Early Value Assessment

MTG589 Digitally Enabled Therapies for Adults with Anxiety Disorder

Final Protocol

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Contents

Abbreviations

Term	Definition
BDD	Body Dysmorphic Disorder
CI	Confidence interval
DHSC	Department of Health and Social Care
EAG	External assessment group
EVA	Early Value Assessment
GAD	Generalised Anxiety Disorder
GP	General Practitioner
IAPT	Improving Access to Psychological Therapies
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
OCD	Obsessive Compulsive Disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitors
VAS	Visual analogue scale
Vs	Versus

Plain English Summary

Anxiety leads to feelings of stress, panic, or fear and can have a serious physical and/or psychological impact. Although feeling anxious at times is perfectly normal, for some people the feelings are more constant and difficult to control. Anxiety can stop people from being able to get on with their normal routines. It can make it difficult for people to work or socialise due to feelings of fear or worry. Anxiety can be an ongoing condition where people feel anxious about lots of different things rather than any one specific thing. This is called Generalised Anxiety Disorder (GAD). Anxiety can also be the main symptom for a number of conditions known as anxiety disorder such as health anxiety, panic disorders, post-traumatic stress disorder (PTSD), social anxiety or phobias.

Anyone can be affected by anxiety and sometimes there is no apparent reason. Although the causes of anxiety are not clear, there are a number of things which can contribute to development of anxiety and anxiety disorders.

There are a number of treatments available to help people manage and ease their symptoms. These can include talking therapies such as cognitive behavioural therapies (CBT), counselling and guided self-help. Medication such as selective serotonin reuptake inhibitors (SSRIs) can also be prescribed.

NICE reviews the evidence for these treatments and therapies and in England, the Improving Access to Psychological Therapies (IAPT) service offers NICE approved therapies. There are a lot of digital technologies (mobile apps, websites) that people can use to access therapy and it is important to know how these technologies work and if they are safe before they are made available in the NHS. This assessment will look at a number of digital therapies to determine whether they are safe for use and report how well they work to treat anxiety. The assessment will also consider the costs of providing digitally enabled therapies and their potential value for money.

Scope of the Early Value Assessment

NICE, together with a number of specialist committee members with expertise in anxiety disorders, patient representatives and other stakeholders, has developed a scope for the assessment of guided digital therapies for adults with anxiety disorder.

The scope outlines the decision problem to be addressed however it should be noted that for an Early Value Assessment (EVA), there may be very limited evidence available and one of the key purposes of the assessment is to highlight where there are gaps which need to be addressed in future research or data collection.

Section 1 and 2 of this protocol are taken from the NICE Final Scope and provides specific details of the decision problem including the technologies to be included in the EVA. The remaining sections outline the specific objectives of the assessment and the methods that will be used to develop the EVA.

1. Background

The primary indication of this early value assessment (EVA) is adults with anxiety disorders.

Anxiety disorders are a major contributor to mental health problems in the UK. Improving and widening services for mental health is a commitment of the NHS, given the high prevalence of these conditions and the importance of early intervention (NHS Long Term Plan). The most recent Adult psychiatric morbidity survey reports that only 1 in 3 people with a common mental health disorder accesses treatment (McManus et al. 2016). Furthermore, early research suggests that the COVID-19 pandemic and subsequent measures have had a significant impact on the mental health of adults in the UK (UK parliament website). In the annual report on the use of Improving Access to Psychological Therapies (IAPT) services in England 2021/22, there were 1.81 million referrals to IAPT services between April 2021 to March 2022. Of these, only 37% completed a course of treatment showing a substantial gap between the number of people referred and the number of people starting treatment (House of Commons library 2021, Nuffield Trust 2022). Additionally, waiting times for NHS psychological therapy vary from 4 days to 86 days in different parts of England (House of Commons library 2021).

Digitally enabled therapies are a treatment option for adults with anxiety disorders. They can potentially improve access to mental health services by offering greater flexibility, more choice and self-management through remote interventions. They can be delivered online or through apps with varying levels of practitioner or therapist support. These therapies generally include modules for the person to work through in

their own time. Some can also monitor a person's progress through self-report questionnaires.

2. Decision Problem

2.1. Population

The target population for this assessment is adults with anxiety disorders.

Anxiety disorders involve excessive fear, worry and anxiety that is severe enough to cause significant distress or impairment in a person's functioning and daily living. Anxiety disorders are one of the most common mental health disorders. In 2010, over 8 million people in the UK had some form of anxiety disorder (Fineberg et al. 2013). Anxiety disorders can have a lifelong course of relapse and remission and commonly occur together or with other conditions such as depression or substance misuse. Anxiety disorders treated in IAPT services include:

Body dysmorphic disorder (BDD)

BDD is characterised by a preoccupation with an imagined defect in one's appearance or excessive concern with a slight physical anomaly. It is characterised by time consuming behaviours such as mirror gazing, comparing features with those of others, excessive camouflaging behaviours to hide the defect, skin picking and reassurance seeking. People with BDD may avoid social situations and intimacy and may experience significant distress and impaired occupational and social functioning. About 0.5% to 0.7% of the population have BDD (CG31 2005).

Generalised anxiety disorder (GAD)

GAD is characterised by persistent and excessive worry about many different things and difficulty controlling that worry. People with GAD often have restlessness, difficulties with concentration, irritability, muscular tension and disturbed sleep. GAD is a common condition, estimated to affect up to 6% of people in England in any given week (McManus et al. 2016). It is said to be underdiagnosed and commonly occurs with depression (NICE 2022).

Health anxiety

Health anxiety involves persistent preoccupation or fear about the possibility of having or getting a serious health problem. This is accompanied by repetitive and excessive health-related behaviours or avoidance behaviours such as avoiding medical appointments. Symptoms cause significant distress or impairment in daily living and functioning. It is suggested that about 1 in 20 people may have some type of health anxiety at any given time (iCope 2022).

Obsessive-compulsive disorder (OCD)

OCD is characterised by the recurrence of either obsessions or compulsions, but more often both. An obsession is an unwanted intrusive thought, image or impulse that repeatedly enters the mind and is difficult to get rid of. Compulsions are repetitive behaviours or mental acts that the person feels driven to perform. It is estimated that around 1 in 100 people in England will have OCD in any given week (McManus et al. 2016).

Panic disorder with or without agoraphobia

The characteristics of panic disorder include repeated and unexpected attacks of intense anxiety followed by at least 1 month of persistent worry of having future attacks. This can result in avoidance of situations that may provoke a panic attack. Panic disorder can be diagnosed with or without agoraphobia (fear of being in situations where escape might be difficult or help would not be available if needed). Up to 2 in 100 people in the UK have panic disorder, with about a third going on to develop agoraphobia (NHS 2018).

Post-traumatic stress disorder (PTSD)

PTSD encompasses psychological and physical problems that develop in response to threatening or distressing events, such as abuse, severe accidents, disasters or military action. It involves repeated and intrusive distressing memories that can feel like a person is reliving or re-experiencing the trauma, emotional detachment and social withdrawal, avoidance behaviours and sleep disturbance. About 4% of people in England will have a diagnosis of PTSD in any given week (McManus et al. 2016).

Social anxiety disorder

Social anxiety disorder is characterised by intense fear of social or performance situations that results in considerable distress and impacts daily functioning. There is a fear doing or saying something that will lead to being judged negatively by others and being embarrassed or humiliated. These feared situations are then avoided or experienced with intense distress. It is estimated that up to 12% of people will have social anxiety disorder in their lifetime with 12-month prevalence rates up to 7% (CG159 2013).

Specific phobias

A phobia is an overwhelming and debilitating fear of an object or situation that is disproportionate to the real threat or danger. This may cause a person to actively avoid the thing that causes anxiety and may restrict daily living. Specific or simple phobias centre around a specific object, animal, situation or activity. Common specific phobias include fear of spiders, heights, flying, visiting the dentist, or bodily fluids. About 2% of people in England have phobias in any given week (McManus et al. 2016).

2.2. Intervention Technologies

NICE will consider digitally enabled therapies that are intended for use by adults and deliver a therapeutic intervention in line with NICE guidelines that can be used in IAPT services with practitioner or therapist support. The technologies must deliver a substantial portion of the therapy through the technology rather than being platforms to support teletherapy. They must also have regulatory approval or are actively working towards regulatory approval, specifically CE or UKCA mark and DTAC where required, and be available for use in the NHS.

This will not include virtual reality therapies as their use in the care pathway will likely differ from online or app-based therapies. In total, 11 digitally enabled therapies for adults with anxiety disorders are included in this EVA:

- **Beating the Blues (365 Health Solutions)** - an online computerised CBT programme for people with mild to moderate depression and anxiety. It has 8 sessions, with each session including 3 or 4 modules that take 10 to 15 minutes to complete. The sessions contain interactive material, videos, and practical hands-on tools that help people to understand their mental health

problems and learn techniques to change their thinking and behaviours. The programme lasts about 8 to 12 weeks and can be accessed using any internet enabled device. Beating the Blues can be used as low intensity unguided self-help or with one-to-one support which allows the patient and practitioner or therapist to see regular progress reports and to adjust the intensity of the course as needed.

- **Cerina (NoSuffering)** - a mental health app that provides disorder-specific psychological support. It has CBT interventions for GAD and obsessive compulsive disorder (OCD) with the latter also including exposure response prevention. Both interventions consist of 7 sessions and include anxiety management exercises, journals and self-care resources. Cerina also uses evidence-based screening measures to measure symptom severity.

- **iCT-PTSD (OxCADAT)** - an internet version of cognitive therapy for posttraumatic stress disorder based on Ehlers and Clark's cognitive model of PTSD. It is delivered in a series of modules alongside therapist support. The order of modules is individualised depending on a person's individual needs and treatment plan. Modules consist of psychoeducation, videos, case examples, monitoring sheets, behavioural experiments and assignments. People can also track progress using measures including GAD-7 and PHQ-9.

- **iCT-SAD (OxCADAT)** - an internet-based programme based on Clark and Wells' cognitive therapy for social anxiety disorder. It is delivered in a series of modules alongside therapist support. Modules consist of psychoeducation, videos, case examples, monitoring sheets and assignments. It also includes video feedback, attention training, behavioural experiments and memory focussed techniques. Therapists can view completed modules and provide support using built-in messaging.

- **Iona Mind (Iona Mind)** - an app-based CBT programme for people with GAD or depression. It is intended to support the delivery of step 2 interventions within IAPT services and can be used with the support of a psychological wellbeing practitioner. It creates personalised support plans to help people achieve their mental health goals through guided exercises and insight into their patterns of thinking. It uses machine learning to anticipate and adapt the programme to a person's needs and has functionality to identify crisis events and provide signposting. Behavioural health can be tracked using clinical measures such as the GAD-7 and PHQ-9. Iona Mind also monitors mood and goal progression.

- **Minddistrict (Minddistrict)** - an online CBT programme for treating mental health conditions. It has a catalogue of modules, diaries and questionnaires that can be used to help people change their behaviour. It has interventions for GAD, health anxiety, social anxiety, OCD, panic disorder and phobia.

Interventions can be personalised by adapting and combining components in line with a person's needs. It can be used as a standalone self-help tool or with practitioner or therapist support including video sessions delivered using the Minddistrict platform. Modules for GAD, OCD and panic disorder are described by the company as IAPT compliant and following NICE guidelines. Versions of these modules are available specifically for IAPT services. The technology can be accessed via a web browser and there is also a smartphone app.

- **Perspectives (Koa Health)** - an online CBT programme with interventions for adults with BDD, OCD and depression. It is a 12-week programme that delivers core components of CBT using treatment modules. Each module includes psychoeducation, interactive exercises and CBT skills. People are also asked to complete weekly questionnaires, including PHQ-2, QIDS-SR and CGI, to track their symptoms. Perspectives also provides information on local emergency services and suicide hotlines should a person need urgent support. It is designed to be used in IAPT services with a practitioner or therapist who monitors progress and provides support via calls or asynchronous messaging. The programme is delivered through a mobile app and includes a web-based administration panel for practitioners or therapists.

- **Resony (RCube Health)** - an automated digital therapeutic designed to improve worry and anxiety and to manage GAD. It is a 6-week programme based on CBT, mindfulness and gratitude journalling. It also includes nondirective resonance breathing, applied relaxation and heart rate variability training. It also provides access to a community of users, to share experiences and provide social support. People can choose specific modules and can monitor progress using the GAD-7 questionnaire and progress dashboard. Resony can be used as a self-help tool for people with worry, anxiety and stress or alongside the supervision of a healthcare professional for people with GAD. It is delivered through an app available for smartphones and tablets.

- **SilverCloud -** offers over 40 internet-based CBT programmes for a range of mental health conditions including depression, phobia, panic, social anxiety, health anxiety, GAD and OCD. SilverCloud offers both supported and self-guided programmes and provides online IAPT counselling. Programmes can be accessed at any time using any smartphone, tablet or computer.

- **Spring** - an online guided self-help programme for people with PTSD. It is audio narrated throughout and includes 8 steps based on core components of CBT with a trauma focus. The programme is interactive and user input dictates feedback to key activities within the programme. Practitioners or therapists can review a person's progress via a healthcare professional

dashboard to help guide the patient through the programme. Spring can be accessed through a computer, tablet or smartphone.

- **Wysa (Wysa)** - an artificial intelligence (AI) based programme that uses CBT techniques along with other psychological approaches to help people build mental resilience and improve their mental wellbeing. It is designed to help people with low mood, stress or anxiety or who wish to improve their emotional resilience. Wysa has a chatbot that uses AI-guided listening to guide people to evidence-based tools and techniques to self-manage their emotions and mental wellbeing. It can also be used with professional human support, including in-app text-based chat sessions with qualified therapists.

2.3. Potential Alternative Technologies

No other commercially available technologies were identified for this topic. This was clarified with specialist committee members who were recruited specifically for this early value assessment.

2.4. Comparators

The comparator for this EVA is the current standard of care provided within the IAPT care pathway; low intensity and high intensity psychological interventions.

2.5. Outcomes

Outcomes will cover several different domains as shown in Table 1

Table 1: EVA outcomes

Intermediate measures for consideration may include: • Patient choice and preferences • Treatment satisfaction and engagement • Intervention adherence and completion • Referral to treatment time • Assessment to treatment time • Intervention-related adverse events • Inaccessibility to intervention (digital inequalities) • Rates of attrition (dropouts) and engagement
Clinical outcomes for consideration may include: • Change in anxiety symptoms • Change in other psychological symptoms • Global functioning and work and social adjustment • Reliable recovery • Reliable improvement • Reliable deterioration

• Rates of relapse including relapse rate and time from remission to relapse
IAPT service level outcomes for consideration include: • Rates of reliable recovery • Rates of reliable improvement • Rates of reliable deterioration
Patient-reported outcomes for consideration may include: • Health-related quality of life • Patient experience

Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:
• Costs of the technologies
• Cost of other resource use (e.g., associated with managing anxiety, adverse events, or complications):
  ○ GP or IAPT appointments
  ○ Medication
  ○ Healthcare professional grade and time

2.6. Care pathway

This assessment will focus on the use of digitally enabled therapies for adults with anxiety disorders in IAPT services. The IAPT programme organises the provision of evidence-based psychological therapies in the NHS to people with anxiety disorders and depression (National Collaborating Centre for Mental Health 2021). IAPT services follow a stepped care approach as recommended in NICE's clinical guideline on common mental health problems. This means offering the least intrusive, most effective intervention first. Generally, the stepped care approach includes:

- Step 1: Identification, assessment, psychoeducation, and active monitoring of known or suspected common mental health disorders.
- Step 2: People with GAD or mild to moderate panic disorder or OCD whose symptoms have not improved after step 1 are offered low intensity interventions such as guided self-help or psychoeducational groups. This is guided by a person's preferences.
- Step 3: People with moderate to severe disorders, marked functional impairment, or whose symptoms have not improved after step 2 are offered high intensity interventions including individual CBT or drug treatment. Treatment choice is based on patient-clinician decision-making. Only step 3 intervention is recommended for social anxiety disorder or PTSD.

- Step 4: Complex drug or psychological treatments involving multiagency teams, crisis services or inpatient care are offered to those with complex treatment-refractory disease with significant functional impairment.

IAPT services deliver low intensity and high intensity psychological interventions at step 2 and step 3 of the care pathway, respectively. Digitally enabled therapies are most commonly offered as a step 2 low intensity intervention. Low intensity interventions are delivered by psychological wellbeing practitioners who facilitate treatment and review progress. There is some variation in NICE-recommended low intensity interventions across disorders:

- GAD: CG113 recommends 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.
- OCD: CG31 recommends 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.
- Panic disorder with or without agoraphobia: CG113 recommends 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.

There is currently no NICE guideline on health anxiety. The NHS suggests that people with health anxiety use self-help and see a GP if symptoms do not improve or worries are significantly impacting daily living (NHS 2020).

The NHS advises that specific phobias can be treated using desensitisation or self-exposure therapy with the help of a professional or a self-help programme (NHS 2022). NICE's 4-year surveillance of CG159 (2017) does not recommend computerised CBT for the routine treatment of specific phobias because of a lack of quality evidence at that time.

In IAPT services, digitally enabled therapies may also be offered as high intensity psychological interventions if they include the same therapeutic content as recommended in the NICE guideline. The IAPT manual states that this should be

supported or delivered by a high intensity therapist trained in the specific therapies. There is variation in NICE-recommended high intensity interventions across disorders:

- BDD: CG31 recommends 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.
- GAD: CG113 recommends 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.
- OCD: CG31 recommends an SSRI or more intensive CBT with ERP for adults with moderate functional impairment or who have not benefited from low intensity treatment. Adults with severe functional impairment should be offered both an SSRI and CBT with ERP.
- Panic disorder with or without agoraphobia: CG113 recommends CBT or an antidepressant for people with moderate to severe panic disorder with or without agoraphobia.
- PTSD: NG116 recommends 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.
- Social anxiety disorder: CG159 recommends 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.

Potential place of digitally enabled therapies in the care pathway

In IAPT services, digitally enabled therapies would be offered after assessment and identification of the appropriate problem descriptor in line with ICD-10. Digitally enabled therapies may be offered as an alternative to existing low intensity or high

intensity interventions for adults with anxiety disorders. The place in the care pathway depends on the specific disorder, healthcare professional assessment and clinical judgement, the content of the intervention, patient preferences and risk, and the level of support needed.

3. Objective

The purpose of the Early Value Assessment is to summarise and critically appraise existing evidence on the clinical-effectiveness and cost-effectiveness of guided digital therapies for adults with anxiety disorder. It should be noted that the purpose of the review is not to compare the technologies with each other. The following objectives are proposed:

Clinical Effectiveness

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

Cost Effectiveness

- Identify and assess economic evidence relating to the use of the included technologies within the scope
- Develop a conceptual economic model, related to the scope, that can be used to inform future research and data collection
- Report available model inputs and evidence gaps
- Report on the technology costs and run a simple model using available inputs, reporting on the plausibility of cost effectiveness

4. Methods

In line with the interim methods statement for early value assessments, while following systematic review methods, the EAG will adopt a pragmatic approach to evidence assessment and appraisal.

4.1. Inclusion Criteria

Full details of the inclusion criteria for the topic are reported in the final scope and summarised briefly in Table 2. While the scope represents the relevant decision problem, there is an acknowledgement that technologies being assessed through the EVA process are likely to have very little evidence available to address the specific decision problem. The inclusion criteria may therefore be necessarily broader than those outlined in the scope. The EAG has noted how the inclusion criteria may broaden to include evidence that does not strictly meet the elements in the scope but where inclusion of such evidence will help identify relevant evidence gaps (table 2).

Table 2: Inclusion Criteria

Decision Problem	Scope	EAG Comment
Population	• Adults over 18 years of age	Some technologies are suitable for use by people under 18 years. If no other evidence is available, the EAG will report the evidence in young people while noting the lack of evidence in adult populations as an evidence gap.
Conditions	• Body Dysmorphic Disorder • Generalised Anxiety Disorder • Health Anxiety • Obsessive compulsive disorder • Panic disorder with/without agoraphobia • Post traumatic stress disorder • Social anxiety disorder • Specific phobias	For any studies which include people with depression and anxiety, the EAG will consider the evidence where the technologies are being used for a diagnosed anxiety disorder. Where a study reports on the use of a technology for anxiety without defining or separating specific anxiety related diagnosis, the EAG will consider this on a case by case basis and include a summary of these as a separate subgroup, highlighting the potential limitations. Studies which report results for anxiety and depression combined will be considered for inclusion on case by case basis.
Setting	Improving access to psychological therapies (IAPT) services	It is likely that technologies are being used outside of IAPT, particularly in the case of non-UK based studies. The EAG will include any relevant evidence, noting the lack of IAPT specific evidence as a gap.

Decision Problem	Scope	EAG Comment
Intervention	Digitally enabled therapies for adults with anxiety disorders that are delivered with practitioner or therapist support. Namely: • Beating the Blues • Cerina • iCT-PTSD for post-traumatic stress disorder • iCT-SAD for social anxiety disorder • Iona Mind • Minddistrict • Perspectives • Resony • SilverCloud • Spring • Wysa	
Comparator	Standard care low intensity and high intensity psychological interventions currently delivered in IAPT services.	Although excluded from the scope, if evidence comparing with standard interventions is limited, the EAG will consider studies comparing technologies with waitlist controls and other non-standard comparators. This will be done on a technology by technology basis.
Outcomes	Intermediate measures for consideration may include: Patient choice and preferences • Treatment satisfaction and engagement • Intervention adherence and completion • Referral to treatment time • Assessment to treatment time • Intervention-related adverse events • Inaccessibility to intervention (digital inequalities) Clinical outcomes for consideration may include: • Change in anxiety symptoms	

Decision Problem	Scope	EAG Comment
	• Change in other psychological symptoms • Global functioning and work and social adjustment Service level clinical outcomes: • Rates of reliable recovery • Rates of reliable improvement • Rates of reliable deterioration • Rates of relapse including relapse rate and time from remission to relapse Patient-reported outcomes for consideration may include: • Health-related quality of life • Patient experience	
Study Design		All study designs will be considered and the decision to include or exclude a study based on design will be made on a technology by technology basis.

4.2. Search strategy

Searches will be developed in MEDLINE (Ovid) by an experienced Information Specialist. Search terms will include free-text terms and controlled terms from databases (e.g. MeSH, Emtree). Searches will be structured around population and intervention concepts as detailed in the inclusion criteria (Section 4.1):

- Population: Anxiety disorders to include:
    - Body dysmorphic disorders (BDD)
    - Generalised anxiety disorder (GAD)
    - Health anxiety
    - Obsessive-compulsive disorder (OCD)
    - Panic disorder with or without agoraphobia
    - Post-traumatic stress disorder (PTSD)
    - Social anxiety disorder
    - Specific Phobias

- Intervention: Guided digital therapies to include:
    - Beating the Blues
    - Cerina
    - iCT-PTSD for post-traumatic stress disorder
    - iCT-SAD for social anxiety disorder
    - Iona Mind
    - Minddistrict
    - Perspectives
    - Resony
    - SilverCloud
    - Spring
    - Wysa

Searches for this topic will be combined with another topic: Digitally enabled therapies for adults with depression (MT588). This is due to an overlap in technologies across both topics and an expected overlap in studies reporting both anxiety and depression. A draft search strategy is provided in Appendix A. A search strategy for both clinical and economic evidence will be created and will be peer-reviewed by a second Information Specialist. The strategy will be translated to each database.

The following bibliographic databases will be searched:

- MEDLINE ALL (Ovid)
- Embase (Ovid)
- PsycInfo (Ovid)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Database of Abstracts of Reviews (DARE, via CRD)
- Health Technology Assessment Database (HTA, via CRD)
- NHS Economic Evaluation Database (NHS EED, via CRD)
- International HTA database (INAHTA)
- PubMed
- Epistemonikos

Additionally, economic studies will be identified from the references of a similar report: Guided dCBT for CYP with mild to moderate anxiety/low mood: an Early Value Assessment (MT580). The economic searches from this report will be updated to identify any literature published since August 2022. A draft economic search strategy is provided in Appendix A. The following databases will be searched:

- Medline ALL (Ovid)
- Embase
- PsycInfo
- ScHARRHUD
- CEA Registry

The following clinical trial registries will be searched:

- ClinicalTrials.gov
- International Clinical Trials Registry Platform (ICTRP)

The EAG will, where possible, confirm directly with companies whether there are any studies planned in the near future.

Relevant guidelines will be identified by searching:

- NICE Guidance

Relevant data regarding adverse effects will be identified by searching MHRA and FDA Manufacturer and User Facility Device Experience (MAUDE). Additionally, company websites will be searched to identify relevant publications and ongoing trials.

4.3. Study selection

Retrieved references will be imported into EndNote and deduplicated. EndNote will also be used to record reviewers' screening decisions. For economic evidence, literature screening will be performed using the main search results in section 4.2, to identify any published economic studies of guided digital therapy for the pre-defined anxiety disorders in the UK. Full economic evaluations (both costs and effects of the intervention are reported) or cost analyses will be included.

Standardly for an early value assessment, one reviewer will screen the titles and abstracts of identified studies against the inclusion and exclusion criteria, followed by screening of the eligible full text articles. A minimum of 10% of records will be independently checked by a second reviewer and where reviewers disagree, consensus will be reached through discussion.

Where time permits, additional searches may be conducted through citation searches and bibliographic searches of included papers. The EAG consider this will not routinely happen but may be considered in the case where there are systematic reviews or narrative reviews that may provide a source of additional evidence as well as providing an opportunity to cross-check the sensitivity of the searches by confirming relevant studies have been identified.

Due to overlap with another topic (Digitally enabled therapies for adults with depression (MT588)) some changes may be made to the planned sifting approach and full details of the final sifting approach will be detailed in the EVA report.

4.4. Data extraction

A standardised data extraction form will be created and piloted. Where available, the following data will be extracted from studies: study information (i.e., author, year) study design, study dates, intervention characteristics (i.e., intervention name, therapist delivering intervention), comparator, participant characteristics (i.e., demographics, anxiety symptoms, psychological symptoms), patient outcomes (e.g., change in anxiety symptoms, change in psychological symptoms, global functioning, work and social adjustment, reliable recovery, reliable improvement, reliable deterioration, rates of relapse, health-related quality of life, treatment satisfaction), adverse events and safety data. For economic literature, data extraction forms will include study design, population, intervention, comparator, analytic approach (trial-based or model-based), costs, outcomes or utilities, other model inputs, results and sensitivity analyses to examine uncertainties.

Data extraction will be conducted by one reviewer and checked by a second.

4.5. Quality assessment

A pragmatic approach to quality assessment will be considered based on the volume and type of evidence identified. It is anticipated that much of the available evidence

will not fully meet the scope criteria and full critical appraisal will not be used. Instead, the EAG will include a discussion on the potential biases in the included studies and how these might impact the key outcomes.

For studies which fully meet the decision problem outlined in the scope, quality assessment will be conducted using the JBI Critical Appraisal Tools, which is a collection of quality assessment tools for differing methodologies. The JBI Critical Appraisal Tools include those appropriate for assessing randomised controlled trials, quasi-experimental studies, cohort studies, cross-sectional studies, case control studies, case series studies, and others.

Key strengths and limitations of the evidence will be presented in the final report and the EAG will include comment on the generalisability of the results to clinical practice in the NHS.

5. Evidence synthesis

The EAG will consider meta-analysis methods to synthesise the relevant clinical evidence. However, due to the nature and purpose of an Early Value Assessment, it is not anticipated that there will be enough data available to conduct a meta-analysis.

Results for both clinical and economic literature will therefore be presented in a suitable tabular format and where appropriate, accompanied by a narrative synthesis of the data. Methodological problems with included studies will be noted and discussed along with any identified risks of bias which may impact study results. A discussion outlining the applicability of the evidence to the scope of the EVA will be included. Evidence gaps will be identified and discussed within the context of the NICE EVA processes to allow expert judgements to be made about what further evidence needs to be collected and how long for.

6. Development of an early economic model

A conceptual cost-effectiveness model will be developed from the UK NHS perspective, which can be used to inform a subsequent full economic evaluation of guided digital therapy for anxiety. This can be a decision analytic model, consisting of a decision tree or a Markov model. This model will incorporate the care pathway of

patients receiving guided digital therapy for anxiety in the UK NHS setting, specifically within the IAPT service. The aim of this conceptual model is to identify model inputs required and the evidence gaps.

The model structure will be adapted based on the existing models used to evaluate cost-effectiveness of anxiety treatments. A rapid review of existing models will be conducted, and relevant findings reported. The model structure will be reviewed by clinical experts for face validity and if the current NHS practice and pathway is appropriately reflected.

The potential model structure and model inputs will be described. Any available model inputs will be reported, and the key evidence gaps identified.

The economic model will be simplified as required to allow generation of preliminary cost-effectiveness findings using the available evidence. Sensitivity analyses including one-way sensitivity analyses, threshold analysis and probabilistic sensitivity analysis may be conducted to determine the impact of uncertainty on cost-effectiveness findings. Value of information analysis will be considered to estimate the return of reducing decision uncertainty through future research.

7. Company Submissions

All data submitted by the company or other stakeholders will be considered by the EAG if received by 23/12/2022. Data received after this date will be considered if practicable and at the discretion of the EAG.

All correspondence with companies will be recorded in a correspondence log for transparency. Any ‘commercial in confidence’ data provided by the company, and specified as such, will be highlighted in blue and underlined in the report and correspondence log. Any ‘academic in confidence’ data provided by the company, and specified as such, will be highlighted in yellow and underlined in the report and correspondence log.

8. Competing Interests of Authors

None

9. Appendices

Appendix A: Draft search strategy in MEDLINE (Ovid)

Ovid MEDLINE(R) ALL <1946 to November 22, 2022>

1	Anxiety/	102027
2	anxiety disorders/	39925
3	(anxiet* or anxious).tw.	252620
4	"generali?ed anxiety disorder*".tw.	9697
5	GAD.tw.	11873
6	"social anxiety disorder*".tw.	3217
7	phobia*.tw.	9537
8	"panic disorder*".tw.	10038
9	"post?traumatic stress disorder*".tw.	22077
10	PTSD.tw.	30465
11	"body dysmorphic disorder*".tw.	1302
12	"obsessive compulsive disorder*".tw.	15322
13	exp Phobic Disorders/	12249
14	Panic Disorder/	7237
15	Stress Disorders, Post-Traumatic/	39852
16	Body Dysmorphic Disorders/	1226
17	Obsessive-Compulsive Disorder/	16142
18	or/1-17	355241
19	Depression/	145419
20	(depression or depressive or depressed).tw.	509140
21	or/19-20	535264
22	18 or 21	742823
23	"beating the blues".af.	40
24	"365 health solutions".af.	0
25	cerina.af.	157
26	(NoSuffering or "no suffering").af.	20

27 iCT-PTSD.af. 3

28 (internet adj2 "cognitive therapy for post traumatic stress disorder").tw. 0

29 iCT-SAD.af. 3

30 (internet adj2 "cognitive therapy for social anxiety disorder").tw. 4

31 OxCADAT.af. 3

32 "iona mind".af. 0

33 Minddistrict.af. 26

34 "mind district".af. 0

35 ("Get.ON" adj2 ("Mood Enhancer" or panic or depression)).af. 10

36 "Koa Health".af.9

37 (Perspectives adj3 Koa).tw. 3

38 Resony.af. 0

39 "RCube health".af. 0

40 (SilverCloud or "silver cloud").af. 56

41 (space adj2 (anxiety or GAD or "health anxiety" or OCD or panic or phobia)).tw. 40

42 (space adj2 depression).tw. 31

43 Wysa.af. 13

44 Spring.af. and ("cognitive behavio* therap*" or cbt or dcbt or ccbt or icbt or "digital therapeutic*" or "digital cbt" or "online cbt" or "comput* cbt" or "internet cbt").tw. 120

45 Deprexis.af. 50

46 ("Ethypharm digital" or "gaia group").af.14

47 23 or 24 or 32 or 33 or 34 or 35 or 36 or 37 or 40 or 43 154

48 22 and 47 114

49 25 or 26 or 27 or 28 or 29 or 30 or 31 or 38 or 39 or 41 or 44 347

50 18 and 49 94

51 42 or 45 or 46 93

52 21 and 51 83

53 48 or 50 or 52 276

54 exp animals/ not humans.sh. 5069381

55 53 not 54 262

56 limit 55 to english language 247

Economics searches

Medline

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>

1 (computer or computerized or computerised or digital or online or internet$ or app or apps).ti,ab. 726287

2 (cognitive adj2 behavio$ adj3 (therap$ or intervention$ or treatment$ or psychotherap$ or programme$1 or program$1 or method$1 or approach$1)).ti,ab. 27053

3 1 and 2 3678

4 (dCBT or cCBT).ti,ab. 268

5 ((gaming or gamified or game format or video game$) and (CBT or cCBT or dCBT or cognitive behavi$)).ti,ab. 116

6 3 or 4 or 5 3793

7 Anxiety/ or Anxiety Disorders/ 133283

8 exp Depressive Disorder/ or Depression/ 249790

9 (anxiet$ or anxious or low mood or depress$).ti,ab. 662705

10 7 or 8 or 9 725340

11 6 and 10 2267

12 economics/ 27477

13 exp "costs and cost analysis"/ 261369

14 economics, dental/ 1920

15 exp "economics, hospital"/ 25651

16 economics, medical/ 9231

17 economics, nursing/ 4013

18 economics, pharmaceutical/ 3089

19 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. 990508

20 (expenditure$ not energy).ti,ab. 35481

21 (value adj1 money).ti,ab. 40

22 budget$.ti,ab. 34192

23 or/12-22 1152950

24 ((energy or oxygen) adj cost).ti,ab. 4644

25	(metabolic adj cost).ti,ab.	1655
26	((energy or oxygen) adj expenditure).ti,ab.	28278
27	24 or 25 or 26	33534
28	23 not 27	1145212
29	letter.pt.	1200171
30	editorial.pt.	627878
31	historical article.pt.	368891
32	29 or 30 or 31	2175992
33	28 not 32	1105779
34	11 and 33	413
35	limit 34 to english language	408
36	limit 35 to yr="2022 - 2023"	40