Health economics report

XR Therapeutics

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1 Executive summary

Under the stepped-care approach set out by National Institute for Health and Care Excellence (NICE) guidelines for most kinds of anxiety there is a clear place for Cognitive Behavioural Therapy (CBT). CBT is the most commonly offered treatment under the NHS Talking Therapies (formerly IAPT) programme. NHS Talking Therapies only supports evidence-based treatments that have been recommended by NICE. NICE have also been very active in recent years in assessing digital interventions particularly using their new Early Value Assessment (EVA) programme.

NICE have been very clear and consistent about the type of evidence that they are looking for in relation to treatments for inclusion in the NHS Talking Therapies programme. The most important form of evidence is of clinical effectiveness in the relevant population. This means that populations should be identified as having a specific type of anxiety disorder rather than being the general NHS Talking Therapies population. RCTs are recommended as the preferred form of evidence with comparator being standard of care in the NHS Talking Therapies (TT) programme. Preferred outcomes are those which align with the current data collected in the TT programme including PHQ9, GAD7 and an appropriate validated measure for the specific anxiety disorder. Some form of follow-up of the trial population to ascertain the longevity of treatment effects, relapse rates and subsequent resource use will ideally take place. The NICE committees have also recommended collecting data on patient experience, resource use and on quality of life. Number and duration of therapy sessions and grade of therapist data should also be collected.

In the economic evaluations which have accompanied the recent EVAs there is generally a recognition that digitally enabled therapy can be cost saving or cost effective but because of the limited clinical effectiveness evidence there is a high level of uncertainty. The cost savings are generally realized because with many digital interventions, the level of therapist and/or the amount of therapist time can be reduced. Although it is recognized that a lifetime horizon would be preferable (in line with NICE's reference case) most of the models have been short term decision trees which aim to capture an element of response/non-response and stepped or subsequent treatment models.

For XR Therapeutics cost savings would be highly likely if, as claimed, equivalent clinical effectiveness could be achieved with a much shorter course of treatment delivered by a lower grade therapist. The early model developed alongside this scoping exercise found that the cost savings were relatively insensitive to clinical effectiveness because the course of treatment is so much cheaper, even with license fees and upfront costs of mini-studio set -up where appropriate.

There is recognition that treatments may need to be adapted for different populations (e.g. neurodivergent) so there is scope to emphasise the usefulness of XR Therapeutics technology in this regard.

Recommendations:

- Build evidence base, RCTs preferred with TT standard of care as comparator
- Focus on specific types of anxiety rather than generalized TT population
- Use outcome measures aligned with TT programme including a validated measure specific to the type of anxiety, measure of work and social functioning (Work and Social Adjustment Assessment), quality of life and patient perceptions
- Follow-up trial participants to track resource use (subsequent treatments), quality of life and relapse
- Collect data on previous history of patients including previous interventions, response and relapse.

2 Introduction

2.1 Purpose of this document

The purpose of this Health Economic Report is to set out the results of an initial health economics scoping review and early modelling exercise for XR Therapeutics Limited (XRT). The report records decisions made in the development of the early model, results and uncertainties, as well as sources of information used and provides recommendations for outcome measures and other data sources which may be useful to collect in real world evidence and any subsequent clinical studies.

2.2 Clinical context

Anxiety is a type of fear usually associated with the thought or threat of something going wrong in the future but it can also arise from something happening right now. In 2021, those aged 16-29 were most likely to have some form of anxiety (28%). This decreased steadily through the age groups with the least likely to have some form of anxiety being those aged 70 and over (5%). Women report higher anxiety levels than men with 37.1% of women reporting some form of anxiety in 2022-3 compared to 29.9% of men. Most people report feeling low or very low levels of anxiety (59.4%) compared to medium or high levels of anxiety (40.5%). (Anxiety: statistics | Mental Health Foundation drawing on information from the Office of National Statistics).

There are several major sub-types of anxiety Types of anxiety disorders - Mental Health UK (mentalhealth-uk.org). Generalised anxiety disorder (GAD) is the most common type and its main symptom is excessive worrying about different activities and events. People with GAD often feel 'on edge' or hyper alert to their surroundings. GAD can affect day to day functioning such as the ability to work, travel, sleep and can also have physical symptoms such as sweating and muscle tension. Comorbidity with depression and more specific forms of anxiety is common. Panic disorder may be diagnosed when a person has regular panic attacks with no particular trigger. It is possible to dissociate during a panic attack and they can be very intense and frightening. Certain situations can cause panic attacks (eg getting in a lift if you have a phobia about small spaces) but this would probably not be diagnosed as panic disorder as it has a specific trigger. Social anxiety disorder (SAD) or social phobia is when you have an intense dread of social situations. People with SAD may experience anxiety when speaking in public or groups, meeting new people, dating or eating or drinking in public. Physical signs of anxiety may be sweating, racing heartbeat, blushing or shaky voice. Health anxiety is the fear that you are ill or going to get ill. Symptoms are constantly checking your body for signs of illness, seeking reassurance, worrying that results are incorrect, obsessively consuming health-related content or avoiding health-related content. Phobias are overwhelming fears of a particular object, situation, feeling or animal. Phobia is more intense than fear. People with phobias may avoid the trigger which may cause issues in their life. Agoraphobia is a fear of being in situations where escape may be difficult or where help may not be available if things went wrong. This might be leaving home, being in public spaces, using public transport or being in crowded spaces. Avoiding these situations can cause difficulties in people's day to day lives.

Other mental health conditions which are related to anxiety disorders are obsessive-compulsive disorder (OCD) and Post Traumatic stress disorder (PTSD). The obsessive part of OCD is a repeated unwelcome thought or image which is disturbing and difficult to ignore. The compulsive part is something which a person may think about or do repeatedly to help relieve the anxiety caused by the obsession. Common types of OCD relate to contamination, safety checks, intrusive thoughts and hoarding. PTSD is caused by a threatening situation such as a car crash or abuse. Anxious feelings continuing long after the threatening situation has passed.

XR Therapeutics current evidence base focuses on patients with autistic spectrum disorder although they are building real world evidence in the neurotypical population. Autism spectrum disorders occur in around 1% of the population and are characterized by social communication difficulties and repetitive behaviours (Maskey et al, 2019b). Anxiety is common in children with ASD with specific fears and phobias one of the most common sub-types (Maskey et al, 2014). Around half of young people with ASD suffer from anxiety (Simonoff et al, 2008). Anxiety disorders are associated with significant social, emotional and economic impact (Ialongo

et al,1995) and if untreated can become chronic with negative effects on other family members (McPheeters et al, 2011). The presence of anxiety symptoms in adolescence is a significant predictor of anxiety disorder in adulthood (Pine et al, 1998) indicating the long-term psychological, social and economic significance of childhood anxiety (van Steensel et al, 2013). Mayes et al, (2013) found that over half of children with ASD had intense fears and phobias. Specific fears and phobias can cause significant distress and have a serious impact on young people with ASD and their families inhibiting the acquisition of education or daily life skills (Leyfer et al, 2006; Mayes et al, 2013). Early intervention allows young people to develop coping skills, potentially reducing the impact of anxiety on school attendance, academic achievement, social participation and future employment (Drahota et al, 2011).

Recent activity in adapting CBT techniques for ASD has demonstrated that there are four aspects to successful adaptation: 1) development of disorder specific hierarchies 2) use of concrete visual tactics 3) incorporation of child specific interests 4) incorporation of parents (Moree and Davis, 2010). Good evidence that CBT can reduce anxiety but mostly evidence on generalized anxiety or social phobia rather than specific fears/phobias. McConachie et al (2013) successfully tackled general and social anxiety in an RCT of group treatment using CBT; 82% of children aged 9-13 had specific phobias at baseline and a similar proportion continued to have this following group CBT, suggesting that specific interventions are required. Graduated exposure is identified as the key therapeutic mechanism in evidence-based treatments for specific phobias and fears (Ollendick and King, 2006). But this is likely to require adaptation for people with ASD as they tend to experience difficulties with imagination. Those with ASD may also need help with recognizing and describing feelings. VRE has been used safely in people without ASD to treat fear of flying and heights (Rothbaum and Hodges, 1999) and fear of public speaking (Slater et al, 2006). VRE has also been used to teach people with ASD various skills including social understanding, facial expressions, road safety and fire alarm procedures (Mitchell et al, 2007; Fabri et al, 2007; Josman et al, 2008).

2.3 Background to the technology

The technology is a treatment for anxiety combining cognitive behavioral therapy (CBT) with graduated exposure in a virtual reality environment (VRE). Initially, the VRE environment was a purpose-built 360 degree seamless screen room where patients would be totally immersed in a VRE tailored to provide exposure to the environment where the patient would feel anxious. Subsequent work demonstrated that the benefits of the graduated exposure with CBT could also be achieved using a flat screen with the patient sitting with the therapist (see Figure 1) or even virtually delivered (now named 'Boundless'). This means that the technology is highly scalable. The technology has been fully developed and is in use in several NHS Trusts as well as being provided privately by XR Therapeutics. The business model with existing NHS Trust customers is that a Trust buys so many hours of screen time (500 or 1,000 hours for example). Each Trust will use a mini studio which is set up with a flat screen TV, an iPad to access the scenes and a sound bar. Set up of the mini studio costs around £4,000 upfront.

Figure 1 - Face to face option - mini suite

2.4 Claims

- VR enabled graduated exposure can reduce number of CBT sessions required to 4 from 6-8 up to 12.
- Therapy can be delivered by a lower grade of therapist than would typically deliver graduated exposure therapy.
- Some patients with ASD who would not otherwise access care are able to do so with VR e.g. overcoming needle phobias so able to access vaccination. XR Therapeutics have used suggestions from the NAS-Good-Practice-Guide-A4.pdf (thirdlight.com) to make therapy more accessible for people with ASD, and have worked with focus groups of autistic people with and without learning disabilities.

2.5 Potential indication/setting/population

The company have indicated that the technology can be used for a wide range of anxiety disorders. Initial published research studies have been limited to patients with ASD but neurotypical patients can also benefit. The initial published research studies were focused on specific anxieties/phobias but the company believes that the technology is effective against a variety of anxiety-related problems and real world evidence collection is underway in these broader populations. Table 1 includes the various settings, populations and indications where the technology can be used. The value proposition remains the same regardless of use case.

Table 1 - Suggested settings and use cases for XR Therapeutics system

Setting	Population	Indication	Benefit over standard of care
• Flat screen face to face in clinic • Virtual (Boundless)	• Adults or children • Neurotypical or neurodivergent	• Specific anxiety/phobia • Social anxiety • Generalised anxiety • Obsessive compulsive disorder • Low mood/depression • Any indication treated using behavioural activation	• Equivalent effectiveness to standard of care • Reduced number of therapy sessions required • Lower grade of therapist can achieve same results

The current evidence base consists of four published studies (Maskey et al, 2014; Maskey et al, 2019a, b and c). The focus of evidence generation to date has been in neurodivergent adults and children with specific phobias. However, real world data is being collected as treatment of neurotypical adults and children is being delivered in NHS clinical services and to private patients treated within XRT.

3 Current and proposed clinical pathways

3.1 Current clinical pathway

Care for patients with anxiety is set out in a number of NICE clinical guidelines which are summarized in section 9.3. Generally care is organized on a stepped basis with step 1 being diagnosis and the provision of educational material. Steps 2 and 3 are delivered within the NHS Talking Therapies (TT) programme (formerly Increasing Access to Psychological Therapies (IAPT)). Patients whose symptoms deteriorate may be moved to Step 4 where care is delivered by specialized mental health services.

The following figure illustrates a typical patient pathway in the TT programme with the patient first receiving low intensity interventions at first (guided self-help) and then moving on to CBT if required. CBT is the most frequently delivered therapy as part of NHS Talking Therapies with just under 2 million appointments out of a total of just over 3.8 million appointments in 2022-23 and 225,000 courses of therapy out of a total of 525,000 (Talking Therapies Annual Report). Digitally enabled therapies are most often offered in step 2 low intensity interventions but can also be offered in step 3 high intensity if they include the same therapeutic content as recommended in the appropriate NICE guideline and are delivered by an appropriately trained high intensity therapist. XR Therapeutics VR tools are used at both steps 2 and 3.

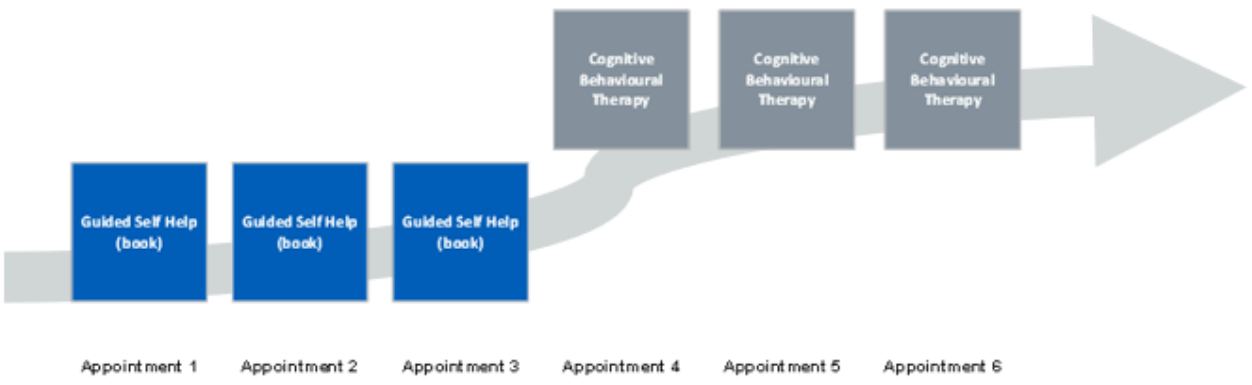


Figure 1: example NHS Talking Therapies patient journey

Additional analysis of therapy-based outcomes in IAPT services - NHS England Digital

The TT programme is strictly quality controlled with all treatments evidence-based and recommended by the National Institute of Health and Care Excellence (NICE). Measurement-based care is practiced throughout with patients and/or carers/supporters completing pre and post treatment measures appropriate to their diagnosis and treatment. The IAPT Manual (england.nhs.uk) provides outcome measures appropriate for each anxiety type and PHQ9 and GAD7 are collected for all patients. Table 9 in the manual has cut-off levels for caseness (when a patient can reliably be said to have a diagnosis) and reliable change index. PHQ9 and the relevant Anxiety Disorder Specific Measure (ADSM) are used to calculate recovery and reliable improvement. Data collection is rigorous.

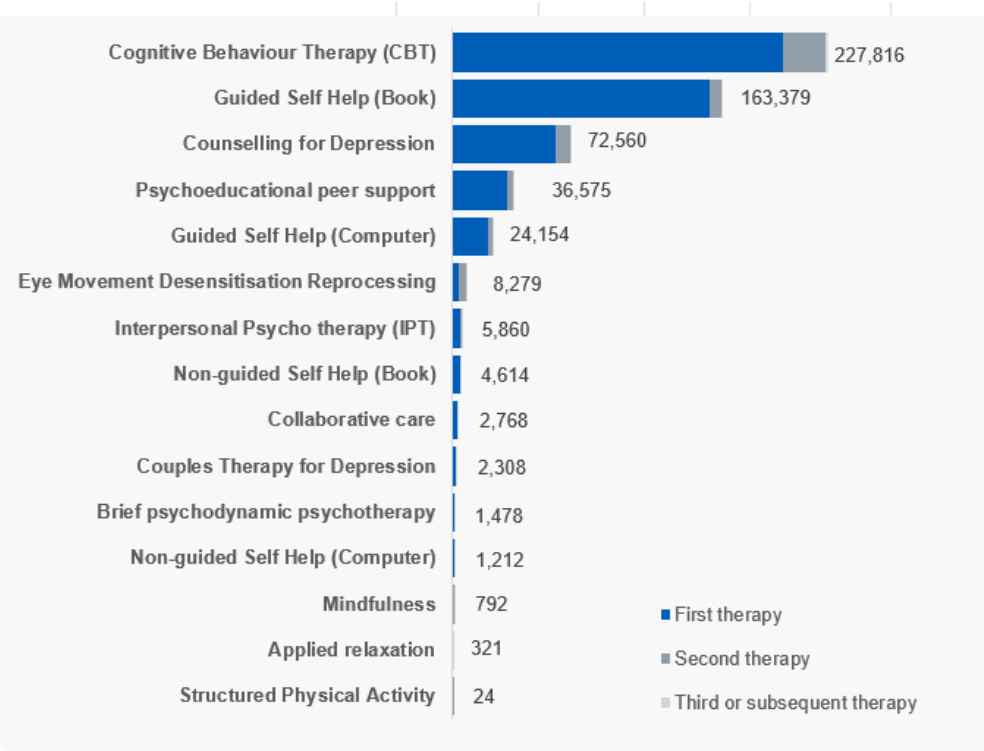


Figure 2: Number of courses of each therapy type and relative position in pathway, England, 2022-23

Although some courses of therapy are given concurrently with other types of therapy, CBT is given alone 95.4% of the time. Thus the recovery rates for CBT are virtually all due to CBT rather than the therapy provided alongside. XR Therapeutics are tools which are used for the delivery of CBT.

3.2 Proposed clinical pathway

The technology could be added in to any CBT treatment. In all cases the proposed treatment sequence would be a single 45 minute preparatory session delivered by the therapist who will deliver the course of therapy. During this preparatory session targets are set and CBT techniques such as breathing and relaxation are taught. This can be delivered face to face with supporters present or via a self-learning package which is sent out ahead of the first VR appointment and completed at home by the patient. The VR scenarios would then be developed and therapy would involve four 20 minute sessions delivered on two days (each day having two sessions separated by a break). Low intensity interventions would be delivered by a psychology assistant (Band 5) and high intensity interventions by a Band 6 or above. Across the sessions the scenario becomes increasingly challenging for the patient. The four therapy sessions are backed up with advice on how to gradually increase the challenge in a real world setting. Parents or supporters can observe and are involved in supporting when practices are transferred to a real world setting. Pre and post intervention questionnaires are completed.

4 Adoption in the NHS

4.1 Introduction

Successful adoption of any intervention or device in the NHS is dependent on the extent and credibility of the claims made for it by its manufacturer. They will need to make a number claims for the technology through their promotional literature and presentations covering areas such as efficacy, user experience and practicality, device safety and cost savings.

The NHS has finite resources. Every pound spent on a new device is a pound that cannot be spent on existing patient care. It is therefore important to be able to demonstrate that money spent on any new device will

bring at least as much patient benefit as a pound spent elsewhere. In general terms a new device or intervention will deliver either improved, equivalent or reduced patient benefit and will be either cheaper, about the same or more expensive. There are therefore potentially nine states such a device or intervention can occupy as shown in the figure below.

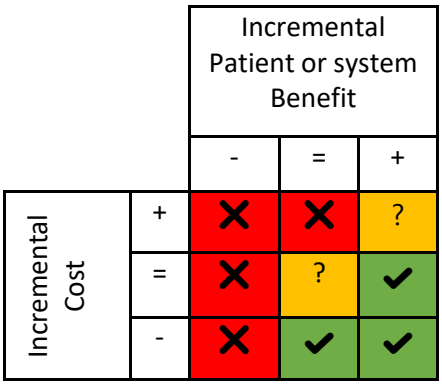


Figure 2 - cost-effectiveness plane showing typical decisions to adopt a technology or not

A device or intervention that delivers reduced patient benefit is unlikely to be adopted into the NHS even if it is cheaper than current care pathways. A device or intervention that brings equivalent patient benefit is only likely to be adopted into the NHS if it cheaper than current care pathways. A device or intervention that delivers improved patient benefit has most potential to be adopted into the NHS if it is the same price or cheaper (green zones in Figure 2 above). It may also be adopted if it is more expensive but more evidence and involved processes of assessment will be involved (amber zones).

The key factor to consider when developing claims is the level of evidence required to support those claims. The amount and level of evidence required is somewhat subjective. It is acknowledged and accepted that large scale, multi-site RCTs are unlikely to be available for most new medical devices: a lower burden of evidence is generally accepted. There is also an unwritten rule that the greater the credible potential benefit (either patient or healthcare system benefit) the lower the required evidence threshold. The claims and evidence generation plan should be in line with the device Technical file. Evidence generation has been extensively discussed in the early value assessments carried out by NICE in recent years. They provide clear guidance about what would be needed for XR Therapeutics to receive NICE approval (which would be required for wholesale adoption in the TT programme). In addition to a solid evidence base, NICE has asked other digital technologies to have DTAC certification which is a requirement by NHS England Transformation Directorate for all digital technologies being used in the NHS whether they are medical devices or not. XR Therapeutics have DTAC and are registered as a Class I medical device. Similarly, the XR Therapeutics platform should meet the requirements of the NICE Evidence Standards Framework for Digital Health Technologies.

4.2 Costs

4.2.1 General points

Costs can be direct and indirect. Direct costs are the costs spent on the medical device and other aspects of the intervention. Indirect costs are costs incurred by the healthcare provider which may be incurred elsewhere in the clinical pathway but that are impacted by the use of a medical device. An example of an indirect cost is a hospital admission for an infection after an initial surgery. Providing information on both direct and indirect costs can help make the full impact of the new device apparent, particularly if cost savings are indirect rather than direct. Where both direct and indirect cost savings can be shown this may be particularly persuasive. It is usual in the UK to consider costs only from a health and social care perspective (ie those costs incurred by the health and social care system) as these are the most relevant costs for the healthcare service decision maker. However, it is also important to take note of costs incurred by patients and carers, including lost working time, as this can help to influence decision makers in some cases.

4.2.2 Direct per patient costs

Table 2 – Direct per patient costs of XRT therapy and standard of care CBT

Cost item	Mini-studio	Boundless	SOC – face to face CBT	SOC – virtual CBT
Initial set up of mini-studio	£4,000	-	-	-
Lifetime of capital item (years)	5	-	-	-
Annual capital cost	£800	-	-	-
XRT charges for accessing scenarios – intentionally left blank in order to estimate head room for licensing costs			-	-
Training cost for XRT	£148	£148		
Total annual costs	£948	£148	-	-
Therapy hours per year	50 weeks x 37.5/2 hours = 937.5	50 weeks x 37.5/2 hours = 937.5 -		
Hours per patient	Initial set up 40 minutes plus 4x20 minutes = 2hrs	Initial set 40 minutes plus 4x20 minutes = 2hrs		
Patients per year (therapy hours per year divided by hours per patient from rows above)	468.75	468.75		
Upfront costs per patient	£2.02	£0.32	-	-
Therapist time – initial meeting – 40 minutes – Grade 7	=40/60 x £63 = £42	=40/60 x £63 = £42	-	-
Therapist time – VRE/CBT sessions (4*20 minutes split over 2 occasions) – Grade 6	=80/60 x £53 = £70.67	=80/60 x £53 = £70.67	-	-
Therapist time – SOC Step 3 (20%) - 8 sessions of 50 minutes – G7 = =8 x 50/60 x £63 = £420 x 20% = £84 Step 2 (80%)- 8 sessions of 30 minutes – G6 8 x 30/60 x £53 x 80% =£170			Total = £254	Total = £254
Total costs per patient	**£114.69**	**£112.98**	**£254**	**£254**

Training for the individual therapist is a two hour workshop with an experienced psychologist then time to read the manual. Assume Grade 8b psychologist trains 4 people at once – 30 mins of time at £84 = £42. Plus 2 hours of the Band 6 at £53 = £148. Assume it needs doing every year. Therapist time from PSSRU. Grade 6 clinical psychology trainee is £53 per hour, grade 7 clinical psychologist £63 per hour. These costs account for indirect time per patient (which is roughly even – ie for every hour of direct time there's 0.91 hours of indirect time). The unit costs of health and social care_Final3.pdf (kent.ac.uk). Per XR Therapeutics SOC sessions would likely be grade 6 for low intensity step 2 interventions, with each appointment lasting 30 minutes. For step 3 high intensity interventions sessions would likely last 50 minutes and be delivered by a Grade 7 member of staff. 8 sessions was the mean number of sessions delivered from the NHS Talking Therapies Annual Report 2022-23. In the absence of information about what proportion of the treatments in standard of care are step 2 or step 3 we will assume that 80% are step 2 interventions and 20% are step 3.

For some indications graded exposure therapy would require set up costs which would not be required using XR Therapeutics virtual reality tool. For example, someone with a dog phobia may require set up of a scenario of gradual exposure to a dog or dogs and this would require significant input from the therapist for preparation and paperwork planning time out the office. We have not included this in our analysis but it would be useful for XR Therapeutics to gather anecdotal evidence of situations where this is the case.

4.2.3 Indirect costs

One potentially significant category of indirect costs is increased physical healthcare costs which tend to be higher among people suffering with anxiety and depression. Melek et al, 2014 found that per member per month physical healthcare costs were $899 for members with mental health or substance abuse disorders compared to $390 for members without mental health or substance abuse disorders. There will be an element of poorer mental health in patients with chronic conditions but there will also be some of this difference which will be explained by poorer mental health leading to worse physical health outcomes. The evidence for these costs is unlikely to be sufficient that it could be included in a model but it is worth making the point that there is likely to be a reduction in physical healthcare costs if recovery from mental health conditions is accelerated.

4.2.4 Societal costs

Costs incurred by patients and carers/supporters may include out of pocket expenses including travel costs getting to appointments, other costs incurred dealing with anxiety including private medical costs or adaptation costs (eg travelling by taxi rather than by bus). If anxiety has resulted in either the patient or a carer/supporter losing wages due to having time off or retiring early then this loss of earnings can be included in a secondary analysis. XR Therapeutics technology may result in a reduced amount of time off for patients/supporters due to the reduction in the number of sessions required and the structure of the sessions in two lots of two sessions. Travel costs may also be reduced if therapy which previously had to be delivered in person can be delivered remotely although much standard of care therapy will also be delivered remotely.

4.3 Budget impact and reimbursement

4.3.1 General points

Budget impact is an important consideration for healthcare service decision makers. The timing of direct and indirect costs and savings impacts upon budget. Where additional costs are incurred upfront, even if they are outweighed by savings at a later date, the case for adoption is less persuasive. It can also be important where costs are incurred and savings delivered. For example, if costs are incurred which need to be met from a diagnostics budget but savings will be made in a pharmaceuticals budget, this can make the case for adoption more difficult.

4.3.2 XRT budget impact

XR Therapeutics agree a rate with customers based on a number of hours access to the VR scenarios. The customer pays on a monthly basis for the hours used based on XR Therapeutics data. The introduction of XR Therapeutics would incur a small amount of additional up front cost if the buyer was interested in the mini studio face to face version. Licensing fees would also be incurred but these may not be charged upfront. XR Therapeutics offer a leasing option for the mini studio and may also absorb the capital cost of the initial set up resulting in no upfront costs for a trust. Savings from introducing XR Therapeutics are in therapist time. Given the scarcity of resource, it is unlikely that any savings would be cash releasing. Therapists' time would be redirected. This should result in additional patients being seen and a reduction in waiting lists.

4.4 Patient benefit

The technology is expected to improve patient health and wellbeing by accelerating recovery. Overall, XRT has the potential to reduce symptoms for mental health conditions and improve quality of life for patients and their friends/family members although this is quite difficult to evidence. A proportion of patients (adults and children) appear to benefit from the treatment with response rates around $^1/_3$ to ½ patients. In an adult study quality of life data was also collected from a small number of patients which may allow a difference to be identified between responders and non-responders.

Outcome measures which have been used in the XR Therapeutics clinical studies to date as well as some potential measures are included in the table below. It is clear from the NICE EVAs (see Section 9.3) that the outcome measures NICE are looking for are those which tie in with the NHS Talking Therapies programme

(PHQ9, GAD7, WSAS, a specific validated measure for the particular indication), and other data such as participation, patient perceptions, quality of life and resource use.

Table 3 - Outcome measures used in Maskey papers and usefulness for health economic analysis

Measure	Reference	Usefulness for HE or otherwise
SCQ – social communication questionnaire – parent	Maskey et al, 2014, 2019b,c	This is a scale used to determine whether a child fits the profile for autistic spectrum disorder (ASD) rather than an outcome measure in the clinical study
Anxiety Disorders Interview Schedule (ADIS)	Maskey et al, 2019b	Widely used standardized clinical interview carried out with parents.
Vineland Adaptive Behaviour Scales (VABS)	Maskey et al, 2019b	Parent interview comparing children's functional skills to age norms – IQ assessment not undertaken as would not be included in current clinical practice.
Social Responsiveness Scale – 2nd edition (SRS-2)	Maskey et al, 2019a	Similar to above but for adults. Used to assess the ASD characteristics of the clinical study participants. 66-75 moderate impairment, 76 or higher severe impairment.
Spence Children's Anxiety Scale (SCAS – P/SCAS – C)	Maskey et al, 2014 Maskey et al, 2019b,c	Used as an outcome measure but likely to capture general rather than specific anxiety. Widely used in ASD studies. NB children rather than adults.
Fear survey schedule of children – revised (FSSC-R)	Maskey et al, 2019b	80 item parent-report questionnaire with an overall intensity and fearfulness score – most commonly used tool for assessment of common fears and phobias.
Children's Assessment of participation and enjoyment (CAPE)	Maskey et al, 2019b	Completed by child at baseline and 9 months and intended to measure any increase in participation in community activities. 50 item child-report of activities.
Beck Anxiety Inventory (BAI)	Maskey et al, 2019a	Used as an outcome measure but likely to capture general rather than specific anxiety (adults). Requires basic reading level.
Generalized anxiety disorder 7 (GAD-7)	Maskey et al, 2019a	Used as an outcome measure but designed to capture general rather than specific anxiety (adults). Standard measure in NHS Talking Therapies.
Patient Health Questionnaire – 9 (PHQ9)	Maskey et al, 2019a	Used as an outcome measure to capture symptoms of depression. Measures overall depression severity as well as the specific symptoms. Standard measure in NHS Talking Therapies.
WHOQOL-BREF	Maskey et al, 2019a	Measure of quality of life 26 items addressing 4 domains (physical health, psychological health, social relationships and environment). 8 adults showed average improvement up to 6 months in the social and environment domains.
Target Behaviour Scores	Maskey et al, 2014, (children) Maskey et al, 2019a (adults) Maskey et al, 2019b,c (children)	Used to measure response to therapy with regard to the specific fear targeted. Involves vignettes at baseline and follow-up points which are then scored on a scale of 1-9 for change from baseline. Change of 1-3 is classed as a responder. Requires review by panel of experts and clinical time for interview and development of vignette.

Confidence Ratings – parent and child, adult and supporter	Maskey et al, 2014. Maskey et al, 2019a/b/c	Used as a tool within the therapy session (adults and children). Visual VAS scale from 1-6 for the specific anxiety trigger. Parent/supporter completes at end of session when observing.

Table 4 - Other outcome measures which could be useful

R-CADS	Revised Children's Anxiety and Depression Scale (RCADS) (corc.uk.net)	47 item, youth self-report questionnaire with sub-scales. Available in child and parent versions. Too developmentally advanced for use with children with learning difficulties unless mild.
ASC-ASD	ASC-ASD Child | Neurodevelopment and Disability | Newcastle University (ncl.ac.uk)	Adapted version of RCADS for children with ASD.
EQ-5D-3L or 5L	EQ-5D-5L | EuroQol	Quality of life measure for use with adults. Erridge (2022) uses EQ5D-5L with patients with autism. There is an adapted version for adults with learning difficulties.
CHU – 9D	CHU9D - Measuring health and calculating QALYs for children and adolescents. available from University of Sheffield Licensing	Quality of life measure for use with children. Has also been validated in children with ASD.
WSAS	Work and Social Adjustment Scale (WSAS) (nhs.wales)	Measure of functioning. Standard measure from NHS Talking Therapies programme.

4.5 Health system benefit

In addition to the patient benefit, health service providers will potentially benefit from having access to XR through:

- A reduction in therapist time in providing CBT, where this service is already provided for patients
- A potential reduction in other services if patient is able to reduce symptoms of specific anxiety

4.6 NICE engagement

NHS Talking Therapies only includes interventions which are recommended by NICE. XR Therapeutics has experience of participating in an Early Value Assessment (HTE15 – VR technologies for treating agoraphobia EVA – Nov 2023). On that occasion NICE recommended that XRT be used in research only because the evidence of effectiveness in this population (those over 18 with diagnosed agoraphobia) was not sufficient. It would be advisable that XRT build up the evidence base for clinical and cost effectiveness in specific populations included in the wider NHS Talking Therapies programme. Although real world evidence is welcomed by NICE, RCT evidence with standard of care as comparator is still seen as more robust and given the quite strong claims made by XRT (equivalent performance from much shorter treatment sequence) the RCT study design may be advisable.

5 Economic evidence

5.1 Introduction to health economic models

A health economic model is developed in order to compare the costs and the outcomes of the clinical pathways with and without the new technology. At the earliest stages of development (up to TRL 4 see DRAFT PROGRAM ANNOUNCEMENT (mtec-sc.org)) there is generally no evidence specific to the technology and often it is unclear which indication or position in the pathway the technology will target. This leads to a large amount of uncertainty which impacts on the appropriate health economic model. It might mean that a number of

simple models are developed to explore different uses of the technology. It is also often appropriate to include a wide range of outcome measures in what is known as a 'cost-consequence' model. This provides decision-makers with information about costs and other outcomes which are of interest to them. It may be possible to also produce a cost-utility model, if information about quality of life is available. It is generally not appropriate to calculate an incremental cost effectiveness ratio (ICER, the principal metric used by NICE for recommendations of cost-effectiveness) at such an early stage of development as the modelling is being used to answer a broader range of questions than the adoption decision which NICE typically consider. Questions which early health economic models (in conjunction with qualitative work alongside) try to answer are:

1. What are the current clinical pathways?
2. How might the technology under consideration change the clinical pathways?
3. What is the 'room for improvement' or size of clinical need?
4. What are the value propositions of the new technology? Eg cost savings, improved health outcomes, system efficiencies.
5. What characteristics does the new technology need in order to deliver claimed value propositions?
6. What is the maximum price the potential improvement in health outcomes adjusted for any cost impact could support (headroom estimate)?

The developer can use the answer to question 6, often called a 'headroom estimate' to decide whether the further development of the technology is likely to offer an acceptable return on investment (ROI). We can provide assistance with an ROI calculation.

5.2 PICO

Population, Intervention, Comparator, Outcomes (PICO) is often used to structure a decision problem to be considered in a health economic model. The PICO will vary depending on the use case. For XR the PICO is set out in Table 5. The model has been set up such that you can select different sub-types of anxiety and this will input the appropriate recovery rate from NHS Talking Therapies data.

Table 5 - PICO for XRT

Population	Patients with various forms of anxiety suitable for treatment with CBT
Intervention	VRE enabled CBT (XR therapeutics)
Comparator	CBT delivered as in SOC
Outcomes	Utilities, Cost, Proportion of patients in recovery

5.3 Analytic approach

XRT are likely to be cost saving over a short time horizon. Although a lifetime horizon is the preferred time horizon for a NICE Reference Case based economic evaluation shorter time horizons can be preferable if the economic case can be made over a shorter time horizon as this will minimize uncertainty. An economic evaluation for XRT would take a health and social care perspective as the base case analysis. A secondary analysis could be undertaken including lost working time but this may not be worth including given that XRT is already likely to be cost saving. We will undertake a cost utility analysis in this early health economic modelling exercise. This means we will report costs and quality adjusted life years and use these to calculate an incremental cost effectiveness ratio, if this is appropriate.

Utility data is available from the literature to populate the model, although the source used in this initial model is based on US population norms. Ideally, utility values for patients before, during and after XR therapy should be collected. CHU-9D has been validated in children with neurodevelopmental disorders including ASD. There is an algorithm from Australian adolescents translating this to utility values (Perry et al, 2024 includes references for algorithms). CHU9D - Measuring health and calculating QALYs for children and adolescents. (sheffield.ac.uk). There is also a UK adult algorithm. You need to register to use the CHU-9D. Figure 3 below from Stevens et al, 2010 gives the content of the CHU9D. Stevens et al, 2010, also contains an algorithm for scoring the content as a utility. O'Dwyer has an adapted EQ5D for adults with learning difficulties. For adults

without learning difficulties, either the EQ5D3L or the EQ5D5L would be ideal instruments for the collection of quality of life data as they are quick and easy to use. EQ5D3L is the preferred measure for NICE submissions but the five level version can be more sensitive and mapping algorithms are available to convert them to the suitable output for NICE submissions. For cost utility analysis both can be used.

Figure 3 Descriptive system

Dimension	Level	Description
Worried	1	I don't feel worried today
	2	I feel a little bit worried today
	3	I feel a bit worried today
	4	I feel quite worried today
	5	I feel very worried today
Sad	1	I don't feel sad today
	2	I feel a little bit sad today
	3	I feel a bit sad today
	4	I feel quite sad today
	5	I feel very sad today
Annoyed	1	I don't feel annoyed today
	2	I feel a little bit annoyed today
	3	I feel a bit annoyed today
	4	I feel quite annoyed today
	5	I feel very annoyed today
Tired	1	I don't feel tired today
	2	I feel a little bit tired today
	3	I feel a bit tired today
	4	I feel quite tired today
	5	I feel very tired today
Pain	1	I don't have any pain today
	2	I have a little bit of pain today
	3	I have a bit of pain today
	4	I have quite a lot of pain today
	5	I have a lot of pain today
Sleep	1	Last night I had no problems sleeping
	2	Last night I had a few problems sleeping
	3	Last night I had some problems sleeping
	4	Last night I had many problems sleeping
	5	Last night I couldn't sleep at all
Daily routine	1	I have no problems with my daily routine today
	2	I have a few problems with my daily routine today
	3	I have some problems with my daily routine today
	4	I have many problems with my daily routine today
	5	I can't do my daily routine today
Work	1	I have no problems with my work today
	2	I have a few problems with my work today
	3	I have some problems with my work today
	4	I have many problems with my work today
	5	I can't do my work today
Able to join in activities	1	I can join in with any activities today
	2	I can join in with most activities today
	3	I can join in with some activities today
	4	I can join in with a few activities today
	5	I can join in with no activities today

5.4 Model structures

See section 10.3 for models identified in NICE HTE9. Figure 2 below is a suggested model structure from the assessment report. Following the Figure are some suggestions for an ideal model structure for anxiety. The benefit of this 15 month decision tree is that it allows for a second same level treatment to be provided for non-responders or those who relapse as well as a further stepped treatment for those who continue to not respond. The hybrid structure then allows the findings to be extended to a full lifetime horizon.

Figure 2: Theoretical hybrid model for anxiety

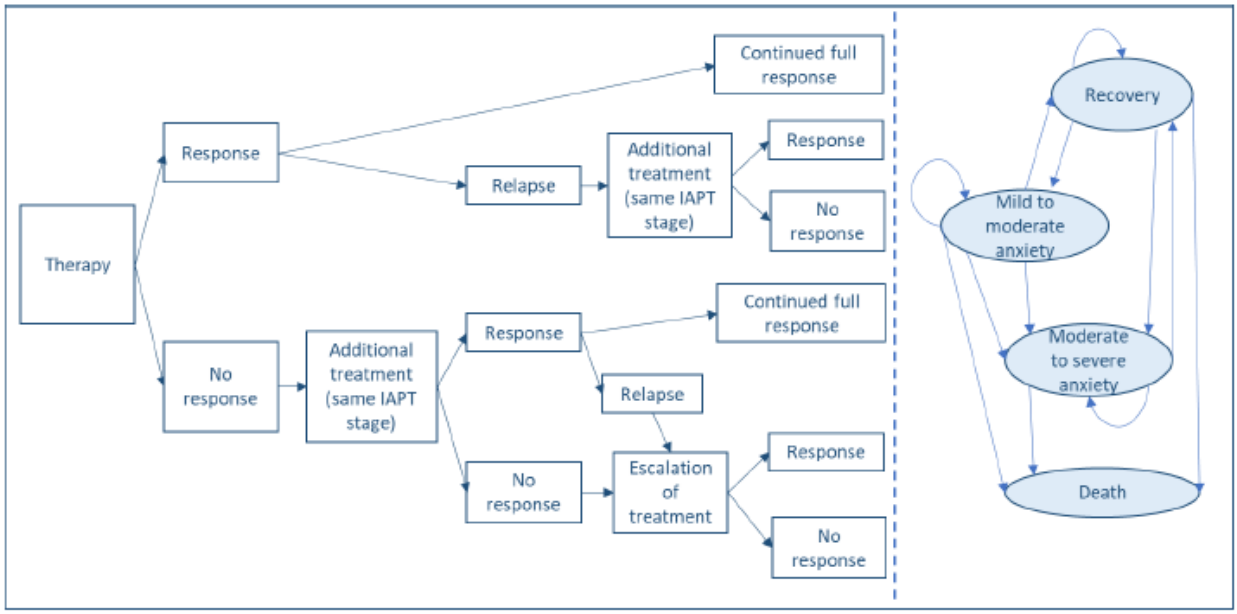


Figure 3: EAG simple decision tree model

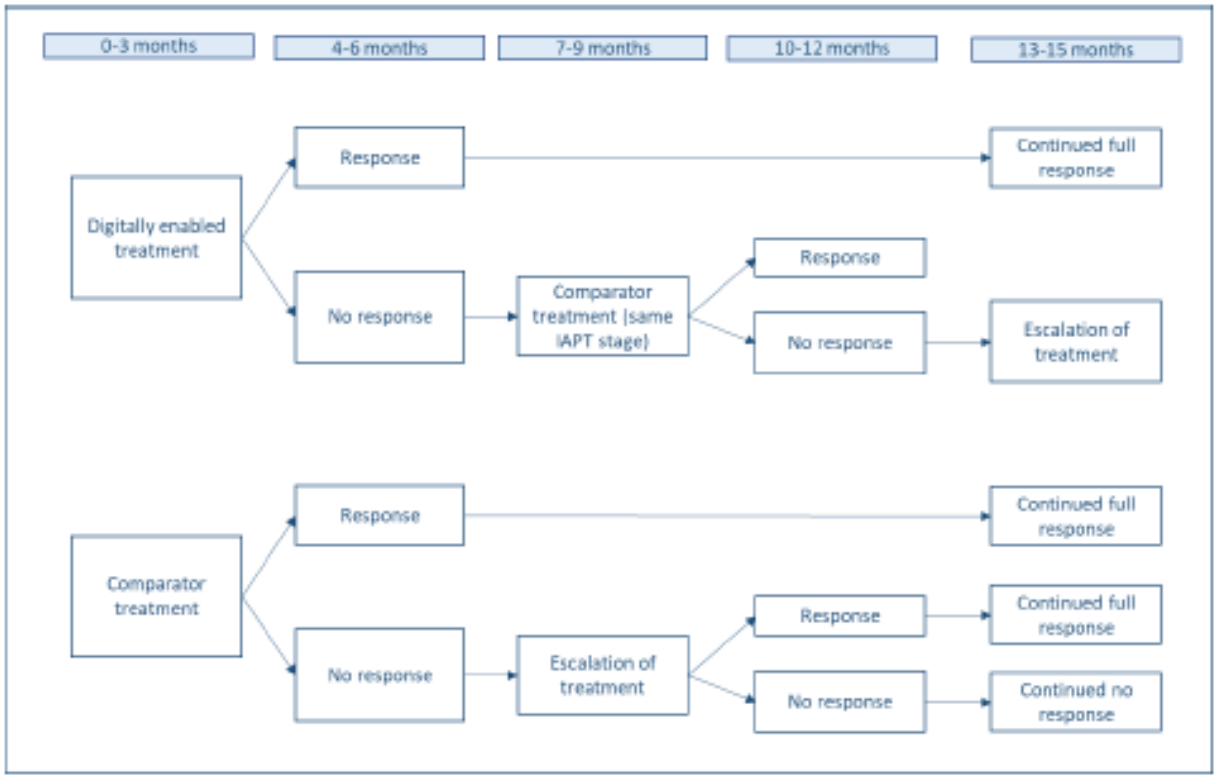


Figure 3 shows the EAG model for HTE9 which is a 15 month decision tree with no follow-up Markov model.

Utility values are used for mild, moderate and severe anxiety. Assumptions that half those having step 2 treatments are mild and half moderate and similar for step 3 between moderate and severe. This model does not consider relapses implying that treatment effect lasts at least one year. Recovery is used rather than reliable recovery although the latter may be more robust. This assessment uses more granular data than publicly available IAPT data in order to model effectiveness of step 2 and step 3 interventions. The EAG recommend a comparator which is a mix of all the other interventions provided by IAPT. Table 17 has key cost parameters which are calculated using time for therapies to be delivered and rates for the bands of therapist from PSSRU data. Clinical effectiveness data for the included digital therapies ranges from 0.464 to 0.818 compared to IAPT recovery rates which range from 0.131 for PTSD to 0.511 for GAD. Costs per patient for licenses are only given for SilverCloud and Spring and they are £49.90 and £40 per user respectively. Other costs are redacted. The snip of section 9.3 from the External Assessment Group for the EVA into digitally enabled therapies for adults with anxiety sets out ideal features of a model together with some potentially relevant sources of data.

NB The IAPT pathway refers to NHS Talking Therapies as it was formerly known as Increasing Access to Psychological Therapies (IAPT).

9.3 *Conceptual modelling*

Existing models have a variety of structures and there is not one single version that is widely accepted. There are however a number of factors that would ideally be included in any model:

- The long-term nature of anxiety disorders
- The possibility that recovery may be followed by relapse or recurrence
- The impact that previous or adjunct treatment may have on the efficacy outcomes (this could be IAPT interventions, medications or others)
- Healthcare and personal social service costs incurred other than direct interventions for anxiety, including those outside the IAPT pathway
- Align with IAPT pathways and definitions, where used for decision making in the IAPT pathway.

Ideally clinical data used in the inputs will:

- be for the anxiety descriptor that is under consideration
- use interventions that are delivered in the same way as described by IAPT (e.g therapist guiding time included)
- be reported using IAPT defined terms, such as caseness thresholds, recovery and reliable recovery
- use of longer term data to demonstrate continued recovery or relapse, with reporting at multiple time points (short and longer-term)
- report ITT results, or according to IAPT manual methods, so that those who drop out, or are missing from the final results are assumed not to experience recovery.
- Include comparators that reflect the most appropriate current treatment, or mix of treatments, usually on the IAPT pathway. These should also be reported fully in any clinical studies.

5.5 Data sources available to support economic evaluation

In an early model, there are typically no clinical data to support the performance of the new technology. Clinical effectiveness in the base case is often assumed from similar technologies or from bench studies.

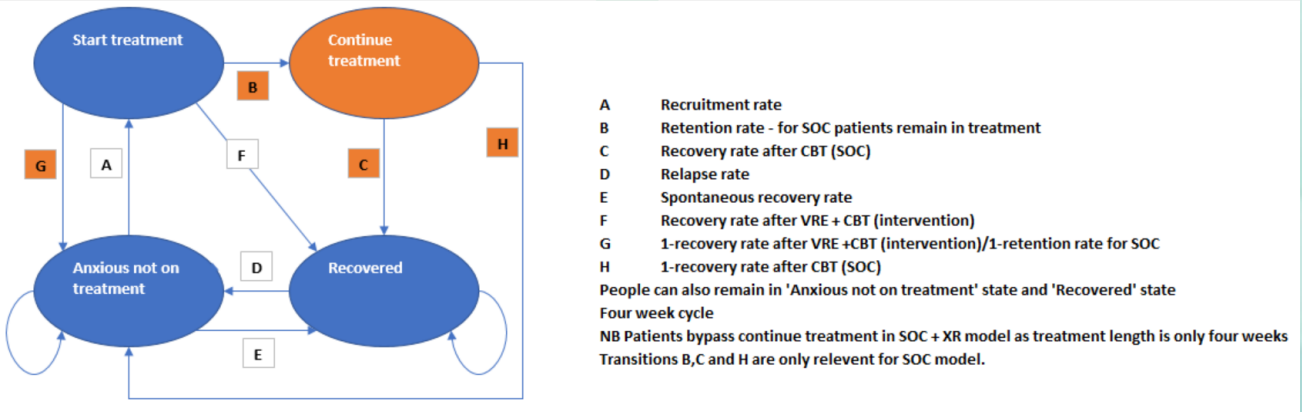
Early economic evaluation is exploratory in nature so whereas a point estimate assumption maybe made for the base case, a full range may be explored in sensitivity analysis or what is known as a threshold analysis may be undertaken to explore how effective the technology has to be compared to the comparator to support a conclusion of cost effectiveness. Cost of the new technology is often not known either at this early stage. We may make an assumption about cost and explore in the same way for clinical effectiveness across a broad range. We may also leave cost out of the early model so that we can reverse engineer what cost would be supported by the value that the technology may bring. Data for other parameters of the model such as costs and utilities (measures of quality of life used in calculating a QALY) are generally sought from the literature. Cost information is also often available from published sources including the NHS National Cost Collection (NHS England » National Cost Collection for the NHS) and the Unit Costs of Health and Social Care 2023 Manual - Kent Academic Repository from the PSSRU at the University of Kent. Registry data is often an important source for population level statistics and NHS Model Hospital and NHS Getting it right first time (GIRFT) often have important bench marking data. The National Institute for Health and Care Excellence (NICE) may also have assessed a similar technology or carried out a comprehensive assessment in the same disease area. The supporting data for these assessments often provide a valuable source for both structure of models and data to populate a model.

6 Methods of and inputs to early health economic model

6.1 Structure of the model

The following figures shows a Markov model suitable for modelling the impact of XR therapeutics. Patients move between the health states on a four week cycle. Patients in the standard of care (SOC) model enter in the Anxious not on treatment health state and then either start treatment or remain in the not on treatment (NOT) state. After starting treatment, patients can either remain in treatment in which case they pass to the Continue treatment health state or stop treatment in which case they return to the NOT state. From Continue treatment patients can either recover or pass back to the NOT state. From Recovered patients can either relapse and pass to the NOT state or remain in the Recovered state. From the NOT state a proportion of patients may spontaneously recover without treatment. The model is slightly simplified when XR is introduced as treatment only requires the Start treatment health state. States and transitions coloured orange are not used in the SOC + XRT model and patients pass straight from Start treatment to Recovered or back to NOT.

Figure 4 –Markov model for cohort of patients entering treatment



The impact of XR Therapeutics will be operationalized primarily through reducing the therapist time and cost attached to the treatment health states. Other parameters may potentially be impacted if XR Therapeutics can justify the impact. For example, recruitment and recovery may be impacted if patients who would not otherwise access treatment would be prepared to undertake treatment given the virtual reality element.

6.2 Inputs to the model

Parameter	Input value	Source
Recruitment rate	0.7	NHS Talking Therapies 2022-3 Annual Report, number starting treatment divided by number referred
Retention rate	0.55	NHS Talking Therapies 2022-3 Annual Report, number completing treatment divided by number starting treatment
Recovery rate	0.526	NHS Talking Therapies 2022-3 Annual Report, figure for 'Anxiety, total'. Drop down available in model to vary response rate
Relapse rate	0.018	Lorimer et al, 2021. O.235 patients relapsed in a 12 month period. 0.235/13 = 0.018
Spontaneous recovery rate	0.038	Mekonen et al, 2020. 0.114 patients relapse over 3 month period. 0.114/3 = 0.038
Impact of XRT on recruitment	1	Assumption
Impact of XRT on retention	1	Assumption
Impact of XRT on recovery	1	Assumption
Impact of XRT on relapse	1	Assumption
Cost of treatment SOC	£254	Calculated for four week period from therapist time requirement – see Costs calculations worksheet
Cost of treatment XRT	£113/£115	Costs provided for virtual and face to face treatment. Differ slightly due to inclusion of mini-studio set up for face to face. Both costs exclude the cost of accessing the VRE scenarios. This is to facilitate a headroom estimate.
Utility for Start treatment	0.516	Morriss et al, 2019 UK patients with moderate to severe anxiety - baseline
Utility for Continue treatment	0.579	Morriss et al, 2019 UK patients with moderate to severe anxiety after 4 weeks of treatment with Alpha Stim
Utility for Recovered	0.855	McNamara et al, 2023. Age population norm for 40-44 age group using male:female ratio of 1:2 from NICE Clinical Knowledge Summary
Utility for anxious not on treatment state	0.516	As start treatment

7 Results of model

7.1 Base case

The base case analysis incorporates the recovery rate for generalized anxiety and compares virtual SOC (CBT) to virtual XRT (Boundless) + CBT. The primary analysis considers a one year time horizon for a cohort of 100 patients who start the model in the Anxious not on treatment (NOT) health state.

Table 6 - Results of the base case analysis for SOC vs SOC + XRT virtual and face to face over 1 year time horizon

	QALYs per 100 patients	Costs per 100 patients	NMB per patient (headroom estimate)	Headroom estimate per patient supported by cost savings
Virtual SOC + XRT	74	£20,496		
Virtual SOC	66	£48,926		
Difference	**7**	**-£28,430**	**£1,781**	**£284**
Face to face SOC + XRT	74	£20,806		
Face to face SOC	66	£48,926		
Difference	**7**	**-£28,120**	**£1,777**	**£281**

NMB – net monetary benefit (difference in QALYs multiplied by threshold, £20,000, plus cost savings), QALY – quality adjusted life year, SOC – standard of care.

The base case results show that SOC + XRT is cost saving because it significantly reduces the amount of sessions of therapy which are required. SOC + XRTalso generates more QALYs as patients progress to the Recovered state more quickly thus adding more QALYs. Moving from virtual to face to face only increases costs slightly as the only incremental costs in this model included are the small set up cost of the mini-studio for face to face provision and some training costs. The cost of buying access to the virtual scenarios is not included as we are using the net monetary value calculated to estimate the headroom available to charge for access to the scenarios. Note that an NMB of approximately £1,700 per patient would support a price in excess of £630,000 for 500 hours of virtual scenarios. This is based on each patient requiring 80 minutes of scenario access (500*60/80*£1700 =£637,000). If the headroom were based on a price needed to allow the technology to be cost saving rather than cost-effective then the price supported would be in excess of £106,500.

It is unlikely that this price level would be acceptable to an NHS Trust. NB digital interventions in the early value assessment of digital interventions for adults with anxiety disorders had prices of £40-£50 per user equating to £15,000-£18,000 for 500 hours access. The following table explores the cost savings provided to an NHS Trust per 100 patients at different price levels for 500 hours access to the XRT scenarios. This analysis only considers virtual provision but results are very similar for face to face. Table 7 shows that significant savings could still be delivered over a range of prices of access for scenarios. NB this is the virtual SOC vs virtual SOC+XRTand assumes equivalent recovery is achieved with SOC+XRT.

Table 7 - scenario analysis based on different price of access to XRT scenarios - virtual

Price per 500 hours access to XRT Scenarios	Cost saving per 100 patients per year	NMB per 100 patients per year valuing each additional QALY at £20,000	License fee per patient per course of therapy	License fee per hour
£0 – base case for headroom analysis	£28,430	£178,059	£0	£0
£5,000	£26,011	£175,641	£13.33	£10
£10,000	£23,592	£173,222	£26.67	£20
£14,500	£21,416	£171,045	£38.67	£29
£25,000	£16,336	£165,965	£66.67	£50
£50,000	£4,242	£153,872	£133.33	£100
£75,000	Additional cost of £7,852	£141,778	£200	£150

The base case model assumes that the shorter provision of therapy with XRT scenarios used in a VR format will achieve equivalent recovery rates to standard of care across all anxiety types. Table 8 explores the reduction in recovery rates which may still be acceptable in order for cost savings to continue to be made and for net monetary benefit to remain positive. Cost of £14,500 for 500 hours of XR scenarios is included in this analysis. This table illustrates that the cost saving is maintained even when XRT has recovery rates 50% of SOC but quality of life gains are reduced to just over 1 QALY per 100 patients per year by this point. Quality of life gains are maintained even when recovery rates are lower using XRT than with SOC because the patients who do recover achieve recovery faster, so spending a greater proportion of their time in the recovered state.

Table 8 - Impact of reducing recovery rates for SOC+XRT - virtual SOC vs virtual SOC+XRT

Impact of XRTon recovery rate (0.9 means XRT's recovery rate is 10% lower than SOC)	Cost savings	Incremental QALYs	NMB per patient
Base case – 1	£21,416	7.48	£1,710
0.9	£19,211	6.54	£1,500
0.8	£16,696	5.46	£1,260
0.7	£13,821	4.23	£984
0.6	£10,533	2.8	£666
0.5	£6,769	1.17	£301

7.2 Results including cost of accessing XRT scenarios

Table 9 - Base case analysis for SOC vs SOC + XRT virtual and face to face over 1 year time horizon

	QALYs per 100 patients	Costs per 100 patients	NMB per patient	Cost saving per patient	Incremental cost effectiveness ratio (ICER)
Virtual SOC + XRT	74	£27,511			
Virtual SOC	66	£48,926			
Difference	**7**	**-£21,416**	**£1,710**	**£214**	**XRT Dominates**
Face to face SOC + XRT	74	£27,820			
Face to face SOC	66	£48,926			
Difference	**7**	**-£21,106**	**£1,707**	**£211**	**XRT Dominates**

NMB – net monetary benefit (difference in QALYs multiplied by threshold, £20,000, plus cost savings), QALY – quality adjusted life year, SOC – standard of care.

Table 9 summarises the results of the health economic model showing that for each cohort of 100 patients using XRT scenarios to deliver CBT would result in additional QALYs generated of 7 in both virtual and face to face settings. The cost savings would be approximately £21,000 per cohort of 100 patients resulting from saved therapist time less additional cost of accessing the XRT scenarios. Valuing the QALYs generated at £20,000 (the lower range of the NICE accepted thresholds) results in a net monetary benefit of just over £1,700. Positive NMB indicates that the use of XRT scenarios would be seen as cost-effective in the UK. XRT is said to dominate SOC as it is both cheaper and more clinically effective. Again this indicates cost-effectiveness of XRT scenarios. All results depend on the assumption that CBT using XRT scenarios is equally effective as standard of care CBT but can be delivered over a reduced number of therapy sessions.

7.3 Exploration of uncertainty

7.3.1 Types of sensitivity analysis

The most fundamental uncertainty is structural uncertainty. This relates to how the scope of the decision model is determined. For example, whether we are modelling the appropriate population or use case or whether we have structured the model appropriately. This type of uncertainty would be addressed by ensuring that the data used in the model reflected the relevant population. The model is populated using a general population but the same structure could be used to explore different populations, indications (e.g. children with ASD with social anxiety) provided that the parameter estimates were tailored accordingly.

There is also uncertainty about the values of the parameter inputs that we have included in the model. In order to deal with this kind of uncertainty, three types of sensitivity analysis can be undertaken: threshold

analysis, probabilistic sensitivity analysis and one way sensitivity analysis. In section 7.1, we have undertaken some threshold analyses varying parameters which are likely to be particularly influential such as cost of XRT and recovery rate. We have not undertaken probabilistic sensitivity analysis (PSA) or one way sensitivity analysis (OWSA) at this stage but it could be undertaken as part of a more detailed and focused modelling exercise. PSA varies the majority of the parameters simultaneously. One way sensitivity analysis varies parameters one at a time over either their confidence interval, if available, or up and down by an arbitrary percentage (here 20%).

7.3.2 Societal perspective scenario

It would be possible to incorporate lost working days and any costs incurred by patients and their carers/supporter into a more detailed analysis.

8 Summary and Recommendations

The initial value proposition for XR Therapeutics is likely to be focused on:

- Reduction in time to complete a course of TT with a lower band of therapist

We would make the following recommendations:

- The reviews and EVAs from NICE have provided a clear expectation regarding the outcomes required to make the case for cost saving/cost effectiveness.
- Outcomes should be clearly related to clinical effectiveness in specific and relevant patient populations rather than generalized populations and aligned to TT data collection
- Validated outcomes including PHQ9, GAD7, WSAS and any condition-specific validated measures should be used and an appropriate comparator would be SOC under the NHS Talking Therapies programme
- Outcomes for HE analysis would also need to include a QoL measure (e.g. EQ5D) and implementation data such as time to complete therapy, band of therapist, other resource use. Therapist time and grade is particularly important given that the cost savings delivered by XRT are based around this claim.
- RCT data is preferred but EVAs also allow for real world evidence and a pragmatic approach may be to blend data collection from both approaches

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10 Literature Reviewed

10.1 **Clinical effectiveness studies** – (review confined to references from grant application, those provided by the project team and any incidental papers identified in the economic evaluation literature review)

Maskey et al, 2014
Nine verbally fluent boys with an ASD diagnosis and no reported learning disability, aged 7 to 13 years, were recruited. Each had anxiety around a specific situation or stimulus. An individualised scene was created in 'wrap-around' VRE. In the VRE participants were coached by a psychologist in CBT (eg relaxation and breathing exercises) while exposure to the phobia/fear/stimulus was increased as the child felt ready. Each child received four 20-30 minute sessions. After participating in the study 8/9 children were able to tackle their phobia situation. 4/9 completely overcame their phobia. Treatment effects were maintained at 12 months. In this study Maskey et al, 2014, investigated whether a combination treatment using a CBT approach with a wrap-round or immersive VRE reduced specific fear or phobia in young people with ASD and whether this would lead to functional improvements in managing real-life anxiety provoking situations. Each child in the study had one assessment and preparation session at home lasting approximately one hour, then four VRE sessions (2 sets of 2 sessions lasting 20-30 minutes each). Confidence ratings and a verbal report of the child facing the real-life situation were provided two weeks after final session. Further follow-up at 6 weeks, 6 months and 12-16 months after final VRE session (anxiety questionnaires and verbal report from parents).
Outcome measure was Spence Children's Anxiety Scale – parent version and child version (ref 34, Maskey et al). This measure was developed to measure anxiety in children in the general population and has 44 items on a 0 (never) to 3 (always) scale and comprises 6 sub-scales including panic attack and agoraphobia, separation anxiety disorder, social phobia, physical injury fears, obsessive compulsive disorder and generalised anxiety disorder. Widely used in ASD studies. Also measured using target behaviours in an approach developed by the Research Units of Paediatric Psychopharmacology. Parents identify one or two problem areas, researchers then write a vignette at the beginning and end of the treatment then expert panel rate the change between the vignettes on a scale of 1 to 9 where 1 is normalised and 9 is disastrously worse. Ratings of 3 or less were deemed to be responders to treatment. Patients and children also rated confidence on a scale of 0 to 6 where 6 is very comfortable, at the beginning and end of treatment sessions and in tackling the

problem in real life. Uses Reliable Change Index to determine whether the change before and after the intervention is significant with an RCI>1.96 deemed significant.

Maskey et al, 2019a

Similar study to 2014 but in adults. 8 adults aged 18-57 years received one psychoeducation session and four 20 minute sessions of graded exposure. All completed all sessions. Outcomes monitored at 6 weeks and 6 months. 5/8 were classified as responders and at 6 months after the end of the intervention were experiencing real-life functional improvements. Target Behaviours with vignettes and expert scoring was primary outcome measure. Used Beck Anxiety Inventory and Generalised Anxiety Disorder 7 (GAD7) to measure anxiety. Patient Health Questionnaire was used for depression. For quality of life used WHOQOL-BREF (self-report, 26 items addressing 4 domains (physical, psychological, social and environment). VAS confidence scales from 0-6 completed by participant and supporter.

TABLE 3. MEAN SCORES FOR WHOQOL-BREF SUBSCALES

Time point	*Mean physical*	*Mean psychological*	*Mean social*	*Mean environment*
Preintervention	39.29 (14.91)	46.35 (15.98)	41.67 (16.06)	53.13 (14.94)
6 Weeks postintervention	31.12 (15.93)	45.83 (15.96)	47.02 (23.41)	57.59 (22.09)
6 Months postintervention	40.6 (16.19)	45.83 (14.26)	51.04 (19.64)	59.77 (19.87)

Higher scores in each subscale indicate higher quality of life.

Maskey et al, 2019[b]

32 participants randomised to treatment or control. Young people with ASD and specific anxiety. One session introducing CBT techniques and four 20 minute VRE sessions delivered by local clinical therapists. Change in Target Behaviour was independently rated. Two weeks after treatment 25% intervention and no control patients were responders. 6 months after treatment 38% (n=6) intervention and no control participants were responders. At 6 months post treatment symptoms had worsened for one intervention and five controls.
8-14 years. Baseline measures: Social Communication Questionnaire (Berumet et al, 1999); Anxiety Disorders Interview Schedule (ADIS, Sliverman 1996) and Vineland Adaptive Beahaviour Sclaes (VABS, Sparrow et al, 2005). Participants recruited between March 2015 and Feb 2016. Mean age 10 years 10 months. 25 boys, 7 girls. Fidelity was high. Overall fidelity was 94.5% (range 84.5%-100%) so all were at least adequate and most were excellent.

Table 4 Target behaviour ratings categories (responder, no change/equivocal, and worse) for immediate treatment group at 2 weeks, 6 months and 12 months post treatment and control group

Target behaviour rating	2 weeks		6 months		12 months
	Treatment	Control	Treatment	Control	Treatment
	n (%)	n (%)	n (%)	n (%)[a]	n (%)[b]
Treatment responder (1.0–3.0)	4/16 (25.0)	0	6/16 (37.5)	0	4/11 (36.4)
No change/equivocal (3.1–5.9)	11/16 (68.8)	13/16 (81.3)	9/16 (56.3)	10/15 (66.7)	7/11 (63.6)
Symptoms worse than at baseline (6.0–9.0)	1/16 (6.3)	3/16 (18.7)	1/16 (6.3)	5/15 (33.3)	0

[a]1 parent vignette missing

[b]5 parent vignettes missing

Table 7 Target behaviour ratings categories (responder, no change/equivocal and worse) for delayed treatment control group at 2 weeks and 6 months after receiving treatment

Target behaviour rating	Control group post treatment	
	2 weeks (n = 15)	6 months (n = 8)
	n (%)	n (%)
Treatment responder (1.0–3.0)	9 (60.0)	5 (62.5)
No change/equivocal (3.1–5.9)	5 (33.3)	3 (37.5)
Symptoms worse than at baseline (6.0–9.0)	1 (6.7)	0

Conclude that Target Behaviour Ratings are the best indicator of real life change as many of the questionnaires are not sensitive to change in the ASD population.

Maskey et al, 2019[c]

Flat screen intervention. 8 young people received one psychoeducation and four 20 minute sessions of flat screen, computer delivered VR graded exposure with CBT. Follow up measures at 6 weeks, 6 months and 12 months after intervention. 4/8 were responders maintained at 12 months. 1 lost to follow up and remaining 3 classed as non-responders. Recruitment was from the Database of children with Autism Spectrum Disorder living in the North East. Clinical multidisciplinary teams in the North East follow best practice guidelines from NICE (NICE, 2011).

Outcome measures were SCAS-P and SCAS –C, Target Behaviours, no baseline score for Target Behaviours as the rating measures change. Confidence measures were taken during each treatment session for child and parent. Parents observing in an adjacent room through a one way mirror.

Spence Children's anxiety scale. For typically developing males aged 8-11 a total score about 40 indicates levels of anxiety above the normal range for that age group. For those aged 12-15 a score above 33 indicates anxiety above the normal range. No indicative cut-off scores are available for children with ASD. The children classed as responders show a decrease in self-reported anxiety symptoms measured with the SCAS at 6 months with this reduction maintained for two children at 12 month follow up. None of the children classified as non-responders showed a reduction in self-reported anxiety.

de Willige GV et al, 2005

Comparison between WHOQol measure and EQ5D finds that WHOQol measure is more sensitive in acute psychiatric patients.

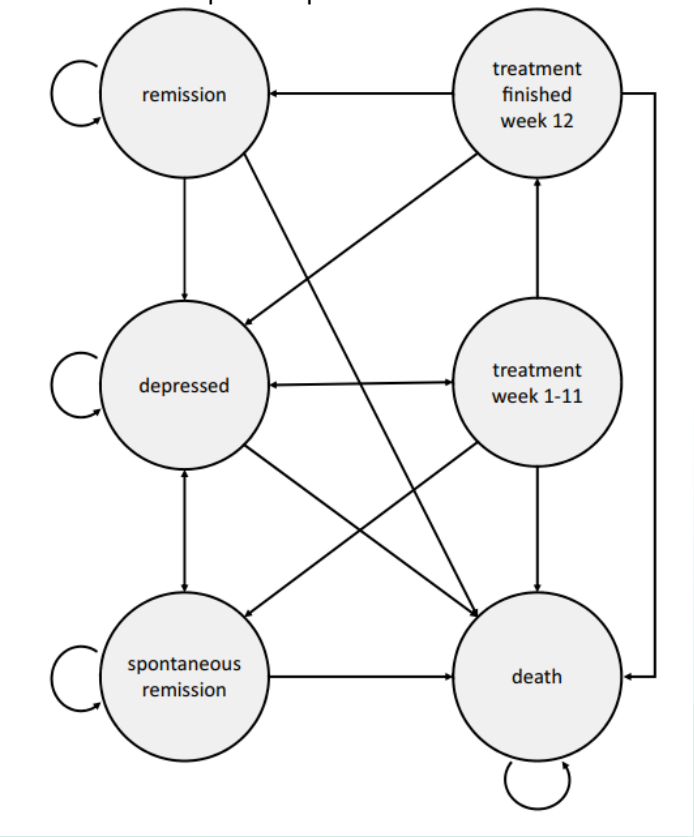
10.2 Economic evaluations

No search for economic evaluations was carried out as part of this scoping review as NICE HTE9 included a review of economic evidence for interventions relating to anxiety. This review will have been comprehensive

and is relatively recent. Papers identified were You 2022, Baumann 2020, Stiles 2019, Jankovic 2022, Mavranezouli 2015, Najafzadeh 2017, Gega 2022, Health Quality Ontario 2019), including 2 HTA reports (Gega 2022 (NIHR); Health Quality Ontario 2019).

Baumann et al, 2022

Model structure Markov with 6 states. 3 year time horizon comparing face to face and internet-based treatment for unipolar depression. Data from literature. PSA found 90% probability of cost-effectiveness.



Gega et al, 2022

HTA report on digital interventions in mental health: evidence syntheses and economic modelling. Found 76 economic analyses including 11 economic models and 65 within trial analyses. Overall results suggested that digital health interventions are likely to be cost-effective compared with no intervention or non-therapeutic control. Compared to face to face therapy or printed manuals the position is unclear and depends more on clinical effectiveness than the costs of the respective interventions. Value of information is high.

Health Quality Ontario, 2017

HTA of internet-delivered CBT for major depression and anxiety disorders: found that compared to wait list iCBT is effective for mild to moderate depression and select anxiety disorders.

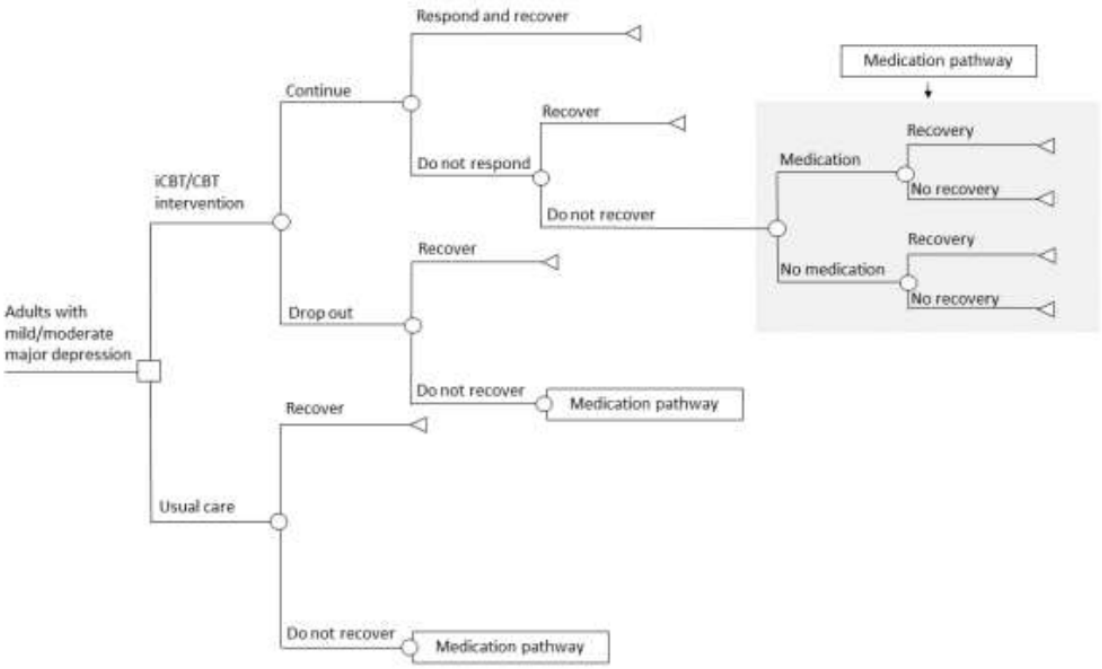


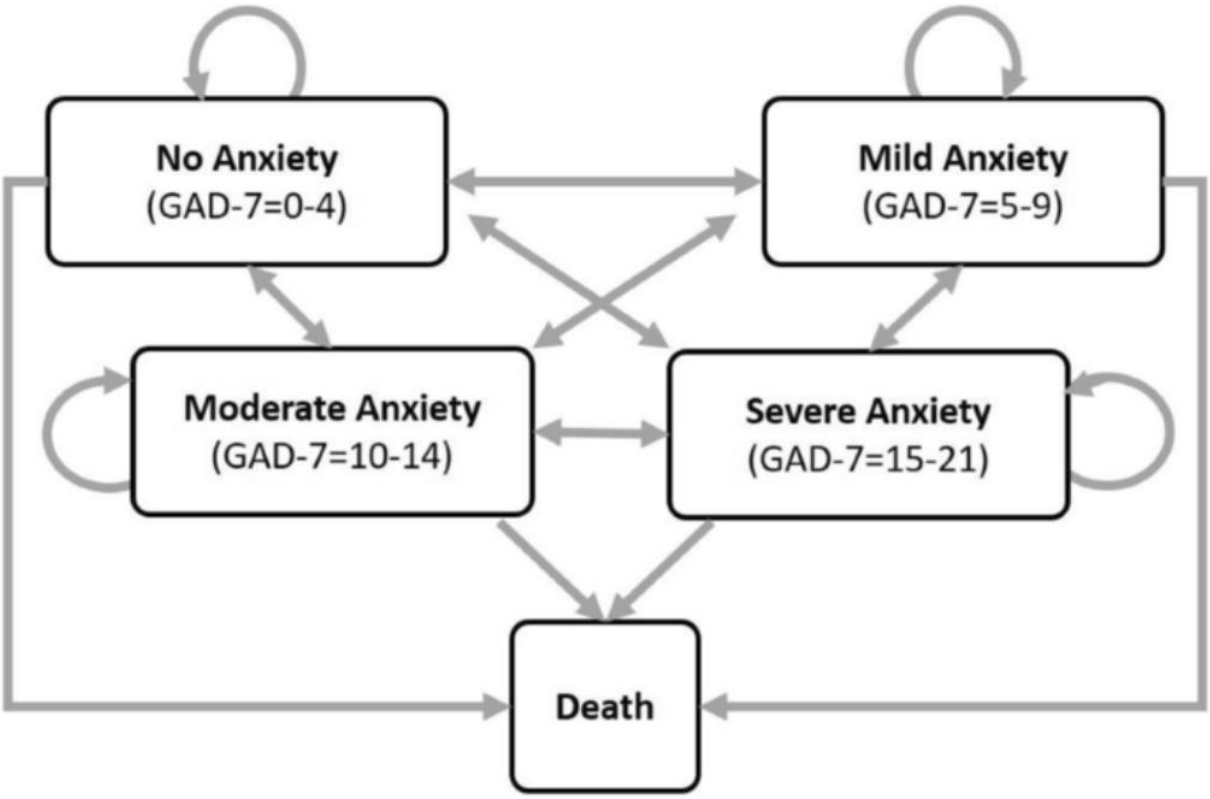
Figure 3: Simplified Model Schematic: Reference Case Analysis

Abbreviation: iCBT, internet-delivered cognitive behavioural therapy.
Note: Figure 3 describes a decision-tree model where the square denotes a decision node, the circle denotes a chance node and the triangle denotes a terminal node (a health state that accumulates utilities and costs associated with a specific pathway and strategy, assuming a 12-month time horizon). The same model structure was applied to the reference case analysis in adults with an anxiety disorder. A person with mild to moderate major depression who enters this model chooses between five different strategies: unguided iCBT, guided iCBT, individual face-to-face CBT, group face-to-face CBT (these four tracks compose the upper branch), and usual care. Within each strategy, pathways account for differences in drop out, response and recovery rates, utilities, and costs. People who respond and recover enter the well health state. People who do not respond are offered medication. Those who recover progress to the better health state associated with increments in health-state utility, and those who do not recover do not accumulate this utility increment (i.e., return to the baseline health state).

Jankovic et al 2022

An open-source decision analytic model was used to extrapolate the results of a network meta-analysis over a patient's lifetime. Digital interventions in generalised anxiety disorder. Found that there was very high Value of Information for further research into the treatment effectiveness of digital interventions. Has some useful input parameters if need to take the model out to lifetime horizon. Utilities data from Revicki et al of 0.72 for no anxiety, 0.64 for mild anxiety, 0.6 for moderate and severe anxiety. Scenarios were explored based on treatment duration. No spontaneous recovery included. Scenarios were treatment duration one year and ten years but very gradual wearing off of treatment effect.

Fig. 1



Mann et al, 2009

Table 6 Summary statistics by severity of depression at baseline and 3 month follow-up

From: Putting the 'Q' in depression QALYs: a comparison of utility measurement using EQ-5D and SF-6D health related quality of life measures

Severity of depression defined by PHQ-9 score	Baseline				Follow-up				Change in mean utility[a]
	n	Mean	SD	Median	*n*	Mean	SD	Median	
Mild (score: 5–9)									
EQ-5D	10	0.645	0.23	0.690	47	0.826	0.16	0.812	0.181
SF-6D	10	0.642	0.09	0.666	47	0.728	0.11	0.696	0.086
Moderate (score: 10–14)									
EQ-5D	24	0.656	0.21	0.689	16	0.706	0.17	0.689	0.050
SF-6D	22	0.601	0.09	0.602	16	0.620	0.07	0.614	0.019
Moderately severe (score: 15–19)									
EQ-5D	39	0.558	0.27	0.689	15	0.388	0.38	0.414	-0.169
SF-6D	37	0.548	0.07	0.557	14	0.557	0.05	0.556	0.009
Severe (score: 20–27)									
EQ-5D	35	0.337	0.29	0.291	14	0.361	0.41	0.362	0.024
SF-6D	33	0.544	0.06	0.557	11	0.479	0.09	0.512	-0.065

n number of patient observations for each utility measure

[a]Mean change in utility = mean utility$_{\text{follow-up}}$ − mean utility$_{\text{baseline}}$

Mavrenouzouli et al, 2015

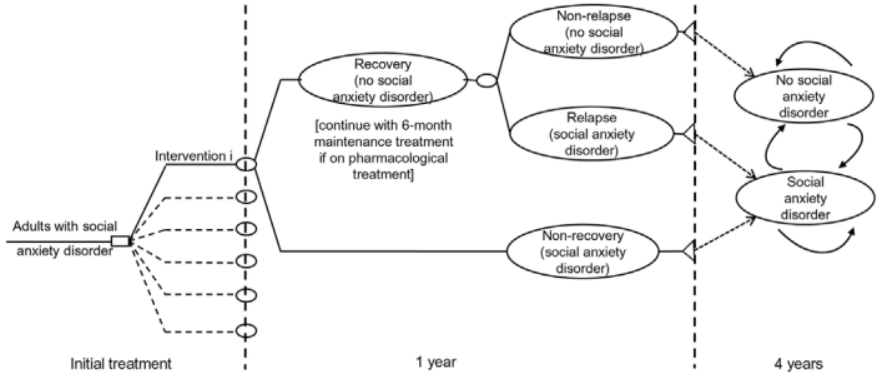


Fig 1. Schematic diagram of the economic model constructed to assess the cost-effectiveness of interventions for social anxiety disorder.

doi:10.1371/journal.pone.0140704.g001

McNamara et al, 2009

Age related population norms for 40-44 year olds Female – 0.846, Male – 0.872

Nafjadzadeh et al, 2017

Implementing a novel pharmacogenetic test to guide drug treatment in anxiety and depression. Complex simulation model including possibilities of remission, response and no response, adverse events, relapse, suicide. Aging, background mortality. 3 year time horizon for the base case analysis.

Prevalence | Background information | Depression | CKS | NICE

Prevalence of depression, ratio of female to male is approximately 2:1.

Stiles et al, 2019

Stepped care versus care as usual in Australian setting in adults with mild to moderate anxiety. Decision tree model over 12 month time horizon. 3 stepped care intervention (guided self-help, face to face CBT then pharmacological therapy). Used epidemiological factors and disutility from the Global Burden of Disease study 2013. Stepped care model found to be cost-effective compared to care as usual.

You et al, 2022

5 year Markov model in students with anxiety comparing face to face to internet-based CBT.
Model inputs of costs and healthcare resource retrospectively collected from a cohort of university students and clinical outcomes and utilities from the literature. Internet based was cheaper and cost-effective over 90% of the time.

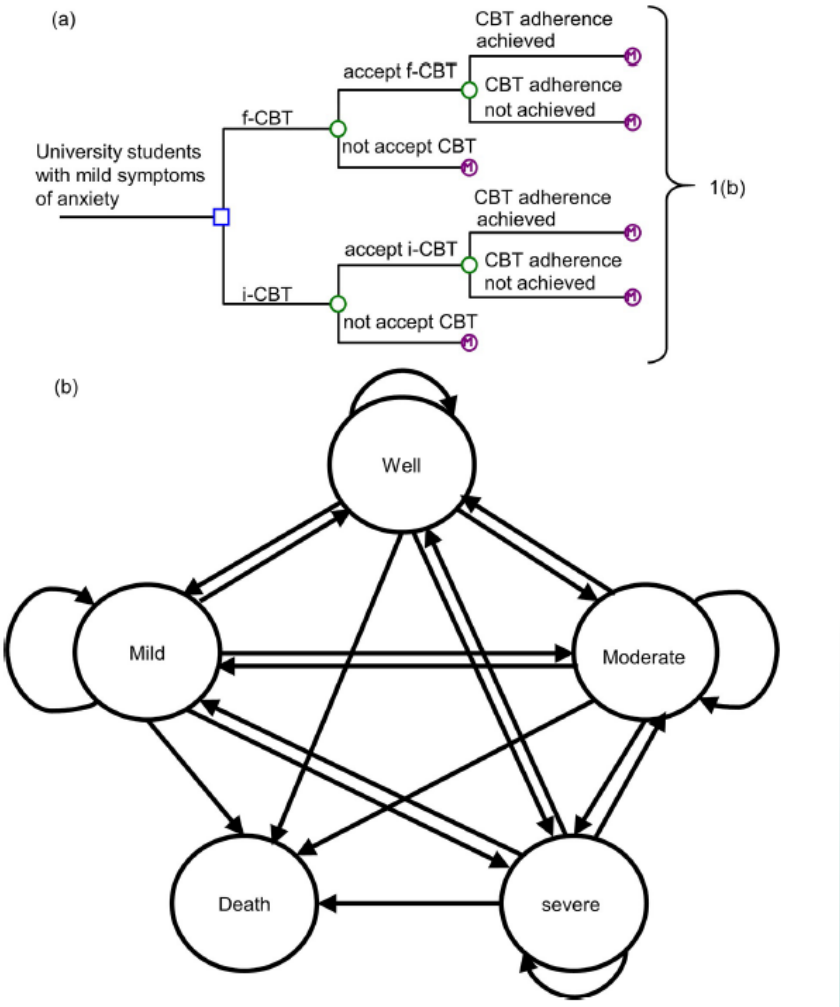


Fig 1. a, b. Simplified Markov model of university students with mild symptoms of anxiety. CBT: cognitive-behavioral therapy; f-CBT: face-to-face cognitive-behavioral therapy; i-CBT: internet-based cognitive-behavioral therapy.

https://doi.org/10.1371/journal.pone.0268061.g001

10.3 NICE content

NICE has 11 products on anxiety

HTE9 May 2023 updated Dec 2023	Digitally enabled therapies for adults with anxiety disorders: early value assessment See detailed notes below
HTE15 November 2023	Virtual reality technologies for treating agoraphobia or agoraphobic avoidance: early value assessment (HTE15) Includes XR Therapeutics – see detailed notes below
HTE3 February 2023	Guided self-help digital cognitive behavioural therapy for children and young people with mild to moderate symptoms of anxiety or low mood: early value assessment See notes below
IPG693 April 2021	Deep brain stimulation for chronic, severe, treatment-resistant obsessive-compulsive disorder in adults Reviewed but nothing relevant for this decision problem.
MTG56 March 2021	Alpha-Stim AID for anxiety disorders

	Important for the model to reflect current clinical practice including drugs and subsequent or concurrent treatments
IPG676 August 2020	Transcranial magnetic stimulation for obsessive-compulsive disorder Use in research only. Needs RCTs measuring concurrent therapies, type, duration and frequency of stimulation, improvements in symptoms, quality of life and duration of effect.
CG113 Jan 2011 updated June 2020	Generalised anxiety disorder and panic disorder in adults: management Recommends a stepped care model. Includes principle that people with mild learning difficulties should be offered the same range of treatments but with adjustments if required. For severe LD, need consultation with relevant specialist.
NG116 Dec 2018	Post-traumatic stress disorder CBT first line treatment where symptoms have lasted more than a month from traumatic event. Typically 8-12 sessions but more if clinically indicated.
CG159 May 2013	Social anxiety disorder: recognition, assessment and treatment Recommends the use of CBT. If drug treatment wanted recommends SSRIs. If CBT and drugs not wanted recommends short term psychodynamic psychotherapy.
CG31 Nov 2005	Obsessive-compulsive disorder and body dysmorphic disorder: treatment Treatment options include psychological interventions and drug treatment (typically SSRIs)
QS53 Feb 2014	Anxiety disorders. 4 quality statements - 1) assessment that distinguishes specific anxiety disorder, severity of symptoms and functional impairment 2) evidence-based psychological interventions 3)not prescribed benzodiazepines or antipsychotics unless clinically indicated 4)response to treatment recorded at every session

HTE9 - Overview | Digitally enabled therapies for adults with anxiety disorders: early value assessment | Guidance | NICE

Part of the pilot trying out the new EVA approach. Gives evidence recommendations and reviews for next three years to see if technologies are fulfilling their potential. Recommended the following as soon as they have DTAC approval and an NHS Talking Therapies for anxiety and depression digitally enabled therapies assessment from NHS England.

- iCT-PTSD (OxCADAT) for post-traumatic stress disorder (PTSD)
- iCT-SAD (OxCADAT) for social anxiety disorder
- Space from Anxiety (SilverCloud) for generalised anxiety symptoms or unspecified anxiety disorder.

Further two could be used once they have DTAC, NHS Talking Therapy and CE or UKCA mark.

- Perspectives (Koa Health) for body dysmorphic disorder (BDD)
- Spring (Cardiff University) for PTSD

Low intensity interventions should be supported by a psychological wellbeing practitioner and high intensity interventions by a high intensity therapist in NHS Talking Therapies.

Further evidence requested on:

Evidence requirement
Rates of recovery
Rates of reliable recovery
Rates of reliable improvement
Rates of reliable deterioration
Rates and reasons for stopping treatment
Rates of relapse
Adverse effects and stepping up of care

Patient experience
Health related quality of life
Resource use during and after treatment including the average number of sessions and level of guidance provided (defined by healthcare professional grade and time)
Baseline data including the demographics and symptom severity of the people using the technology and risk classification

Page 112 – tips on evidence generation from EAG report

Table 34: Evidence Generation

Population	• Studies should clearly report on participant diagnosis - focusing on actual diagnoses of GAD, or differentiating from anxiety symptoms as reported from the GAD-7 • Reporting of results should be split by diagnosis or descriptor – rather than grouping people who are experiencing anxiety and/or depression symptoms • Use of IAPT recommended tools / measures to assess caseness
Interventions	• Some interventions are lacking in any clinical evidence, and others have very limited evidence, or no relevant comparative evidence • Clear reporting of therapist involvement and level of qualification • Consistent use of guided element as per IAPT protocol
Comparators	• Lack of comparators based on appropriate treatments (rather than waiting list, or treatment as usual that includes waiting list, or has little specification of treatments) •
Outcomes	• Reporting of recovery or reliable recovery data • Consistent reporting of ITT, or based on IAPT criteria • Relapse rates and longer term follow up • Consistent use of guided element as per IAPT protocol • Safety/Adverse Events
Economic	• Robust clinical evidence as outlined above • Inclusion of quality of life outcomes and utilities

Other technologies were recommended for research only with ethics clearance once they have regulatory approval:

- Cerina (NoSuffering), Iona Mind (Iona Mind), Minddistrict (Minddistrict), Resony (RCube Health) and Wysa (Wysa) for generalised anxiety disorder (GAD) or generalised anxiety symptoms
- Cerina, Minddistrict and Space from OCD (SilverCloud) for obsessive compulsive disorder (OCD)
- Minddistrict and SilverCloud programmes for health anxiety, panic disorder with or without agoraphobia, social anxiety disorder and phobias.

Overview suggests that there is potential that digitally enabled therapies are cost-effective.

Useful discussion of comparators. Generally comparator will be SOC low or high intensity treatment offered in NHS TT which varies depending on the condition.

- BDD: high intensity psychological interventions include individual or group CBT with exposure and response prevention (ERP).
- GAD: low intensity interventions include individual guided or unguided self-help or psychoeducation groups. High intensity psychological interventions include CBT and applied relaxation.
- Health anxiety: high intensity CBT for health anxiety.
- OCD: low intensity interventions include brief individual or group CBT with ERP. High intensity psychological interventions include more intensive CBT with ERP.

- Panic disorder with or without agoraphobia: low intensity interventions include guided or unguided self-help. High intensity psychological interventions include individual CBT.
- PTSD: high intensity psychological interventions include individual trauma-focused CBT, eye movement desensitisation and reprocessing (EMDR) or supported trauma-focused computerised CBT.
- Social anxiety disorder: high intensity individual CBT for social anxiety disorder (based on the Clark and Wells model or the Heimberg model) as first-line treatment. CBT-based supported self-help or short-term psychodynamic psychotherapy may be offered if individual CBT is declined.

Committee discussion was broadly supportive of digitally-enabled treatment as it offered more flexible and accessible treatment for more patients. Also noted that they may save therapist time which could then be allocated elsewhere in the service to increase access or reduce waiting times.

3.5 Recommended that technologies should be integrated into a service's system rather than being a stand-alone technology. More information on implementation in the adoption report within the supporting documents. 1 Purpose of this document | Tools and resources | Digitally enabled therapies for adults with anxiety disorders: early value assessment | Guidance | NICE

3.12 – costs and resource use – mentions a simple decision tree model showing that digitally enabled therapies could be a cost effective option. The committee believed that it was likely that digitally enabled therapy is cost effective because it uses less therapist time but that it may be more costly in the long run if the clinical effectiveness is not as good.

3.15 – evidence gap overview – importance of comparing against NHS TT standard of care.

Review of EAG report for HTE9 assessment-report (nice.org.uk)

Patchy evidence of UK relevant clinical effectiveness evidence at the time of the review for all technologies. Recommends high quality RCTs for the missing indications in a UK NHS setting. Only considers adults.

Table 1 has decision problem. Note outcome measures section and importance of collecting Global Functioning and Work and Social Adjustment data.

Useful summary of relevant clinical guidelines in Table 3 – copied below.

Table 3: Relevant NICE Guidelines

Guideline	Condition	Recommendation
NICE CG31	Body Dysmorphic Disorder	• Individual or group CBT with ERP that addresses key features of BDD for adults with mild functional impairment • Adults with moderate functional impairment should be offered either a selective serotonin reuptake inhibitor (SSRI) or more intensive individual CBT with ERP, while those with severe impairment should be offered both an SSRI and CBT with ERP
NICE CG113	Generalised anxiety disorder	Low intensity • Individual guided self-help, individual unguided self-help, or psychoeducational groups • Guided or unguided self-help for GAD should include written or electronic materials based on the principles of CBT • Interventions should be completed over at least 6 weeks with guided self-help including 5 to 7 sessions with a trained practitioner. High Intensity • CBT or applied relaxation if a person chooses a high intensity psychological intervention. • This would usually consist of 12 to 15 weekly sessions each lasting an hour • Drug treatment may be offered to some people who prefer it to therapy
NICE CG31	Obsessive Compulsive Disorder	Low Intensity • Low intensity interventions as a first line treatment for people with mild functional impairment and/or who prefer a low intensity approach • This includes brief individual CBT including exposure and response prevention (ERP) using structured self-help materials or by telephone, or group CBT with ERP. High Intensity • SSRI or more intensive CBT with ERP for adults with moderate functional impairment or who have

Guideline	Condition	Recommendation
		not benefited from low intensity treatment • Adults with severe functional impairment should be offered both an SSRI and CBT with ERP
NICE CG113	Panic Disorder with or without agoraphobia	Low Intensity • Guided or unguided self-help for people with mild to moderate panic disorder • People with moderate to severe panic disorder with or without agoraphobia would usually be offered step 3 interventions High Intensity • CBT or an antidepressant for people with moderate to severe panic disorder with or without agoraphobia
NICE NG116	Post-traumatic stress disorder	• Individual trauma-focused CBT as first line treatment • Eye movement desensitisation and reprocessing (EMDR) or supported trauma-focused computerised CBT may be offered to some adults who present more than 3 months after a traumatic event if they prefer it to face-to-face treatment. This should be based on a validated programme delivered over 8 to 10 sessions, with guidance and support from a trained practitioner
NICE CG159	Social Anxiety Disorder	• Individual CBT specifically developed to treat social anxiety disorder as first line treatment • CBT-based supported self-help may be offered to people who decline individual CBT. This should include up to 3 hours of support to use CBT-based self-help materials over 3 to 4 months • People who decline either treatment may be offered drug treatment or short-term psychodynamic psychotherapy where appropriate

Summary of clinical evidence important points to note:

- RCTs preferred with relevant NHS Talking Therapies comparator
- Outcome measures consistent with IAPT and relevant to disorder
- Collecting QoL with EQ5D, collecting WASA and Patient Experience Questionnaire
- Record therapist time and grade
- Follow-up not commented on specifically by EAG but their model was a one-year time horizon.

Economic evidence identified by the EAG. 8 published economic modelling studies for any intervention into the management of anxiety. (You 2022, Baumann 2020, Stiles 2019, Jankovic 2022, Mavranezouli 2015, Najafzadeh 2017, Gega 2022, Health Quality Ontario 2019), including 2 HTA reports (Gega 2022 (NIHR); Health Quality Ontario 2019) These studies were conducted in the UK (n=3), Australia, Germany, US, Canada and Hong Kong. EAG also looked at modelling for 3 NICE clinical guidelines (CG159 SAD, CG113 GAD, NG222 Depression in adults). Economic models varied in structure from decision tree to Markov model or both and one discrete event simulation. Time horizons varied significantly from 7 months, 3-5 years and lifetime. Perspectives were societal or health service. Acceptance and adherence rates were only incorporated into one

model. Many were not specific to a particular disorder and majority included only a single intervention per arm without referral to other interventions except medication. Gega is a UK HTA and took a Markov model with 3 month cycles and lifetime horizon with health states of mild/moderate, severe and no anxiety. Health Quality Ontario conducted a simplified decision model with a Markov microsimulation model.
Table 13 copied below summarises findings of previous modelling exercises. Interestingly, the cost effectiveness is driven by clinical effectiveness rather than cost.

Table 13: Summary of HTA and NICE Guidance

	Interventions and population	Modelling approach	Key findings	Key limitations
Gega 2022 (NIHR)	GAD Supported and unsupported therapy, face to face individual and group therapy, medication and usual care	Markov model, lifetime horizon (Jankovic 2022)	Effectiveness results were inconclusive due to uncertainty about appropriate comparators. Digital interventions were likely to be cost effective compared to no intervention, or non-therapeutic controls. This was less clear compared to face to face therapy or printed manuals. Cost effectiveness was driven by how effective technologies were, rather than how much they cost. Clinical effectiveness was also a key driver of uncertainty.	Pooled evidence for similar interventions Single treatment only per pathway Likely to be heterogeneity in patient pathway
Ontario HTA	Usual care vs interventions including guided digital CBT and face to face CBT. Depression and anxiety (modelled separately)	Decision tree (12 months) and Markov. 1 week cycle, lifetime horizon	Guided digital CBT was likely to be good value for money compared to waiting list, but effectiveness was uncertain compared to face to face or group CBT. Exploratory analysis of digitally enabled therapies in a stepped care model appeared to present good value for money compared to usual care (including medication and GP follow up)	Pooled evidence for similar interventions Primary modelling was for a single intervention during pathway. Secondary modelling considered a stepped pathway
CG113	GAD Considers low and high intensity psychological interventions. Modelling is for	Cost analysis: decision tree (35 weeks) for low intensity intervention	Digitally delivered CBT was found to be cost effective compared to a waitlist. It was noted that this does not represent routine practice in the NHS for GAD.	Single treatment only per pathway Waitlist comparators in clinical studies Study population with mixed anxiety disorders

	Interventions and population	Modelling approach	Key findings	Key limitations
	low intensity psychological interventions compared to waiting list.	s		Study reporting: use of continuous outcomes and inconsistent definitions of response and remission
CG159	SAD Compares psychological and pharmacological interventions	Hybrid model, decision tree (12 weeks) and Markov (5 years) (Mavranezouli 2015)	CT (Clark & Wells) was most cost effective due to higher effectiveness and lower risk of relapse compared ot medication. For interventions ranked by NMB, Internet based self help ranked 7th (with support) and 20th (without support)	Single treatment only per pathway Limited data available for recovery Lack of robust evidence on the relative risk of relapse

EAG preferred the hybrid model proposed by Health Quality Ontario as it allowed short term aspects such as treatment switching to be captured but still models out to lifetime.

Table 14 includes 4 economic evaluation studies. Key points are:

- One study completely redacted
- Mostly within trial analyses
- Interventions 8 weeks with 1 year follow up for SilverCloud, short course for Spring,
- Comparators waitlist control for SilverCloud, 12 sessions of 60-90 mins F2F for Spring
- Spring much cheaper but not achieving equivalent clinical effectiveness
- Criticism of waitlist control, heterogeneous population (especially mixing depression and anxiety),

Table 18: Key Utility Parameters

Variable	Value	Distribution	Source	EAG commentary on availability, quality and reliability of the source/s
Utilities used to calculate model inputs				
No anxiety	0.720	B(14, 5)	NIHR HTA report (Gega 2022)	These are reported in the HTA report (Gega 2022), but are derived from Revicki et al 2012 and Revicki et al. 2008. There is limited information on how the utilities reported in the paper were valued.
Mild anxiety	0.640	B(14, 8)		
Moderate anxiety	0.600	B(14, 9)		
Severe anxiety	0.530	B(13, 11)		
All anxieties other than SAD and PTSD				
Prior to treatment	0.620			Mean of mild and moderate anxiety
Responded to treatment	0.680			Mean of mild and no anxiety
Did not respond to treatment	0.620			Mean of mild and moderate anxiety
PTSD and SAD				
Prior to treatment	0.565			Mean of moderate and severe anxiety
Responded to treatment	0.620			Mean of mild and moderate anxiety
Did not respond to treatment	0.565			Mean of moderate and severe anxiety

HTE15 – VR technologies for treating agoraphobia EVA – Nov 2023

gameChangeVR can be used in the NHS while more evidence is generated to treat severe agoraphobic avoidance in people with psychosis aged 16 and over. More research is needed on the following VR technologies: Amelia Virtual Care to treat agoraphobia, gameChangeVR to treat mild to moderate agoraphobic

avoidance in people with psychosis aged 16 and over, XR Therapeutics to treat agoraphobia. More evidence is needed on:

- Clinical effectiveness including long term benefit and who may benefit most
- Rates of relapse or worsening of symptoms, including use and effectiveness of extra VR sessions
- Adverse effects
- Resource use including maintenance and lifespan of any equipment and mental health professional grade and time needed to deliver treatment or support.

Version of XR that was assessed was the Blue Room.
3.7 lack of evidence of effectiveness of XR Therapeutics in patients with agoraphobia. Only evidence reviewed was single arm ASD n=8.
8.6.4 Highlights lack of improvement in the 8 adult patients on PHQ9, GAD-7 or BAI and quality of life measurements (apart from a small improvement on the social sub-scale). EAG not convinced that lack of SS results was due to measures being unsuitable for people with autism. Also summarised the papers in children and noted that there was improvement on the target behaviours scale but not across all measures.

HTE3 – guided self help for children and young people with mild to moderate anxiety or low mood

Evidence Generation report lists as essential evidence of clinical effectiveness using validated clinical outcomes such as Revised Children's Anxiety and Depression Scale (RCADS) and the strengths and difficulties questionnaire (SDQ). Evidence that supports decision making is:

- Separate evidence for neurodivergent CYP
- Levels of user engagement and rates and reasons for stopping treatment
- Health related quality of life – committee recommended CHU-9D

CG113 GAD
Stepped care model

The stepped-care model

Focus of the intervention	Nature of the intervention
STEP 4: Complex treatment-refractory generalised anxiety disorder (GAD) and very marked functional impairment, such as self-neglect or a high risk of self-harm	Highly specialist treatment, such as complex drug and/or psychological treatment regimens; input from multi-agency teams, crisis services, day hospitals or inpatient care
STEP 3: GAD with an inadequate response to step 2 interventions or marked functional impairment	Choice of a high-intensity psychological intervention (cognitive behavioural therapy [CBT]/applied relaxation) or a drug treatment
STEP 2: Diagnosed GAD that has not improved after education and active monitoring in primary care	Low-intensity psychological interventions: individual non-facilitated self-help, individual guided self-help and psychoeducational groups
STEP 1: All known and suspected presentations of GAD	Identification and assessment; education about GAD and treatment options; active monitoring

1.3 is a stepped care model for people with panic disorder.

- Step 1 – recognition and diagnosis
- Step 2 – treatment in primary care
- Step 3 – review and consideration of alternative treatments
- Step 4 – review and referral to specialist mental health services
- Step 5 – care in specialist mental health services.

CBT comes in at step 3. 7-14 hours is recommended. But recognised that shorter courses may work for some people and 7 hours of treatment may be integrated with self-help materials.

10.4 Other useful sources

Anything from Model Hospital/GIRFT

NHS Talking Therapies Annual Report and statistics for 2022/23 available at psych-ther-2223-out-ther-data-tables.xlsx (live.com) and NHS Talking Therapies, for anxiety and depression, Annual reports, 2022-23 - NHS England Digital

Recovery rate

Diagnosis[7]	Total finishing a course of treatment[4]	Therapy-Based Recovery[5]	
		Count	Rate
Total	281,968	93,683	45
Depression	100,421	31,226	43.9
Anxiety (Total)	161,819	57,579	46.3
Agoraphobia	2,371	579	31.7
Social phobias	15,017	4,873	37
Specific (isolated) phobias	4,235	1,620	59.1
Panic disorder [episodic paroxysmal a	7,259	2,521	46.4
Generalised Anxiety Disorder	67,682	25,662	52.6
Mixed anxiety and depressive disorder	5,581	1,877	44.9
Obsessive-compulsive disorder	13,983	5,445	45.3
Post-traumatic stress disorder	30,441	10,204	40.4
Hypochondriacal disorders	7,096	2,547	41
Other anxiety or stress related disorde	8,154	2,251	46.7
Body Dysmorphic Disorder	355	143	49.1
Chronic Fatigue Syndrome	54	17	44.7
Irritable Bowel Syndrome	72	25	49
MUS not otherwise specified	0	0	-

Number of appointments

Problem descriptor[2]	Cognitive Behaviour Therapy (CBT)		
	Count Treatment Appointments	Count Courses of Therapy[3]	Mean Treatment Appointments
Total	**1,891,879**	**227,816**	**8.3**
Depression	620,578	77,167	8
Agoraphobia	16,465	1,992	8.3
Social phobias	126,772	13,699	9.3
Specific (isolated) phobias	37,116	3,900	9.5
Panic disorder [episodic paroxysmal anxiety]	50,517	6,013	8.4
Generalised Anxiety Disorder	431,826	54,328	7.9
Mixed anxiety and depressive disorder	36,084	4,538	8
Obsessive-compulsive disorder	132,798	13,093	10.1
Post-traumatic stress disorder	235,504	26,754	8.8
Hypochondriacal disorders	58,977	6,566	9
Other anxiety or stress related disorder	41,979	5,535	7.6
Body Dysmorphic Disorder	3,353	331	10.1
Chronic Fatigue Syndrome	376	44	8.5
Irritable Bowel Syndrome	512	62	8.3
Other Mental Health problems	18,184	2,264	8
Other recorded problems	2,355	378	6.2
Invalid/Unspecified	4,219	503	8.4
Unknown	74,264	10,649	7

Recommendations for therapy types for different disorders

	Depression	Depression with LTC	Generalised Anxiety Disorder	Panic Disorder	Obsessive-Compulsive Disorder	Post-Traumatic Stress Disorder	Social Anxiety	Chronic Fatigue	Irritable Bowel Syndrome	Medically Unexplained Symptoms
Low Intensity Therapies										
Guided Self Help (Book)	Yes		Yes	Yes	Yes					
Non-guided Self Help (Book)			Yes	Yes						
Guided Self Help (Computer)	Yes		Yes	Yes	Yes					
Non-Guided Self Help (Computer)			Yes	Yes						
Behavioural Activation (Low Intensity)	Yes									
Structured Physical Activity	Yes									
Psychoeducational peer support			Yes	Yes						
High Intensity Therapies										
Applied relaxation			Yes							
Behavioural Activation (High Intensity)	Yes									
Couples Therapy for Depression	Yes									
Collaborative care		Yes								
Counselling for Depression	Yes									
Brief psychodynamic psychotherapy	Yes									
Eye Movement Desensitisation Reprocessing						Yes				
Mindfulness	Yes									
Cognitive Behaviour Therapy (CBT)	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Interpersonal Psychotherapy (IPT)	Yes									

Price estimates sent through by Morag 20 Sept 2024

Licensing Model					
Annual Cost	£60,000	£114,000	£174,000	£240,000	£270,000
Per month	£5,000	£9,500	£14,500	£20,000	£22,500
Hours	150	300	500	750	1000
Hourly rate	£33.33	£31.67	£29.00	£26.67	£22.50