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Early Value Assessment consultation:

Supporting documentation – Committee papers

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

1. **Front sheet**
2. **Assessment report** – an independent report produced by an external assessment group (EAG) who have reviewed and critiqued the available evidence.
3. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
4. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
5. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.

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

Digitally enabled therapies for adults with depression [MTG588]

External Assessment Group report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Early Value Assessment Programme

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Date completed	27/01/2023

Contains confidential information: Yes

Number of attached appendices: 8

Purpose of the assessment report

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

Declared interests of the authors

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

None.

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Responsibility for report

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

Contents

Abbreviations

Term	Definition
BA	Behavioural activation
BDI	Beck Depression Inventory
CBT	Cognitive behavioural therapy
dCBT	Digital cognitive behavioural therapy
CEA	Cost-effectiveness analysis
CE mark	*Conformité européenne* (European conformity) marking
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence interval
CORE-OM	Clinical Outcomes in Routine Evaluation – Outcome Measure
CRD	Centre for Reviews and Dissemination
CYP	Children and young people
dCBT	Digital cognitive behavioural therapy
DET	Digitally enabled therapies
DTAC	Digital Technology Assessment Criteria
EAG	External assessment group
EE	Economic evaluation
EQ-5D	EuroQoL-5 dimensions
EVA	Early value assessment
FCBT	Face-to-face cognitive behavioural therapy
GAD	Generalised Anxiety Disorder assessment
GP	General practitioner
HRQoL	Health-related quality of life
HRSD	Hamilton Rating Scale for Depression
HTA	Health technology assessment
IAPT	Improving Access to Psychological Therapies
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	Interquartile range
ITT	Intention to treat
GP	General practitioner
MADRS	Montgomery-Asberg Depression Rating Scale
MAUDE	Manufacturer and User Facility Device Experience
MeSH	Medical subject headings

MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
N/A	Not applicable
NG	NICE guideline
NGA	National Guidelines Alliance
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLM	National Library of Medicine
PenTAG	Peninsula Technology Assessment Group
PEQ	Patient Experience Questionnaire
PHQ	Patient Health Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSW	Propensity score weighting
PWP	Psychological wellbeing practitioner
QALY	Quality-adjusted life year
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self Report
RCT	Randomised controlled trial
SCM	Specialist Committee Member
SD	Standard deviation
SG	Standard gamble
SIGN	Scottish Intercollegiate Guidelines Network
TAU	Treatment as usual
UK	United Kingdom
UKCA	United Kingdom Conformity Assessed marking
US	United States
VAS	Visual analogue scale
Vs	Versus
WHO	World Health Organization
WSAS	Work and Social Adjustment Scale

Executive summary

Quality and relevance of clinical evidence

For certain technologies (Beating the Blues, Space from Depression and Deprexis) there was substantial evidence from randomised controlled trials, potentially beyond what may be expected for an early value assessment (EVA). However, there are a number of evidence gaps in respect of the clinical evidence base as it pertains to the decision problem. Currently, there is little or no evidence on the other technologies of interest; where evidence is available, there is very little comparative evidence and there was a mismatch between comparators identified in the scope and comparators used in the trials. Categorisation of depression in included studies did not correspond to the definitions in the NICE guideline. In over half of included studies, the population was not restricted to depression and included other affective disorders. A minority of studies were conducted in an IAPT setting. Differences in health system organisation and treatment pathways may limit generalisability of international evidence. Published evidence was not available for all scoped outcomes. There was limited adverse event or other patient safety data reported in the eligible studies identified by the EAG. Clinical measures are reported heterogeneously, though some measures are frequently reported across studies. Included studies mostly suffered from methodological limitations, and bias in effect estimates could not be ruled out as a result. It is important to note that baseline severity characteristics differed between studies conducted in IAPT settings and routine practice data from the IAPT database.

Quality and relevance of economic evidence

Early decision modelling suggests there is a *prima facie* case for digital cognitive behavioural therapy (dCBT) interventions to be cost-effective in less severe depression, but there is considerable uncertainty around this. However, dCBT interventions appear unlikely to be the most cost-effective option in more severe depression, where a problem solving intervention generates a higher net monetary benefit. There is one RCT with a corresponding economic evaluation (REEACT) conducted in an IAPT population using a stepped care model that did not show a statistically significant clinical or economic benefit of Beating the Blues over usual GP care alone. In this study treatment with dCBT using Beating the Blues was dominated

by usual care which included access to IAPT (including dCBT) and secondary mental health services. Adherence to dCBT was low in this study (only 18% completed all 8 sessions). Usual care was numerically both less expensive and generated better outcomes than Beating the Blues. There is a lack of evidence to determine whether one dCBT intervention is more cost-effective than another. There are likely to be unrecoverable costs associated with a decision to implement these treatments which may be sizeable and should be considered within negotiations.

Evidence Gap Analysis

Key evidence generation should focus on the scoped interventions compared to the scoped comparators in an IAPT setting with depression severity categorized as per NICE guidelines. The best study design for generating this evidence is a randomized controlled trial, and a pragmatic design would be appropriate. A pragmatic RCT is one set within everyday clinical practice with follow-up data collected ideally from existing routine data sources, although this can be supplemented with additional questionnaires and measurements as required. Cluster rather than individual randomization would further simplify the design but reduces the statistical power of the study. The EAG emphasises the importance of randomised comparisons as observational cohort studies typically lead to exaggerated estimates of effect, compared with RCTs; the key IAPT RCT (on Beating the Blues) did not show a statistically significant effect on outcomes, contrary to evidence from a non-randomised controlled pilot trial and other non-randomised studies. The most suitable study designs should be decided taking into account feasibility and stakeholder input.

1 Decision problem

Table 1 details the final scope issued by NICE for this EVA, defined per element of assessment.

Table 1: Summary scope of the assessment

Element of assessment	Final scope issued by NICE	Clinical advice to the EAG comment
Population	Adults with depression who have been referred to IAPT services	No comment

Element of assessment	Final scope issued by NICE	Clinical advice to the EAG comment
Interventions (proposed technologies)	Digitally enabled therapies for facilitating guided self-help in people with depression. These technologies have been designed to be used with support by healthcare professionals: • Beating the Blues • Minddistrict • Space from Depression • Wysa • Deprexis • Iona Mind • Perspectives	No comment
Comparator	Standard care according to NICE's clinical guideline on depression in adults: treatment and management[2]. The recommended treatment options for less severe depression include: • Guided self-help • Group cognitive behavioural therapy (CBT) • Group behavioural activation (BA) • Individual CBT • Individual BA • Group exercise • Group mindfulness and meditation • Interpersonal psychotherapy • Selective serotonin reuptake inhibitors • Counselling • Short-term psychodynamic psychotherapy For more severe depression include: • Combination of individual CBT and an antidepressant • Individual CBT • Individual BA • Antidepressant medication • Individual problem-solving • Counselling • Short-term psychodynamic psychotherapy • Interpersonal psychotherapy • Guided self-help • Group exercise	The most appropriate comparator would be either face-to-face individual high intensity CBT or other treatment modalities such as telephone, video conference or face-to-face guided self-help or other groups and courses. Waitlist and usual care are often no psychological therapy and thus a good replacement for inactive placebo. It was noted that waitlist may reflect the real-life alternative patients face.
Healthcare setting	Improving access to psychological therapies (IAPT) services	No comment
Outcomes	Intermediate measures for consideration may include: • Patient choice and preferences • Treatment satisfaction and engagement	No comment

Element of assessment	Final scope issued by NICE	Clinical advice to the EAG comment
	• 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 depression symptoms • 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)	No comment
	Patient-reported outcomes for consideration may include: • Health-related quality of life • Patient experience	No comment

	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 depression, adverse events or complications):
	  ○ GP or IAPT appointments
	  ○ Medication
	  ○ Health professional grade and time
		No comment

Time horizon	The time horizon for estimating the clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	No comment

Abbreviations: BA, Behavioural Activation; CBT, Cognitive Behavioural Therapy; EVA, Early Value Assessment; GP, General Practitioner; NICE, National Institute for Health and Care Excellence; IAPT, Improving Access to Psychological Therapies

2 Overview of the technology

2.1 *Purpose of the medical technology*

Depression is a common and important health condition for the NHS. It is the leading cause of disability and premature death in those aged 18-44[3]. The Improving Access to Psychological Technologies (IAPT) initiative set targets to provide access to services for 25% of people with common mental health conditions each year and reduce waiting times to within 6 weeks for 75% of patients by 2020-2021[4]. However, between April 2021 and March 2022, only 37% completed a course of therapy, showing a substantial gap between referrals and treatment[5] [6]. Reasons may include inappropriate referral (with IAPT therapies being unsuitable for the patient's clinical need) and long waiting lists, which were estimated as being up to 86 days in some parts of England[5].

Digitally enabled therapies represent another treatment option for adults with depression. They may be delivered online or via smartphone apps and allow people to access self-help for their mental health condition with varying levels of support from a health professional. These therapies may offer greater patient choice and service flexibility and reduce waiting lists by improving productivity in care provision.

2.2 *Product properties*

This scope focuses on digitally enabled therapies for treating and managing depression in adults that meet the following criteria:

- Intended for use by adults
- Deliver a therapeutic intervention in line with NICE guidelines that can be used in IAPT services with practitioner or therapist support
- Deliver a substantial portion of the therapy through the technology rather than being platforms to support teletherapy
- Meet the standards within the digital technology assessment criteria (DTAC), including the criteria to have a CE or UKCA mark where required. Products may also be considered if they are actively

working towards required CE or UKCA mark and meet all other standards within the DTAC.

- Are available for use in the NHS.

Technologies included in this EVA are also expected to complete the IAPT Digitally Enabled Therapies (DET) assessment criteria at an appropriate point.

In total, seven digitally enabled therapies designed to treat adults with symptoms of depression were included in the final scope.

2.2.1 Space from Depression (SilverCloud)

Space from Depression is an online CBT programme for adults with low mood and depression. It aims to teach users skills and strategies to manage depression. The programme comprises modules that contain quizzes, videos, information, personal stories, interactive activities, homework suggestions and summaries. In addition, the interventions incorporate mindfulness tools and resources, positive psychology, and motivational interviewing techniques. It can be used as a supported or a self-guided programme within IAPT services. Practitioners or therapists can guide people through the programme using built-in messaging within the platform. SilverCloud recommends that all programmes are used with a supporter who regularly reviews progress, provides feedback and unlocks content. Silvercloud has other programmes which can be used for a range of other mental health conditions, including a programme for anxiety and depression combined. However, experts state that the programmes for individual indications are primarily used in IAPT services. SilverCloud has screening tools incorporated into the programme, including the PHQ-9, which can be used to flag risk and send risk alert emails to the user's supporter or relevant members of the care team. Programmes can be accessed at any time using any smartphone, tablet, or computer.

2.2.2 Minddistrict (Minddistrict)

Minddistrict is an online CBT programme intended for treating psychological health conditions, including mild-to-moderate depression. It has a catalogue of modules, diaries, and questionnaires that can be combined and edited to suit the needs of each person. These include modules on mindfulness and self-help short courses that support everyday issues. Minddistrict can be used as a

standalone self-help tool or in a therapist-guided model of care, which allows practitioners to use video calling within the platform. The company state that the IAPT depression module has been designed to treat mild-to-moderate depression in adults. This consists of 7 sessions that are usually completed in 6 weeks. In this IAPT version, the Minimum Data Set is included in the module, with the PHQ-9 questionnaire included to allow services to automatically collect outcomes. The technology can be accessed via a web browser and there is also a smartphone app.

2.2.3 Beating the Blues (365 Health Solutions Ltd.)

Beating the Blues is an online CBT program for individuals with mild to moderate depression and anxiety. Each of the 8 sessions comprise 3 or 4 modules each taking 10 to 15 minutes to complete. The sessions contain both reading material and practical hands-on tools and lasts 8 to 12 weeks. It can be used according to the user's preferences with any computer, laptop, smartphone or tablet with internet access.

2.2.4 Deprexis (Ethypharm Digital Therapy)

Deprexis is a web-based program based on elements from CBT intended to help those with unipolar depression or depressive disorders. It is intended to be used as a supplement to care-as-usual. Deprexis integrates 10 modules on topics related to depression. During these modules, the technology adapts its approach according to the needs and preferences of the user. Worksheets, exercises, audio sequences, short texts and illustrations are also available to in order to guide people through the program. It can be used according to the user's preferences with any computer, laptop, smartphone or tablet with internet access. Progress can be tracked using the PHQ-9 questionnaire and moodcheck (to monitor mood). These questionnaires (in addition to progression charts) can then be downloaded to be shared with a healthcare professional.

2.2.5 Wysa (Wysa Ltd.)

Wysa is an artificial intelligence-based app for people with mild to moderate depression and anxiety. It has a collection of CBT-based self-help programmes that are designed to be used with practitioner or therapist support. This includes a web-based therapist companion portal that lets practitioners and therapists

review a person's engagement and recommend programmes. Wysa has an AI-guided chatbot that uses natural language processing to encourage self-reflection and help users engage with the mental health tools. It has built in mental health assessment which collects outcome data such as the PHQ-9 questionnaire. Wysa includes a risk alert system and pathway that provides grounding exercises, a crisis care plan and crisis numbers for emergency support. In addition to the patient app, Wysa also has a web-based AI-supported e-triage tool that collects data based on questions from the referral form for IAPT services.

2.2.6 Iona Mind (Iona Mind)

Iona Mind is an app-based CBT programme for people with depression or generalised anxiety disorder. It is designed to be used alongside therapist support. 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. Progress can be tracked using screening measures such PHQ-9. It also monitors mood and goal progression. The app additionally has functionality to identify crisis events and provide signposting.

2.2.7 Perspectives (Koa Health)

This technology was removed from the evaluation after scope publication as regulatory approval is not currently being sought in this population.

3 Comparator

Guided self-help digital CBT technologies could be a first line treatment prior to more intensive interventions or used as an alternative to standard care for adults with depressive symptoms. The scoped comparator was other treatments recommended by NICE guidelines for the relevant depression severity level, with treatment options as outlined in Table 1. SCM advice to the EAG indicated that the comparator should be face-to-face high intensity CBT or guided self-help, courses or groups using different treatment modalities (telephone, video conference or face-to-face) and that usual care and waitlist would act as a good substitute for inactive placebo and may reflect the real-life

alternative. Thus ideally, all interventions listed as both intervention and comparators in Table 1 should be compared against each other.

4 Clinical context

The target population for this assessment is adults with depressive symptoms in the IAPT setting.

According to ICD-11 criteria, depression is defined as the presence of low mood or decreased interest in activities of daily living that persists most of the day, almost every day, for a 2-week period, accompanied by other symptoms which may include:

- Reduced ability to concentrate and sustain attention or marked indecisiveness
- Beliefs of low self-worth or excessive or inappropriate guilt
- Hopelessness about the future
- Recurrent thoughts of death or suicidal ideation or evidence of attempted suicide
- Significantly disrupted sleep or excessive sleep
- Significant changes in appetite or weight
- Psychomotor agitation or retardation
- Reduced energy or fatigue

Depression severity exists as a continuum along three dimensions relating to: a) symptom frequency and intensity, b) duration of disorder, c) impact on personal and social functioning.

The most recent NICE guideline[2] on the treatment and management of depression in adults has adopted a binary classification into less severe and more severe depression. The former category encompasses subthreshold and

mild depression (scoring less than 16 on PHQ-9) and the latter encompasses moderate and severe depression (scoring 16 or more on PHQ-9). However, it was considered that the clinical evidence available to inform this appraisal would be aligned to these groups due to the NICE guideline being recently updated.

4.1 *Care pathway*

The current NICE guideline for the treatment and management of depression in adults recommends that decision making about which treatments to initiate should take into account a variety of factors, including patient needs, any physical health problems, any coexisting mental health conditions, factors affecting the patient's likely engagement with proposed treatments, previous treatment history, and any disabilities, language or communication difficulties that may be a barrier to the delivery of any particular treatment options. Additionally, it is recommended to match treatment to the needs and preferences of the person with depression as far as possible and also to use the least intrusive and most efficient treatment that is clinically appropriate or that has worked for the patient in the past.

As part of the treatment pathway for all people with depression, it is recommended to review how well the treatment is working after 2 to 4 weeks, monitor and evaluate adherence to treatment plans, monitor for adverse events, monitor for suicidal ideation especially early in the treatment programme, and consider routine outcome monitoring and follow-up using appropriate validated outcome tools.

Current NICE guidelines divide treatment options into two categories by depression severity. The following treatments are recommended and the ordering in the list can be taken to reflect a ranked order of preference.

<u>Less severe depression</u>

- Guided self-help
- Group cognitive behavioural therapy (CBT)

- Group behavioural activation (BA)
- Individual CBT
- Individual BA
- Group exercise
- Group mindfulness and meditation
- Interpersonal psychotherapy
- Selective serotonin reuptake inhibitors
- Counselling
- Short-term psychodynamic psychotherapy

More severe depression

- Combination of individual CBT and an antidepressant
- Individual CBT
- Individual BA
- Antidepressant medication
- Individual problem-solving
- Counselling
- Short-term psychodynamic psychotherapy
- Interpersonal psychotherapy
- Guided self-help
- Group exercise

Current NICE guidelines recommend guided self-help for both more and less severe depression but note that it should be considered as the first option for less severe depression as it is the least intrusive and most resource efficient option, while it may be less suitable for more severe depression and other treatment options with greater therapist contact should be considered first. It is

noted in the guideline that within an IAPT context, where considered clinically appropriate, digitally enabled therapies may provide faster access to treatment and reduce waiting lists. The stepped care model allows patients to be referred to a more intensive therapy if it is considered that there is a clinical need.

One SCM advised that the treatment pathway in the NICE guidelines very closely matches routine NHS practice. However, other SCM advice was that due to limited resources, high demand and long waiting times, treatments offered may differ from the guidelines, for example Step 2 treatments being offered where Step 3 may be more appropriate, while digital therapies may be given precedence in order to manage waiting lists, and that additionally IAPT services may see more people with moderate-to-severe depression than anticipated in the NICE guidelines.

Benchmarking data from the NHS Digital IAPT database show that CBT was the most common treatment across IAPT services in 2021 and 2022 (55,587 courses of therapy), followed by guided self-help using a book (42,652), counselling (29,802), guided self-help using a computer (7,022 – the most relevant category for this appraisal), interpersonal psychotherapy (3,536), non-guided self-help using a book (924), non-guided self-help using a computer (332), and mindfulness (288). These values are not reported separately by level of depression.

4.1.1 Current use of dCBT technologies

Information available to the EAG indicated that where digitally enabled mental health therapies are used currently in the IAPT setting these are generally SilverCloud products, such as Space from Depression. Based upon information supplied by the company [redacted]. The manufacturer of Beating the Blues indicated that its product receives minimal use in IAPT settings but is widely used in Scotland and Northern Ireland. The EAG did not have information to determine whether this different pattern of usage is attributable to differences in health system organisation, commercial factors, or whether there is something about the content of Beating the Blues that makes it particularly amenable for depression

as encountered in Scotland and Northern Ireland. Among SCMs responding to the EAG, two were familiar with Space from Depression (SilverCloud Health) and one was familiar with Beating the Blues. None reported seeing any other guided digital therapies used within IAPT settings.

While the IAPT manual states that the interventions under consideration would be delivered by a Band 5 PWP, one SCM advised was that Band 5 staff would not be suitable for the delivery of dCBT interventions. If there was a discrepancy between the level of expertise and training needed in the manual and in routine practice, this may have implications for resource at a health system level.

4.2 *Patient issues and preferences*

Digitally enabled therapies are delivered via computers, tablets and/or smartphones and can therefore be accessed remotely. Digitally enhanced therapies are more resource efficient and can therefore increase capacity and the timeliness of available support and reduce waiting lists in the context of IAPT services with an increasing demand for treatment for depression but limited resource capacity to deliver traditional face-to-face CBT. Digitally enabled therapies can therefore offer an additional treatment option and increase patient choice.

Patient preferences will differ with regard to digitally enabled therapies. Some patients who are regular users of digital technologies may prefer digitally enabled therapies due to potential greater flexibility and privacy, but some regular users of digital technologies may prefer more clinician-led approaches. There may be some concerns about the level of support provided in a digitally enabled therapy and concerns around data security and quality control. Not all patients will be confident with using digital technologies and this may disproportionately affect older people and those from more socially deprived backgrounds. The Ofcom Adults' Media Use and Attitudes report[7] states that 6% of households did not have access to the internet at home in 2021, with this being associated with increased age, greater social deprivation and greater financial vulnerability. Ofcom[7] estimate that 21% of internet users exclusively access the internet using a smartphone. Furthermore, depending on people's

living situations and triggers for depression, they may not be able to access therapy within the house, and this could cause particular challenges for users in rural areas where access to smartphone data and WiFi networks, for example in natural environments, such as parks, woodland, fields and on riverside walks, can be limited.

5 Special considerations, including issues related to equality and equity

A number of potential equality issues have been identified. Women are nearly twice as likely on average to be diagnosed with depression than men. This may relate in part to cultural factors and differences in treatment-seeking behaviour. Increased social deprivation is also associated with higher depression rates. Ethnic, religious or cultural backgrounds may influence people's perceptions about mental health issues. People with ADHD and learning difficulties and non-English speakers are also significant groups who may struggle to access dCBT in its current form. In addition, there may be overlap between depression and long-term health conditions such as chronic pain; evidence considering specific physical health conditions has not been considered within this EVA as the scope was limited to depression as the primary diagnosis but could be a topic for future research.

Digitally guided therapies require internet access via a computer, tablet and/or smartphone. There may therefore be barriers to access to these therapies for those with low familiarity with or poor access to the requisite technological devices. Overcoming these barriers would increase resource costs. Additional support in using digitally guided therapies may be needed for people with visual, hearing or cognitive impairment, problems with manual dexterity, and/or who are unable to read or understand health-related information presented in English.

6 Potential implementation issues

The EAG noted several potential implementation issues related to greater adoption of digitally enabled therapies for adults with depression. Barriers to patient access to required technology would need to be addressed, including the particular challenges of rural communities. Training would be required for those facilitating digitally enabled therapies. Costs may differ between technologies and smaller service areas may have higher costs per user due to not needing as many licences for the technology. Three therapies [redacted] and Space from Depression) provided a volume banded pricing structure, and the lowest band price per user was up to [redacted] times the highest volume band. Digitally enabled therapies need to be able to identify potential risks for patients. Some digitally enabled therapies have inbuilt processes to flag the need for greater intervention. Lastly, the interventions within the scope have varying levels of integration with existing recording systems currently in use within the UK e.g. IAPTus and PCMis, the implications of which for implementation will need assessment.

7 Other issues for consideration

Characteristics of digital technologies

Digitally enabled therapies included in the scope are heterogeneous in terms of delivery mode (computer, app), the focus of the content and the extent of practitioner support. Some technologies can be used in both a guided or non-guided context, while only guided use is within the scope of the present appraisal. It is important to note that the availability and extent of guiding or support available may differ between studies on the same technology. Wysa and Iona Mind use artificial intelligence (AI) as part of the support available to users. Technologies included in this EVA will complete the IAPT DET assessment criteria. This includes validation of clinical content in line with NICE guidelines and assessment of clinical effectiveness. Passing this assessment will be a requirement to proceed to evidence generation stage of the EVA.

Population

Most technologies are designed for mild to moderate depression. The NICE guideline has subdivided depression into less severe (subthreshold and mild) and more severe (moderate and severe) depression. This leads to a mismatch in severity categorisation between the guidelines and the trial evidence. Most of the available evidence will span the two categories in the NICE guideline, for which different recommendations are offered. It should be noted that people with depression often have other mental health issues such as anxiety. IAPT services so far have been designed to treat the person's 'main' presenting problem, such as depression, rather than having a combined focus on anxiety and depression. In many included studies, the intervention is positioned with the aim of treating anxiety and/or depression in a mixed population. SCM advice to the EAG was that mixed anxiety and/or depression populations are not a concern since the symptoms often overlap and there is a very high comorbidity between anxiety and depression (estimated to be about 80%). However, clinical practice often focuses on treating one of anxiety or depression, depending which is identified as the primary presenting symptom.

Evidence

This appraisal will consider a range of evidence types including RCTs, real world evidence and benchmarking against published NHS Digital metrics. The depth and quality of the evidence base varies from technology to technology. Some trials were conducted in a UK IAPT setting, but other studies were conducted in other settings in Scotland or internationally. Comparators vary between trials, but commonly include waitlist control which was not a scoped comparator for this appraisal, but may reflect the realities of a service with high demand but constrained resources. Study populations are heterogeneous and may include mixed populations of people with one or both of anxiety and depression rather than being specific to depression. This assessment will evaluate the clinical and potential cost effectiveness of digitally enabled therapies as an alternative to standard care in IAPT services.

Care pathway

Digitally enabled therapies can be used at different points along the care pathway. The points at which a particular technology may be appropriate will depend on the content of the intervention. Treatments should be used in accordance with NICE guidelines with treatment selection guided by healthcare professional assessment, patient risk and patient choice.

8 Clinical evidence selection

8.1 *Search strategy*

Search strategies used were based on those devised during the initial scoping searches by NICE Information Services, with some amendments. The search strategies used relevant search terms, comprising a combination of indexed keywords (e.g., Medical Subject Headings, MeSH) and free-text terms appearing in the titles and/or abstracts of database records and were adapted according to the configuration of each database. No date or publication status (published, unpublished, in-press, and in-progress) limits were applied. The searches were limited to English language studies. Searches were carried out jointly with Cedar, who are carrying out a review for dCBT for anxiety in adults, in parallel with this one.

Following deduplication, a total of 1694 records of potentially relevant evidence on clinical and/or cost effectiveness, 53 additional records of potentially relevant economic evaluations and 130 trial registry entries were retrieved. Databases searched were Medline, Embase, PsycInfo, Cochrane, CRD, INAHTA, PubMed, Epistemonikos, CEA Registry and ScHARRHUD. Additional trial registries searched were Clinicaltrials.gov (NLM) and ICTRP (WHO). The websites of the individual companies were searched; NICE and SIGN websites were searched for related Guidelines; MAUDE and MHRA were searched for adverse events data; the company submission references were also scanned and 24 potential additional references were identified for screening.

In addition, further economics papers were identified for the cost effectiveness systematic review by scanning the studies used in the previous report *MT580*

Guided dCBT for CYP with mild to moderate anxiety/low mood: an Early Value Assessment[8]. These searches were also updated by broadening them to all digital interventions for adults (not just the specific ones in the scope) but adding the health economics filters from the Centre for Reviews and Dissemination at http://www.crd.york.ac.uk/crdweb/searchstrategies.asp and were limited to 2022 only.

The search terms for the Medline search strategies for clinical and cost-effectiveness evidence are presented in Appendix A and B (Section 16), respectively.

8.2 *Study selection*

The abstracts and titles of references retrieved by the electronic searches were screened for relevance. Full paper copies of potentially relevant studies were obtained. The retrieved articles were assessed for inclusion against pre-specified inclusion/exclusion criteria. At each stage of screening, 50% of records were independently screened by a second reviewer. Discrepancies were resolved by discussion, with involvement of a third reviewer, where necessary. All duplicate papers were excluded.

This assessment looked across a range of evidence types including RCTs, real world evidence and benchmarking against NHS Digital published metrics. Evidence considered included evidence of clinical effectiveness.

The following study types were excluded:

- Animal models
- Pre-clinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as meeting abstracts only, where insufficient methodological details are reported to assess the study and its outcomes Information provided by the companies that is considered relevant was considered regardless
- Studies not available in the English language.

Eligible studies assessed a scoped intervention (Beating the Blues, Minddistrict, Space from Depression, Wysa, Deprexis, Iona Mind) in a population of adults with depression, or a mixed population of adults with depression and/or anxiety. Mental health conditions secondary to another medical condition such as Parkinson's disease or epilepsy were not considered due to the quite different nature of depression in these conditions.

As this was an EVA, studies were not excluded if the comparator did not match the scope or if the outcomes did not match the scope, provided the outcomes appeared reasonable and could offer useful information in the context of the appraisal. This approach was agreed in discussion with the NICE technical team.

A PRISMA flow diagram is provided as Appendix 16.3.

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

Due to time and resource constraints, in light of the volume of evidence available across a range of technologies, the EAG was not able to conduct formal risk of bias assessment. Generally, RCTs or meta-analyses of RCTs could be considered more robust than other study types, but it depends on the details of how each study was conducted, and how well the trial setting reflects routine clinical practice in terms for example of eligible population and staff attention, which could affect generalisability.

9 Clinical evidence review

The EAG identified a total of 46 papers, including one [redacted] that was under review and supplied by SilverCloud Health as academic in confidence, that were relevant to the present decision problem. These comprised 32 unique studies.

Table 2 presents a detailed overview of the study design and characteristics of each included study.

Table 2: Included studies

Papers	Study name	Country	IAPT?	Method	Sample	Intervention	Comparator	Outcomes
Beatty et al, 2022[10]	Not stated	International	No	Mixed methods	1205 people who screened positively for depression or anxiety on PHQ-4	Wysa (AI-guided)	None	Therapeutic alliance, acceptability of conversational agent
Beevers et al, 2017[11]; Mullarkey et al, 2020[12]	NC/T01818453	USA	No	Parallel-group pragmatic RCT	376 people with depression (QIDS-SR >=10)	Deprexis (self-guided)	Waitlist	Depression severity, 50% or greater reduction in depression severity, depression remission (HRSD <=7), Quick Inventory of Depression Symptoms
Berger et al, 2011[13]	Not stated	Switzerland and Germany	No	RCT	128 people with depression (BDI-II >13)	Deprexis (low-intensity therapist-guided self-help)[a]	Deprexis (unguided), waitlist	BDI-II, general psychopathology, interpersonal problems, quality of life
Berger et al, 2018[14]	Not stated	Germany	No	Pragmatic RCT	98 people with a unipolar affective disorder	Deprexis plus psychotherapy	Psychotherapy	BDI-II, anxiety symptoms, somatic symptoms, quality of life

Papers	Study name	Country	IAPT?	Method	Sample	Intervention	Comparator	Outcomes
					(BDI-II >13)			
Boschloo et al, 2019[15]; Kaiser et al, 2021[16]; Klein et al, 2016[17]; Klein et al, 2017[c18];Nolte et al, 2021[19]; Schneider et al, 2018[20]; Schuster et al, 2020[21]	EVIDENT	Germany	No	Pragmatic RCT	1013 people with mild-to-moderate depression as per PHQ-9	Deprexis – whether or not participants received clinician guidance depended on baseline score	Care as usual	PHQ-9, HDRS-24, QIDS-C16, Questionnaire for the Evaluation of Psychotherapeutic Progress, quality of life, remission rates
Cavanagh et al, 2006[22]/2009[23]	Not stated	UK	No (before IAPT)	Naturalistic open trial	219 people with anxiety and/or depression	Beating the Blues (results sent to a health professional after every session)	None	CORE-OM, Work and Social Adjustment scale, Attitudes to dCBT Questionnaire, Opinions about Psychological Problems Questionnaire, Patient Feedback Scale for dCBT
Cavanagh et al, 2011[24]	Not stated	UK	Yes	Implementation study	510 referrals for depression and/or anxiety	Beating the Blues (progress and outcomes reviewed by service volunteer or service coordinator)	None	PHQ-9, GAD-7, CORE-OM, Work and Social Adjustment Scale, Patient Experience Questionnaire

Papers	Study name	Country	IAPT?	Method	Sample	Intervention	Comparator	Outcomes
Cientanni et al, 2019[25]	Not stated	UK	No (Scotland)	Real-world evidence	1158 people with mild-to-moderate depression (suspected diagnosis by referring clinician)	Beating the Blues (routine contact with service coordinator differed across Health Boards)	None	CORE-OM
Du et al, 2021[26]	Not stated	UK	No (Scotland)	Qualitive	33 people with mild-to-moderate anxiety and/or depression	Beating the Blues	None	Patient experience and acceptance
Duffy et al, 2020[27]	Not stated	UK	Yes	Open naturalistic study	124 people on a waiting list for high intensity CBT for depression and/or anxiety	Space from Depression (with integrated risk management) – analysis of completers vs dropouts	None	Depression, anxiety, functioning
Enrique et al, 2019[a] ; [28] [29]Richards et al, 2015[b30]	ISRCTN03704676	Ireland	No	RCT plus secondary analysis	188 people with BDI-II >=14 and <=29	Space from Depression (with support)	Waitlist	BDI-II, GAD-7, Work and Social Adjustment Scale, platform usage, reliable change

Papers	Study name	Country	IAPT?	Method	Sample	Intervention	Comparator	Outcomes
Gilbody et al, 2015[31]; Littlewood et al, 2015[32]	REEACT	UK	Yes	Pragmatic RCT	691 people with PHQ-9 score >=10	Usual care from GP plus Beating the Blues; Usual care from GP plus MoodGYM	Usual care from GP	Improvement in depression (PHQ-9), CORE-OM, quality of life, treatment preference, acceptability, user experience, adverse events
Gräfe et al, 2020[33 34]	RKS00003564	Germany	No	Pragmatic RCT	3,805 people with PHQ-9 score >4	Deprexis plus care as usual	Care as usual plus a brochure with general information about depressive disorders	Depression severity, functional impairment, Work and Social Adjustment Scale, quality of life
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inkster et al, 2018[35]	Not stated	International	No	Mixed methods	129 users of the Wysa app	Wysa (AI-guided)	None	Mood improvement, user experience, user engagement
Jonassaint et al, 2017[36]	Online Treatment for Mood and	USA	No	RCT	704 people with moderate	Beating the Blues, or Beating the	Usual care	User engagement, decrease in

Papers	Study name	Country	IAPT?	Method	Sample	Intervention	Comparator	Outcomes
	Anxiety Disorders Trial				depression and/or anxiety (PHQ-9 or GAD-7 score >=10)	Blues plus internet support group		depression and/or anxiety symptoms
Karyotaki et al, 2018[37]	Not stated	International	No	IPD meta-analysis	13 trials including 3805 participants with depression	Self-guided internet CBT interventions	Waitlist, treatment as usual, attention placebo or other non-active controls	BDI-I, BDI-II, CES-D, or PHQ-9, analysed using reliable change index
Karyotaki et al, 2021[38]	Not stated	International	No	IPD meta-analysis	39 trials including 9751 participants with depression	Guided and unguided internet CBT interventions	Other forms of guided or unguided internet CBT or any type of control intervention (treatment as usual, waitlist)	PHQ-9
Klein et al, 2020[39]	Not stated	Germany	No	Uncontrolled observational study	104 people with a depressive disorder	Deprexis plus usual care	None	MADRS short version, PHQ-9, Clinical Global Impression scale, Sheehan Disability Scale, Client Satisfaction Questionnaire, 2 items from

Papers	Study name	Country	IAPT?	Method	Sample	Intervention	Comparator	Outcomes
								Compulsive Internet Use Scale, adverse events
McCrone et al, 2004[40], Proudfoot et al, 2004[41]	Not stated	UK	No (before IAPT)	RCT	274 people with depression or anxiety	Beating the Blues (results were automatically sent to a health professional after each session)	Usual care	Change in depression level (BDI), Beck Anxiety Inventory, Work and Social Adjustment Scale, Attributional Style Questionnaire
McMurchie et al, 2013[42]	Not stated	UK	No (Scotland)	Non-randomised pilot study	57 people with depression or depression co-morbid with anxiety	Beating the Blues plus treatment and usual	Treatment as usual	Geriatric Depression Scale, Geriatric Anxiety Scale, CORE-34
Malik et al, 2022[43]	Not stated	International	No	Qualitative thematic analysis	41,114 user reviews	Wysa (AI-guided)	None	User feedback
Meyer et al, 2009[44]	ISRCTN 64953693	Germany	No	RCT	396 adults from internet depression forums	Deprexis plus treatment as usual	Treatment as usual (delayed access to Deprexis)	Depression (BDI), social functioning (Work and Social Adjustment Scale), programme acceptability, subjective benefit

Papers	Study name	Country	IAPT?	Method	Sample	Intervention	Comparator	Outcomes
Meyer et al, 2015[45]	Not stated	Germany	No	RCT	163 people exceeding threshold for severe depression (PHQ-9 >15)	Deprexis plus usual care	Usual care/waitlist	PHQ-9, GAD-7, PHQ-15, quality of life, treatment satisfaction, alliance/ helpfulness
Moritz et al, 2012[46]	NCT 01401296	Germany	No	RCT	210 people with elevated depression symptoms	Deprexis	Waitlist	BDI, Dysfunctional Attitude Scale, Rosenberg Self-Esteem Scale, quality of life, subjective benefit
Ormrod et al, 2010[47]	Not stated	UK	Probably (not stated)	Pilot study	16 people with a diagnosis of depression	Beating the Blues (a health professional greeted participants at all sessions and monitored outcomes)	None	BDI
Palacios et al, 2022a[48]	Not stated	UK	Yes	Naturalistic cohort study	21,215 people with depression and/or anxiety	Guided self-help, internet-delivered CBT (Space from Depression, Space from Anxiety), psychoeducational group therapy	None (all seen as interventions)	PHQ-9, GAD-7, Work and Social Adjustment Scale
Palacios et al, 2022b[49]/	ISRCTN 91967124	UK	Yes	Pragmatic RCT	361 people referred to	Space from Depression,	Waitlist	PHQ-9, GAD-7, Work and Social

Papers	Study name	Country	IAPT?	Method	Sample	Intervention	Comparator	Outcomes
Richards et al, 2020[50]					IAPT stage 2 with depression and anxiety	Space from Anxiety, Space from Depression and Anxiety (supported by Psychological Wellbeing Practitioners)		Adjustment Scale, reliable recovery from depression and anxiety
Pittaway et al, 2010[51]	Not stated	UK	Probable (not stated)	Comparative clinical feasibility study	100 people with mild to moderate anxiety and/or depression	Beating the Blues (supervision in first session then minimal contact), workbooks on overcoming depression and anxiety, Livinglifetothefull website	None	CORE-OM, participant feedback on usefulness
Rollman et al, 2018[52]	NCT 01482806	USA	No	RCT	704 people with anxiety, generalised anxiety, panic and/or depression	Care manager guided computerised CBT (Beating the Blues); care manager guided computerised CBT plus internet support group	Usual care	Patient-Reported Outcomes Measurement Information System (depression and anxiety), quality of life, health service use
Simmonds-Buckley et al, 2020[53]	Not stated	International	No	Meta-analysis	24 studies assessing anxiety, depression	NHS-recommended e-therapies for anxiety,	Controls varied, including in the same meta-analysis	Patient reported outcomes of anxiety, depression and/or stress

Papers	Study name	Country	IAPT?	Method	Sample	Intervention	Comparator	Outcomes
					and/or stress	depression and/or stress		
Twomey et al, 2017[54]/ 2020[55]	Not stated	International	No	Meta-analysis (original and update)	12 RCTs on a total of 2901 people with depression	Deprexis	Waitlist, delayed access, no treatment, treatment as usual, or active control interventions (computerised or not)	Self-reported or clinician-rated depression measures

Abbreviations: BDI, Beck Depression Inventory; dCBT, Computerised Cognitive Behavioural Therapy; CES-D, Center for Epidemiologic Studies Depression Scale; CORE-OM, Clinical Outcomes in Routine Evaluation – Outcome Measure; GAD, Generalised Anxiety Disorder assessment; HRSD, Hamilton Rating Scale for Depression; IAPT, Improving Access to Psychological Therapies; MADRS, Montgomery-Asberg Depression Rating Scale; PHQ, Patient Health Questionnaire; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Report; RCT, Randomised controlled trial; UK, United Kingdom; USA, United States.[a] = The background of the supporter was not low-intensity.

Among the 32 unique studies, seven were conducted in an IAPT or probable IAPT setting. We assigned studies as 'probable IAPT' if they did not specifically mention IAPT but were conducted in England during the period of IAPT's operation as the principal relevant mental health services offering. This ensured we did not miss relevant studies, since setting is of particular importance in this appraisal. However, the potential limitation is that it is not confirmed that 'probable IAPT' studies took place within an IAPT setting and that other care pathways could have been used as well or instead. Among these seven studies, four assessed Beating the Blues and three assessed Space from Depression. Two of these were RCTs, one assessing each of these two technologies, one against usual GP care and one against waitlist control. These comparators are conceptually similar, as in neither case were participants receiving specialist psychological treatment. Information on what usual care comprised was generally lacking across studies, so it was not possible to systematically profile what treatment patients in the control arms may have received. Meta-analyses broadly relevant to the decision problem were also included, as they can provide relevant contextual information and may be useful for modelling purposes. However, the focus in the clinical section was on the specific key studies identified by the EAG.

9.1 *Overview of methodologies of all included studies*

All relevant studies described in Table 2 had some methodological limitations or misalignment with the scope of the NICE decision problem.

9.1.1 Study design, intervention and comparator

There were a total of 32 unique studies, of which seven were contacted in an IAPT setting or probable IAPT setting – when the study was conducted in England in appropriate services over the time period IAPT has been in operation but the paper did not specifically mention IAPT. Four studies (Karyotaki et al, 2018[37]; Karyotaki et al, 2021[38]; Simmonds-Buckley et al, 2002[53]; Twomey et al, 2017[54]; Twomey et al, 2020[55]) were meta-analyses. The

two papers by Twomey et al (2017[54], 2020[55]) reflect an original and updated version of the same meta-analysis.

There were a total of 14 RCTs, of which two were conducted in the IAPT setting. These are REEACT (n=691) (Gilbody et al, 2015[31]; Littlewood et al, 2015[32]), which is a pragmatic RCT comparing Beating the Blues plus usual GP care with usual GP care alone (there is a second intervention arm MoodGYM which is out of scope for this appraisal) and ISRCTN 91967124 (n=361) (Palacios et al, 2022[49]; Richards et al, 2015[30]), which is a pragmatic RCT of Space from Depression (and other non-scoped interventions) with waitlist control. The REEACT study imposed no constraints on usual GP care in the control or intervention groups, this included the use of antidepressants, counselling, psychological services (including IAPT services and therefore potentially dCBT (19% of the usual care group), or secondary care mental health services. Such services were used by similar proportions of participants across each of the three groups. Of those participants who started the programmes only 18% completed all eight sessions of Beating the Blues. Remaining studies were predominantly single-arm studies without a direct comparator.

There was RCT evidence available for Space from Depression, Beating the Blues and Deprexis, and for the first two of these technologies, there was also RCT evidence available within the IAPT setting. For Wysa, there were three eligible studies, of which two (Beatty et al, 2022[10]; Inkster et al, 2018[35]) were mixed methods studies and one (Malik et al, 2022[43]) was a qualitative study. None of these studies were conducted in an IAPT setting. No eligible studies were identified by the EAG for Minddistrict or Iona Mind.

Among the 14 RCTs identified by the EAG as eligible for this appraisal, all used usual care or waitlist control as the comparator, with the exception of Berger et al (2011)[13] which included unguided Deprexis alongside waitlist control as a comparator, Berger et al (2018)[14] in which the comparator arm was psychotherapy alone, and RKS00003564 (Gräfe et al, 2020[33] [34]) which supplemented usual care with an informational brochure on depression.

Evidence gap: Eligible evidence was not available for Minddistrict or Iona Mind. No evidence in the IAPT setting was available for Deprexis. There was poor alignment between scoped comparators and comparators in the published literature, in which the sole comparator in 11 out of 14 RCTs was usual care or waitlist control. Only one study (Berger et al, 2018[14]), in Germany, used a scoped comparator in the form of psychotherapy.

9.1.2 Participants and setting

A minority of studies (7 out of 32 studies) were conducted in an IAPT setting or probable IAPT setting. There was IAPT RCT evidence for two technologies: Space from Depression and Beating the Blues. Due to the particularities of how IAPT services are organised, international evidence may be less directly applicable to the present decision problem.

All included studies described participants who are broadly relevant to the decision problem, although the inclusion criteria for participants and comparators had to be expanded versus the NICE scope to capture sufficient evidence. While the scoped population was adults with depression, it was necessary to include studies with a mixed population of anxiety and/or depression, noting that some participants within these studies may not have had depression according to clinical criteria.

In 18 out of the 32 included studies (56%), the population was not restricted to depression and there were adults with anxiety and other affective disorders included. No included studies reported depression categorised as less severe and more severe depression defined in the NICE guidelines. Interventions were generally designed predominantly for people with mild-to-moderate depression, which spans the two categories in the NICE guidelines.

Depression severity in the included studies was generally aligned to mild-to-moderate, although there were some people with greater depression severity included in some studies. Studies did not typically present subgroup results by depression severity. Therefore, it was not feasible for the EAG to conduct clinical subgroup analyses by depression severity. SCM advice to the EAG was

that the misalignment between interventions and the NICE guidelines regarding how to categorise depression severity has arisen due to a change of approach in the most recent NICE guidelines which has been done to help with resources, and that studies on mild-to-moderate depression, spanning the NICE guideline categories of less and more severe depression can still be relevant.

The EAG considered generalisability to the UK setting to be satisfactory for IAPT studies – concerns about depression severity profiling notwithstanding – but that international trials may have limited generalisability to the IAPT setting. This may relate partly to differences in health system organisation and differences in treatment pathways. Translation of technologies may impact upon generalisability of international evidence. Furthermore, it should be noted that the US version of Beating the Blues is structurally different from the UK version which restricts generalisability of US-based studies of this technology. There is a moderate degree of similarity but some key differences regarding the degree of interactivity and linearity, meaning that it is uncertain whether the UK and US versions of Beating the Blues should be considered as the same technology. Neither RCT conducted in an IAPT setting stated that it excluded potential participants who did not have personal access to required technical devices. The REEACT study clarified that while most participants had access to their own device or through a close relative, some participants accessed therapy through a central location such as a community library.

SCM advice to the EAG from one advisor was that the stepped care model is a NICE innovation and a concept used in the NHS, so treatment approaches may differ internationally. SCM advice was that in terms of population, Scotland (for Beating the Blues) and Germany (for Deprexis) can be considered generally similar to the target English population.

Evidence gap: Categorisation of depression in included studies did not correspond to the NICE guideline. In over half of included studies, the population was not restricted to depression and included other affective disorders.

Generalisability gap: A minority of studies were conducted in an IAPT setting. Differences in health system organisation and treatment pathways may limit generalisability of international evidence.

9.1.3 Outcomes

As the present appraisal is an EVA, a wide range of potentially relevant outcomes were listed on the final scope and these were listed as outcomes that the appraisal 'may include' rather than being exhaustive. Therefore, no studies were excluded on outcomes, provided the outcomes could be considered broadly relevant to the present appraisal. The EAG identified the key studies for detailed assessment for each technology, based on a preference for studies conducted within the IAPT context and studies near the top of the hierarchy of evidence (such as RCTs) where available and then assessed whatever outcome data were available within these key studies, supplementing this with additional data from other studies where it was considered appropriate.

None of the included studies reported on all outcomes included in the NICE scope, but all reported some outcomes of interest. The most commonly reported outcomes were depression severity, as well as anxiety severity where the study used a mixed population of anxiety and/or depression. The most commonly used outcome measures for depression were the PHQ-9[56] and the Beck Depression Inventory-II (BDI-II)[57], although other measures were used including BDI-I[58], Hamilton Rating Scale for Depression (HRSD)[59], Quick Inventory of Depressive Symptomatology (QIDS)[60]and Center for Epidemiologic Studies Depression Scale (CES-D)[61]. In total, excluding meta-analyses, [redacted] studies used PHQ-9 and 9 studies used a version of the Beck Depression Inventory. Quality of life measures, scores on the Work and Social Adjustment Scale (WSAS)[62] and measures of patient experience were also reported by multiple studies. Very limited adverse event or other or other patient safety outcomes were available. This may be because adverse event data are most frequently collected for pharmacological and surgical interventions and also because interventions were generally developed principally for mild-to-moderate depression.

SCM advice to the EAG was that PHQ-9 is the standard depression outcome in IAPT, HRSD is used in the majority of drug trials, BDI was used in the original studies of CBT by Beck, and all three are good rating scales. CES-D was seen as unfamiliar. SCM advice to the EAG was also that CBT has not usually been associated with any side effects or adverse events, but PHQ-9 should be monitored for any increase in suicidality. No responding SCMs raised concerns regarding the outcome measures.

Evidence gap: Published evidence was not available for all scoped outcomes. In particular, while the EAG was asked in particular to look for any available safety data, very limited adverse event or other safety data were reported in the eligible studies identified by the EAG.

Heterogeneity issue: Clinical measures are reported heterogeneously, though some measures are frequently reported across studies.

9.2 *Critical appraisal of studies*

No formal risk of bias assessment was conducted. The EAG noted that many available studies were single arm, which precludes comparative assessment of clinical effectiveness against a direct comparator. There were however 14 relevant RCTs among the 32 included studies, although only two were conducted in the IAPT population. Many were pragmatic RCTs, which may be beneficial for generalisability. However, it is a limitation in the context of the scoped comparators (alternative active treatments for less severe and more severe depression according to NICE guidelines) that only one study (Berger et al, 2018[14]), conducted in Germany, used an active targeted treatment for depression (in this case psychotherapy) as a comparator. The pivotal IAPT REEACT RCT for Beating the Blues, which did not show statistical significant benefit for Beating the Blues over usual GP care experienced low participant engagement rates. It is important to consider levels of support offered within the REEACT trial. The study states that it proactively offered a high level of technical support and weekly encouragement to use the packages. However, in contrast to current practice, the REEACT trial purposely did not augment structured psychological therapy over the telephone using trained

psychological therapists or PWPs. Indeed, the mean number of minutes of technical support calls for Beating the Blues participants in the REEACT trial (6.2, 2-8 minutes) is lower than in IAPT RCT evidence for Space from Depression (six online reviews of 15 minutes each over the 8-week period). Therefore, the level of support in the REEACT trial may not have been as high as initially suggested. The company has said that on the basis of the findings of REEACT, the support systems have been enhanced since 2015.

Methodological gap: More high-quality randomised controlled trials are required specifically addressing the decision problem, with particular reference to the IAPT setting and scoped comparators

9.3 *Results from the evidence base*

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

Space from Depression

Within the IAPT setting, evidence was available from one RCT ISRCTN 91967124 (Palacios et al, 2022[48]; Richards et al, 2015[30]) comparing Space from Depression (and other non-scoped SilverCloud products) with waitlist control and two naturalistic cohort studies (Duffy et al, 2020[27]; Palacios et al, 2022[48]).

ISRCTN 91967124 observed a significant interaction between time and group (Space from Depression vs waitlist control) for PHQ-9 (b = −2.75; SE = 0.64; 95% CI −4.00, −1.50; p < 0.0001) and GAD-7 (b =−2.79; SE = 0.61; 95% CI −4.00, −1.58; p < 0.0001) and WSAS (b = −2.65, SE = 0.99, 95% CI −4.59, −0.72; p = 0.075). At post-treatment (8-week), 46.4% (90/194) of the intervention arm and 16.7% (15/90) control-arm participants recovered. 63.4% (123/194) of the intervention-arm and 34.4% (31/90) control-arm participants showed significant improvement. Reliable recovery (both criteria fulfilled) in the intervention-arm was 40.7% (79/194), and 13.3% (12/90) in the control arm – p<0.01 for all between group differences. In the later publication (Palacios et al,

2022[49]), 89 participants met the criteria for reliable recovery from depression and anxiety at the post-treatment assessment, of which 29.2% relapsed within the 9-month period, with 70.8% remaining in remission at 9 months post-treatment.

Duffy et al (2020)[27] presented a comparison of completers versus dropouts within Space from Depression, which the EAG considered not to be a helpful comparison in this context. Palacios et al (2022)[49] found that average treatment effect of Space from Depression compared to non-digital guided self-help was: PHQ-9 1.26 (1.08-1.44); GAD-7 1.17(1.00-1.34); WSAS 0.86 (0.58-1.14), all p<0.0001 favouring Space from Depression. Average treatment effect compared to psychoeducational group therapy was: 1.71 [1.27–2.15], 1.90 [1.50–2.31], 1.96 [1.35–2.57], all p<0.0001 favouring Space from Depression.

While data on work and[49] social functioning were available in an IAPT setting (Palacios et al, 2022), quality of life and patient experience data were not available in this setting.

An Irish RCT of Space from Depression against waitlist control ISRCTN 03704676 (Enrique et al, 2019[28 29]; Richards et al, 2015[30]) found that post-intervention scores were lower in the intervention group than waiting list group for BDI-II (d=0.5, p<0.01), GAD-7 (d-0.32, p<0.01) and Work and Social Adjustment Scale (d=0.40, p<0.01), with 'reliable change' in BDI-II occurring in 29.5% of the intervention group versus 7.6% of the control group. Participants with reliable change had more log-ins, used more tools, viewed a higher percentage of the program, and got more reviews from their supporter compared with those who did not. No significant difference in change in quality of life scores was however found between the Space from Depression and waitlist control arms.

No patient experience data were identified by the EAG for Space from Depression within the searches performed. Additional papers were provided by the company during final review.[63-66] These could not be fully reviewed due to the timeframe available.

Richards et al 2016[63] collected 282 online self-report questionnaires and found that most respondents were satisfied with the programme (*n* = 191), felt supported (*n* = 203), reported positive gains and impact resulting from use of the programme, and perceived these to be likely to be lasting effects (*n* = 149). A number of respondents felt their needs were not met by the intervention (n = 64); for this group suggestions for improvements centred on the programme's structure and how supporter feedback is delivered. Richards et al 2018 [64] collected information for 88 patients using an online Helpful Aspects of Therapy questionnaire and found that role of the supporter was as a key ingredient in online delivery. Negative impacts associated with hindering events included disappointment, frustration/irritation, confusion, mood deterioration and being self-critical/blaming. Jardine et al[65] found that whilst dCBT on the whole provides a positive, supportive and therapeutic experience for clients; managing expectations, polarized preferences, momentary help-seeking and long-term support were important aspects of the experience to consider in future design.

Minddistrict

The EAG did not identify any eligible evidence for Minddistrict from the systematic search. Minddistrict did supply very basic IAPT data in the company submission without providing a reference. The EAG did not consider this to be an eligible study due to lack of information. The only available data were that there was an average recovery rate of 72% based on data from two of the UK customers who use the Minddistrict platform. No information was provided as to how many total customers there are and how representative these two were. The customer Making Space reported an 80% recovery rate and the customer West London reported a 65% recovery rate.

For Minddistrict, the company submission indicates there are ongoing trials but no AIC manuscripts were sent to the EAG. Two papers were available, both of which the EAG considered not to be relevant to the current decision problem. Cook et al (2019)[67] was conducted in a population solely of ruminating university students, while Topper et al (2017)[68] was conducted in a population of adolescents and young people (secondary school pupils aged 15-18, plus

first year university students with a maximum age of 22), which it was agreed was not appropriate for this appraisal.

Beating the Blues

Within the IAPT setting, evidence was available from one RCT called REEACT (Gilbody et al, 2015[31]; Littlewood et al, 2015[32]), one comparative clinical feasibility study compared to non-scoped interventions (Pittaway et al, 2010[51]), and two single arm studies (Cavanagh et al, 2011[24]; Ormrod et al, 2010[47]).

In the REEACT trial, there was no evidence of a statistically significant improvement in PHQ-9 at four months compared to usual GP care (odds ratio of being depressed (PHQ>=10): 1.19 (95%CI 0.75 to 1.88); p= 0.46). Fifty percent of participants on Beating the Blues remained in depression at four months compared to 44% on usual GP care. No evidence of a statistically significant difference in PHQ-9 scores had emerged at the 12 and 24 month follow-ups either. There was no evidence of a statistically significant difference in quality of life measures between arms.

The Beating the Blues intervention received positive patient acceptability ratings and participants generally expressed a preference to be randomised to computerised CBT rather than usual GP care.

Considering the other three available studies within the IAPT setting, Pittaway et al (2010)[51] found a highly significant reduction (t (49) = 9.150; p ≤0.001) in CORE-OM scores from baseline to week eight, but that this fall was not significantly different between participants in the Beating the Blues, workbooks and internet support group arms. The response rate in the feedback survey was only 27%, but among respondents, 73% of participants said they would recommend Beating the Blues to others. In Cavanagh et al (2011)[24], mean PHQ-9, GAD-7, CORE-OM and Work and Social Adjustment Scale scores improved post treatment compared to pre-treatment (p<0.001), with a mean difference on PHQ-9 between pre- and post-test of 9.4. Among participants completing the Patient Experience Questionnaire, 90% were mostly or very

satisfied with their experience. In Ormrod et al (2010), there was a significant effect of time ($F(1, 15) = 13.1$, $p < 0.01$) on BDI scores.

All three Scottish studies identified by the EAG were on Beating the Blues (Cientanni et al, 2019[25]; Du et al, 2021[26]; McMurchie et al, 2013[42]). Cientanni et al (2019)[25] in a single arm study found a mean CORE-OM score reduction of 0.72 (SD=0.62) from pre-to post treatment ($p<0.001$, Cohen's $d=1.32$). McMurchie et al (2013)[42] in a non-randomised controlled pilot trial compared to treatment as usual found participants on Beating the Blues had greater reduction in GDS (mean difference 8.2 vs 1.7, repeated measures ANOVA for time x group $p<0.001$), GAI (mean difference 5.0 vs 1.4, $p<0.01$) and CORE-34 (mean difference 17.5 vs 2.5, $p<0.001$). Du et al (2021)[26] conducted a qualitative study among 33 people with mild-to-moderate depression and/or anxiety. Limited information about the study setting was provided, which is especially a limitation for qualitative research. It is stated that the study was conducted in 'three NHS services' in Scotland, but no information is provided regarding geographical context, in particular urban vs rural settings, which could be important for the interpretation and generalisability of findings. Du et al (2021)[26] identified six emergent themes around user engagement and acceptance: (1) information dissemination; (2) expectations and the impact of waiting for eating the Blues; (3) impact of locations on experience of Beating the Blues; (4) preference for home access; (5) desire for better human support; and (6) desire for additional application support features. Non-IAPT evidence, except for evidence in Scotland, may be less useful especially for Beating the Blues, given differences in product versions internationally. The UK version is structured differently than the US version and differs in the extent of linearity and interactivity.

Deprexis

No evidence was identified within the IAPT setting. However, a meta-analysis was available (Twomey et al, 2020[55]) of 12 RCTs assessing a total of 2,901 people with depression globally. The meta-analysis showed that Deprexis was more effective than comparators (which varied within the meta-analysis, see

Table 34) in improving depressive symptoms (g=0.51, 95%CI 0.40-0.62, I^2 = 26%).

The EAG also separately identified 8 eligible RCTs on Deprexis. There was considerable overlap with the studies included by Twomey et al (2020)[55], but some differences relating to inclusion criteria and search date. It should be noted that evidence for Deprexis was generally from a German context. These separate RCTs can provide information on additional relevant outcomes not assessed in the Twomey et al (2020)[55] meta-analysis. The summary here therefore focuses on other measures besides improvement in depressive symptoms. Quality of life, interpersonal functioning and/or work and social functioning were assessed by all Deprexis studies apart from NCT01818453 (Beevers et al, 2017[11]; Mullarkey et al, 2020[12]). Across studies, a statistically significant benefit for Deprexis on these outcomes against assessed comparators was observed with a high level of consistency. It was noted that in Berger et al (2018)[14], which was the only included study to assesses a scoped comparator that a statistically significant beneficial effect of Deprexis plus psychotherapy against psychotherapy alone was only found for health-related quality of life and not physical quality of life.

Available evidence on subjective patient experience of Deprexis was generally favourable. For example, Meyer et al (2009)[44] found that 83% of participants who provided feedback said that they liked the programme and 82% considered that it had helped them. Most participants said they would recommend Deprexis to people with mild-to-moderate depression, but only a minority would recommend it to people with severe depression; in Meyer et al (2015)[45], 71% of participants reported the programme to be helpful; and in Moritz et al (2012)[46], 53.5% of completing participants considered the programme to be good or very good, 91.6% would recommend it for mild depression, 77.5% for moderate depression and 40.0% for severe depression, 47.5% believed that Deprexis had reduced their depressive symptoms, and 73.2% were satisfied with the programme and that it provided at least as helpful advice as a 'real' therapist. The inherent contradiction in some of these numbers reflects the challenge of collecting and analysing quantitative data on subjective participant

experience. One non-randomised study on Deprexis was available (Klein et al, 2020[39]) in a German setting and did not add to the evidence base beyond what was already available, with the exception of for adverse events (see Section 10).

Wysa

Three eligible studies were identified (Beatty et al, 2022[10]; Inkster et al, 2018; Malik et al, 2022). None were considered to be key studies or were conducted in the IAPT setting. Of these studies, two (Beatty et al, 2022; Inkster et al, 2018[35]) were mixed methods and one (Malik et al, 2022[43]) was qualitative.

Only one study (Inkster et al, 2018[35]) reported an effectiveness outcome, 'mood improvement' using the PHQ-2, with high users of Wysa (engaging on the app on 2 screening days and at least once in between) showing greater improvement than low users, mean (SD) improvement 5.84 (6.66) vs 3.52 (6.15), Mann Whitney p=0.03. This study was conducted online internationally among 129 users of the Wysa app and did not have a control arm.

Across all three studies, patient experiences with Wysa and patient feedback were generally positive. In Malik et al (2022)[43], emergent themes included the engaging exercises, interactive interface, artificial intelligence conservational ability, being non-judgemental, improvement in mental health and convenient access.

Iona Mind

No eligible evidence was identified. No empirical studies were available, only conceptual and theoretical pieces and an IAPT research proposal.

9.4 *Benchmarking against NHS Digital IAPT database*

The EAG considered key variables from the NHS Digital IAPT database provided by NICE. Of particular interest were: i) current mix of computerised support vs comparator treatments, ii) mean number of appointments for computerised support vs comparator treatments, iii) mean starting PHQ-9, iv) Cohen's d effect size for PHQ-9, v) rate of therapy-based recovery, vi) rate of reliable recovery, vii) rate of improvement, vii) rate of deterioration, viii) rate of

no change. Item i) was used to inform writing about the clinical context. Other items were tabulated below and used to compare to studies conducted in the IAPT setting.

Based on the information in Table 3, there was some evidence that included studies may have had higher baseline PHQ-9 scores (indicating greater depression severity), greater effect sizes for PHQ-9 and superior recovery rates (both indicating greater benefit of treatment) than observed in routine practice as reflected in the IAPT database.

Table 3: Comparison of key parameters in the NHS Digital IAPT database and included IAPT studies

Parameter/Study	NHS Digital IAPT database	Cavanagh et al, 2011[24]	REEACT/Gilbody et al 2015[31]/Littlewood et al., 2015[32]	Palacios et al, 2022a[48]	ISRCTN 91967124/Palacios et al, 2022b[48]/Richards et al, 2020[50]	Duffy et al, 2020[27]	Ormrod et al, 2010[47]	Pittaway et al, 2010[51]
Mean number of appointments for computerised support vs comparator treatments	• Guided self-help (book) 4.6 • Non-guided self-help (book) 2.9 • **Guided self-help (computer) 3.9** • Non-guided self-help (computer) 3.6 • Counselling 7.1 • Mindfulness 5.9 • CBT 7.8 • Interpersonal psychotherapy 10.1	Not presented	Not presented.	Of those attending at least 2 appointments Guided self-help (book- GSH) 4.9 SilverCloud Space from Depression or Anxiety dCBT 5.6 Psychoeducational group therapy (PGT) 4.7	Silvercloud (Space from Depression, Space from Anxiety, Space from Anxiety and Depression) 4.7 (SD=2.4) online reviews. Waitlist control: not presented.	SilverCloud 3.4 (SD=2.0)	Not presented	Not presented

Mean starting PHQ-9 (SD)	• Guided self-help (book) 14.5 (5.6) • Non-guided self-help (book) 15.4 (5.9) • **Guided self-help (computer) 13 (5.7)** • Non-guided self-help (computer) 11.1 (5.7) • Counselling 13.9 (5.8) • Mindfulness 10.7 (5.4) • CBT 15 (5.8) Interpersonal psychotherapy 15.1 (5.8)	Beating the Blues (BtB) all: 14.4 (6.6) Of those who attended at least 2 sessions of dCBT: 14.1 (6.5)	BtB 16.78 (4.21) Usual GP care (includes IAPT) 16.32 (4.52) MoodGYM 16.87 (3.99) Total 16.65 (4.25)	GSH 14.4 (5.9) dCBT 12.8 (5.6) PGT 13.3 (6.2)	Silvercloud 14.4 (4.9) Wait list 14.2 (5.1)	Silvercloud 15.6 (5.5)	Not presented	Not presented – CORE-OM measured.
Cohen's d effect size for PHQ-9	• Guided self-help (book) 0.8 • Non-guided self-help (book) 0.6 • **Guided self-help**	BtB. Of those who attended at least 2 sessions of dCBT: 0.8	Not presented	GSH 0.92 (95%CI 0.89-0.94) dCBT 1.06 (1.03-1.09) PGT 0.80 (0.75, 0.86)	Not presented	SilverCloud 0.61	Not presented	Not presented

	(computer) 0.6 • Non-guided self-help (computer) 0.6 • Counselling 0.8 • Mindfulness 0.3 • CBT 0.8 • Interpersonal psychotherapy 1							
Rate of therapy-based recovery	• Guided self-help (book) 43.7% • Non-guided self-help (book) 26.6% • **Guided self-help (computer) 39.1%** • Non-guided self-help (computer)- 46.2% • Counselling 47.7% • Mindfulness 27.9%	BtB. Of those who attended at least 2 sessions of dCBT: 50% stated, but not clearly calculated in expected way	Using PHQ9 threshold of 10+ for caseness. Results at 4 months (earliest time point). BtB 50% Usual GP care (includes IAPT) 56% MoodGYM 51%	GSH 50% dCBT 65% PGT 41%	Using defined thresholds as set by IAPT being PHQ-9 ≥ 10 and/or GAD7 ≥ 8) Silvercloud 46.4% Waitlist 16.7%	Amongst those with data 22/99 = 22.2%	Based on BDI, not comparable.	Not presented

	• CBT 44.1% • Interpersonal psychotherapy 47.5%							
Rate of reliable recovery	• Guided self-help (book) 38.7% • Non-guided self-help (book) 24% • **Guided self-help (computer) 32.9%** • Non-guided self-help (computer) 38% • Counselling 42.2% • Mindfulness 20.5% • CBT 39.5% • Interpersonal psychotherapy 43.9%	Not presented	Not presented	GSH 41% dCBT 50% PGT 30%	Silvercloud 40% Waitlist 13.3%	SilverCloud: 20/99 = 20.2%	Based on BDI, not comparable.	Not presented
Rate of improvement	• Guided self-help (book) 53%	Not presented	Not presented	GSH 59% dCBT 67% PGT 49%	Using a score change of PHQ-9 ≥ 6 and/or GAD-7 ≥ 4 Silvercloud 63.4% Waitlist 34.4%	SilverCloud 58/100 = 58%	Based on BDI, not comparable.	Not presented

	• Non-guided self-help (book) 43.7% • **Guided self-help (computer) 43.8%** • Non-guided self-help (computer) 40.1% • Counselling 55.7% • Mindfulness 28.5% • CBT 54.5% • Interpersonal psychotherapy 58.3%							
Rate of deterioration	• Guided self-help (book) 7.3% • Non-guided self-help (book) 10.5% • **Guided self-help (computer) 7.2%** • Non-guided self-help	Not presented	Not presented	Not presented	Completers only (increases of PHQ-9 ≥6 and/or GAD-7≥ 4). Silvercloud 5.2% Waitlist 12.2%	Not presented	Based on BDI, not comparable.	Not presented

	(computer) 7.8% • Counselling 6% • Mindfulness 10.4% • CBT 6.6% • Interpersonal psychotherapy 6.1%							
Rate of no change	• Guided self-help (book) 38.6% • Non-guided self-help (book) 44.5% • **Guided self-help (computer) 42.3%** • Non-guided self-help (computer) 50% • Counselling 36.5% • Mindfulness 53.1% • CBT 36.7%	Not presented.	Not presented	Not presented	Not presented	Not presented	Based on BDI, not comparable.	Not presented

	• Interpersonal psychotherapy 33.9%							

10 Adverse events

Very limited adverse event or other patient safety data were reported in any eligible studies identified by the EAG.

In the REEACT trial, total adverse events were similar between arms. There were nineteen serious adverse events in the Beating the Blues arm, of which 18 were deemed unrelated to the intervention and one could not be determined due to limited information. Two patients died while in the trial (Gilbody et al, 2015[31]).

In Klein et al (2020)[39], two adverse incidents (feeling of paralysis and increase in depressive symptoms) and one serious adverse event (acute suicidality) were reported by the treating physicians. Only the feeling of paralysis (which spontaneously recovered after a few hours) was considered to be causally related to Deprexis by the treating physician. The patient reporting an increase in depressive symptoms felt overwhelmed by Deprexis.

SCM advice was generally that adverse events are not typically a major concern for dCBT interventions. However, it is important to monitor for changes in suicidality. The vast majority of studies did not report conducting such monitoring or the outcomes thereof.

For SilverCloud, Richards et al (2020) state that there were no serious adverse events. No adverse event or other patient safety data were available from any other studies. Deterioration in itself was considered to be a response rate outcome rather than an adverse event.

Evidence gap: Very limited published safety evidence was available for any of the scoped interventions in the context of the treatment of adults with depression.

11 Evidence synthesis

Findings across studies are presented and discussed in narrative form. It was not feasible to undertake meta-analysis within the constraints of this EVA. The EAG noted the existence of a fairly recent published meta-analysis on Deprexis by Twomey et al (2020)[55]. Especially with regard to other interventions, there were relatively few RCTs and there was considerable statistical and clinical heterogeneity between studies. Considering NICE technical team advice to focus on studies in the IAPT setting, meta-analyses of international trials may be of limited utility in the context of the present decision problem. There are no published Deprexis studies in the IAPT setting and there is insufficient evidence to conduct an IAPT-specific meta-analysis for any of the scoped technologies.

12 Economic evidence

12.1 *Published economic evidence*

The search for economic evidence was conducted alongside the search for clinical evidence and is detailed in Section 8 and Section 16.2 (Appendix B). A total of 11 publications of direct relevance and 25 publications of indirect relevance to the economic analysis were identified.

Due to the anticipated scarcity of evidence for the specific interventions of interest, economic studies in adults with depression were included regardless of whether a specific intervention within the scope was listed as they are highly likely to provide information of indirect relevance. Studies of direct and indirect relevance to the decision problem are summarized in Table 4.

Directly relevant studies are those providing an analysis for one of the interventions included within the decision problem. Indirectly relevant studies are those reporting economic analyses in a related area or patient group as these may provide useful background on, for example, model structure or other insight into input parameters. Given the purpose of the review was to inform an initial assessment of economic potential and gap analysis a formal quality assessment of studies was not conducted.

In addition to the published evidence identified within the economic searches the economic model produced for the treatment of a new episode of depression as part of guideline on depression in adults (NG222)[1] was provided to the EAG. The economic model for NG222 was developed by the National Guidelines Alliance (NGA)[2], a collaborating centre wholly funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists until 1st April 2022. On 1st April 2022, NGA became part of NICE.

Direct evidence for economic outcomes in adults

Five economic evaluations alongside clinical trials were identified which provided evidence for 3 of the interventions included within the scope: Beating the Blues, Space from Depression and Deprexis. In addition a previous NICE technology appraisal (TA51 and update paper[69]) looked at the evidence available at the time for Beating the Blues.

Beating the Blues

Two UK economic evaluations alongside RCTs have been reported for this treatment. The two evaluations came to very different conclusions with the latter RCT which was conducted in a population more generalisable to the IAPT population in UK practice considering it to be unlikely that Beating the Blues would be cost-effective vs usual GP care. The authors of a later publication[50] consider that this less positive result may be down to the stepped-care model within which these interventions were embedded, with contextual factors favouring the deployment and uptake of the interventions (i.e. trained personnel for the use of dCBT, routine outcome monitoring). The current NICE guideline NG222[1] is less definitive on the use of stepped care compared to previous guidance instead now recommending: “Commissioners and providers of mental health services should consider using models such as stepped care or matched care for organising the delivery of care and treatment of people with depression.” We understand though that IAPT is currently delivered via a stepped care model and therefore would expect the results of the REEACT study to be of most relevance. There are, however, a number of potential issues with that study including use of dCBT in the comparator arm (19%) and low

adherence to dCBT offered in the intervention arm (18% completed all 8 sessions). A summary of each of the studies is provided below.

The first of these, McCrone et al,[40] reports the cost-effectiveness of treatment with Beating the Blues based upon data from 12 general practices in Southeast England in adults with a diagnosis of depression, mixed depression and anxiety, or anxiety disorders. The study reported data for 274 patients with 8 month follow-up. Utility values used to calculate the QALYs were based on an assumed score of 0.59 for a day with depression, and a score of 1 for a depression-free day with depression days calculated using a straight-line interpolation between visits. A high level of missing data was reported as a limitation of the study. The improvement in QALYs with Beating the Blues over standard care was 0.032 (3%). At the submitted licence cost there was a 99% chance of the intervention being cost-effective at a willingness to pay of £15,000 per QALY and 85% at £5,000 per QALY. The mean increase in service costs was £40 and the mean difference in QALYs was 0.032 in favour of Beating the Blues which leads to an ICER of £1,250. Data were not reported separately by primary diagnosis.

The REEACT RCT[32 70 71] focused on patients with a PHQ-9 score of ≥10, consistent with the IAPT criteria for depression 'caseness' and was the first study of dCBT based on a large (n=691) NIHR-funded independent pragmatic trial run at sites across England. This RCT assessed the cost-effectiveness of treatment with free (MoodGYM) and commercial (Beating the Blues) programmes for depression in adults as an adjunct to GP care with 2-year follow-up. Neither dCBT programme was found to be cost-effective compared with usual GP care alone. Adherence was found to be low (less than 20% of patients on dCBT completed the treatment). Again, the magnitude of the differences in costs and QALYs between all groups was small. In this case, however, Beating the Blues was dominated by usual care with a mean difference in QALYs of -0.0435 and a mean difference in costs of £104.24 at a licence cost of £50 per patient based on a £250 fee per 5 courses of therapy, which allows the treatment of 5 patients with a full course of dCBT each. At a £20,000 per QALY threshold, usual GP care alone had the highest probability

of being cost-effective (0.55) followed by MoodGYM (0.42) and Beating the Blues (0.04).

NICE TA51[72 73] and its update (TA97) provided an economic evaluation for dCBT for depression and anxiety including Beating the Blues (and a number of treatments outside of the scope) for less severe depression. These pieces of guidance were withdrawn in July 2018 to allow OCFighter to be considered for an IAPT assessment briefing. This information was superseded by the inclusion of digital self-help options within the NICE guideline on depression in adults (NG222)[1], where treatment modalities rather than individual interventions were reviewed. The model structure used can be viewed as a predecessor to the NG222 model and was a decision tree based upon depression severity (minimal, mild, moderate, severe) pre and post treatment and compliance with treatment using individual level data from the trial reported by McCrone et al[40] for Beating the Blues. Relapse was incorporated 6 months post treatment completion based upon general literature rates. The Beating the Blues package was estimated to be cost-effective with an ICER of £1,801 vs TAU at a licence cost of £104.62 per patient. The authors note that there is a considerable amount of uncertainty around the cost of the licence per patient due to uncertainty in the throughput of people receiving dCBT. In this case licences were being considered on the basis of an NHS wide or per site licence fee rather than a fee per user. This was one of the main drivers of cost, at the time was a major unknown and remains unclear to date.

Space from Depression

One UK economic evaluation alongside an RCT was identified[50] which provided an evaluation of the clinical and cost-effectiveness of internet-delivered interventions for symptoms of depression and anxiety disorders in an IAPT stepped care setting using the SilverCloud Space from Depression and Space from Anxiety systems. The study only reported results for the combined population and not separately by primary diagnosis which is not in line with the scope for this EVA, although it is acknowledged that in practice there is considerable overlap between depression and anxiety populations.

The study was a parallel-groups, RCT (n=361; n=169 with depression) run by Berkshire NHS Trust examining the effectiveness and cost-effectiveness of dCBT against a waitlist control group. The dCBT treatments were of 8 weeks duration and supported by regular post-session feedback by Psychological Wellbeing Practitioners. Assessments were conducted at baseline, during, and at the end of the 8-week treatment and at 3, 6, 9, and 12-month follow-up. Participants in the waitlist control group completed measures at baseline and week 8, at which point they received access to the treatment (and were not followed up). The EQ-5D-5L and Re-QOL questionnaires were included as well as clinical outcomes.

Intention-to-treat analyses showed significant interaction effects for the PHQ-9 and GAD-7 in favour of dCBT at 8-weeks and further improvements were observed up to 12-months. Over 8-weeks the probability of cost-effectiveness was 46.6% if decision makers are willing to pay £30,000 per QALY (ICER £29,764) at an estimated dCBT intervention cost of £94.63 per person, increasing to 91.2% when the control-arm's outcomes and costs were extrapolated over 12-months.

Deprexis

Two economic evaluations alongside RCTs were identified, both conducted in Germany. Both studies found evidence that use of Deprexis had the potential to reduce costs with the larger study finding a significant reduction in total included costs alongside a significant improvement in quality-of-life vs usual care. Neither study, however, included the direct costs associated with use of Deprexis (e.g. the licence costs).

The largest study reported by Gräfe et al 2020[33 34] is a 12 week pragmatic RCT (n=3,805) of Deprexis + care as usual vs care as usual aiming to determine whether Deprexis was cost saving to German Statutory Health Insurance for patients with mild/moderate depression. The study included patients with a PHQ-9 of greater than 4 which is less than the IAPT cut-off (10). The average PHQ-9 score reported was 12 (it is not reported whether this is mean or median).

In both groups, total costs of statutory health insurance decreased during the study period, but changes from baseline differed significantly. In the intervention group total costs decreased by 32% from €3139 per year at baseline to €2119 in the study year (vs. a mean reduction in total costs of 13% in the control group). The analysis did not include the licence cost for Deprexis or outpatient treatment costs. In order for treatment with Deprexis to be cost neutral the licence cost and cost of any difference in outpatient treatment would need to be less than ~€580. The difference in total health care costs remained statistically significant if the licence fee was less €34.

In comparison to the control group, the intervention group also showed a significantly greater reduction in depression severity, and impairment in functioning and a significantly greater increase in health-related quality of life. A significant difference on the EQ-5D-3L was noted up to 9 months follow-up (Cohen's d 0.09).

The smaller study[74] is still considerably larger than any of the UK evaluations (n=1,013) and consists again of a 12 week RCT comparing Deprexis + care as usual vs care as usual in patients with PHQ-9 scores of between 5 and 14. Patients were recruited from inpatient and outpatient settings, health insurance companies and online forums. The study aimed to examine the potential for Deprexis to reduce disease-related costs for patients with mild/moderate depression. Crossover was allowed after 12 weeks with follow-up for up to 6 months post enrolment reported.

In both groups total direct health care costs decreased during the study period, but changes from baseline did not significantly differ between study groups. Costs for psychotherapeutic treatment decreased in the intervention group, costs increased in the control group (− 16.8% (€80) vs. + 14.7% (€60)); p = 0.008). Again the analysis did not include the licence cost for Deprexis. Here the cost of Deprexis would only need to be €6 for treatment to no longer be cost saving when comparing the change in mean treatment costs from 6 months pre-enrolment to 6 months post-enrolment between groups (albeit that this would not be a significant difference).

Indirect evidence for economic outcomes in adults

As noted within the previous EVA for children and young adults[8] the Li 2022[75] systematic review provides the most up to date summary of the evidence base available for economic outcomes more generally in depression. A total of 15 studies reported the cost-utility of dCBT in the treatment of depression (mostly mild to moderate) from a social or health system perspective, with a time horizon of 3 to 60 months. Eleven studies showed that dCBT alone or combined with usual care was more cost-effective than usual care alone; of the 11 studies, 7 studies focused on guided dCBT, and the other 3 studies focused on unguided or minimally supported dCBT. Two studies showed that guided dCBT did not seem to be any more cost-effective than usual general practice care. Another 2 studies compared the cost-effectiveness of guided dCBT with unguided dCBT for depression; 1 study showed guided dCBT was more cost-effective than unguided dCBT (guided dCBT was dominated), whereas the other study indicated that guided CBT was not more cost-effective than unguided informational websites. The authors concluded that there was fair or high-quality evidence that CBT monotherapy or combination therapy for adult depression was cost-effective.

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

Similar to the conclusions in the previous EVA for children and young adults[8]; review papers indicated that key issues in interpreting the cost-effectiveness evidence available included the transferability of trial results to routine clinical practice, the effectiveness of blended formats and stepped care models and the appropriate comparator (active treatment such as face to face therapy or waiting list).

Learnings from the models presented include:

- dCBTthe wide variety of potential approaches to costing dCBT dependent on how the programme is set up and charged to the NHS[76]

- the need to consider continuation with / adherence to treatment[76] and the wider treatment pathway (e.g. medication, stepped care)[1]

- potential approaches to consideration of differential wait times between internet-based and face to face care and the need to consider the potential for spontaneous remission

- dCBTconsiderable uncertainty around the cost of licensing per patient due to uncertainty in the throughput of people receiving dCBT[73]

- the key role that individual values and goals and treatment preferences play in treatment take up and outcomes in practice which cannot be accounted for within modelling[1]

- a general paucity of health economic data for model population and complete lack of data for the impact of interventions on caregivers. NG222[1] includes a broader set of model inputs but does not consider caregivers within the assessment either.

Table 4: Narrative summary of economic studies of direct relevance

Study ID	Title	Study type	Treatment	Population
Duarte 2017[70] and Littlewood 2015[32] and Duarte 2014[71]	Cost-effectiveness of computerized cognitive–behavioural therapy for the treatment of depression in primary care: findings from the Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy (REEACT) trial	EE alongside RCT	Beating the Blues	More severe depression[1]
Kaltenthaler 2006[73] Update to NICE TA51[69] reported in Kaltenhalter 2002[72]	Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation	HTA	Beating the Blues (and a number of treatments outside of the scope)	Less severe depression[1 31]
McCrone 2004[40]	Cost-effectiveness of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial	EE alongside RCT	Beating the Blues	Mixed severity depression
Richards 2020[50]	A pragmatic randomised waitlist-controlled effectiveness and cost-effectiveness trial of digital interventions for depression and anxiety	EE alongside RCT	Space from Depression	Combined results presented for depression and anxiety IAPT step 2 service so expected to be less severe patients
Gräfe 2020[33 34]	Health economic evaluation of an internet intervention for depression (deprexis), a randomised controlled trial	EE alongside RCT	Deprexis	German patients receiving Statutory Health Insurance Less severe depression

Study ID	Title	Study type	Treatment	Population
Gräfe 2019[74] and Gräfe 2017[77]	Health economic evaluation of a web-based intervention for depression: the EVIDENT-trial, a randomised controlled study	EE alongside RCT	Deprexis	German patients recruited from inpatient and outpatient settings, health insurance companies and online forums Less severe depression

Table 5: Narrative summary of economic studies of indirect relevance

Study ID	Title	Study type	Narrative summary
Palmqvist 2007[78]	Internet-delivered treatments with or without therapist input: does the therapist factor have implications for efficacy and cost?	Editorial	Discusses the Kaltenhalter systematic review and advises that other costs than licensing associated with dCBT in general practice are the hardware/computer costs, the costs of screening for suitable clients and the cost for clinical support where applicable. The cost of the clinical support will vary greatly according to the profession of the supporting staff (e.g., a licenced psychologist will cost more than a nurse, who in turn costs more than a psychology student). Given the availability of CBT principles in published self-help books and the accelerating computer literacy among staff and the general public, it is possible that in the future healthcare companies and institutions might prefer to develop their own dCBT or internet-delivered programs, thus avoiding the licence cost in the long run. However, the costs of providing clinical support will continue to play a role in future applications. This will make dCBT less cost effective. In conclusion, at present it is premature to draw any firm conclusions regarding the cost-effectiveness of internet-delivered dCBT.
Gerhards 2010[79]	Economic evaluation of online computerised cognitive–behavioural therapy without support for depression in primary care: randomised trial	EE alongside RCT	Economic evaluation of online computerised cognitive–behavioural therapy (dCBT; Colour Your Life) without support for adults with depression in primary care based on an RCT (n=303) with 12 month follow-up alone or in combination with treatment as usual vs treatment as usual in the Netherlands. Study used a societal perspective and found that costs were lowest in the dCBT group and there were no significant group differences in effectiveness or quality of life. The authors comment that all treatments showed low adherence rates and modest improvements in depression and quality of life. In fact the EQ-5D remains around 0.70 for all 3 arms for all timepoints. Adherence to treatment was low which may mean that outcomes reflect the natural course of the disease rather than treatment received.

Study ID	Title	Study type	Narrative summary
Hollinghurst 2010[80]	Cost-effectiveness of therapist-delivered online cognitive–behavioural therapy for depression: randomised controlled trial	EE alongside RCT	Economic evaluation of online CBT (intervention as described by Judith Beck) vs usual care for adult depression at 8 months alongside an RCT in the UK (n=297). Online CBT was more expensive than usual care, although the outcomes for the CBT group were better. Cost per QALY gain based on complete case data was £17 173, and £10 083 when missing data were imputed (NHS perspective).
Kraepelien 2018[81]	Cost-effectiveness of internet-based cognitive–behavioural therapy and physical exercise for depression	EE alongside RCT	Economic evaluation of a randomised controlled trial (N=945) in Sweden comparing dCBT with physical exercise and treatment as usual (TAU) in adults. The dCBT programme was based on routine care in Sweden. The primary analysis (3 month, health care provider perspective) showed that incremental cost per QALY gained was €8817 for dCBT and €14 571 for physical exercise compared with TAU. At the established willingness-to-pay threshold of €21 536 (£20 000) per QALY, the probability of dCBT being cost-effective is 90%, and for physical exercise is 76%, compared with TAU.
Titov 2015[82]	Clinical and Cost-Effectiveness of Therapist-Guided Internet-Delivered Cognitive Behavior Therapy for Older Adults With Symptoms of Depression: A Randomised Controlled Trial	EE alongside RCT	Economic evaluation of an RCT (n=54) conducted in Australia in older adults (aged 60+) using the Managing Your Mood Course (five-lesson intervention delivered over 8 weeks with telephone and email support from a therapist) vs waitlist control including follow-up at 3 and 12 months. The treatment group had slightly higher Quality-Adjusted Life-Years (QALYs) than the control group at posttreatment (estimate: 0.012; 95% CI: 0.004 to 0.020) and, while being a higher cost (estimate $52.9 l 95% CI: − 23.8 to 128.2), the intervention was cost-effective according to commonly used willingness-to-pay thresholds in Australia.
Warmerdam 2010[83]	Cost-Utility and Cost-Effectiveness of Internet-Based Treatment for Adults With Depressive Symptoms: Randomised Trial	EE alongside RCT	This study aims to evaluate the relative cost-utility and cost-effectiveness of (1) Internet-based cognitive behavioural therapy, (2) Internet-based problem-solving therapy, and (3) a waiting list for adults with depressive symptoms based on an RCT (n=263, 12 weeks). Internet based CBT was based on the Dutch Coping with Depression" course. Cost-utility analysis showed that cognitive behavioural therapy and problem-solving therapy had a 52% and 61% probability respectively of being more cost-effective than waiting when the willingness to pay is €30,000 per QALY. Comparing both Internet-based treatments showed no clear preference for one or the other of the treatments. This study showed that a brief intervention based on problem-solving therapy seems to be a good alternative for Internet-based cognitive behavioural therapy in terms

Study ID	Title	Study type	Narrative summary
			of cost-effectiveness. The generic nature of problem-solving therapy makes it suitable as a first step in a stepped care model. This would enable therapists to free up their limited resources and direct these to people presenting with more complex and severe symptomatology.
Baumann 2020[84]	Cost–Utility of Internet-Based Cognitive Behavioral Therapy in Unipolar Depression: A Markov Model Simulation	EE decision model	This study reports the outcomes from a Markov model comparing internet-based CBT with face to face CBT (FCBT) in Germany considering differential waiting times (3 vs 20 weeks) using a societal perspective. The authors modelled a time horizon of 3 years using six states (remission, depressed, spontaneous remission, undergoing treatment, treatment finished, death) with transition probabilities using meta-regression per transition which is then essentially used within a naïve comparison. QoL and cost data are obtained from the literature. dCBT generated 0.260 QALYs and saved €2536 per patient compared to FCBT. PSA suggested that dCBT is highly likely to be more effective (91.5%), less costly (76.0%), and the dominant strategy (69.7%) compared to FCBT. Scenario analysis revealed that the base-case results are robust to variations in time-to-treatment differences with the factor having the most impact being wait times.
	The precision of health state valuation by members of the general public using the standard gamble	Health state valuation	Vignette study using SG with UK general population for five comparisons of the outcomes of treatments, based on health state descriptions (n=27 to 59). The mean utility differences between groups was: 0.23 for computerised cognitive behavioural therapy for depression (n=41, P<0.001). The computerised CBT for depression exemplar was based on the parallel group RCT by Selmi et al. This showed a significant difference of 7.5 points between treatment and control groups on the Beck Depression Inventory (BDI). Health states were developed for the BDI categories of moderate, mild and minimal depression, targeting the mid-point in the ranges within each BDI category. The vignettes were reviewed by a consultant psychiatrist and a family physician, who confirmed that they depicted the target condition and appropriately described levels of severity. The outcomes according to the original health states are not reported.
Health Quality, Ontario 2019[76]	Internet-Delivered Cognitive Behavioural Therapy for Major Depression and Anxiety Disorders: A Health Technology Assessment	HTA assessment	HTA of internet-delivered CBT for Major Depression and Anxiety Disorders conducted by Health Quality Ontario. Concluded that compared with waiting list, guided dCBT improves symptoms of mild to moderate major depression and select anxiety disorders and guided dCBT represents the most economical option for the short-term treatment of adults with mild to moderate major depression or anxiety disorders. For adults with mild to moderate major depression, guided dCBT was associated with increases in both quality-adjusted survival (0.04 quality-adjusted life-years [QALYs]) and cost ($1,257), yielding an ICER of $31,575 per QALY gained (Canadian dollars) when compared with usual care. In adults with anxiety disorders, guided dCBT was also associated with increases in both quality-adjusted survival (0.03 QALYs) and cost ($1,395),

Study ID	Title	Study type	Narrative summary
			yielding an ICER of $43,214 per QALY gained when compared with unguided dCBT. In this population, guided dCBT was associated with an ICER of $26,719 per QALY gained when compared with usual care. The probability of cost-effectiveness of guided dCBT for major depression and anxiety disorders, respectively, was 67% and 70% at willingness-to-pay of $100,000 per QALY gained. Guided dCBT delivered within stepped-care models appears to represent good value for money for the treatment of mild to moderate major depression and anxiety disorders. However, participants reported important barriers and limitations to using dCBT, including the need for a computer, internet access, and computer literacy, as well as the ability to understand complex written information. Participants found that the cost of treatment, the number of sessions in a course of treatment, and the lack of follow-up support were also substantial drawbacks for dCBT.
NICE NG222 2022[1]	Depression in adults: treatment and management	HTA assessment	This guideline covers identifying, treating and managing depression in people aged 18 and over. It includes an economic assessment for the treatment of new episodes of depression split by less and more severe depression. The assessment considers a range of pharmacological, psychological and physical interventions for adults treated in primary care including generic dCBT without or with minimal support and generic dCBT with support. The model used within this assessment was provided to the EAG and consists of a decision tree followed by a 3-state state transition model (2 years follow-up following 12 weeks of acute treatment). The model considers discontinuation and response in completers (50% improvement on any measure) and relapse post treatment. Efficacy data were derived from the guideline systematic review and NMAs. The cost year was 2020. The cost of provision of a computerised CBT programme per client by the main provider of digital mental health programmes comprised a fixed fee of £39, which is independent of the number of sessions attended (committee's expert advice). The annual costs (£14) of hardware and capital overheads (space around the PC) were based on reported estimates made for the economic analysis undertaken to inform the NICE Technology Appraisal on computerised CBT for depression and anxiety (Kaltenthaler 2006). The analysis found that dCBT with and without support had a mean rank of between 7 and 8 out of 16 potential interventions for less severe depression and a positive NMB vs TAU. For adults with more severe depression dCBT with support had a mean rank of 7.28 out of 20 and dCBT without support had a mean rank of 12.15. Again both interventions had a positive NMB vs TAU.

Study ID	Title	Study type	Narrative summary
Foroushani 2011[85]	Meta-review of the effectiveness of computerised CBT in treating depression	Meta-analysis	A thorough search and analysis of reviews of efficacy of computerised cognitive behaviour therapy (dCBT) published between 1999 and February 2011. The search yielded twelve systematic reviews from ten studies covering depression. The meta-review supports the efficacy of dCBT for treatment of depression; however there is limited information on different approaches, whose relative cost-effectiveness remains to be demonstrated. Only one study Kaltenthaler et al. 2006 was found which addressed cost-effectiveness for the Beating the Blues package (£1,250 per QALY estimate from a review which excluded 'commercially-sensitive' information).
Marks 2003[86]	Pragmatic evaluation of computer-aided self-help for anxiety and depression	Open pragmatic evaluation	Provides a "rough" cost comparison based solely on assumed unit costs and assumptions around admin and overheads within taking into account outcomes
Antle 2019[87]	Dissemination of computer-assisted cognitive-behaviour therapy for depression in primary care	Protocol	Planned RCT with 240 patients randomly assigned to computer-assisted cognitive-behaviour therapy (investigator designed) or treatment as usual based on patients >18 yrs old from 5 primary care clinics in Kentucky. Planned follow-up up to 6 months including dCBT program completion and satisfaction rates, CSQ-8, PHQ-9, Automatic Thoughts Questionnaire, Computer Attitudes Questionnaire, Satisfaction with Life Scale and cost effectiveness analysis with a societal perspective. Enrolment was planned to continue until March 2019 but the study does not yet appear to have reported.
Kumar 2017[88]	The Effectiveness of Internet-Based Cognitive Behavioral Therapy in Treatment of Psychiatric Disorders	Review	Literature search using PubMed and Google Scholar investigating dCBT's role in treating and controlling psychiatric illnesses which concludes that dCBT is useful in treating mental health and medical illnesses with psychiatric comorbidities and has also been found to be cost-effective for patients and society. The date of the search and methodology used is not clear. The review is focused on the implications for the rural US and of low relevance considering this. The cost-effectiveness papers discussed include are Romero-Sanchez 2017 for major depression.
Peck 2007[89]	Computer-guided cognitive– behavioural therapy for anxiety states	Review	Narrative review which concludes that all the RCTs and other trials conducted to date indicate that outcomes using dCBT are comparable to those obtained with FTF treatment. dCBT programmes also appear to be cost-effective (based on the NICE review of TA51). However more trials are needed, with greater numbers of participants and with FTF therapy as a comparator, to examine outcomes and cost-effectiveness in more detail.

Study ID	Title	Study type	Narrative summary
Schroder 2016[90]	Internet interventions for depression: new developments	Review	This review summarizes the current body of evidence and highlights pros and cons of Internet interventions. It considers that despite profound evidence for the efficacy of Internet interventions, it is yet to be shown that results can be transferred into routine clinical and that more research on the cost effectiveness of blended formats is needed.
Arnberg 2014[91]	Internet-Delivered Psychological Treatments for Mood and Anxiety Disorders: A Systematic Review of Their Efficacy, Safety, and Cost-Effectiveness	SR	Systematic review funded by the Swedish Council on Health Technology Assessment of efficacy, safety and cost-effectiveness of internet delivered psychological treatments for mood and anxiety disorders. Searches conducted in March 2013 and used PubMed, Cochrane Library, CINAHL, PsycINFO, Psychology and Behavioural Sciences Collection (PBSC), TRIP database and CRD. Identified 52 RCTs of which 12 were excluded due to high risk of bias. Five cost-effectiveness studies were identified and three were excluded due to high risk of bias due to incomplete information on costs (Bergstrom 2010, Mihalopoulos 2005 and Titov 2009, none of which are included in the current review). The included trials mainly evaluated internet-delivered cognitive behavioural therapy (I-CBT) against a waiting list in adult volunteers and were primarily conducted in Sweden or Australia. For adults, the quality of evidence was graded as moderate for the short-term efficacy of I-CBT vs. waiting list for mild/moderate depression in adults (d = 0.83; 95% CI 0.59, 1.07). The quality of evidence was graded as low/very low for other interventions, noninferiority, adverse events, and cost-effectiveness. The two cost-effectiveness studies included were Hedman 2011 and Hollinghurst 2010 (assessed separately here) both of which were found to have a moderate risk of bias
Donker 2015[92]	Economic evaluations of Internet interventions for mental health: a systematic review	SR	Systematic review funded by the Black Dog Institute, University of New South Wales, and VU University Amsterdam, of economic evaluations alongside RCTs for internet interventions for mental health. Searches covered 1990 - 2014 and used Medline, EMBASE, the Cochrane Central Register of Controlled Trials, NHS Economic Evaluations Database, NHS Health Technology Assessment Database, Office of Health Economics Evaluations Database, Compendex and Inspec. 16 papers met the inclusion criteria, 4 of which described treatment for depression (Warmerdam 2010, Hollinghurst 2010, Gerhards 2010 and Phillips 2014). In terms of quality the authors considered that ten of the included studies (62.5%) adhered to >=75% of the guidelines and therefore achieved a rating of good quality using the Drummond checklist rather than CHEERS (which the authors considered difficult to use). The authors conclude that "Results of guided Internet interventions being cost-effective are promising with most studies adhering to publication standards, but more economic evaluations are needed in order to determine cost-

Study ID	Title	Study type	Narrative summary
			effectiveness of Internet interventions compared to the most cost-effective treatment currently available."
Hedman 2012[93]	Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost-effectiveness	SR	This review aimed to determine the applications, clinical efficacy and cost-effectiveness of dCBT. Results showed that dCBT has been tested for 25 different clinical disorders. Most randomised controlled trials have been aimed at depression, anxiety disorders and chronic pain. Comparison to conventional CBT showed that dCBT produces equivalent effects. Cost-effectiveness data were relatively scarce but suggested that dCBT has more than 50% probability of being cost effective compared with no treatment or to conventional CBT when willingness to pay for an additional improvement is zero. The 3 studies assessing cost-effectiveness in depression where Gerhards 2010, Hollinghurst 2010 and Warmerdam 2010.
Li 2022[75]	Economic Evaluation of Cognitive Behavioural Therapy for Depression: A Systematic Review	SR	This review aimed to aimed to conduct a systematic review of cost-utility studies of internet-based and face-to-face cognitive behavioural therapy (CBT) for depression from childhood to adulthood. A structured search for cost-utility studies concerning CBT for depression was performed in 7 databases from their inception to July 2020. Two reviewers independently screened the literature, abstracted data, and assessed quality using the Consolidated Health Economic Evaluation Reporting Standards and Quality of Health Economic Studies checklists. The primary outcome was the incremental cost-effectiveness ratio (ICER) across all studies. Cost data were inflated to the year 2020 and converted into US dollars. Thirty-eight studies were included in this review, of which 26 studies (68%) were deemed of high methodological quality and 12 studies (32%) of fair quality. Despite differences in study designs and settings, the conclusions of most included studies for adult depression were general agreement; they showed that face-to-face CBT monotherapy or combination therapy compared with antidepressants and usual care for adult depression were cost-effective from the societal, health system, or payer perspective (ICER 2$241 212.4/quality-adjusted life-year [QALY] to $33 032.47/QALY, time horizon 12-60 months). Internet-based CBT regardless of guided or unguided also has a significant cost-effectiveness advantage (ICER $37 717.52/QALY to $73 841.34/QALY, time horizon 3-36 months). In addition, CBT was cost-effective in preventing depression (ICER $23 932.07/QALY to $26 092.02/QALY, time horizon 9-60 months). A total of 15 studies reported the cost-utility of dCBT in the treatment of adults' depression from a social or health system perspective, with the time horizon from 3 to 60 months. The depressive symptoms of most participants were mild/moderate. Eleven studies showed that dCBT alone or combined with usual care was more cost-effective than usual care alone; of the 11 studies, 7

Study ID	Title	Study type	Narrative summary
			studies focused on guided dCBT, and the other 3 studies focused on unguided or minimally supported dCBT. In addition, 2 studies showed that guided dCBT did not seem to be any more cost-effective than usual general practice care. Another 2 studies compared the cost-effectiveness of guided dCBT with unguided dCBT for depression; 1 study showed guided dCBT was more cost-effective than unguided dCBT (guided dCBT was dominated), whereas the other study indicated that guided CBT was not more cost-effective than unguided informational websites.
Musiat 2014[94]	Collateral outcomes in e-mental health: a systematic review of the evidence for added benefits of computerized cognitive behaviour therapy interventions for mental health.	SR	Systematic review of the evidence for added benefits of computerized cognitive behaviour therapy interventions for mental health conducted in January 2013 using Medline and Web of Science. Thirteen of the included studies included some form of economic evaluation of the tested intervention 3 of which were for depression (Gerhards 2010, Hollinghurst 2010 and McCrone 2004). The first 2 are included separately in our review, the latter reported a comparison of dCBT + TAU with TAU which found that at $6168 per QALY: dCBT was cost-effective with 85% probability, at $18503 per QALY: dCBT cost-effective with 99% probability based on an economic evaluation alongside a RCT (n=174, 8 month follow-up, 12 general practices in SE England). The authors conclude that: "On balance, the results from the economic evaluation of e-mental health interventions suggest that dCBT is a cost-effective alternative to usual care, achieving results that are similar to, or better than, usual care, at lower direct costs." Limitations noted were that studies did not include in their calculations those costs that are required to be met by the patients and none of the studies reported the development costs of the intervention nor licence costs nor incorporated them into the cost-effectiveness analysis despite these being potentially significant.

Abbreviations: dCBT, Computerised Cognitive Behavioural Therapy; CHEERS, Consensus on Health Economic Evaluation Reporting Standards; EE, Economic Evaluation; FCBT, Face-to-Face Cognitive Behavioural Therapy; FTF, Face to Face; HTA, Health Technology Assessment; dCBT, Internet Cognitive Behavioural Therapy; ICER, Incremental Cost-Effectiveness Ratio; NIHR, National Institute for Health and Care Research; OCD, Obsessive-Compulsive Disorder; QALY, Quality Adjusted Life Year; RCT, Randomised Controlled Trial; SG, Standard Gamble

12.2 *Conceptual modelling*

The primary purpose of this analysis was to assess whether there is a plausible prima facie case for cost-effectiveness of the digitally enabled therapies in adults with depression, and to identify where there is greatest value in future research to reduce uncertainty.

An early value assessment for three of the therapies within scope is provided using an adaptation of the economic model for NICE's guideline on depression in adults (NG222[1]). Only three therapies could be assessed quantitatively as these were the only treatments for which both sufficient comparative and cost data were available. Other treatments are considered qualitatively. The NG222 model was developed by the National Guidelines Alliance (NGA)[2], a collaborating centre wholly funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists until 1st April 2022. On 1st April 2022, NGA became part of NICE.

12.2.1 Population

In line with the NG222[1] model and the final scope we consider separately the populations of less severe depression (<16 on the PHQ-9 based either on the mean reported or mapping from other scales) and more severe depression (≥16 on the PHQ-9 scale). Where data were not available on the PHQ-9, alternate scales were mapped using the thresholds presented in Appendix A (page 204) of Evidence Review B.

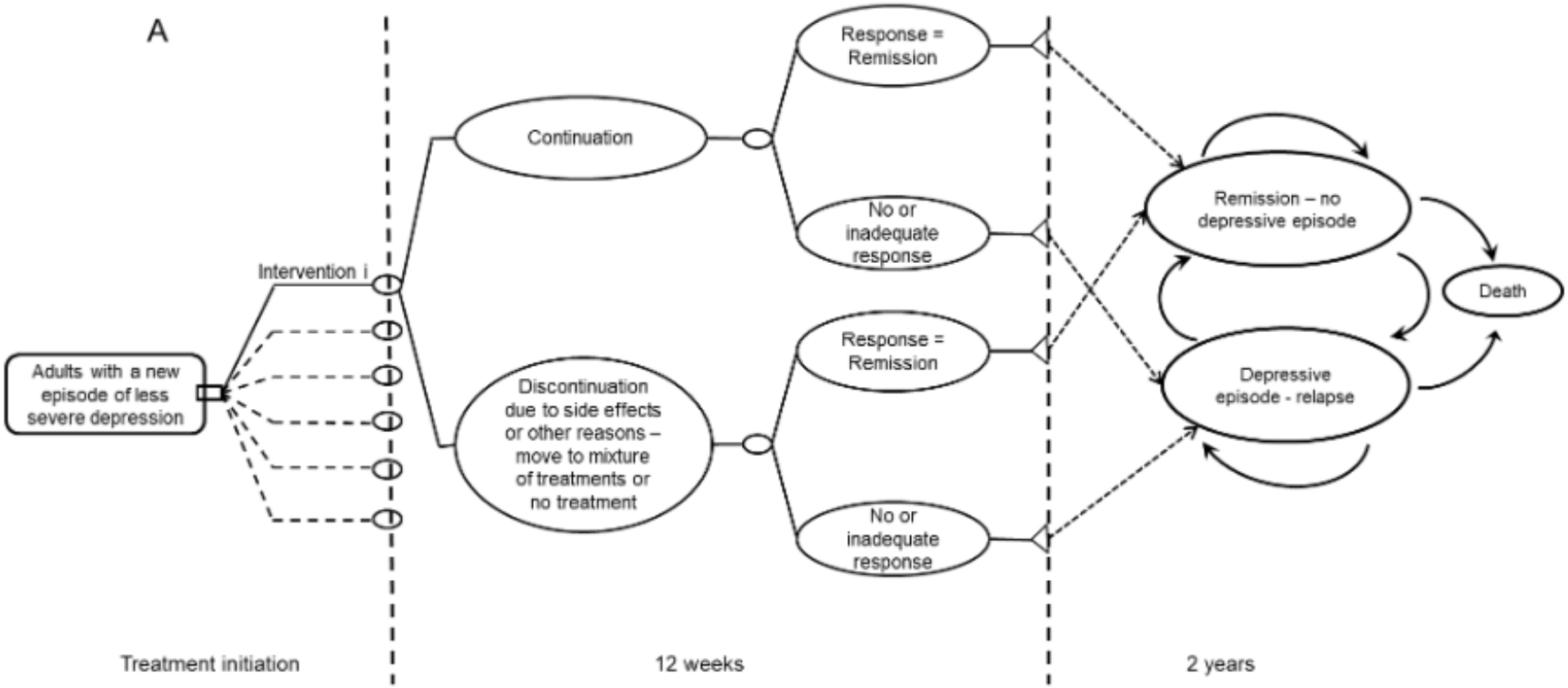
For the majority of the studies available for interventions within our scope considered patients with less severe depression. This is in line with the expected use of these interventions. There were three studies that presented evidence on patients with more severe depression specifically; Twomey et al[55] and Moritz et al[46], who presented a disaggregated analysis, and Meyer 2015[45], who included a population of more severe depression. In Meyer, the definition of severe depression was slightly lower than the scoped definition of PHQ-9 score of ≥ 15. However, baseline mean score was 16.62 for the treatment group

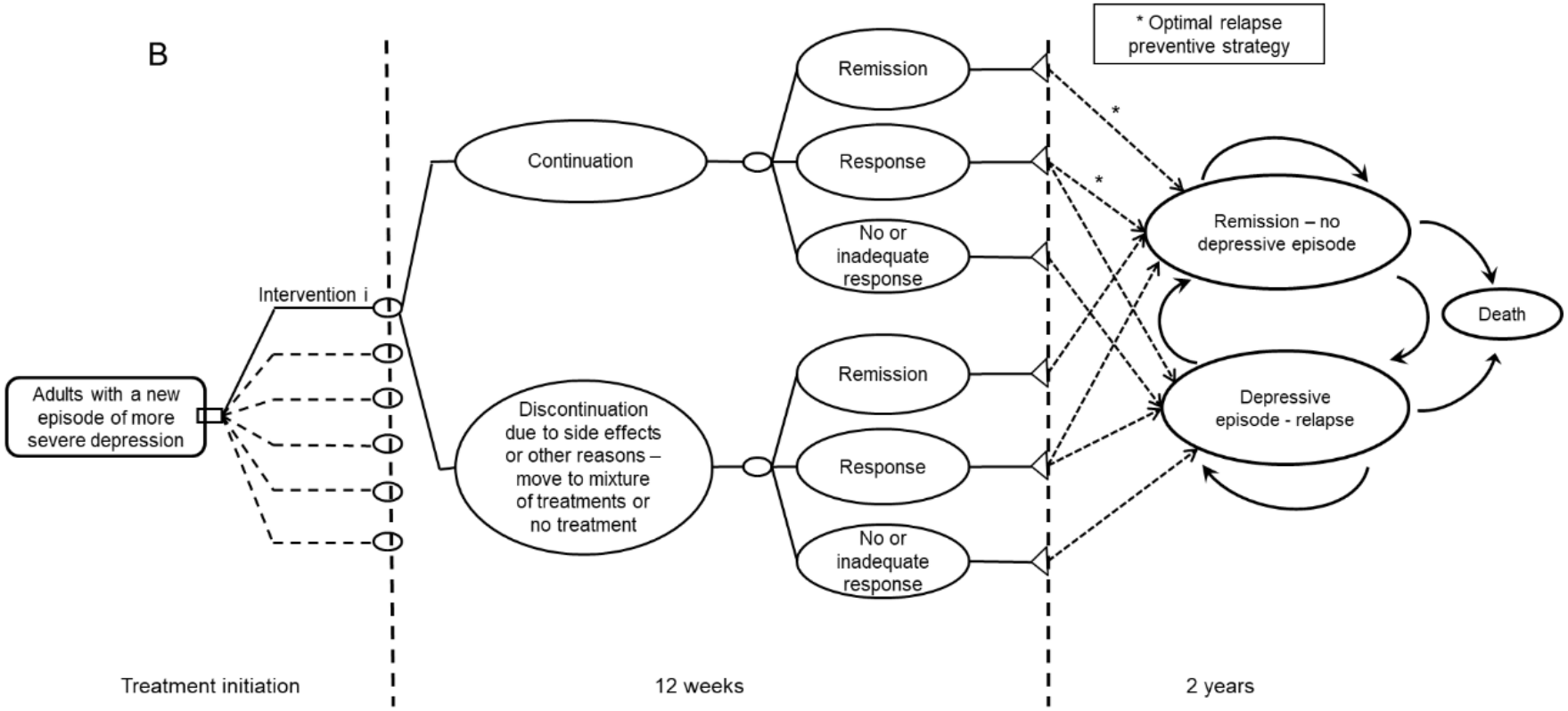
and 17.20 for the control group, so the population still fell within the original definition.

12.2.2 Model structure

For adults with a new episode of less severe depression the model first assesses whether the patient completes treatment or not at 12 weeks, then whether or not the patient responds at the same timepoint (defined as a 50% or more improvement from baseline on any depression scale) and then whether or not the patient relapses by 2 years (Figure 1). For patients with more severe depression an additional component is included whereby response is split into remission (using the same cut-off level as that which was used within the original paper or no longer meeting diagnostic criteria per the original paper) and response (defined in the same manner as for less severe depression).

Figure 1: Schematic diagram of the structure of the economic model of treatments for adults with a new episode of (A) less severe depression and (B) more severe depression





Source: Figure 63, NICE NG222[1] Evidence Review B

The model comprises an initial decision tree for the first 12 weeks followed by a Markov model with year cycles with a half-cycle correction applied. In each model cycle, people entering the Markov component of the model could either remain in the same 'entrance' state, move between the remission and the depressive episode states, or move to the death state (absorbing state). Within the remission and depressive episode states, people entered tunnel states, so that the time they remained in every state (one or two years) could be estimated and a time-dependent probability of relapse or remission, respectively, could be applied. Death was considered only in the Markov component of the economic model.

Costs and benefits were both discounted at a rate of 3.5% as recommended in the NICE manual[95].

Considering the learnings from the wider economic literature review (Section 12.1) the NG222[1] model has the benefit of considering adherence to treatment and the impact of this on response, spontaneous remission and it also incorporates an element of stepped care (use of natural history data to inform relapse prevention rates including the potential for an optimal scheme for patients with more severe depression with repeated relapses). It does not incorporate the following elements:

- ability to explore the impact of differential wait times between internet-based and face to face care
- exploration of assumptions for costs specific to dCBT such as licensing and set-up costs
- ability to explore different approaches to stepped care
- incorporation of the impact on caregivers
- exploration of broader definitions of response and patient benefit

12.2.3 Comparators

The majority of the comparators included within the NICE scope are also included within the NG222[1] model (Table 6 and Table 7), with the exception of guided self-help outside of dCBT. Effectiveness data for the generic dCBT with

support for less severe depression in the NG222 model is based upon a class effect with all guided self-help as there were no studies for this intervention. As a result, this has not been included as a comparator in the EAG analysis due to concerns over the reliability of these estimates.

Table 6: Comparison of scoped comparators for less severe depression with those included in NG222[1]

Scoped comparator	NG222 model comparator
Guided self-help	Generic computerised CBT without support*
Group cognitive behavioural therapy (CBT)	Group CBT (under 15 sessions)
Group behavioural activation (BA)	Group BA
Individual CBT	Individual CBT (under 15 sessions)
Individual BA	Individual BA
Group exercise	Supervised high intensity group exercise
Group mindfulness and meditation	Group mindfulness-based cognitive therapy (MBCT)
Interpersonal psychotherapy	Individual interpersonal psychotherapy (IPT)
Selective serotonin reuptake inhibitors	Sertraline
Counselling	Non-directive/supportive/person-centred counselling
Short-term psychodynamic psychotherapy	Individual short-term psychodynamic psychotherapy (PDPT)

*Included as validation within this analysis

Table 7: Comparison of scoped comparators for more severe depression with those included in NG222[1]

Scoped comparator	NG222 model comparator
N/A	Generic computerised CBT with and without support*
Combination of individual CBT and an antidepressant	CBT individual (equal to or over 15 sessions) + escitalopram [combined individual CT/CBT and antidepressant
Individual CBT	Individual CBT (equal to or over 15 sessions)
Individual BA	Individual BA
Antidepressant medication	Escitalopram [SSRIs] Lofepramine [TCAs] Duloxetine [serotonin and norepinephrine reuptake inhibitors (SNRIs)]

	Mirtazapine [own class] Trazodone [own class]
Individual problem-solving	Individual problem solving
Counselling	Non-directive/supportive/person-centred counselling
Short-term psychodynamic psychotherapy	Individual short-term psychodynamic psychotherapy (PDPT)
Interpersonal psychotherapy	Individual interpersonal psychotherapy (IPT)
Guided self-help	Generic computerised CBT*
Group exercise	Supervised high intensity group exercise

*Included as validation within this analysis

12.2.4 Model Inputs

12.2.4.1 Clinical Parameters

Clinical parameters were taken from the key studies for each of the scoped interventions where available and, in line with the NG222[1] model structure, focused on patient response, discontinuation, and additionally for severe depression, remission from depressive symptoms.

Identification of key studies for inclusion in the economic analysis

Key studies were selected from those reported within the clinical evidence review informed by company submissions and the literature undertaken by the EAG.

Key studies were those based on the population the study was conducted on (for example the UK, IAPT population), the availability of results reported, and if the studies were randomised controlled trials with relevant comparators. For a full table detailing the rationale behind study selection, see Table 32. Though not used in the NG222[1] model, a waitlist control was assessed as a relevant comparator on the basis that most studies used this, and odds ratios were able to be transformed be consistent with the comparators used in the NG222 model.

As noted previously, only three interventions were able to be incorporated into the model based on the RCT data available; Space from depression, Beating the Blues and Deprexis. There were two studies (Cook et al, 2019[67] and Topper

2017[68]) that were available for Minddistrict, however, these related to a student only population and basic, unreferenced, data was provided on recovery rates within IAPT. Similarly, for Wysa there were multiple studies available, but they were either a comparison on usage patterns with no effect size provided, or for use on depressive symptoms on orthopaedic patients only. Minddistrict and Wysa have therefore been evaluated narratively only in Section 12.3.4.

None of the key studies identified were included in the original NG222[1] model analysis as part of generic computerised CBT. This includes the REEACT study. Beating the Blues was considered within previous modelling for TA51.

The EAG's comment on data availability and quality is seen in Table 8. As discussed in the clinical evidence review section 9.3 the main limitation in the evidence was that there were no studies across any of the inventions that evaluated the technology in an IAPT population versus treatment as usual in a UK setting. As noted previously there were also few studies reporting data specific to more severe depression.

The majority of the studies reported comparison to waitlist control, the treatment effects in the economic analysis were therefore applied relative to GP care (less severe population) or no treatment (more severe population). The exception to this was Proudfoot 2004[41] which compared to usual care including referral for counselling. Here the calculated treatment effect was applied relative to treatment as usual (TAU) from the NG222[1] model.

Table 8: Included studies

Source	Depression severity/Parameter	EAG commentary on availability, quality and reliability of the source/s
Space from Depression		
Richards 2020[50]	Mild/Moderate	The EAG considered the study to be a moderately reliable source, but with concerns over the lack of differentiation between severity of depressive symptoms.
Richards 2015[30]	Mild/Moderate.	Low/medium quality and generalisability to the scope. Not IAPT population though discussed.
Beating the Blues		
Proudfoot 2004[41]	Does not distinguish. Baseline mild/moderate.	Trial reported only the mean of the available post-randomisation BDI scores finding that the TAU group had a significantly higher BDI score than the treatment

Source	Depression severity/Parameter	EAG commentary on availability, quality and reliability of the source/s
		group. The EAG considered this study to have a high risk of bias due to unclear reporting on baseline BDI scores and poor quality statistical methods for comparative analysis.
Littlewood 2015[32]	Does not distinguish. Baseline mild/moderate	UK IAPT population based, and funded by the NIHR HTA programme. The EAG considered the study to be highly generalizable to the UK population, but only applicable to mild/moderate patients.
Deprexis		
Berger 2011[13]	Does not distinguish. Baseline mild/moderate	The EAG considered there to be a moderate risk of bias due to generalisability and aggregated results reporting.
Meyer 2015[45]	Severe only	A notable area of uncertainty was that less than 50% of the users completed more than three sessions. The EAG therefore considered the trial to have a moderate risk of bias due to the specificity of severe depression, but highlights generalisability concerns with respect to an NHS population compared to a German based trial.
Meyer 2009[44]	Does not distinguish. Baseline mild/moderate	German based study. Reported an odds ratio of significant reduction in depressive symptoms in the abstract, but did not report elsewhere in the study, and Cohens-d effect sizes transformed to ORs by the EAG did not correspond to reported ORs. The EAG considered this study to have a high risk of bias.
Moritz 2012[46]	Reports effect sizes disaggregated by severity, but does not distinguish for discontinuation.	The EAG noted that response to treatment may differ between severity classes, but the study did differentiate between severity in reporting outcomes.
Klein 2016[17]	Mild/Moderate Only	The EAG considered this study to have a low risk of bias, but noted generalisability issues due to a purely German-based study.
Twomey 2020[55]	Reports effect sizes disaggregated by severity. Discontinuation per study not reported.	The EAG agreed with quality ratings in the meta-analysis for the above studies, notably, Moritz et al was negatively ranked in the allocation concealment and completeness of data categories. The lead author of this paper disagreed and argued for a positive ranking in all categories, which was rejected by Twomey et al. The quality and availability of the meta-analysis is limited by the limitations and bias of included studies and there is no evidence of study weighting due to quality.

Accounting for multiple sources of evidence

For all three interventions more than one key study was identified. As there was no clear indicator of one most relevant study for any of the interventions base case results are presented as a weighted average of each of the included individual studies according to sample size. Results are presented for each treatment in each key study in Appendix F.

Classification of depression severity

Depression severity and response were measured on either the PHQ-9 or the Becks Depressive Inventory scale (BDI) for all included studies. In accordance with the existing NG222[1] model, those studies with a mean baseline of a PHQ-9 score of ≥16 were categorised as studies examining severe depression, and those with a mean baseline score of 9-15 were categorised as mild/moderate. For BDI-I, the NG222 model defined severe depression to be a score of 22 or higher, and for BDI-II, severe depression was defined at 30 or higher.

Response

The existing NG222[1] model evaluated dichotomous response at 12 weeks in completers within the network meta-analysis using log odds ratios, whereas most of the included studies reported effect sizes using Cohen's D, or Hedges' G in the ITT population. Given that this analysis is for early value assessment it has been assumed that the effect size in the ITT population is similar to the effect size in completers. This was considered a reasonable approximation as the NG222 model analysis showed little difference in outcomes when considering imputed data analysis rather than completers' data only. Within this analysis response was assessed at 12 weeks, or where not available in the studies, the next nearest time point.

Cohen's D effect sizes were transformed into odds ratios using R-studio using the 'esc' package; prior to conversion to log odds ratios[96]. Richards et al 2015[30], Proudfoot et al 2004[41] and Littlewood et al 2015[32] did not report effect sizes. For these three papers the EAG therefore first calculated Cohens D by dividing the difference in means between the treatment group by the pooled standard deviation prior to calculation of odds ratios.

Twomey et al[55] reported the effect size using Hedge's G, which uses the *weighted* pooled standard deviation to divide the difference in means. However, as Twomey et al is a meta-analysis containing only summary reporting, the EAG were not able to access the data required to transform the effect size in odds ratios. It was therefore assumed that the two effect sizes were substitutes,

and the Hedges G effect size was used in place of the Cohens D effect size when calculating the odds ratio in this instance.

Where available, the same process was followed to calculate confidence intervals, and the confidence intervals were used to calculate the deviation using the formula (upper CI – lower CI)/3.92 which assumes a normal distribution. Where the confidence intervals were not available in the studies, an arbitrary 20% of the mean was used to calculate the standard deviation.

Table 9 presents the response parameters used within the economic analysis. The presented odds ratios can be interpreted as follows:

- Odds Ratio = 1: the odds of response are equal for dCBT compared to treatment as usual as defined within the NG222 guidelines
- Odds Ratio > 1: the odds of response are higher for dCBT than treatment as usual as defined within the NG222 guidelines (i.e. beneficial effect)
- Odds Ratio < 1: the odds of response are lower for dCBT than treatment as usual as defined within the NG222 guidelines (i.e. detrimental impact)

The larger the standard deviation, the greater the uncertainty around the result.

Table 9: Response Parameters

Source	Mean Odds Ratio (SD)	Mean Log Odds Ratio (95% CI)	Population
Space from Depression			
Richards 2020[50]	2.71 (0.58)	0.84 (-0.54, 2.11)	Less severe depression ITT
Richards 2015[30]	0.76 (0.15)	-0.44 (-1.78, 0.83)	Less severe depression ITT
Beating the Blues			
Proudfoot 2004[41]	2.08 (0.42)	0.73 (0.23, 1.06)	Less severe depression Per protocol (completers)
Littlewood 2015[32]	0.84 (0.20)	-0.33 (-1.75, 0.99)	Less severe depression ITT
Deprexis			
Berger 2011[13]	4.51 (0.87)	1.35 (-0.01, 2.64)	Less severe depression ITT
Meyer 2009[44]	3.19 (19.20)	3.03 (-0.53, 2.34)	Less severe depression ITT
Meyer 2015[45]	2.81 (0.97)	0.79 (-0.82, 2.09)	More severe depression ITT
Moritz 2012[46]	3.56 (0.68)	1.11 (-0.24, 2.40)	Less severe depression

Source	Mean Odds Ratio (SD)	Mean Log Odds Ratio (95% CI)	Population
			ITT
	1.52 (0.30)	0.18 (-1.06, 1.40)	More severe depression ITT
Klein 2016[17]	2.03 (15.64)	0.55 (-0.85, 1.86)	Less severe depression ITT
Twomey 2020[55]	2.43 (19.21)	0.73 (-0.55, 1.98)	Less severe depression ITT
	2.71 (0.46)	0.76 (-0.49, 1.95)	More severe depression ITT

Where information was not available in the publication standard deviation was calculated from presented data assuming a normal distribution

Discontinuation

Discontinuation was assessed using data for post-intervention dropouts. None of the key studies reported comparative effects discontinuation. Log odds ratios were therefore calculated, along with the associated standard errors and confidence intervals, by the EAG using the number of participants who discontinued from both the treatment group and the control group in each paper. The Twomey et al meta-analysis did not present discontinuation data. The EAG therefore calculated a weighted average of the other four included papers for Deprexis to represent discontinuation within the meta-analysis.

Table 10 presents the discontinuation parameters used within the economic analysis. Here a log odds ratio that is negative can be interpreted as an increased odds of discontinuation compared to treatment as usual as defined in the NG222 guidelines, whereas a positive log odds ratio represents a reduced odds of discontinuation.

Table 10: Discontinuation Parameters

Variable	Mean Log Odds Ratio (SD)	Mean Log Odds Ratio (95% CI)	Population
Space from Depression			
Richards 2020[50]	-1.73 (0.49)	-2.55 (-7.59, 1.02)	Less severe depression ITT
Richards 2015[30]	-0.04 (0.27)	-0.86 (-7.58, 1.01)	Less severe depression ITT
Beating the Blues			
Proudfoot 2004[41]	0.56 (0.30)	0.56 (-0.26, 0.86)	Less severe depression ITT

Variable	Mean Log Odds Ratio (SD)	Mean Log Odds Ratio (95% CI)	Population
Littlewood 2015[32]	0.05 (0.41)	-0.76 (-5.72, 2.75)	Less severe depression ITT
Deprexis			
Berger 2011[13]	1.11 (1.52)	-3.14 (-8.28, 0.62)	Less severe depression ITT
Meyer 2009[44]	0.63 (0.29)	-0.30 (-4.69,3.79)	Less severe depression ITT
Meyer 2015[45]	0.87 (0.40)	0.96 (0.53, 1.38)	More severe depression ITT
Moritz 2012[46]	0.63 (0.36)	-0.19 (-5.5 0, 3.033)	Combined population ITT
Klein 2016[17]	0.09 (0.15)	-0.72 (-5.69, 2.78)	Less severe depression ITT

Where information was not available in the publication standard deviation was calculated from presented data assuming a normal distribution

Remission

None of the highlighted key studies reported remission rates for patients with more severe depression therefore it is assumed that remission rates are the same as patients receiving generic computerised CBT in the NG222[1] model (100% of responders).

Limitations of the analysis

There are a number of limitations which should be considered when interpreting the outputs of the early value assessment which stem from uncertainty in interpretation of clinical parameters. Many of these limitations are consistent with the limitations flagged within the economic analysis conducted for NG222[1].

Firstly, the estimation of outcomes is based upon data that was not in the correct format in the available studies. For example, the original NG222[1] NMA of response outcomes included a mixture of dichotomous response data (those who discontinued were considered to be non-responders) and continuous data where the trial did not report dichotomous data. Our analysis then required the informal addition of studies reporting outcomes in a variety of manners to a variety of quality levels into this network.

Secondly, as there are various measures for the level of depression in the study population (most commonly PHQ-9 and BDI-II), the scales had to be mapped

across to define the health states. In line with NG222[1] these measures are then used to classify patients as having more or less severe depression based upon baseline means (or medians). Particularly where study baselines are close to the cut off used this means that the evidence included in the analysis may not be fully reflective of the intended population. Only 3 papers identified for our interventions were available for patients with more severe depression. This paucity of evidence is in line with the NG222 guidance which only identified 3 studies for generic computerised CBT (2 with support and one without). Finally, the NG222 model's ability to incorporate stepped care and relapse prevention treatment was relatively limited. Specialist Committee Member advice indicates that a repeat session could be offered to patients whose symptoms recur, or alternatively patients may move on to high intensity CBT.

There were also limitations within the EAG's update to the model which should be considered when interpreting the results. Firstly, the data was not available in the correct format to calculate response for completers of the treatment, meaning that the data were based upon the response for the intention to treat (ITT) population. Given the analysis presented within NG222 [1] this is considered unlikely to have a major impact. Secondly, as none of the papers identified in the more severe depression population included data on remission an assumption that this was the same as generic computerised CBT in the NG222[1] model was required. Thirdly, the EAG considered the control groups in the key studies identified for our treatments of interest to be a limitation to the accuracy of this model. For all trials included aside from Proudfoot et al[41] where the comparator was treatment as usual, all studies used a waitlist control. This meant that to have comparable parameters in the model, the odds ratio generated for the studies was added to the OR comparing TAU to a 'do nothing' / 'GP care' option in the original model. This may bias the results as the treatment options have not been directly compared to the scoped comparator in this study.

Finally, consistent with the NG222[1] model benchmarking data for the IAPT population was not used directly within the economic as the data are not available in the format required for model input. In particular the way the

benchmarking data handle earlier cessation of treatment does not align; this was discussed at length in the development of the NG222 guideline.

12.2.4.2 Resource use and cost

The licence costs and the professional support required for each intervention can be seen in Table 11. Unit costs are provided in Table 12.

Table 11: Resource Use and Costs

	Space From Depression	Beating the Blues	Deprexis	Iona Mind	Minddistrict	Wysa
Existing licence cost exc VAT (Mean, Min, Max)	£3.75 - £6.25 (banded based on usage)	[redacted]	£270	Not provided	[redacted]	[redacted]
Duration of intervention	8 weeks	8-10 weeks	8-12 weeks	5-6 weeks	6 weeks	Dependent upon intended use (e-triage or treatment)
Resource required	Access to a computer, tablet or smartphone Push notifications via the SilverCloud App, email, or SMS	Computer, laptop, tablet or compatible smart device	Access to a computer, tablet or smartphone Compatible browser* SMS or email for personalized messages	Tablet or smartphone	Access to a computer, tablet or smartphone	Tablet or computer App is downloaded so may not require continuous internet access.
	Internet connection (8 wks)	Internet connection (8-10 wks)	Internet connection (10 wks)	Requirement for continuous internet access unclear	Internet connection (6 wks)	Requirement for continuous internet access unclear
	6 sessions of 15 minutes with a PWP	60 minute telephone call with a PWP over 8-10 period	5 minute interaction after 3 weeks, plus a 30 minute initiation and completion therapy calls	Typically 5-6 sessions of 30 minutes with a PWP	6 sessions of 30 mins with a therapist (trained CBT therapist)	Step 2: two review calls 30-45 mins Step 3: weekly/fortnightly calls 30-45 mins with a PWP

Costs used in model base case: Space from Depression: £5.13 (Mean), Beating the Blues: [redacted] (Mean) Deprexis: £270.
* Chrome 86, Edge 86, Internet Explorer 11, Mozilla 82, Safari 14

Table 12: Unit Costs

Item	Point estimate Cost	Distribution	Source / Notes
Tablet computer or smart phone	£80	N(80,8)	Representative cost from large online retailer, January 2023. 10" Android tablet with sim card slot. A basic smart phone is similar cost
Data sim card, per month	£20	N(20,2)	Representative cost from price comparison website, January 2023. Unlimited 5G data-only plan, 1m contract
Psychological wellbeing practioner, Band 5	50	N(50, 2.5)	Unit costs 2020 as in the NG222[1] model.

Abbreviations: N, Normal distribution

Licence costs

The licence costs provided are based upon existing costs supplied by the companies in consultation responses. These are to be considered indicative at best as negotiations are ongoing in relation to final pricing. In particular, the cost for Deprexis has been specified at £270, but it was highlighted by the company that this the price for a private purchase of the intervention. The company highlighted that the NHS price would be much lower and competitive with other products in this review. However, the company did not provide an estimation of this lower cost, and therefore the £270 is reflected in the model.

Three programs (Space from Depression, [redacted]) provided a tiered licence costs depending on the number of users, with, in the case of Space from Depression, a 5% allowance for growth of users across the licence period. As of the most recent data (2021-2022 data published September 2022), there were 203,387 people in contact with adult mental health services in the UK[97] with a primary diagnosis of depression receiving interventions considered as comparators within the scope or computerised CBT (14,222 patients). [redacted], but for Space from Depression, at 14,222 patients would mean the cost is in the second tier at £4.99 if only existing patients transferred to use the new systems. Within the model we have used costs based on the mid-point or mean within the base

case analysis. [redacted]

NHS support time

The majority of the companies consulted expected that use of their technologies would be in conjunction with support from a psychological wellbeing practitioner (Band 5). Advice from one Specialist Committee Member, however, indicated that whilst guided self help is provided by Band 5 practitioners, Band 5 staff would not be able to support digital CBT and instead a Band 6 practitioner would be required. Within the model base case we follow company advice on the requirements for resourcing, within sensitivity analysis we explore a scenario assuming that a Band 6 practitioner is required.

Computing equipment and internet access costs

All dCBT interventions by definition require access to computing equipment and an internet connection. The cost of these resources were added to licence costs in the NG222[1] model, as well as the costs of support from NHS staff. In the NG222 model, the cost of generic computerised CBT for a first visit was £78, which comprised of £39 per patient per licence and £14 per patient for the cost of hardware & capital overheads (here it was assumed that patients would be given access to computer equipment at a location provided by the NHS) plus half an hour of PWP (Band 5) time at £50.

The EAG instead used the estimated cost of a tablet computer or smart phone, (£80), per month cost of a sim card (£20) and mobile internet connection for the duration of the interventions in order to address equity concerns around digital exclusion, provide a more conservative estimate and as not all treatments specified delivery outside of use as an app. These were added to the licence costs and the estimated cost of a PWP's time. The unit costs used are in line with the earlier EVA for dCBT in children and young adults[8]. A limitation of this approach is the use of an average cost of a tablet computer and sim card cost, which are both highly variable costs and the assumption that the NHS will provide all users with the technology, whereas in real-world practice, this may not be needed. As highlighted in section 4.2, 6% of households did not have

internet access, 7% of the population did not own a smartphone, and 21% of internet users exclusively accessed the internet using a smartphone. However, these figures are for the general population, and as internet access is associated with increased age, greater social deprivation, and greater financial vulnerability, this figure is likely to be great amongst a depressed population. The EAG acknowledge that the incorporation of tablet/laptop and SIM card costs is a conservative inclusion into the model, and costs are likely to be less. However, relative to other parameters in the model, these costs constituted a very small proportion of the costs, thus the resulting impact of this inclusion is likely to be small. See Table 16 for a full breakdown of the costs.

Training, set-up and administrative costs

Training, set-up and administrative costs for NHS staff were not included in the model. Specialist Committee Member advice indicates that the number of administrative staff needed would be expected to increase if these interventions were introduced due to an increase in the number of patients receiving therapy and the number of PHQ-9 questionnaires being completed. Information provided in the company submissions indicates that training and consultation costs for set-up could be sizeable. For example, [redacted]

These costs should be considered in full in addition to the licence fee during pricing negotiations and later economic evaluation. These costs should also be of particular note within Committee deliberations as these costs are not recoverable if the systems are not fully implemented post the EVA.

Other costs

All other costs, including those associated with comparator therapies, were taken from NG222[1]. These can be found on pages 344 – 351 of the NG222 report.

12.2.4.3 Health State Utilities

Table 13 reports the utility values included within this model based upon NG222[1] which were identified via systematic review. The identified data came from studies reporting utility data for depression-related health states that were generated using the EQ-5D and the UK population tariff, as recommended by NICE. The authors of the NG222 guideline did not consider utility data to be a key area requiring additional research. Scenario analysis demonstrated little sensitivity to use of alternative value sets in less severe depression for more severe depression high intensity high intensity psychological interventions became less cost-effective than GP care and the rankings of pharmacological interventions and cCBT with support were substantially improved when utility values were used from an alternate source with a much smaller sample size (Mann 2009, n=141) with a reduced difference between remission and more severe depression.

Table 13: Utility values included within the model based on NG222[1]

Health state	Utility (SE)	Source
Less severe depression	0.60 (N/A)	NG222[1] original sources Sapin 2004[98], Sobocki 2006[99], Kolovos 2017[100]
More severe depression	0.42 (N/A)	NG222[1] original sources Sobocki 2006[99] & 2007[101], Kolovos 2017[100]
Acute remission: more severe depression and response less severe depression	0.85 (0.011)	NG222[1] original source Sapin 2004[98], Soini 2017[102]
Acute response: more severe depression	0.72 (0.034)	NG222[1] original source Sapin 2004[98]
Remission in Markov component	0.81 (N/A)	NG222[1] original sources Sobocki 2006[99] & 2007[101].
Utility decrement for patients experiencing side effects from medication	-0.09 (0.035)	NG222[1] original source Sullivan 2004[103]

N/A; uncertainty was not included within the economic analysis

12.2.5 Approach to Analysis

We conduct a cost utility analysis reporting net benefit at a willingness to pay threshold of £20,000 per QALY gained and analysis of uncertainty.

Probabilistic analyses are presented in all cases with 10,000 simulations from input distributions.

12.3 *Results from the economic modelling*

Mean cost, QALYs, net monetary benefit (+/-95%CI) at a willingness to pay threshold of £20,000/QALY and ranking in terms of net monetary benefit are reported in section 12.3.1. All results are reported for a cohort of 1,000 patients. The net monetary benefit is calculated as the incremental benefits multiplied by the willingness to pay (WTP) threshold (assumed to be £30,000 per QALY), minus incremental costs.

An indicative breakdown of costs and QALYs is provided for one treatment each for less severe and more severe depression to demonstrate the key model drivers.

One way sensitivity analyses exploring the impact of the cost of a telephone consultation with low and high cost staff, and the per-user licence cost of the dCBT interventions are in Section 12.3.3. Scenario analyses were conducted deterministically due to the run-time involved in the probabilistic analyses, however, this is not expected to impact on the conclusions as the probabilistic and deterministic analysis results were similar. A brief commentary follows in Section 12.3.4. Results are presented for the less severe and more severe depression populations.

12.3.1 Base Case Results

In less severe depression (Table 14) the results of the probabilistic analysis placed analyses based on individual dCBT treatments reported as low as at the bottom of the list and as high as 5th best in terms of mean NMB. Generic computerized CBT as analysed within the guidelines fell within the mid-range of the papers for the individual treatments considered within this scope of this EVA indicating that the results of the guideline are expected to be reasonably generalizable. As can be seen in Figure as the willingness to pay threshold increases use of face to face group CBT becomes increasingly cost-effective. The difference in the NMB between the most cost-effective and least cost-

effective intervention within the overall treatment pathway was, however, than 5%. Overall we would interpret these results as demonstrating that there is the plausibility for dCBT to be cost-effective in less severe depression but that considerable uncertainty surrounds the economic case.

When looking at individual papers per treatment the level of uncertainty around relative clinical effectiveness for dCBT treatments and the impact of that on cost-effectiveness becomes even more clear (Appendix F). Deterministic base case results may be found in Appendix F and are consistent with the probabilistic results.

Table 14: Base case results, Less Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY	Mean NMB Rank
CBT group	[redacted]	[redacted]	[redacted]	[redacted]
BA group	[redacted]	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]	[redacted]
Sertraline	[redacted]	[redacted]	[redacted]	[redacted]
Space From Depression	[redacted]	[redacted]	[redacted]	[redacted]
MBCT group	[redacted]	[redacted]	[redacted]	[redacted]
Generic computerized CBT	[redacted]	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]	[redacted]
Deprexis	[redacted]	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]	[redacted]
Beating the Blues	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; MBCT, Group mindfulness-based cognitive therapy NB, net benefit; OSI, Online support and intervention for anxiety; QALY, quality-adjusted life years; TAU, treatment as usual
*This paper reports results using the REEACT study which found use of dCBT to be less effective than GP care

In more severe depression (Table 15) the results of the probabilistic analysis placed Deprexis (the only treatment with evidence in this subgroup) towards the bottom end of the rankings list (mean NMB ranking of 11.36 out of 16). As can be seen in Figure problem solving was considered to be the most cost-

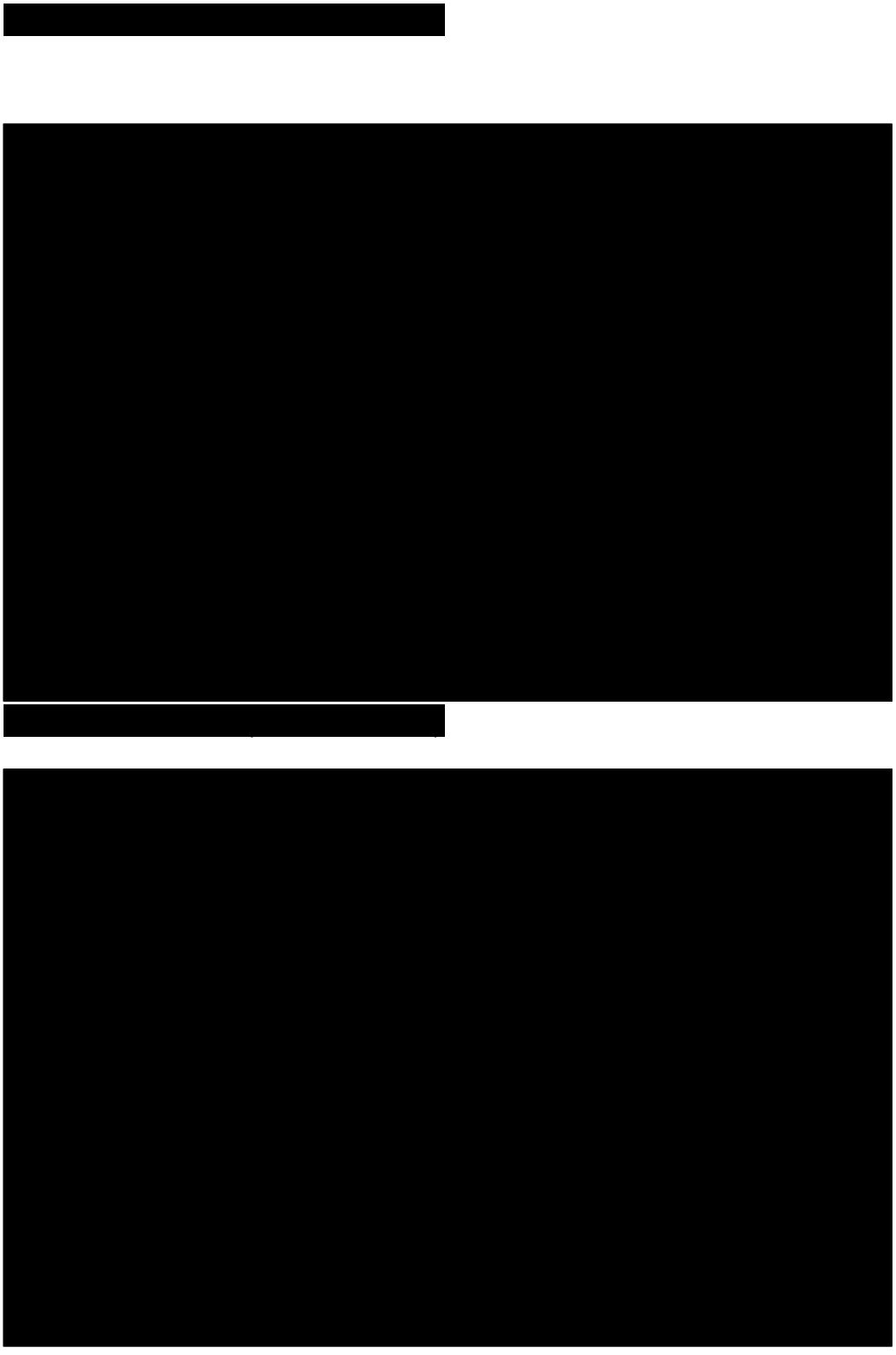
effective by a good margin at all tested willingness to pay thresholds. The difference in the NMB between the most cost-effective and least cost-effective option was 9%. Generic computerized CBT with support resulted in a marginally higher net monetary benefit than Deprexis, but generic computerized CBT with no support offered a lower NMB than Deprexis, highlighting the importance of the provision of support for patients with more severe depression. Individual studies for Deprexis all ranked poorly in terms of NMB. This indicates that dCBT is unlikely to be the most cost-effective treatment for more severe depression.

Table 15: Base case results: More Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY	Mean NMB Rank
Problem solving	[redacted]	[redacted]	[redacted]	[redacted]
CBT individual + escitalopram	[redacted]	[redacted]	[redacted]	[redacted]
Duloxetine	[redacted]	[redacted]	[redacted]	[redacted]
Mirtazapine	[redacted]	[redacted]	[redacted]	[redacted]
Escitalopram	[redacted]	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]	[redacted]
Lofepramine	[redacted]	[redacted]	[redacted]	[redacted]
Trazodone	[redacted]	[redacted]	[redacted]	[redacted]
Generic computerized CBT with support	[redacted]	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]	[redacted]
Deprexis	[redacted]	[redacted]	[redacted]	[redacted]
Generic computerized CBT without support	[redacted]	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; NB, net benefit; QALY, quality-adjusted life years; TAU, treatment as usual

Figure 2: Cost effectiveness Acceptability Curves



12.3.2 Cost and QALY Breakdown

To demonstrate the drivers of costs and QALYs associated with the included dCBT studies, cost and QALY breakdowns have been provided for representative studies for less severe and more severe depression.

The major cost components for the interventions are GP costs for follow-up for non-completers who respond to subsequent therapy (£82 1/£1,835, 44.72%), and the cost of a non-remitted episode for those with more severe depression (£1,042/£2,390, 44%). The costs added by the EAG which directly relate to dCBT treatments make up 13% (£239/£1,835) of the costs for mild depression and 19% (£463/£2,390) of the costs for severe depression. This demonstrates that the key cost driver relates to effectiveness and what is used as the next step in the treatment pathway for patients who do not respond rather than costs specific to dCBT.

Response to the treatment is also a key driver of patients' quality of life, which is reflected by the difference in utilities and therefore QALYs between responders and non-responders. In less severe depression quality of life is only impacted by response, in more severe depression the depth of response and whether or not remission is achieved (and therefore follow-up treatment is required) is also a major driver of QALY gains; this is an area where there is considerable uncertainty for dCBT treatments currently as none of the included trials reported this data.

Table 16: Cost/QALY Breakdown, Less Severe (Beating the Blues, Proudfoot, 2004)

Individual costs per patient	**Mean**	
Licence costs (one off)	[redacted]	
Tablet or laptop (one off)	£80.00	
SIM card (1 month)	£20.00	
PWP costs (per hour)	£49.59	
Cost of discontinuation (one off)	£223.05	
Depressive episode costs for those moving into remission in year 2 (annual)	£1,103.20	
Depressive episode costs (annual)	£1,449.84	
Remission/recovery costs (annual)	£532.73	

Cost of antidepressant therapy for those attaining remission on subsequent therapy (1 year)	£136.19	
Cost breakdown by health states (discounted)	**Per 1,000 patients**	**Per patient**
GP costs	[redacted]	[redacted]
Tablet or laptop	[redacted]	[redacted]
SIM Card	[redacted]	[redacted]
PWP time	[redacted]	[redacted]
Licence	[redacted]	[redacted]
Cost of subsequent treatment after discontinuation	£91,159.20	£91.16
Cost of follow-up: non-completers who respond to subsequent therapy	£820,806.60	£820.81
Costs of non-response	£684,716.17	£684.72
Total Cost (discounted)	**£1,835,308.49**	**£1,835.31**
Utilities		
Baseline	0.60	
Remission (and response)	0.85	
QALYS per patient	**Undiscounted**	**Discounted**
Remission with no further treatment	1.034	1.017
Non-remitted episode	0.514	0.505

Table 17: Cost/QALY Breakdown, More Severe (Deprexis, Meyer 2015)

Individual costs	**Mean**	
Licence costs	£29.00	
Tablet or laptop	£80.00	
SIM card	£20.00	
PWP costs	£49.59	
Cost of discontinuation	£223.05	
Depressive episode costs for those moving into remission in year 2 (annual)	£1,103.20	
Depressive episode costs (annual)	£1,449.84	
Remission/recovery costs (annual)	£532.73	
Cost of antidepressant therapy for those attaining remission on subsequent therapy (1 year)	£136.19	

Cost breakdown by health states (discounted)	Per 1,000 patients	Per patient
GP costs	£39,000.00	£39.00
Tablet or laptop	£80,000.00	£80.00
SIM Card	£37,191.96	£37.19
PWP time	£36,868.38	£36.87
Licence	£270,000.00	£270.00
Cost of subsequent therapy	£81,784.22	£81.78
Cost of follow-up: non-completers who respond to subsequent therapy	£310,850.24	£310.85
Costs of maintenance mindfulness-based CBT	£259,887.32	£259.89
Costs of maintenance CBT	£232,915.55	£232.92
Costs of non-response	£1,041,583.60	£1,041.58
Total Cost (discounted)	**£1,835,308.49**	**£1,835.31**
Utilities		
Baseline	0.42	
Remission	0.85	
Response not reaching remission	0.72	
QALYS per patient	**Undiscounted**	**Discounted**
Maintenance CBT group	0.226	0.222
Maintenance mindfulness-based CBT	0.227	0.223
Remission with no further treatment	0.373	0.366
Non-remitted episode	0.557	0.547

12.3.3 Scenario analyses

Table 18 and Table 19 show the using a Band 6 rather than Band 5 staff cost for dCBT appointments had minimal impact. For less severe depression, compared to the deterministic base case analysis, there was some change in the ranking of treatments within this scenario analysis. With Band 6 pricing, Richards 2015 had a lower NMB than generic computerized CBT, whereas with Band 5 pricing this was higher. This is likely due to the unguided nature of generic computerized CBT in the NG222[1] guideline, meaning that clinical input was only required during the first meeting, reducing the overall cost compared to other, guided interventions. For more severe depression there was a minimal difference in the NMB in the interventions, and no change in the ranking.

Table 18: Scenario analysis: Use of Band 6 rather than Band 5 staffing cost for dCBT appointment: Less Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY
CBT group	[redacted]	[redacted]	[redacted]
BA group	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]
DPX (Berger 2011[13])	[redacted]	[redacted]	[redacted]
MBCT group	[redacted]	[redacted]	[redacted]
Generic computerized CBT	[redacted]	[redacted]	[redacted]
SfD (Richards 2020[50])	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]
SfD (Richards 2015[30])	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012[46])	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]
Sertraline	[redacted]	[redacted]	[redacted]
BtB (Proudfoot 2004[41])	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020[55])	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]
DPX (Meyer 2009[44])	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]
DPX (Klein 2016[17])	[redacted]	[redacted]	[redacted]
BtB (Littlewood 2015[32])	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; NB, net benefit; QALY, quality-adjusted life years; TAU, treatment as usual

Table 19: Scenario analysis: Use of Band 6 nurse rather than Band 5 staffing cost for dCBT appointment: More Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY
Problem solving	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]
Exercise Group	[redacted]	[redacted]	[redacted]
dCBT with support	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020[55])	[redacted]	[redacted]	[redacted]
DPX (Meyer 2015[45])	[redacted]	[redacted]	[redacted]
Duloxetine	[redacted]	[redacted]	[redacted]

	Cost	QALYs	Mean NMB £20,000 per QALY
CBT individual + escitalopram	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]
Mirtazapine	[redacted]	[redacted]	[redacted]
Escitalopram	[redacted]	[redacted]	[redacted]
Lofepramine	[redacted]	[redacted]	[redacted]
Trazodone	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012[46])	[redacted]	[redacted]	[redacted]
dCBT	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; NB, net benefit; QALY, quality-adjusted life years; TAU, treatment as usual

Using the upper and lower bounds of the licence costs provided for the included studies resulted in a minimal difference in the NMB, and has not changed the ranking of NMB for either of the severity groups (Table 20 to Table 23). This is in part due to the largest evidence base being for Deprexis, which did not have a variable cost (£270), though the company highlighted that £270 was the maximum licence fee. For the other interventions, the change in cost was relatively small, and resulted in a change in NMB of between [redacted] overall, highlighting the small impact of licence fees within the economic analysis.

Table 20: Scenario Analysis: Higher Licence costs: Less Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY
CBT group	[redacted]	[redacted]	[redacted]
BA group	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]
DPX (Berger 2011[13])	[redacted]	[redacted]	[redacted]
MBCT group	[redacted]	[redacted]	[redacted]
SfD (Richards 2020[50])	[redacted]	[redacted]	[redacted]
Generic computerized CBT	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]

CBT individual	[redacted]	[redacted]	[redacted]
SfD (Richards 2015[30])	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012[46])	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]
Sertraline	[redacted]	[redacted]	[redacted]
BtB (Proudfoot 2004[41])	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020[55])*	[redacted]	[redacted]	[redacted]
DPX (Meyer 2009[44])	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]
DPX (Klein 2016[17])	[redacted]	[redacted]	[redacted]
BtB (Littlewood 2015[32])	[redacted]	[redacted]	[redacted]

Table 21: Scenario Analysis: Higher Licence Costs: More Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY
Problem solving	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]
Exercise Group	[redacted]	[redacted]	[redacted]
dCBT with support	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020[55])	[redacted]	[redacted]	[redacted]
DPX (Meyer 2015[45])	[redacted]	[redacted]	[redacted]
Duloxetine	[redacted]	[redacted]	[redacted]
CBT individual + escitalopram	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]
Mirtazapine	[redacted]	[redacted]	[redacted]
Escitalopram	[redacted]	[redacted]	[redacted]
Lofepramine	[redacted]	[redacted]	[redacted]
Trazodone	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012[46])	[redacted]	[redacted]	[redacted]
dCBT	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]

Table 22: Scenario Analysis: Low Licence Costs: Less Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY
CBT group	[redacted]	[redacted]	[redacted]
BA group	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]
DPX (Berger 2011[13])	[redacted]	[redacted]	[redacted]
MBCT group	[redacted]	[redacted]	[redacted]
SfD (Richards 2020[50])	[redacted]	[redacted]	[redacted]
Generic computerized CBT	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]
SfD (Richards 2015[30])	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012[46])	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]
Sertraline	[redacted]	[redacted]	[redacted]
BtB (Proudfoot 2004[41])	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020[55])*	[redacted]	[redacted]	[redacted]
DPX (Meyer 2009[44])	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]
DPX (Klein 2016[17])	[redacted]	[redacted]	[redacted]
BtB (Littlewood 2015[32])	[redacted]	[redacted]	[redacted]

Table 23: Scenario Analysis: Low Licence Costs: More Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY
Problem solving	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]
Exercise Group	[redacted]	[redacted]	[redacted]
dCBT with support	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020[55])	[redacted]	[redacted]	[redacted]
DPX (Meyer 2015[45])	[redacted]	[redacted]	[redacted]
Duloxetine	[redacted]	[redacted]	[redacted]
CBT individual + escitalopram	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]
Mirtazapine	[redacted]	[redacted]	[redacted]

	Cost	QALYs	Mean NMB £20,000 per QALY
Escitalopram	[redacted]	[redacted]	[redacted]
Lofepramine	[redacted]	[redacted]	[redacted]
Trazodone	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012[46])	[redacted]	[redacted]	[redacted]
dCBT	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]

12.3.4 Commentary

Our analyses demonstrate that there is a there is a plausible prima facie case for the cost-effectiveness of the digitally enabled therapies in adults with depression in less severe depression. For more severe depression, dCBT without support has a lower NMB than other possible options in this analysis, and while a positive NMB shows a cost-effective result compared to existing care, it is unlikely to be the *most* cost-effective alternative. These results are broadly in line with the conclusions of the NG222[1] assessment.

As in NG222, the results of the analysis are characterised by considerable uncertainty, as reflected in the wide 95% credible intervals (CrI) around the rankings of interventions.

The modelled outcomes broadly align with the outcomes of the available economic evaluations alongside clinical trials (EEACTs) in that, barring the REEACT study, dCBT treatments were generally considered to be plausibly cost-effective for less severe depression.

The evidence base in this early value assessment is too uncertain to draw any inferences around whether one dCBT intervention is more or less cost-effective than another.

Scenario analysis (Section 12.3.3) showed that the results are relatively insensitive to whether a Band 5 or Band 6 staff member provided support and licence costs within the range provided by the manufacturers.

There are differences in the length of the course of treatment, level of support from health-care practitioners and licence fees for the various treatments under evaluation. The three treatments which are seeking an indication in depression and could not be included within the early economic assessment generally had shorter course lengths which may reduce the cost to the NHS. The evidence is too uncertain to know whether a longer course or increased direct support leads to improved cost-effectiveness.

The three interventions with a strong enough evidence based were evaluated quantitatively in the model, but this form of evaluation was not possible for Iona Mind, MindDistrict or Wysa due to a lack of evidence. There was no evidence available for either licence costs or effectiveness provided for Iona Mind, so while using an arbitrary mean cost of interventions would have allowed model evaluation, as efficiency was a key driver of results in the model, no evaluation was possible. Similarly, while MindDistrict licence costs [redacted], there was no robust clinical evidence identified to include within the economic analysis. With respect to Wysa, the potential licence costs were provided to the EAG in a format that didn't allow for a direct comparison with the other technologies evaluated. [redacted] The relative clinical effectiveness of Wysa compared to the modelled interventions is uncertain, since the only study which provided data on improvement on a relevant scale, the Inkster et al (2018) study, used the PHQ-2 which does not provide comparable results to the PHQ-9. Any mapping based on single-arm evidence would appear tenuous.

Based on the available evidence, it is not possible to conclude definitively how the clinical effectiveness (and therefore cost-effectiveness) of the three therapies that could not be included in the economic model compares to those that could be modelled. Poorer and more limited evidence may reflect research issues, rather than indicating that these interventions are less effective or cost-effective.

13 Interpretation of the evidence

13.1 *Interpretation of the clinical and economic evidence*

Following systematic searches, 32 unique clinical studies were included, of which seven were conducted in an IAPT or probable IAPT setting ('IAPT studies'). Of these IAPT studies, 4 assessed Beating the Blues and 3 assessed Space from Depression. There was one IAPT RCT for Beating the Blues with a comparator of usual GP care and one IAPT RCT for Space from Depression with a comparator of waitlist control. There is also an Irish RCT available for Space from Depression against waitlist control. There was no IAPT evidence for other interventions. Evidence from RCTs conducted in a German setting as well as a meta-analysis was available for Deprexis. RCTs were generally compared to non-scoped comparators (usual care or waitlist control) with only one RCT (a German trial of Deprexis[14]) using a scoped comparator in the form of psychotherapy. Available relevant evidence on Wysa was all mixed methods or qualitative. No relevant empirical evidence was identified for Minddistrict or Iona Mind. Evidence was not available for all scoped outcomes and safety data were rarely reported.

The EAG considered that there were two interventions for which there is relatively high-quality clinical evidence, especially for key outcomes such as improvement in depressive symptoms. Deprexis was the intervention for which the EAG considered there was the greatest volume of robust evidence, although health system differences between the IAPT setting and Germany are a limiting factor for generalisability of German RCT evidence, although there are likely to be relatively limited differences in terms of population factors. The EAG was also satisfied that there was good evidence for a benefit of Space from Depression, based on an IAPT RCT and an Irish RCT, which both showed a significant benefit of intervention over control for depressive symptoms (PHQ-9 or BDI-II) as well as the Work and Social Adjustment Scale. For a third intervention, Beating the Blues, the EAG considered there was some evidence of clinical effectiveness, but there was greater uncertainty. For Beating the Blues, the REEACT trial [31 32] did not show evidence of a statistically significant

benefit on PHQ-9 at 4, 12 or 24 months, nor a difference in quality of life, over and above usual GP care. The next most robust clinical effectiveness evidence for Beating the Blues came from a non-randomised pilot-controlled trial in Scotland[42] which found a statistically significantly greater reduction in depressive symptoms for patients on Beating the Blues compared to usual care. Although there are some differences in the organisation of mental health services between Scotland and England, the population would be expected to be broadly comparable. It was noted across studies that Beating the Blues received positive user feedback.

The five identified previous economic evaluations alongside clinical trials for the products within the scope were conducted in the UK and Germany and generally considered treatment with dCBT to be cost-effective vs usual care or waitlist control. The exception was the REEACT study which found Beating the Blues to be dominated by usual care (in line with reduced clinical effectiveness). The authors of a later publication[50] consider that this less positive result may be down to the stepped-care model within which these interventions were embedded, with contextual factors favouring the deployment and uptake of the interventions (i.e. trained personnel for the use of dCBT, routine outcome monitoring). The current NICE guideline NG222[1] is less definitive on the use of stepped care compared to previous guidance instead now recommending: "Commissioners and providers of mental health services should consider using models such as stepped care or matched care for organising the delivery of care and treatment of people with depression." We understand though that IAPT is currently delivered via a stepped care model and therefore would expect the results of the REEACT study to be of most relevance. Within this study there was low adherence to dCBT (only 18% completed all 8 sessions) which is likely to have had considerable impact on outcomes. The comparator, usual care, included a mix of alternatives which were similarly used in both arms and also dCBT which 19% of patients in the usual care arm received.

The results of the quantitative early value assessment are presented for the three therapies within scope where sufficient evidence was available (Space from Depression, Beating the Blues and Deprexis) using the NG222[1] model.

Results demonstrate that there is a there is a plausible prima facie case for the cost-effectiveness of the digitally enabled therapies in adults with depression in less severe depression. In more severe depression it would appear unlikely that dCBT will provide the most cost-effective option based upon current analyses.

The evidence base in this early value assessment is too uncertain to draw any inferences around whether one dCBT intervention is more or less cost-effective than another.

The costs of the different interventions are broadly similar and fairly minimal, the key components being licensing costs (still being negotiated), mental health professional contact time, equipment to provide digital access and set-up, administration and training costs for NHS staff (these last being unable to be quantified within the analysis.

There are differences in the length of the course of treatment, level of support from health-care practitioners and licence fees for the various treatments under evaluation. The three treatments which could not be included within the early economic assessment generally had shorter course lengths which may reduce the cost to the NHS. The evidence is too uncertain to know whether a longer course or increased direct support leads to improved cost-effectiveness. It is also unknown how much the qualifications of the professional impact on effectiveness (e.g., PWP vs Band 6) within expert committee member advice indicating a higher level of qualification is required than indicated by the companies. The impact on the cost component of the analysis of this is, however, expected to be limited.

13.2 *Integration into the NHS*

Information available to the EAG suggests that digitally enabled therapies currently used within IAPT are typically from the Silver Cloud product range, including within the present scope Space from Depression. The manufacturer of Beating the Blues confirmed that present use of this technology within IAPT settings in England is very low, although its use is widespread within Scotland and Northern Ireland. All relevant Scottish studies were on Beating the Blues

and evidence in this context provides useful insight into real-world clinical effectiveness and user experience. While the evidence base for Deprexis is largely in a German context, the EAG was informed by the manufacturer that it is conducting a pilot of how this intervention may work in UK practice, focusing on GPs in North Warwickshire.

Guided digital therapies are already used in the IAPT setting within the NHS in England. Any change would be introducing a wider range of digital therapies or increasing the scale on which such therapies are used, rather than introducing a fundamentally new treatment. This would reduce implementation challenges, although it would be important to ensure sufficient appropriate staff resource and training to deliver such interventions. There are some challenges relating to access to digital technologies and service providers would have to consider supply of relevant equipment or signposting to relevant community resources, such as libraries, where equipment can be accessed, noting potential concerns regarding opening hours, access for patients who work during the day, and confidentiality.

13.3 *Evidence gap analysis*

A summary of evidence gaps, pertaining to the intermediate and final outcomes from the scope, and those pertaining to decision modelling are summarised in Table 24.

Evidence was focused around certain key outcomes and therefore there is limited information about many additional scoped outcomes.

A narrative assessment of evidence gaps in other methodological areas besides outcomes is presented in Section 13.4.

It should be noted that while there is a large body of evidence for Deprexis, it does not come from an IAPT setting. This was considered a generalisability issue rather than an outcome gap.

Table 24: Evidence Gap Analysis

Outcomes	Space from Depression	*Minddistrict*	*Beating the Blues*	*Deprexis*	*Wysa*	*Iona Mind*
Clinical trials						
Intermediate outcome: Patient choice and preferences	No studies **RED**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**
Intermediate outcome: Treatment satisfaction and engagement	No studies **RED**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**
Intermediate outcome: Intervention adherence and completion	Multiple studies **GREEN**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**	No studies **RED**
Intermediate outcome: Referral to treatment time	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**
Intermediate outcome: Assessment to treatment time	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**
Intermediate outcome: Intervention-related adverse events	No studies **RED**	No studies **RED**	One RCT **AMBER**	One study **AMBER**	No studies **RED**	No studies **RED**
Intermediate outcome: Inaccessibility to intervention (digital inequalities)	No studies **RED**	No studies **RED**	One study **AMBER**	Multiple studies from one trial **AMBER**	No studies **RED**	No studies **RED**
Intermediate outcome: Rates of attrition (dropouts) and engagement	Multiple studies **GREEN**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**	No studies **RED**
Clinical outcome: Change in depression symptoms	Multiple studies **GREEN**	No studies **RED**	Inconsistent trial evidence **AMBER**	Wide-ranging RCT evidence **GREEN**	One single-arm study **AMBER**	No studies **RED**

Outcomes	Space from Depression	*Minddistrict*	*Beating the Blues*	*Deprexis*	*Wysa*	*Iona Mind*
Clinical outcome: Change in other psychological symptoms	Multiple studies GREEN	No studies RED	Inconsistent trial evidence AMBER	Wide-ranging RCT evidence GREEN	No studies RED	No studies RED
Clinical outcome: Global functioning and work and social adjustment	Multiple studies GREEN	No studies RED	One single-arm study AMBER	Wide-ranging RCT evidence GREEN	No studies RED	No studies RED
Clinical outcome: Rates of reliable recovery	Multiple studies GREEN	No studies RED	Multiple studies GREEN	Multiple studies GREEN	No studies RED	No studies RED
Clinical outcome: Rates of reliable improvement	Multiple studies GREEN	No studies RED	Multiple studies GREEN	Multiple studies GREEN	No studies RED	No studies RED
Clinical outcome: Rates of reliable deterioration	Two single-arm studies AMBER	No studies RED	One study AMBER	Multiple studies GREEN	No studies RED	No studies RED
Clinical outcome: Rates of relapse (including relapse rate and time from remission to relapse)	One study AMBER	No studies RED	No studies RED	No studies RED	No studies RED	No studies RED
Patient reported outcomes: Health-related quality of life	One RCT, no effect RED	No studies RED	Inconsistent trial evidence AMBER	Multiple studies GREEN	No studies RED	No studies RED
Patient reported outcomes: Patient experience	No studies RED	No studies RED	Multiple studies GREEN	Multiple studies GREEN	Multiple studies GREEN	No studies RED

Models and economic outcomes	
Effectiveness evidence: Comparative data	No direct comparisons of effect of the target interventions and either each other, an active control or treatment as usual in an IAPT population. Is one dCBT intervention more effective than another and TAU? RED

Effectiveness evidence: Comparative data	Is one dCBT intervention more effective than another and face to face CBT? **RED**
Effectiveness evidence: Follow-up times and lengths	Follow-up times vary across the source studies, which are crudely equalized to 12 weeks in the decision model. Common FU times are required, along with longer term follow-up data (to 2 years). **RED**
Effectiveness evidence: Impact of stepped care	The optimal treatment pathway following dCBT (repeat session, movement onto high intensity CBT?) and the impact of stepped care on treatment effectiveness are unclear. **AMBER**
Effectiveness evidence: Discontinuations / withdrawals	Withdrawals are currently accounted for a crude assumption of similar relative effectiveness for completers and the ITT population. Future studies should report withdrawal rates, reasons for discontinuation and response in both the ITT population and completers. **AMBER**
Effectiveness evidence: Population	Crude assumptions were required based upon mean or median baseline scores to determine whether patients were classified as having more or less severe depression. There were also fewer papers available considering more severe depression. Reporting by subgroup is required in future studies. **RED**
Effectiveness evidence: Differential wait times	The potential for, and impact of, differential wait times on outcomes for dCBT compared to TAU is unclear. **RED**
Effectiveness evidence: Network meta-analysis	A formal update of the NG222[1] meta-analysis is suggested once suitable evidence is available for specific treatments. **AMBER**
Effectiveness evidence: NHS Digital data	NHS Digital data could not be used within the current economic analysis as the publicly available data does not provide sufficient granularity and the manner in which patients who discontinue are handled differs from the economic analysis in the NG222[1] guideline. Ideally such data would be used to supplement future analysis. **AMBER**
Clinical outcome and costs: Qualifications of mental health contact	What type of support worker is required for dCBT treatments (Band 5 or Band 6) and how does this impact on effectiveness? **AMBER**
Clinical outcome and costs: Schedule of mental health contact	The optimal schedule for mental health contact (frequency and duration of contacts) is unknown along with the impact of this on cost-effectiveness. **RED**

Costs: Set up, administration and training costs	The costs associated with system set-up and integration with NHS systems, day to day administration and training of NHS staff to roll out dCBT are unclear. These costs are unrecoverable and could be substantial. **RED**
Costs: Licence costs and patient numbers	Licence costs are currently unknown and are expected to be based upon the volume of usage which is also uncertain. **AMBER**
Costs: Method of provision of access	The method to be used to provided patients who do not have the required hardware and internet connection at home with access is currently unclear. This impacts upon costs and also equality of access. **AMBER**
HRQoL: Caregivers	The impact of treatment on caregiver quality of life has not been included in prior modelling. **AMBER**
HRQoL: Definition of response and benefit	Exploration of broader definitions of response and patient benefit was suggested within the NG222[1] model following patient commentary that the current definition (50% improvement on any scale) is too narrow and not fully reflective of patient experience. **AMBER**

13.4 *Ongoing studies*

The EAG did not identify any additional ongoing studies besides what the companies had supplied. Ongoing studies as supplied by the companies are listed below in **Table 25. Ongoing studies**

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Table 25. Ongoing studies

Space from Depression	***Minddistrict***	***Beating the Blues***	***Deprexis***	***Wysa***[C]	***Iona Mind***
One under review manuscript)	STEPPS – feasibility study with an expected publication date at submission of September 2022. Young people with bipolar depression.	The company states that [redacted]	No ongoing trials were noted in the company submission.	Meheli S, Sinha C, Kabada M.[104] This study has now been published since the company submission.	No ongoing trials at the time of submission.
One previously under review study that is now published [48].	University of Exeter 2 – starts October 2022, rumination in a student population			[redacted]	Imminent (early 2023) pilots within some IAPT settings (single arm pre-post) to assess effectiveness on IAPT minimum data set at Step 2
[redacted]	TRENT – testing the depression module in adults, expected completion February 2023.[b]			[redacted]	
[redacted]				[redacted]	

Space from Depression	*Minddistrict*	*Beating the Blues*	*Deprexis*	*Wysa*[C]	*Iona Mind*
[redacted]				[redacted]	
[redacted]				[redacted]	
				[redacted]	
				[redacted]	
				[redacted]	
				[redacted]	
				[redacted]	

Space from Depression	*Minddistrict*	*Beating the Blues*	*Deprexis*	*Wysa*[C]	*Iona Mind*
				[redacted]	
				[redacted]	
				[redacted]	

a = A protocol for this study has been published [109]. While not in the IAPT setting, it appears relevant to the present scope. b=may be relevant to the present scope, but cannot be confirmed without additional information. c = these works were not considered relevant to the present scope on grounds of population.

13.5 *Summary and conclusions of evidence gap analysis*

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

Population gaps

- A minority of clinical studies were conducted in the IAPT setting
- Differences in health system organisation and treatment pathways may limit generalisability of international evidence
- In over half of included studies, the population was not restricted to depression and included other affective disorders (although SCM advice was that co-morbidity of depression and anxiety is so high that this may not be a major concern)
- Categorisation of depression in included studies did not correspond to the NICE guideline

Intervention gaps

- There is no evidence on some technologies of interest
- There is uncertainty about the most appropriate and effective health professional to deliver the interventions and how this fits into the health system, including with regard to resource and training

Comparator gaps

- There is a mismatch between comparators in the scope and in the included studies. Only one study used a scoped comparator – psychotherapy – in a German RCT of Deprexis[14].

Outcome gaps

- Published evidence was not available for some outcomes. There was also heterogeneity in how clinical measures are reported, though some key measures (such as PDQ-9 and BDI-II) are frequently reported

- Limited adverse event and safety data were reported in the eligible studies identified by the EAG

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

In addition to the gaps in clinical evidence there are considerable uncertainties around the overall cost of rolling out the dCBT interventions (setup, training, administration and licence fees) which will need resolving as part of negotiations with NHSE.

13.6 *Key areas for evidence generation*

The EAG considered that the important area for evidence generation is more studies using appropriate designs, which could include randomised controlled trials (RCTs), potentially using pragmatic or clustered designs, specifically focusing on the scoped interventions compared to the scoped comparators in an IAPT setting with depression severity categorized as per NICE guidelines. Considering the benchmarking data, it is important as far as possible to ensure populations in future studies to be used to inform UK practice match those in the IAPT database. Even among studies within the IAPT population, the correspondence between studies and the database was only moderate.

Specific evidence generation recommendations are summarised in Table 26.

Table 26: Evidence generation recommendations

Research question	Recommended study design	Outcomes
1. Is Beating the Blues effective in an IAPT setting?	Further RCT in a different IAPT setting. Sample stratified by less severe and more severe depression.	IAPT core data set
2. What is the relative effectiveness of all dCBT interventions compared with	Ideally a multi-arm RCT in an IAPT setting with all interventions. Failing this series of RCTs comparing technologies with active	IAPT core data set

each other, and relevant control?	comparators can be meta-analysed. Sample stratified by less severe and more severe depression. Relevant control depends where in the pathway it is intended to use digitally enabled therapies – as an alternative to face-to-face CBT or as an earlier step in the process.	
3. Is a band 5 PWP as effective as a band 6 at supporting dCBT?	Ideally RCT of all dCBT interventions with two different support levels in an IAPT setting. Sample stratified by less severe and more severe depression. Qualitative study to assess patient and healthcare professional experiences	IAPT core data set, participant perspectives

14 Conclusions

14.1 *Conclusions from the clinical evidence*

A total of 32 unique studies were available for consideration. The EAG was aware of a small number of ongoing studies which could be considered likely to provide evidence to address the present decision problem. Seven studies were conducted in an IAPT or probable IAPT setting. There were a total of 14 RCTs available, of which two were IAPT studies, one each on Space from Depression and Beating the Blues. RCT evidence was available for three interventions: Space from Depression, Beating the Blues and Deprexis.

The greatest volume of RCT evidence was available for Deprexis, although this was largely in a German context. RCT evidence supporting a benefit of Space from Depression was found both in the IAPT setting and in Ireland. There was an RCT of Beating the Blues in an IAPT setting, but it did not show evidence of a significant benefit versus control. However, evidence from a Scottish setting, including a non-randomised pilot controlled trial, did support a beneficial effect of Beating the Blues on depressive symptoms and quality of life. For all other scoped interventions, either limited or no relevant clinical evidence was available.

With the exception of one German Deprexis study compared to psychotherapy, RCTs were compared to usual care or waitlist control, which were not scoped

comparators, but could – according to SCM advice to the ERG – be useful substitutes for an inactive placebo arm. No studies compared scoped digitally enabled therapy interventions to each other.

There was some evidence that included studies may have had higher baseline PHQ-9 scores (indicating greater depression severity), greater effect sizes for PHQ-9 and superior recovery rates (both indicating greater benefit of treatment) than observed in routine practice as reflected in the IAPT database.

14.2 *Conclusions from the economic evidence*

The results of the early value assessment indicate that there is a there is a plausible prima facie case for the cost-effectiveness of the digitally enabled therapies in adults with depression in less severe depression. In more severe depression it would appear unlikely that dCBT will provide the most cost-effective option based upon current analyses.

The evidence available is, however, limited in quantity and quality and no strong conclusions should be drawn from these analyses.

The costs of implementing these therapies would appear to be minimal on a per patient basis with the provision of support via NHS personnel being the key determinant of cost. Licence costs are expected to depend upon the level of uptake; this should therefore be carefully monitored if these treatments are recommended during the EVA.

The costs of system set up, increased administrative burden and training of NHS staff could not be estimated but may be sizeable and should be considered in full in addition to the licence fee during pricing negotiations and later economic evaluation. These costs should also be of particular note within Committee deliberations as these costs are not recoverable if the systems are not fully implemented post the EVA.

The greatest value is to be obtained from research into the effectiveness of dCBT interventions relative to one another and to active control (such as face to face CBT). There is limited evidence on the longer-term (to 2 years)

effectiveness of all interventions, therefore any RCTs should plan follow-up to at least this length. There is limited evidence addressing the optimal use of such systems within a stepped care pathway which would be of particular benefit given this is how IAPT services are currently offered. Any data collected (including via NHS digital) should be collected and reported in such a way that outcomes are able to be evaluated for patients based upon their adherence to treatment. Finally, inclusion of the impact of reduction in depression symptoms on caregivers would be of benefit in future evaluations, particularly for more severe depression.

14.3 *Summary of the combined clinical and economic sections*

There are three interventions for which RCT evidence is available. Deprexis has the greatest volume of evidence, although this is largely from a German context. The effectiveness of Space from Depression is supported by an RCT in the IAPT setting and an Irish RCT. There is a RCT for Beating the Blues in an IAPT setting, although this did not find any benefit over and above control with GP usual care. However, evidence from a Scottish setting, including a non-randomised pilot controlled trial found a consistent benefit for Beating the Blues. Relevant evidence is not available or very limited for the other interventions.

Early decision modelling suggests there is a *prima facie* case for dCBT interventions to be cost-effective in less severe depression, but there is considerable uncertainty around this. It is unknown whether one intervention is more cost-effective than another. There are likely to be unrecoverable costs associated with a decision to implement these treatments which may be sizeable and should be considered within negotiations.

Key evidence requirements are: i) to assess whether Beating the Blues is effective in an IAPT setting given positive evidence supporting this intervention in a Scottish setting but negative results from an IAPT RCT, ii) assess whether other interventions are effective in an IAPT setting iii) determine the relative effectiveness of all dCBT interventions compared to each other and relevant control, considering where in the pathway these technologies are to be used,

and iv) determine the optimal frequency and type of support and the level of training required for staff members to support dCBT programmes v) determine what the care pathway should be for patients not responding to dCBT.

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16 Appendices

16.1 *Appendix A: Searches for clinical effectiveness evidence*

Table 30: Resources searched for clinical effectiveness studies

Database/Resource	Host	Date Searched	Results
MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	Ovid	23.11.22	247
Embase	Ovid	23.11.22	362
APA PsycINFO	Ovid	23.11.22	398
CDSR / CENTRAL	Cochrane Library: Wiley	23.11.22	241
INAHTA HTA database	https://database.inahta.org/	23.11.22	13
CRD	www.york.ac.uk/crd	23.11.22	20
PubMed	https://pubmed.ncbi.nlm.nih.gov/	23.11.22	313
Epistemonikos	https://www.epistemonikos.org	23.11.22	100
Company websites		16.11.22	116
ClinicalTrials.gov	http://www.clinicaltrials.gov/	23.11.22	55
WHO ICTRP	https://trialsearch.who.int/	23.11.22	75
Total records retrieved			1940
Total records after deduplication			1694

Also searched NICE Guidelines (9), SIGN Guidelines (0), MAUDE (0) and MHRA (0).

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 dCBT or dCBT 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

Embase <1974 to 2022 November 22>

1 Anxiety/ 259704
2 anxiety disorder/ 89008
3 (anxiet* or anxious).tw. 355537
4 "generali?ed anxiety disorder*".tw. 13031
5 GAD.tw. 17664
6 "social anxiety disorder*".tw. 3983
7 phobia*.tw. 12794
8 "panic disorder*".tw. 13048
9 "post?traumatic stress disorder*".tw. 25731

10 PTSD.tw. 39557
11 "body dysmorphic disorder*".tw. 1677
12 "obsessive compulsive disorder*".tw. 20892
13 exp phobia/ 35341
14 panic/ 25681
15 posttraumatic stress disorder/ 74592
16 body dysmorphic disorder/ 3448
17 obsessive compulsive disorder/ 28550
18 generalized anxiety disorder/ 14076
19 social anxiety/ 729
20 or/1-19 555175
21 depression/ 446162
22 (depression or depressive or depressed).tw. 682442
23 or/21-22 816413
24 20 or 23 1114339
25 "beating the blues".af. 51
26 "365 health solutions".af. 0
27 cerina.af. 193
28 (NoSuffering or "no suffering").af. 27
29 iCT-PTSD.af. 2
30 (internet adj2 "cognitive therapy for post traumatic stress disorder").tw. 0
31 iCT-SAD.af. 2
32 (internet adj2 "cognitive therapy for social anxiety disorder").tw. 4
33 OxCADAT.af. 1
34 "iona mind".af. 0
35 Minddistrict.af. 8
36 "mind district".af. 0
37 ("Get.ON" adj2 ("Mood Enhancer" or panic or depression)).af. 10
38 "Koa Health".af. 10
39 (Perspectives adj3 Koa).tw. 2
40 Resony.af. 0
41 "RCube health".af. 0
42 (SilverCloud or "silver cloud").af. 70
43 (space adj2 (anxiety or GAD or "health anxiety" or OCD or panic or phobia)).tw. 51
44 (space adj2 depression).tw. 30
45 Wysa.af. 3
46 Spring.af. and ("cognitive behavio* therap*" or cbt or dcbt or dCBT or dCBT or "digital therapeutic*" or "digital cbt" or "online cbt" or "comput* cbt" or "internet cbt").tw. 213
47 Deprexis.af. 60
48 ("Ethypharm digital" or "gaia group").af. 29
49 25 or 26 or 34 or 35 or 36 or 37 or 38 or 39 or 42 or 45 154
50 24 and 49 121
51 27 or 28 or 29 or 30 or 31 or 32 or 33 or 40 or 41 or 43 or 46 491
52 20 and 51 164
53 44 or 47 or 48 111
54 23 and 53 95
55 50 or 52 or 54 371
56 limit 55 to english language 362

APA PsycInfo <1806 to November Week 2 2022>

1 Anxiety/ 72807
2 anxiety disorders/ 20407
3 (anxiet* or anxious).tw. 240939
4 "generali?ed anxiety disorder*".tw. 9047
5 GAD.tw. 5555
6 "social anxiety disorder*".tw. 3921
7 phobia*.tw. 14047
8 "panic disorder*".tw. 11626
9 "post?traumatic stress disorder*".tw. 33157
10 PTSD.tw. 39717
11 "body dysmorphic disorder*".tw. 1543
12 "obsessive compulsive disorder*".tw. 18225
13 exp phobias/ 14015
14 Panic Disorder/ 7921
15 posttraumatic stress disorder/ 38061
16 body dysmorphic disorder/ 1313
17 obsessive compulsive disorder/ 15535
18 generalized anxiety disorder/ 3451
19 health anxiety/ 633
20 social anxiety/ 5730
21 or/1-20 309597
22 depression/ 26720
23 (depression or depressive or depressed).tw. 343507
24 or/22-23 344120
25 21 or 24 539329
26 "beating the blues".af. 76
27 "365 health solutions".af. 1
28 cerina.af. 33
29 (NoSuffering or "no suffering").af. 18
30 iCT-PTSD.af. 0
31 (internet adj2 "cognitive therapy for post traumatic stress disorder").tw. 0
32 iCT-SAD.af. 1
33 (internet adj2 "cognitive therapy for social anxiety disorder").tw. 3
34 OxCADAT.af. 7
35 "iona mind".af. 0
36 Minddistrict.af. 4
37 "mind district".af. 0
38 ("Get.ON" adj2 ("Mood Enhancer" or panic or depression)).af. 20
39 "Koa Health".af. 2
40 (Perspectives adj3 Koa).tw. 1
41 Resony.af. 1
42 "RCube health".af. 0
43 (SilverCloud or "silver cloud").af. 23
44 (space adj2 (anxiety or GAD or "health anxiety" or OCD or panic or phobia)).tw. 54
45 (space adj2 depression).tw. 18
46 Wysa.af. 23
47 Spring.af. and ("cognitive behavio* therap*" or cbt or dcbt or dCBT or dCBT or "digital therapeutic*" or "digital cbt" or "online cbt" or "comput* cbt" or "internet cbt").tw. 335
48 Deprexis.af. 254
49 ("Ethypharm digital" or "gaia group").af. 8
50 26 or 27 or 35 or 36 or 37 or 38 or 39 or 40 or 43 or 46 150
51 25 and 50 98

52 28 or 29 or 30 or 31 or 32 or 33 or 34 or 41 or 42 or 44 or 47 451
53 21 and 52 143
54 45 or 48 or 49 274
55 24 and 54 206
56 51 or 53 or 55 434
57 limit 56 to english language 398

Cochrane Library

#1 MeSH descriptor: [Anxiety] explode all trees 9306
#2 MeSH descriptor: [Anxiety Disorders] explode all trees 7991
#3 (anxiet* or anxious) 68087
#4 "generalised anxiety disorder*" OR "generalized anxiety disorder*" 3553
#5 GAD 2999
#6 "social anxiety disorder*" 1100
#7 phobia* 2962
#8 "panic disorder*" 2450
#9 "posttraumatic stress disorder*" OR "post traumatic stress disorder*". 5971
#10 PTSD 5518
#11 "body dysmorphic disorder*" 161
#12 "obsessive compulsive disorder*" 2939
#13 MeSH descriptor: [Phobic Disorders] explode all trees 1477
#14 MeSH descriptor: [Panic Disorder] explode all trees 989
#15 MeSH descriptor: [Stress Disorders, Post-Traumatic] explode all trees 3190
#16 MeSH descriptor: [Body Dysmorphic Disorders] explode all trees 81
#17 MeSH descriptor: [Obsessive-Compulsive Disorder] explode all trees 1159
#18 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 77725
#19 MeSH descriptor: [Depression] explode all trees 14311
#20 (depression or depressive or depressed) 102081
#21 #19 or #20 102081
#22 #18 or #21 141056
#23 "beating the blues" 47
#24 "365 health solutions" 0
#25 cerina 5
#26 (NoSuffering or "no suffering") 141
#27 iCT-PTSD 0
#28 (internet NEAR/2 "cognitive therapy for post traumatic stress disorder") 0
#29 iCT-SAD 0
#30 (internet NEAR/2 "cognitive therapy for social anxiety disorder") 5
#31 OxCADAT 1
#32 "iona mind" 0
#33 Minddistrict 4
#34 "mind district" 0
#35 ("Get.ON" NEAR/2 ("Mood Enhancer" or panic or depression)) 29
#36 "Koa Health" 2
#37 (Perspectives NEAR/3 Koa) 0
#38 Resony 0
#39 "RCube health" 0
#40 (SilverCloud or "silver cloud") 12

#41 Wysa 3
#42 Spring AND ("cognitive behavio* therap*" or cbt or dcbt or dCBT or dCBT or "digital therapeutic*" or "digital cbt" or "online cbt" or "comput* cbt" or "internet cbt") 33
#43 deprexis 58
#44 ("Ethypharm digital" or "gaia group") 4
#45 (space NEAR/2 (depression or anxiety or GAD or "health anxiety" or OCD or panic or phobia)) 18
#46 #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 322
#47 #22 and #46 241
[152 in CENTRAL 89 in CDSR]

CRD

1	MeSH DESCRIPTOR anxiety EXPLODE ALL TREES	314
2	MeSH DESCRIPTOR Anxiety Disorders EXPLODE ALL TREES	380
3	((anxiet* or anxious))	1762
4	("generalised anxiety disorder*") OR ("generalized anxiety disorder*")	95
5	(GAD)	32
6	("social anxiety disorder*")	31
7	(phobia*)	95
8	("panic disorder*")	121
9	("posttraumatic stress disorder*") OR ("post traumatic stress disorder*")	182
10	(PTSD)	106
11	("body dysmorphic disorder*")	6
12	("obsessive compulsive disorder*")	119
13	MeSH DESCRIPTOR Phobic Disorders EXPLODE ALL TREES	47
14	MeSH DESCRIPTOR Panic Disorder EXPLODE ALL TREES	55
15	MeSH DESCRIPTOR Stress Disorders, Post-Traumatic EXPLODE ALL TREES	139
16	MeSH DESCRIPTOR Body Dysmorphic Disorders EXPLODE 1	0
17	MeSH DESCRIPTOR Obsessive-Compulsive Disorder EXPLODE 1	57
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	2001
19	MeSH DESCRIPTOR Depression EXPLODE 1	639
20	((depression or depressive or depressed))	3049
21	#19 OR #20	3049
22	#18 OR #21	3937
23	("beating the blues")	7
24	("365 health solutions")	0
25	(cerina)	0
26	(NoSuffering) OR ("no suffering")	0
27	(iCT-PTSD)	0

28	((internet NEAR2 "cognitive therapy for post traumatic stress disorder"))	0
29	(iCT-SAD)	0
30	((internet NEAR2 "cognitive therapy for social anxiety disorder"))	0
31	(OxCADAT)	0
32	("iona mind")	0
33	(Minddistrict)	0
34	("mind district")	0
35	(("Get.ON" adj2 ("Mood Enhancer" or panic or depression)))	0
36	("Koa Health")	0
37	((Perspectives NEAR3 Koa))	0
38	(resony)	0
39	("RCube health")	0
40	(silver cloud) OR ("silver cloud")	0
41	((space NEAR2 (anxiety or GAD or "health anxiety" or OCD or panic or phobia)))	0
42	((space NEAR2 depression))	0
43	(Wysa)	0
44	(spring) AND (("cognitive behavio* therap*" or cbt or dcbt or dCBT or dCBT or "digital therapeutic*" or "digital cbt" or "online cbt" or "comput* cbt" or "internet cbt"))	1
45	(deprexis)	0
46	("Ethypharm digital") OR ("gaia group"):TI	0
47	MeSH DESCRIPTOR Cognitive Behavioral Therapy EXPLODE ALL TREES	28
48	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47	36
49	#22 AND #48	20

INAHTA

Line	Query	Hits
48	#47 AND #18	13
47	#46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23	106
46	"Ethypharm digital" or "gaia group"	0
45	Deprexis	0
44	(Spring) AND ("cognitive behavio* therap*" or cbt or dcbt or dCBT or dCBT or "digital therapeutic*" or "digital cbt" or "online cbt" or "comput* cbt" or "internet cbt")	0
43	Wysa	0
42	(space) AND (depression)	0

41	(space) AND (anxiety or GAD or "health anxiety" or OCD or panic or phobia)	2
40	SilverCloud or "silver cloud"	0
39	"RCube health"	0
38	Resony	0
37	(Koa) AND (Perspectives)	1
36	"Koa Health"	0
35	(Get.ON) AND ("Mood Enhancer" or panic or depression)	8
34	"mind district"	0
33	Minddistrict	0
32	"iona mind"	0
31	OxCADAT	0
30	iCT-SAD	0
29	(internet) AND (cognitive therapy for social anxiety disorder)	0
28	(internet) AND (cognitive therapy for post traumatic stress disorder)	1
27	iCT-PTSD	0
26	NoSuffering or "no suffering"	91
25	Cerina	0
24	"365 health solutions"	0
23	"beating the blues"	3
22	#21 OR #18	576
21	#20 OR #19	418
20	depression or depressive or depressed	402
19	"Depression"[mh]	136
18	#17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	286
17	"Phobia, Social"[mh]	1
16	"Obsessive-Compulsive Disorder"[mh]	8
15	"Panic Disorder"[mh]	5
14	"Stress Disorders, Post-Traumatic"[mh]	36
13	"Body Dysmorphic Disorders"[mh]	0
12	"obsessive compulsive disorder*"	12
11	"body dysmorphic disorder*"	1
10	PTSD	27
9	"post?traumatic stress disorder*"	27
8	"panic disorder*"	4
7	phobia*	11
6	"social anxiety disorder*"	2
5	GAD	4
4	"generali?ed anxiety disorder*"	0
3	anxiet* or anxious	223
2	"Anxiety Disorders"[mh]	42
1	"Anxiety"[mh]	72

PubMed

#28	Search: #4 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	313
#27	Search: (spring AND ("cognitive behavio* therap*" or cbt or dcbt or dCBT or dCBT or "digital therapeutic*" or "digital cbt" or "online cbt" or "comput* cbt" or "internet cbt")) AND anxiety	35
#26	Search: "gaia group"	15
#25	Search: "ethypharm digital"	2
#24	Search: deprexis	52
#23	Search: Wysa	13
#22	Search: "silver cloud"	3
#21	Search: silvercloud	67
#20	Search: "RCube health"	0
#19	Search: "RCube health" - Schema: all	0
#18	Search: resony	0
#17	Search: resony - Schema: all	0
#16	Search: (perspectives[Title/Abstract] AND koa[Title/Abstract])	10
#15	Search: "koa health"	15
#14	Search: minddistrict	53
#13	Search: "iona mind"	2
#12	Search: OxCADAT	3
#11	Search: iCT-SAD	3
#10	Search: iCT-PTSD	2
#9	Search: nosuffering	0
#8	Search: nosuffering - Schema: all	0
#7	Search: cerina AND anxiety	2
#6	Search: "365 health solutions" and (anxiety or depression)	9
#4	Search: "beating the blues" and (anxiety or depression)	36

Epistemonikos

(title:((title:("beating the blues" OR "365 health solutions" OR cerina OR nosuffering OR "no suffering" OR iCT-PTSD OR iCT-SAD OR OxCADAT OR deprexis OR "Ethypharm digital" OR "gaia group" OR minddistrict OR "mind district" OR "space from depression" OR "space from anxiety" OR silvercloud OR "silver cloud") OR abstract:("beating the blues" OR "365 health solutions" OR cerina OR nosuffering OR "no suffering" OR iCT-PTSD OR iCT-SAD OR OxCADAT OR deprexis OR "Ethypharm digital" OR "gaia group" OR minddistrict OR "mind district" OR "space from depression" OR "space from anxiety" OR silvercloud OR "silver cloud"))) OR abstract:((title:("beating the blues" OR "365 health solutions" OR cerina OR nosuffering OR "no suffering" OR iCT-PTSD OR iCT-SAD OR OxCADAT OR deprexis OR "Ethypharm digital" OR "gaia group" OR minddistrict OR "mind district" OR "space from depression" OR "space from anxiety" OR silvercloud OR "silver cloud") OR abstract:("beating the blues" OR "365 health solutions" OR cerina OR nosuffering OR "no suffering" OR iCT-PTSD OR iCT-SAD OR OxCADAT OR

deprexis OR "Ethypharm digital" OR "gaia group" OR minddistrict OR "mind district" OR "space from depression" OR "space from anxiety" OR silvercloud OR "silver cloud")))) OR (title:(Wysa OR "iona mind" OR "Get.ON" OR "koa health" OR "koa perspectives" OR resony OR "RCube health") OR abstract:(Wysa OR "iona mind" OR "Get.ON" OR "koa health" OR "koa perspectives" OR resony OR "RCube health")) OR (title:(space AND (anxiety OR GAD OR "health anxiety" OR OCD OR panic OR phobia OR depression)) OR abstract:(space AND (anxiety OR GAD OR "health anxiety" OR OCD OR panic OR phobia OR depression))) OR (title:((internet OR spring) AND ("cognitive behaviour therapy" OR cbt OR dcbt OR dCBT OR dCBT OR "digital therapeutic*" OR "digital cbt" OR "online cbt" OR "comput* cbt" OR wellmind OR "online mindfulness" OR "mindfulness course" OR "mindfulness based cognitive therapy" OR MBCT)) OR abstract:((internet OR spring) AND ("cognitive behaviour therapy" OR cbt OR dcbt OR dCBT OR dCBT OR "digital therapeutic*" OR "digital cbt" OR "online cbt" OR "comput* cbt" OR wellmind OR "online mindfulness" OR "mindfulness course" OR "mindfulness based cognitive therapy" OR MBCT))) AND (title:(anxiety OR phobia OR panic OR "post tramatic stress disorder" OR PTSD OR "body dysmorphic disorder" OR "obsessive compulsive disorder") OR abstract:(anxiety OR phobia OR panic OR "post tramatic stress disorder" OR PTSD OR "body dysmorphic disorder" OR "obsessive compulsive disorder")) AND (title:(depression OR depressed OR depressive) OR abstract:(depression OR depressed OR depressive))

16.2 *Appendix B: Searches for cost-effectiveness evidence*

Table 31: Resources searched for cost-effectiveness

Database/Resource	Host	Date Searched	Results
MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	Ovid	29.11.22	40
Embase	Ovid	29.11.22	18
APA PsycINFO	Ovid	29.11.22	10
CEA Registry	www.cearegistry.org	29.11.22	6
ScHARRHUD	www.scharrhud.org/	29.11.22	0
Total records retrieved			74
Total records after deduplication			53

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$1)).ti,ab. 27053
3 1 and 2 3678
4 (dCBT or dCBT).ti,ab. 268
5 ((gaming or gamified or game format or video game$) and (CBT or dCBT 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

Embase <1974 to 2022 November 28>

1 (computer or computerized or computerised or digital or online or internet$ or app or apps).ti,ab. 931565
2 (cognitive adj2 behavio$ adj3 (therap$ or intervention$ or treatment$ or psychotherap$ or programme$1 or program$1 or method$1 or approach$1)).ti,ab. 37848
3 1 and 2 4602
4 (dCBT or dCBT).ti,ab. 434
5 ((gaming or gamified or game format or video game$) and (CBT or dCBT or dCBT or cognitive behavi$)).ti,ab. 176
6 3 or 4 or 5 4853

7 anxiety/ or anxiety disorder/ 339946
8 depression/ 446921
9 (anxiet$ or anxious or low mood or depress$).ti,ab. 885019
10 7 or 8 or 9 1059530
11 6 and 10 2751
12 health-economics/ 34895
13 exp economic-evaluation/ 341870
14 exp health-care-cost/ 327275
15 exp pharmacoeconomics/ 223818
16 (expenditure$ not energy).ti,ab. 47921
17 (value adj2 money).ti,ab. 2838
18 budget$.ti,ab. 44957
19 or/12-18 775606
20 letter.pt. 1248380
21 editorial.pt. 744742
22 note.pt. 916306
23 20 or 21 or 22 2909428
24 19 not 23 656155
25 (metabolic adj cost).ti,ab. 1775
26 ((energy or oxygen) adj cost).ti,ab. 4899
27 ((energy or oxygen) adj expenditure).ti,ab. 35822
28 25 or 26 or 27 41313
29 24 not 28 655598
30 exp animal/ 29411432
31 exp animal-experiment/ 2928971
32 nonhuman/ 7111933
33 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. 6273170
34 30 or 31 or 32 or 33 31572692
35 exp human/ 24374590
36 exp human-experiment/ 604085
37 35 or 36 24376819
38 34 not (34 and 37) 7196992
39 29 not 38 636636
40 11 and 39 264
41 limit 40 to (english language and yr="2022 -Current") 18

APA PsycInfo <1806 to November Week 3 2022>

1 (computer or computerized or computerised or digital or online or internet$ or app or apps).ti,ab. 252712
2 (cognitive adj2 behavio$ adj3 (therap$ or intervention$ or treatment$ or psychotherap$ or programme$1 or program$1 or method$1 or approach$1)).ti,ab. 37356
3 1 and 2 2924
4 (dCBT or dCBT).ti,ab. 206
5 ((gaming or gamified or game format or video game$) and (CBT or dCBT or dCBT or cognitive behavi$)).ti,ab. 129
6 3 or 4 or 5 3028
7 exp Anxiety/ or exp Anxiety Disorders/ 134889
8 exp "Depression (Emotion)"/ or exp Major Depression/ 177416
9 (anxiet$ or anxious or low mood or depress$).ti,ab. 473455

10 7 or 8 or 9 506849
11 6 and 10 1836
12 "costs and cost analysis"/ 18662
13 "Cost Containment"/ 699
14 (economic adj2 evaluation$).ti,ab. 2085
15 (economic adj2 analy$).ti,ab. 1702
16 (economic adj2 (study or studies)).ti,ab. 926
17 (cost adj2 evaluation$).ti,ab. 394
18 (cost adj2 analy$).ti,ab. 4251
19 (cost adj2 (study or studies)).ti,ab. 996
20 (cost adj2 (effectiv$ or benefit$ or utili$ or minimi$ or consequence$ or comparison$ or identificat$)).ti,ab. 22429
21 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. 243492
22 or/12-21 245661
23 (task adj2 cost$).ti,ab,id. 769
24 (switch$ adj2 cost$).ti,ab,id. 1533
25 (metabolic adj cost).ti,ab,id. 112
26 ((energy or oxygen) adj cost).ti,ab,id. 309
27 ((energy or oxygen) adj expenditure).ti,ab,id. 2998
28 or/23-27 5405
29 (animal or animals or rat or rats or mouse or mice or hamster or hamsters or dog or dogs or cat or cats or bovine or sheep or ovine or pig or pigs).ab,ti,id,de. 378653
30 editorial.dt. 44328
31 letter.dt. 25566
32 dissertation abstract.pt. 541765
33 30 or 31 or 32 611659
34 22 not (28 or 29 or 33) 201241
35 11 and 34 263
36 limit 35 to (english language and yr="2022 -Current") 10

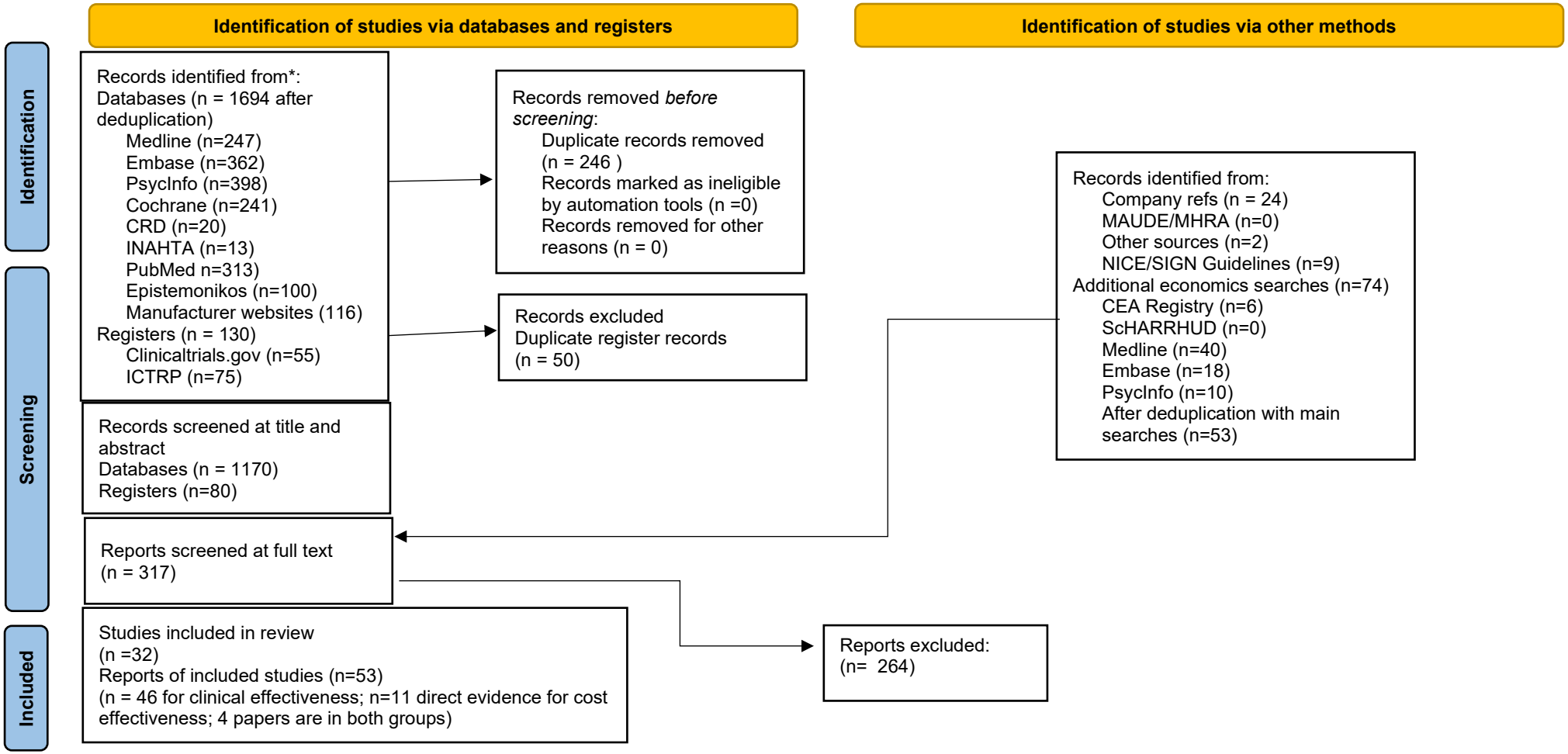
ScHARRHUD

((“cognitive behaviour therapy” or “cognitive behavior therapy” or CBT) and (internet or digital))

CEA Registry

((“cognitive behaviour therapy” or “cognitive behavior therapy” or CBT) and (internet or digital))

16.3 *Appendix C: PRISMA flow diagram*



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

16.4 *Appendix D: List of excluded studies and studies awaiting assessment*

Table 27: List of excluded full-text studies with reasons

Excluded study	Reason for exclusion
Health, Silvercloud et al, 2017	No results
ISRCTN 91947481, 2007	Full text inaccessible
ISRCTN 98677176, 2011	Full text inaccessible
ISRCTN 91967124, 2017	Duplicate
Lewis et al, 2018	Intervention
Lim et al, 2022	Intervention
Luebeck, 2010	No results
Luebeck, 2012	Duplicate
Malik et al, 2022	Study design*
Mathiasen et al, 2022	Intervention
Mayo-Wilson et al, 2014	Intervention
Mayo-Wilson et al, 2013	Intervention
Mediavilla et al, 2022	No results
Medicine et al, 2019	No results
Meyer et al, 2019	Lacking detail
Meyer et al, 2019	Lacking detail
Mitchell, 2009	Population
Mitchell et al, 2007	Population

Excluded study	Reason for exclusion
Moshe et al, 2021	Intervention
Mourad et al, 2021	Population
NICE, 2006	Full text inaccessible
NCT 01401296, 2011	No results
NCT 01482806, 2011	Duplicate
NCT 01990053, 2013	No results
NCT 02178631, 2014	Duplicate
NCT 02150577, 2014	Population
NCT 03062215, 2017	Intervention
NCT 03271645, 2017	No results
NCT 03068676, 2017	No results
NCT 04428450, 2020	Duplicate
NCT 05533190, 2022	No results
NCT 05234970, 2022	No results
NCT 01636752, 2012	Duplicate
NCT 01990053, 2013	No results
NCT 02178631, 2014	Duplicate
NCT 03062202, 2017	No results
NCT 03068676, 2017	No results
NCT 04428450, 2020	Duplicate
NCT 05533190, 2022	No results

Excluded study	Reason for exclusion
Newby et al, 2015	Intervention
Norton et al, 2014	Intervention
NTR 2621, 2010	No results
NTR 2503, 2010	Full text inaccessible
NTR 4408, 2014	Full text inaccessible
Olthuis et al, 2016	Intervention
Pittsburgh et al, 2012	Duplicate
Proudfoot et al, 2003	Duplicate
Proudfoot et al, 2003	Study design
Richards et al, 2017	No results
Richards et al, 2012	Intervention
Richards et al, 2018	Study design
Richards et al, 2016	Full text inaccessible
Richards et al, 2018	Study design
Richards et al, 2016	Study design
Richards et al, 2015	Population
Richter et al, 2022	Population
Rodriguez-Pulido et al, 2020	Intervention
Rollman et al, 2016	Lacking detail
Saddichha et al, 2014	Intervention
Simon et al, 2021	Intervention

Excluded study	Reason for exclusion
So et al, 2013	Intervention
Spek et al, 2007	Intervention
Strauss et al, 2014	Intervention
Svardman et al, 2022	Intervention
Sztein et al, 2018	Intervention
Treanor et al, 2021	Intervention
Vallury et al, 2015	Intervention
Van Ballegooijen et al, 2014	Intervention
Van den Berg et al, 2004	Study design
Waller et al, 2009	Intervention
Wells et al, 2018	Intervention
Wright et al, 2019	Intervention
Xiang et al, 2020	Intervention
Young et al, 2022	No results

This table includes records from the database that was full text screened by PenTAG. We do not have access to reasons for exclusion for records screened by Cedar. * = This study was re-added on pragmatic grounds due to limited evidence available for this technology and as it had been flagged as a key study by the company.

Table 28: List of studies awaiting assessment

The EAG was able to assess all studies retrieved and therefore there are no studies awaiting assessment.

16.5 *Appendix E: Risk of bias of included studies*

No formal assessment of risk of bias could be undertaken within the work scope of this EVA. The EAG has commented in the report on key matters relating to internal validity and external validity (generalisability to NHS practice in the IAPT setting) in the context of the eligible evidence base identified for this appraisal.

16.6 *Appendix F: Identification of key studies for use within economic analysis*

Table 29: Identification of Key Studies

Study ID	**Title**	**Key study**	**Justification**
Space from depression			
Palacios (2022)[48]	Comparison of Outcomes Across Low-Intensity Psychological Interventions for Depression and Anxiety within a Stepped-Care Setting: A Naturalistic Cohort Study Using Propensity Score Modelling	No	Cohort study using PSW for comparison rather than RCT, secondary analysis of the effect sizes based upon other included RCTs. Comparison to guided self-help bibliotherapy and psychoeducational group therapy. Provides data only for combined population with depression and anxiety.
Richards 2020[50]	A pragmatic randomised waitlist-controlled effectiveness and cost-effectiveness trial of digital interventions for depression and anxiety.	Yes	RCT, UK based, effectiveness and CE reported against a waitlist control.
Palacios 2022[49]	Durability of treatment effects following internet-delivered cognitive behavioral therapy for depression and anxiety delivered within a routine care setting	No	RCT in the IAPT population, however, reporting on the relapse and remission rates post-treatment, rather than efficacy of intervention.
Enrique 2021[110]	Are changes in beliefs about rumination and in emotion regulation skills mediators of the effects of internet-delivered cognitive-behavioral therapy for depression and anxiety? Results from a randomised controlled trial	No	Secondary Analysis of Richards et al. Study on the beliefs of users, rather than effect of the intervention on depression scores.
Eilert 2022[111]	Following up internet-delivered cognitive behaviour therapy (CBT): A longitudinal qualitative investigation of clients' usage of CBT skills	No	Qualitative follow-up study, no effect sizes or discontinuation rates reported.

Study ID	Title	Key study	Justification
Duffy 2020[27]	Internet-delivered cognitive behavior therapy as a prequel to face-to-face therapy for depression and anxiety: a naturalistic observation.	No	Naturalistic Observation Study, no effect sizes or discontinuation rates reported.
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Richards 2015[30]	A randomised controlled trial of an internet-delivered treatment: its potential as a low-intensity community intervention for adults with symptoms of depression	Yes	RCT based in Ireland with effect sizes and discontinuation rates reported, waitlist comparator.
Richards 2016[113]	Effectiveness of an internet-delivered intervention for generalized anxiety disorder in routine care: a randomised controlled trial in a student population	No	Student only population
Salamanca-Sanabria, 2020[114]	A culturally adapted cognitive behavioral internet-delivered intervention for depressive symptoms: randomised controlled trial	No	Student only population
Palacios, 2018[115]	Supported internet-delivered cognitive behavioral therapy programs for depression, anxiety, and stress in university students: open, non-randomised trial of acceptability, effectiveness, and satisfaction	No	Student only population
Deprexis			
Berger 2011[13]	Internet-Based Treatment of Depression: A Randomised Controlled Trial Comparing Guided with Unguided Self-Help	Yes	RCT reporting effect size and discontinuation rates. A comparison of guided help selected for model use due to the NICE scope.
Meyer 2015[45]	Effects of an Internet intervention (Deprexis) on severe depression symptoms: Randomised controlled trial	Yes	For severe depression only, RCT reporting effect size and discontinuation.
Zwerenz 2017[116]	Online self-help as an add-on to inpatient psychotherapy: efficacy of a new blended treatment approach.	No	Focused only on inpatients and the Deprexis as an add on to existing inpatient care.
Berger 2018[14]	Evaluating an e-mental health program ("deprexis") as adjunctive treatment tool in psychotherapy for depression: Results of a pragmatic randomised controlled trial.	No	Patients with unipolar affective disorder only

Study ID	Title	Key study	Justification
Meyer 2009[44]	Effectiveness of a novel integrative online treatment for depression (Deprexis): randomised controlled trial.	Yes	An RCT reporting efficacy and discontinuation. Based in a German population.
Moritz 2012[46]	A randomised controlled trial of internet-based therapy in depression.	Yes	RCT versus a waitlist. Reported mild/moderate and severe depression in subgroups.
Klein 2016[17]	Effects of a psychological internet intervention in the treatment of mild to moderate depressive symptoms: results of the EVIDENT study, a randomised controlled trial.	Yes	Mild/moderate depression only, German population, but reporting of effect size and discontinuation against a waitlist.
Beevers 2017[11]	Effectiveness of an internet intervention (Deprexis) for depression in a United States adult sample: A parallel-group pragmatic randomised controlled trial.	No	US only population, and the RCT was group based rather than on an individual basis.
Klein 2020[39]	Feasibility, effectiveness and safety of the self-management intervention deprexis in routine medical care: results of an uncontrolled observational study. Internet Interventions	No	Observational study with no comparator.
Twomey 2020[55]	Effectiveness of a tailored, integrative Internet intervention (deprexis) for depression: Updated meta-analysis.	Yes	Meta-analysis reporting Hedges-g effect size, that captures most of the included above studies. Waitlist comparator in an international population.
Minddistrict			
Cook, 2019[67]	Randomised Controlled Trial of Web-Based Rumination-Focused Cognitive Behavioral Therapy for High-Ruminating University Students	No	Students
Topper, 2017[68]	Prevention of anxiety disorders and depression by targeting excessive worry and rumination in adolescents and young adults: A randomised controlled trial	No	Secondary School and university Students
Beating the Blues			
Proudfoot 2004[41]	Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: Randomised controlled trial	Yes	UK based RCT reporting clinical outcomes.
Littlewood 2015[32]	A randomised controlled trial of computerised cognitive behaviour therapy for the treatment of depression in primary care: the Randomised Evaluation of the	Yes	NHS/IAPT setting, RCT, with informative data and reporting of mild/moderate and

Study ID	Title	Key study	Justification
	Effectiveness and Acceptability of Computerised Therapy (REEACT) trial		severe depression in subgroups.
WYSA			
Inkster 2018[35]	An empathy-driven, conversational artificial intelligence agent (WYSA) for digital mental well-being: real-world data evaluation mixed-methods study.	No	Major depression, and a comparison on usage patterns
Leo 2022a[117]	A Digital Mental Health Intervention in an Orthopedic Setting for Patients With Symptoms of Depression and/or Anxiety: Feasibility Prospective Cohort Study	No	Orthopedic patients
Leo 2022b[118]	Digital Mental Health Intervention Plus Usual Care Compared With Usual Care Only and Usual Care Plus In-Person Psychological Counseling for Orthopedic Patients With Symptoms of Depression or Anxiety: Cohort Study	No	Orthopedic patients
Beatty 2022[10]	Evaluating the Therapeutic Alliance With a Free-Text CBT Conversational Agent (WYSA): A Mixed-Methods Study.	No	Evaluating the usage and does not give an effect size. No comparator group.
Malik 2022[43]	Evaluating User Feedback for an Artificial Intelligence–Enabled, Cognitive Behavioral Therapy–Based Mental Health App (WYSA): Qualitative Thematic Analysis	No	Qualitative Analysis
Meheli 2022[104]	Understanding People With Chronic Pain Who Use an Artificial Intelligence Cognitive Behavioral Therapy–Based Mental Health App (WYSA): Mixed Methods Retrospective Observational Study	No	Patients have chronic pain, not depression
Sinha 2022[119]	Adherence and Engagement With a Cognitive Behavioral Therapy–Based Conversational Agent (WYSA for Chronic Pain) Among Adults With Chronic Pain: Survival Analysis	No	Patients have chronic pain, not depression
[redacted]	[redacted]	[redacted]	[redacted]
Gupta 2022[120]	Delivery of a Mental Health Intervention for Chronic Pain Through an Artificial Intelligence–Enabled App (WYSA): Protocol for a Prospective Pilot Study	No	Protocol for pilot study

Study ID	Title	Key study	Justification
[redacted]	[redacted]	[redacted]	[redacted]
Kuchlous 2020[121]	Short Text Intent Classification for Conversational Agents. In 2020 IEEE 17th India Council International Conference (INDICON)	No	Conference abstract.
Inkster 2020[122]	Digital health management during and beyond the COVID-19 pandemic: Opportunities, barriers, and recommendations.	No	Focused only on health during covid-19.

16.7 *Appendix F: Additional cost-effectiveness results*

Table 30: Base case results (Probabilistic, Individual studies, Less Severe Depression, 1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY	Mean NMB Rank
CBT group	[redacted]	[redacted]	[redacted]	[redacted]
BA group	[redacted]	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]	[redacted]
DPX (Berger 2011[13])	[redacted]	[redacted]	[redacted]	[redacted]
Sertraline	[redacted]	[redacted]	[redacted]	[redacted]
SfD (Richards 2020[50])	[redacted]	[redacted]	[redacted]	[redacted]
SfD (Richards 2015[30])	[redacted]	[redacted]	[redacted]	[redacted]
MBCT group	[redacted]	[redacted]	[redacted]	[redacted]
Generic computerized CBT	[redacted]	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]	[redacted]
BtB (Proudfoot 2004[41])	[redacted]	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012[46])	[redacted]	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020[55])	[redacted]	[redacted]	[redacted]	[redacted]
DPX (Meyer 2009[44])	[redacted]	[redacted]	[redacted]	[redacted]
DPX (Klein 2016[17])	[redacted]	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]	[redacted]
BtB (Littlewood 2015[32])*	[redacted]	[redacted]	[redacted]	[redacted]

Table 31: Base case (Probabilistic, Individual studies, More Severe Depression 1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY	Mean NMB Rank
Problem solving	[redacted]	[redacted]	[redacted]	[redacted]
CBT individual + escitalopram	[redacted]	[redacted]	[redacted]	[redacted]
Duloxetine	[redacted]	[redacted]	[redacted]	[redacted]
Mirtazapine	[redacted]	[redacted]	[redacted]	[redacted]
Escitalopram	[redacted]	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]	[redacted]
Lofepramine	[redacted]	[redacted]	[redacted]	[redacted]
Trazodone	[redacted]	[redacted]	[redacted]	[redacted]
Generic computerized CBT with support	[redacted]	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020[55])	[redacted]	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]	[redacted]
DPX (Meyer 2015[45])	[redacted]	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012[46])	[redacted]	[redacted]	[redacted]	[redacted]
Generic computerized CBT without support	[redacted]	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]	[redacted]

Table 32: Deterministic Cost-effectiveness Results. Less Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY
CBT group	[redacted]	[redacted]	[redacted]
BA group	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]
DPX (Berger 2011)	[redacted]	[redacted]	[redacted]
MBCT group	[redacted]	[redacted]	[redacted]
SfD (Richards 2020)	[redacted]	[redacted]	[redacted]
dCBT	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]

CBT individual	[redacted]	[redacted]	[redacted]
SfD (Richards 2015)	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012)	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]
Sertraline	[redacted]	[redacted]	[redacted]
BtB (Proudfoot 2004)	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020)	[redacted]	[redacted]	[redacted]
DPX (Meyer 2009)	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]
DPX (Klein 2016)	[redacted]	[redacted]	[redacted]
BtB (Littlewood 2015)	[redacted]	[redacted]	[redacted]

Table 33: Deterministic Cost-effectiveness Results. More Severe Depression (1,000 patients)

	Cost	**QALYs**	**Mean NMB £20,000 per QALY**
Problem solving	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]
dCBT with support	[redacted]	[redacted]	[redacted]
DPX (Twomey 2020)	[redacted]	[redacted]	[redacted]
DPX (Meyer 2015)	[redacted]	[redacted]	[redacted]
Duloxetine	[redacted]	[redacted]	[redacted]
CBT individual + escitalopram	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]
Mirtazapine	[redacted]	[redacted]	[redacted]
Escitalopram	[redacted]	[redacted]	[redacted]
Lofepramine	[redacted]	[redacted]	[redacted]
Trazodone	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]
DPX (Moritz 2012)	[redacted]	[redacted]	[redacted]
dCBT	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]

16.8 *Appendix G. Additional study results*

Table 34: Study results

Papers	Study	Intervention	Results
Cavanagh et al, 2006[22]/2009[23]	Not stated	**Beating the Blues**	*Cavanagh et al, 2006[22]:* Summary: Improvements in CORE-OM (ITT LOCF analysis mean difference = 0.29, 95%CI = 0.22-0.36, p<0.001) and WSA (ITT LOCF analysis mean difference = 2.34, 95%CI = 1.47-3.21, p<0.001) were seen post-treatment, compared to pre-treatment. As would be expected, effect sizes were larger in analysis of completers only. *Cavanagh et al, 2009[23]:* Attitudes to dCBT Questionnaire, Opinions about Psychological Problems Questionnaire, Patient Feedback Scale for dCBT – feedback and attitudes were generally positive. It is notable that two of the questionaries were specifically designed for the intervention.
Cavanagh et al, 2011[24]	Not stated	**Beating the Blues**	**Summary**: 84% (295) of suitable participants started Beating the Blues. 265 (89.8%) of these completed 2 sessions. 156 (52.9% completed all 8 sessions). Amongst those completing at least 2 sessions mean PHQ-9, GAD-7, CORE-OM and Work and Social Adjustment Scale scores improved post treatment compared to pretreatment (ITT, LOCF analysis, all p<0.001). The mean difference for the PHQ 9 was 9.4. 112 service users completed Patient Experience Questionnaires – 90% (101) of these were mostly or very satisfied with their experience.
Cientanni et al, 2019[25]	Not stated	**Beating the Blues**	**Summary:** 9736 patients were referred. 1157 (21.7%) completed the information required for this study. Of these 278 (24%) completed all 8 sessions. The mean CORE-OM score change was a 0.72 (SD=0.62) reduction from pre-to post treatment (p<0.001, Cohen's d 1.32).
Du et al, 2021[26]	Not stated	**Beating the Blues**	**Summary:** 6 themes emerged around engagement and acceptance: (1) information dissemination; (2) expectations and the impact of waiting for BTB; (3) impact of locations on experience of BTB; (4) preference for home access; (5) desire for better human support; and (6) desire for additional application support features.
Gilbody et al, 2015[31]; Littlewood et al, 2015[32]	REEACT	**Beating the Blues**	*Gilbody et al, 2015[31]* There was no improvement in PHQ-9 at four months compared to usual GP care (odds ratio of being depressed (PHQ>=10): 1.19 (95%CI 0.75 to 1.88); p= 0.46) nor compared to MoodGYM (OR: 0.91 (90%CI=0.62 to 1.34)). 50% remained depressed in the BtB group, compared to 44% in usual GP care and 49% in MoodGYM group. There was no evidence of a difference at 12 and 24 months either. Results were robust to sensitivity analysis, mixed models adjusted for baseline characteristics and analyses treating PHQ-9 and CORE-OM scores as a continuous outcome variables. 24% of participants had dropped out by 4 months.

Papers	Study	Intervention	Results
			Total adverse events were similar between groups. There were 19 serious adverse events in the BtB group, with 18 determined unrelated to the intervention and the other one unable to be determined due to limited information. 2 patients died. *Littlewood et al, 2015*[32] Quality of life measures were similar in the three groups. Participants generally expressed a preference to be randomised to computerised CPT than usual GP care. A qualitative description of acceptability is provided.
Jonassaint et al, 2017[36]	Online Treatment for Mood and Anxiety Disorders Trial	**Beating the Blues**	**User engagement** "African Americans were less likely than White people to start session 1 of the dCBT programme (75% *v.* 87%; *P*=0.01). Among those who started the programme, compared with White people, African Americans completed slightly fewer sessions at 6 months (mean 4.7 *v.* 5.5; *P*=0.03). After adjusting for age, gender, education, pharmacotherapy and baseline PHQ-9 depression scores, African Americans still trended towards being less likely than White people to complete all eight sessions" **Depression and/or anxiety symptoms** Of those participants who started the dCBT programme, African Americans trended towards a greater decrease in depressive symptoms compared with White people (estimated 8-session change: −6.6 *v.* −5.5; *P*=0.06) but similar decline in anxiety (estimated 8-session change: −5.3 *v.* −5.6; *P*=0.80) over the course of the eight dCBT sessions.
McCrone et al, 2004[40], Proudfoot et al, 2004[41]	Not stated	**Beating the Blues**	**BDI-II, Beck Anxiety Inventory, Work and Social Adjustment Scale, Attributional Style Questionnaire** 406 were invited to participate, 274 commenced the trial. 146 were allocated to Beating the Blues and 128 to treatment as usual. 132 and 116 completed pre-treatment assessment, respectively. 92 and 93 completed post treatment assessment respectively. Mean post-treatment BDI scores in intervention group was 11.6 (SD9.6) and in control was 16.2 (10.1) – t-test p value for between group difference p=0.0006. Between group differences were also tested for the other measures: BAI p=0.06, WASA p=0.002, ASQ CoNeg p<0.001, ASQCoPos p<0.008 – directions of effect all favouring the intervention, effect sizes not calculated.. Average satisfaction ('How satisfied are you with the treatment you have had for your anxiety/depression in this study?', 0 (not at all) to 8 (totally satisfied).)in the computerised therapy group was 1.68 (95% CI 0.82–2.54) points higher than in the treatment-as-usual group at 2 months after randomisation.

Papers	Study	Intervention	Results
McMurchie et al, 2013[42]	Not stated	**Beating the Blues**	**Geriatric Depression Scale, Geriatric Anxiety Scale, CORE-34** A total of 77 individuals met the inclusion/exclusion criteria, and 58 agreed to be referred to the study. From the total number of participants recruited to the study (58), the total number who opted for BTB and then started at least one session was 33, resulting in an uptake rate of 56.9%. 24 participants completed all 8 sessions. One month after the end of treatment, the intervention group (n=33) had greater reductions than the control group (n=20) for GDS (mean difference 8.2 vs 1.7, repeated measures ANOVA for time x group p<0.001), GAI (mean difference 5.0 vs 1.4, p<0.01) and CORE-34 (mean difference 17.5 vs 2.5, p<0.001) When clinically significant improvement was defined as a reduction of at least 2 SDs below the pretreatment mean, 14/33 of the treatment group and 2/20 had a clinically significant improvement in GDS at the 3 month follow-up (Chi-squared test for between group different p=0.007).
Ormrod et al, 2010[47]	Not stated	**Beating the Blues**	**Summary:** 23 participants recruited. 16 completed the programme and study. Mean BDI scores reduced from 33.9 (SD 8.8) to 26.1 (SD 11.3) from pre-post programme. In one-way repeated measures ANOVA there was a statistically significant effect of time on BDI, $F(1, 15) = 13.1$, $p < 0.01$.
Pittaway et al, 2010[51]	Not stated	**Beating the Blues**	**CORE-OM** Of the 100 participants who consented to take part in the study, 38 did not complete the programme and 12 were excluded from the analysis because they did not meet the referral criteria, leaving data for 50 service users (BtB = 16 completers; workbooks = 15 completers; internet = 19 completers). Drop-out rates were comparable for each of the three self-help CBT interventions (BtB = 12 non-completers; workbooks = 11 non-completers; internet = 15 non-completers). A paired t-test indicated that there was a highly significant reduction in CORE–OM scores for the completers at week eight compared to that at entry ($t (49) = 9.150$; $P \leq 0.001$). At entry M = 2.07 (SD = 0.68; 95%, confidence interval (CI) = 1.88–2.27), and at week eight M = 0.98 (SD= 0.64; 95%, CI = 0.78–1.15). An ANCOVA indicated that while controlling for initial scores, there was no significant difference in the CORE–OM scores at week eight between the three self-help CBT tools (BtB, workbooks and internet) ($F (2,46) = 0.655$; $P = 0.524$).

Papers	Study	Intervention	Results
			The overall mean difference in CORE score for each of the three self-help interventions were as follows: BtB = 1.13 (SD 0.69; 95%, CI 0.75–1.49); workbook = 1.02 (SD 0.78; 95%, CI 0.59–1.45); internet = 1.14 (SD 1.04; 95%, CI 0.63–1.63). Paired t-tests indicated that these differences were significant for each of the interventions. **participant feedback on usefulness** 28 of 88 participants completed questionnaires for feedback at 6 months. Of these 73% reported that they woud recommend it to others.
Rollman et al, 2018[123]	NCT 01482806	**Beating the Blues**	**Patient-Reported Outcomes Measurement Information System (depression and anxiety), quality of life** On the PROMIS depression scale, at 6 months patients receiving dCBT alone reported a −2.43 (95% CI, −4.16 to −0.69; *P* = .006) improvement compared to usual care. This value was −2.30 (95% CI, −4.21 to −0.4; *P* = .02) for the PROMIS anxiety scale. Significant differences were not seen in the SF-12 mental health composite scale. **6-Month Health Services Use** Primary care physicians and care manager contacts with patients via telephone and email were similar by intervention arm – 3 contacts for dCBT alone group and 3 contacts for usual care group.
Simmonds-Buckley et al, 2020[53]	Not stated	**Beating the Blues**	**Patient reported outcomes of anxiety, depression and/or stress** SMD (Hedges g) for BtB compared to control on depression outcomes posttreatment is 0.55(0.00-1.10) based on 5 comparisons (I2 of 89% is significant for heterogeneity) and for Headspace compared to control is 0.36 (0.22-0.49) based on 3 comparisons. For anxiety/stress outcomes SMD for BtB posttreatment is 0.40 (0.35 to 0.45) based on 3 comparisons.
Beevers et al, 2017[11]; Mullarkey et al, 2020[12]	NCT01818453	Deprexis	*Beevers et al, 2017[11]* **Summary:** Controlling for pre-treatment depression severity in a multiple imputation intention to treat analysis, self-reported depression severity was lower in the Deprexis group than the waiting list control at the end of the 8 week treatment (b 3.87, SE 0.53, z 7.22, p .001, Cohen's d 0.80, 95% CI [.56, 1.04]). Treatment response (50% reduction QIDS-SR) and remission (HRSD <=7) were more common too. **Depression severity**

Papers	Study	Intervention	Results
			QIDS-SR: Multiple imputation ITT analyses: Using pretreatment QIDS-SR as a covariate in a linear regression, results indicated a significant treatment group difference for postassessment QIDS-SR, b 3.87, SE 0.53, z 7.22, p .001, Cohen's d 0.80, 95% CI [.56, 1.04]). HRSD: Using pretreatment HRSD as a covariate in a linear regression, results indicated a significant treatment group difference for posttreatment HRSD ,b4.58,SE0.72,t6.28,p.001,Cohen's d 0.68,95%CI[.44,.92]. **50% or greater reduction in depression severity** A logistic regression with pretreatment QIDS-SR as a covariate found a significant effect of treatment condition on the dichotomous outcome of treatment response, beta=2.47, SE=0.52, z=4.78, p=0.001. **depression remission (HRSD <=7)** A logistic regression with pretreatment HRSD as a covariate found a significant effect of treatment condition -on remission (b2.23, SE=0.49, z=4.47, p=0.001.) *Mullarkey et al, 2020*[12] **Quick Inventory of Depression Symptoms** Network analysis: Deprexis directly improved sadness and indecision. In turn anhedonia, middle insomnia, self-dislike, suicidality, slowness. Agitation, early insomnia and 6 other symptoms did not improve.
Berger et al, 2011[13]	Not stated	Deprexis	**Summary**: In ANCOVA analyses using baseline values as covariates, BDI scores improved more in the unguided and guided self-help (Deprexis) groups than the wait list controls (Cohen's d = 0.66 for unguided vs control and 1.14 for guided vs control, both p<0.009). However there was not strong evidence of a difference between unguided and guided groups (Cohen's d = -0.3, p=0.88). A 'significant' difference between guided and control groups was also seen in BSI (d = 0.81, p=0.004), IIP (d= 0.65, p = 0.005) and quality of life (d=1.02, p=0.001). No 'significant' differences were found between guided and unguided groups in any measures. *Treatment satisfaction:* Mean CSQ-8 was 3.12 in guided group (SD=0.44, n=25) and 2.86 (SD=0.53, n=22) in the unguided group. Effect size d =0.54, p=0.8) BDI-II Pretreatment to posttreatment score Unguided SH: -9.0 (Cohen's d=0.80, no Cis) Guided SH: -11.5 (d = 1.24) Control: -1.3 (d=0.14) Between group effect size Unguided vs guided: -0.3 Unguided vs control = 0.66 Guided vs control = 1.14 general psychopathology Change in Brief Symptom Inventory U: -0.39 d = 0.64 G: -0.49 d =0.80 C: -0.03 d=0.06 Effect size UvG = -0.15 UvC = 0.61 GvC = 0.81 interpersonal problems Inventory of Interpersonal Problems U = -1.22 (d=0.35) G = -0.35 (d=0.61) C = +0.01 (d=-.02) Effect size UvG = 0.23 UvC = 0.39 GvC = 0.65

Papers	Study	Intervention	Results
			quality of life WHOQOL-BREFOverall +10.5(d= 0.57) +19.5 (d=1.0) +1.9 (d=0.11) Effect size UvG d=0.35 UvC = 0.59 GvC = 1.02
Berger et al, 2018{Berger, 2018 #168	Not stated	**Deprexis**	**Summary:** For the psychotherapy plus Deprexis group versus the psychotherapy only group there was a greater reduction in average BDI-II (d=0.51, 95%CI 0.11-0.91, ITT mixed-model repeated measures ANOVA p<0.05), mental health related quality of life and somatic symptoms. There was not a statistically significant difference in anxiety score, or physical health related quality of life. BDI-II Within group effect size (estimated means – Cohen's d, 95%ci) Intervention: 0.94 (0.54-1.36) Control: 0.38 (-0.02-0.79) Effect: 0.51 (0.11-0.91) Quality of life SF-12MH I 1.30 (0.87-1.72) C 0.49 (0.09-0.89(Effect 0.55 (0.14-0.95) anxiety symptoms I 0.54 (0.14-0.93) C 0.30 (-0.11-0.70 Effect 0.31 (-0.09 – 0.71) Quality of life SF-12PH I -0.01(-0.40-0.38) C -0.02 (-0.42-0.39) Effect 0.07 (-0.33 – 0.47 somatic symptoms (PHQ-15), I 0.58 (0.18-0.97) C 0.09(-0.32-0.49) Effect (0.27(-0.13-0.66) Therapeutic alliance also available
Boschloo et al, 2019[15] ; Kaiser et al, 2021[16] ; Klein et al, 2016[17]; Klein	EVIDENT	**Deprexis**	*Boschloo 2019[15]:* **Summary:** There was a greater reduction in depressive symptoms in the Deprexis group than the control group (difference in difference of mean PHQ-9 = 1.61, Cohen's d = 0.38, unpaired T-test for change scores p<0.001). Please note: patients with baseline PHQ score of 5-9 received unguided versions of the intervention. Also has a network analysis.

Papers	Study	Intervention	Results
et al, 2017[c 18]; Nolte et al, 2021[19]; Schuster et al, 2020[21]			PHQ-9 Change Intervention: 2.83 (sd=4.10) Control: 1.22 (sd=4.31) Cohen's d 0.38 *Kaiser 2021[16]*: Presents a network analysis to examine the symptom-specific effects of the intervention– omit? PHQ9 Cohen's d: −0.40[−0.54;−0.26] SF-12mental:−0.45[−0.30;−0.16] SF12:physical:−0.08[−0.22;0.06] *Klein 2016[17]:* **Summary**: In the ITT linear mixed models analysis, on average PHQ scores decreased by 1.57 (95%CI 1.07-2.07) points more in the Deprexis group than the care as usual group (Cohen's d = 0.39, 95% CI: 0.13–0.64, p<0.001). Differences in change in HDRS-24, QIDS-C16, SF-12mh and FEP-2 also reportedly favoured the intervention (p<0.01) however confidence intervals for the effect size overlapped the null for HDRS-24, QIDS-C16 and SF12-mh. Please note that slightly different results are presented in Table 2 of Klein et al 2017 – e.g. for PHQ Cohen's d = 0.36, 95% CI: 0.06–0.67, p<0.001 – reasons unclear. Average PHQ9 suicidality item and worsening of PHQ9 were lower at posttreatment in the Deprexis group than control group (107/509, 21% worsened in the intervention group and 165/504, 32.7% in the control group), however it is not clear how the suicidality item differed from baseline. **Post-assessment (3months)** **intervention (n = 509)** | **CAU (n = 504)** | **Cohen's *d*** | **95% CI** PHQ-9: 7.54±4.04 | 9.15±4.30 | 0.39 | 0.13 to 0.64 HDRS-24: 12.82±7.49 | 14.25 ±7.96 | 0.19 | −0.29 to 0.66 QIDS-C16: 6.73 ±4.44 | 7.22 ±4.38 | 0.11 | −0.16 to 0.38 SF-12 mental health: 37.26± 10.06 | 35.19±8.87 | 0.22 | −0.37 to 0.80 SF-12 physical health: 47.74±9.58 | 47.21 ±9.45 | 0.06 | −0.53 to 0.64 FEP-2: 2.56±0.61 | 2.74±0.62 | 0.30 | 0.26 to 0.33 *Klein 2017[18]:* **Summary:** 40.9% (208/509) experienced remission in the Deprexis group with an average time to remission of 9.35 months (±3.56), compared to 33.7% (170/504) in the control group with an average time to remission of 10.09 months (±3.08). The unadjusted Cox regression hazard ratio was 1.31 (95% CI,

<table>
<tr><th>Papers</th><th>Study</th><th>Intervention</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td>1.07–1.61; p = 0.009) and log-rank test indicated a statistically significant difference (χ2 (1) = 7.43, p = 0.006).

Nolte 2021[19] = subgroup analysis
Schuster 2020[21] = subgroup analysis – helpful even in those receiving outpatient psychotherapy.</td></tr>
<tr><td>Gräfe et al, 2020[33 34]</td><td>RKS00003564</td><td>Deprexis</td><td>Small-medium effect sizes for differences in depression severity (d=0.37 [0.29, 0.44), p<0.001), functional impairment, Work and Social Adjustment Scale and quality of life were seen post-assessment between the intervention (Deprexis) and control groups, favouring the control group. These differences reduced in magnitude at 3 months and 9 months.

<table>
<tr><th></th><th colspan="2">Post-assessment</th><th colspan="2">3-monts follow-up</th><th colspan="2">9-monts follow-up</th></tr>
<tr><th></th><th>Cohen's d</th><th>95% - CI</th><th>Cohen's d</th><th>95% - CI</th><th>Cohen's d</th><th>95% - CI</th></tr>
<tr><td>PHQ-9</td><td>0.37</td><td>0.29 - 0.44</td><td>0.23</td><td>0.15 - 0.31</td><td>0.15</td><td>0.07 - 0.23</td></tr>
<tr><td>SF-12 physical summary scale</td><td>0.18</td><td>0.10 - 0.25</td><td>0.09</td><td>0.01 - 0.17</td><td>0.14</td><td>0.05 - 0.22</td></tr>
<tr><td>SF-12 mental summary scale</td><td>0.33</td><td>0.25 - 0.40</td><td>0.22</td><td>0.15 - 0.30</td><td>0.09</td><td>0.01 - 0.18</td></tr>
<tr><td>EQ-5D-3L</td><td>0.14</td><td>0.07 - 0.22</td><td>0.10</td><td>0.02 - 0.17</td><td>0.09</td><td>0.01 - 0.18</td></tr>
<tr><td>WSAS</td><td>0.23</td><td>0.15 - 0.31</td><td>0.15</td><td>0.07 - 0.23</td><td>0.12</td><td>0.02 - 0.24</td></tr>
</table>

Cohen's d was calculated as the difference between the mean of the intervention and control group, divided by the pooled standard deviation of both groups. The effect sizes are defined as small (d=0.2), medium (d=0.5) and large (d=0.8).</td></tr>
<tr><td>Klein et al, 2020[39]</td><td>Not stated</td><td>Deprexis</td><td>Summary: Of 104 patients recruited, 87 (83.6%) used deprexis at least once. Only 7 patients received the guided version (8%). Over the 12 weeks reductions were seen in PHQ-9 (d = 1.29, 95% CI 0.60–1.97, p < 0.0001), svMADRS (Cohen's d = 1.42, 95% CI 0.08–2.76, p < 0.0001) and SDS (d = 1.33, 95% CI 0.38–2.28 p < 0.0001,)

From the CSQ-4 “55 patients (68.75%) reported that “most (or all) of my needs have been met”, 75 answered that the intervention “helped (a great deal)” (93.75%) and 69 patients said they would (definitely) use the intervention again (86.25%).”</td></tr>
</table>

Papers	Study	Intervention	Results
			Self-reported total internet usage did not change substantially during the study period, generally slightly reducing. Also reported are Clinical Global Impression scale, 2 items from Compulsive Internet Use Scale Two adverse incidents (feeling of paralysis and increase in depressive symptoms) and one serious adverse event (acute suicidality) were reported by the treating physicians. Only the feeling of paralysis (which spontaneously recovered after a few hours) was considered to be causally related to Deprexis by the treating physician. The patient reporting an increase in depressive symptoms felt overwhelmed by Deprexis.
Meyer et al, 2009[44]	ISRCTN 64953693	**Deprexis**	**Depression (BDI), social functioning (Work and Social Adjustment Scale)** 320 adults were randomised to 9-week Deprexis program and 76 to treatment as usual with delayed access at 9-weeks. Of these 159 in the immediate intervention group and 57 in the delayed intervention group remained in the study at 9 weeks. Between 30% and 50% of participants were lost between any two assessment time-points, and fewer than 50% of the users completed more than 3 sessions. At 9 weeks, a greater reduction in BDI was seen in the immediate treatment group than delayed treatment group (LOCF ITT analysis d=0.30, 95%CI 0.05-0.55). Greater reduction in WSA was also seen (LOCF ITT repeated measures ANOVA analysis d = 0.36, CI 95% = 0.10 - 0.61). Similar reductions in BDI and WSA scores were seen in the delayed treatment group once they had completed the Deprexis intervention. **programme acceptability, subjective benefit** 164 (83%) participants who completed feedback said they liked the programme. 167 (82%) said they thought it helped them. The majority said that they would recommend the intervention to those with mild and moderate depression, but fewer than 50% would recommend it to those with severe depression.
Meyer et al, 2015[45]	Not stated	**Deprexis**	**PHQ-9, GAD-7, PHQ-15, quality of life** 78 participants were randomised to treatment with 61 (78% completing post-intervention questionnaires at 3 months. 85 were randomised to control with 73 (86%) completing post treatment questionnaires. In ITT analyses, standardised between group difference in PHQ-9 was 0.57 (0.22-0.92) favouring intervention (linear mixed effect model analysis for time by treatment condition interaction for the PHQ-9 at post-treatment ($F_{1,155.6}$= 9.00, p<0.01)). For GAD-7 d=0. 27 (−0.09 to 0.63), PHQ-15 0.06 (-0.30 to 0.41), SF12 mental 0.14 (-0.22 to 0.51) and SF12 physical 0.03 (-0.34 to 0.39). **treatment satisfaction**

Papers	Study	Intervention	Results
			For 60 patients in the treatment group, treatment satisfaction measured by the ZUF-8 post treatment (mean 24.17, SD 4.82) was similar to that from a normative sample of 664 inpatients from psychosomatic hospitals in Germany (mean = 25.12, SD 4.63). **alliance/ helpfulness** 62 participants completed the HAQ-11 for a helpfulness rating on average 3 weeks after programme access, with 71% of these reporting a more positive than negative impression of the program's helpfulness (score greater than zero on HAQ-11.
Moritz et al, 2012[46]	NCT01401296	**Deprexis**	**BDI, Dysfunctional Attitude Scale, Rosenberg Self-Esteem Scale, quality of life** 105 were randomised to Deprexis and 105 to waiting list. 78.1% of the intervention group and 85.7% of the wait list group completed the study. Standardised between-group difference in BDI score change was d = 0.36 in intention to treat analysis (ANCOVA, p = 0.03). Between group effect sizes and p-values from ITT ANCOVA analyses are as follows: Rosenberg self-esteem scale d = 0.38, p = 0.03, Suicide Behaviours Questionnaire revisited d = 0.20, p > 0.2, Dysfunctional Attitudes Scale d = 0.54, p= 0.001, and WHOQOL-BREF total score d = 0.40, p = 0.02. **Subjective benefit** 53.5% of completers from the treatment group (n=80) reported that they found the program very good or good. 91.6% would recommend it for mild depression, 77.5% for medium severity and 40.9% for severe depression. 47.9% believed their depressive symptoms had decreased due to Deprexis. 73.20% said they were satisfied with the programme and that the program provided advice at least as helpful advice as real therapist
Karyotaki et al, 2018[37]	Not stated	**Meta-analysis**	BDI-I, BDI-II, CES-D, or PHQ-9, analysed using reliable change index *Please note that this study includes other technologies.* Clinically significant deterioration Overall 7.2% (276/3805) ddCBT 5.8% control 9.1% Odd ratio 0.62 (0.46–0.83) p=0.001 (n=3795) any deterioration 30.1% (1143/3805) 26.2% self-guided ddCBT

Papers	Study	Intervention	Results
			35.3% control Odds ratio 0.65 (0.55–0.76) p=<0.001 (n=3795) Complete case analysis – Clinically significant deterioration (n=2818) dCBT 6.1% control 9.1% OR 0.61 (0.46–0.83) p=0.001 any deterioration dCBT 26.5% control 36.6% OR 0.66 (0.56–0.77) p=<0.001
Karyotaki et al, 2021[38]	Not stated	**Meta-analysis**	PHQ-9 No technology specific results are reported.
Twomey et al, 2017[54]/ 2020[55]	Not stated	**Meta-analysis (Deprexis)**	**Self-reported or clinician-rated depression measures** 12 studies were included in the meta-analysis with n=2901 in total. The estimated effect size for depression reduction post treatment is g=0.51, 95%CI0.40-0.62, I2 = 26%.)
Duffy et al, 2020[27]	Not stated	**Space from Depression**	**Summary**: this study compared completers vs dropouts. This is not a helpful comparison in this context.
Enrique et al, 2019[a 28 29]; Richards et al, 2015[b30]	ISRCTN03704676	**Space from Depression**	*Richards et al, 2015[b30]:* **Summary**: 133 were allocated to the intervention group, 96 included in the active intervention and 60 included in the post-intervention analysis (compared to 129, 92 and 92 respectively for the waiting list control group. In ITT using maximum likelihood method to calculate missing data, post-intervention scores were lower in the intervention group than waiting list group for BDI-II (d=0.5, p<0.01), GAD-7 (d-0.32, p<0.01) and Work and Social Adjustment Scale (d=0.40, p<0.01). Per protocol analysis results were consistent with these. The authors defined a reliable change in the BDI-II as a reduction of 9 points or greater. This occurred for 29.5% (n=28) in the treatment group at 7.6% (n=7) of the waiting list group (p<0.001). *Enrique et al, 2019[a29]* A total of 89 participants obtained a reliable change (RC), and 127 participants did not. Those in the RC group significantly spent more time, had more log-ins, used more tools, viewed a higher percentage of the program, and got more reviews from their supporter compared with those who did not obtain an RC.

Papers	Study	Intervention	Results
			Enrique et al, 2019b No significant difference in change in quality of life was observed between Space for Depression and waiting list control.
[redacted]	[redacted]	[redacted]	[redacted]
Palacios et al, 2022a[48]	Not stated	**Space from Depression**	**PHQ-9, GAD-7, Work and Social Adjustment Scale** In pairwise comparisons using propensity score stratification, the average treatment effect of dCBT compared to non-digital guided self-help was: PHQ-9 1.26 (1.08-1.44); GAD-7 1.17(1.00-1.34); WSAS 0.86 (0.58-1.14), all p<0.0001 favouring dCBT. Average treatment effect compared to psychoeducational group therapy was: 1.71 [1.27–2.15], 1.90 [1.50–2.31], 1.96 [1.35–2.57], all p<0.0001 favouring dCBT.
Palacios et al, 2022b[49]/ Richards et al, 2020[50]	ISRCTN 91967124	**Space from Depression**	PHQ-9, GAD-7, Work and Social Adjustment Scale, reliable recovery from depression and anxiety Richards 2020[50] Random intercept linear mixed models including maximum likelihood estimation indicated a significant interaction effect of time-by-group for PHQ-9 (b = −2.75; SE = 0.64; 95% CI −4.00, −1.50; p < 0.0001) and GAD-7 (b =−2.79; SE = 0.61; 95% CI −4.00, −1.58; p < 0.0001) and WSAS (b = −2.65, SE = 0.99, 95% CI −4.59, −0.72; p = 0.075). Significant improvement and recovery were defined as follows: a) significant improvement: a score change of PHQ-9 ≥ 6 and/or GAD-7 ≥ 4, provided they do not reliably deteriorate on either measure (b) recovery: moving from 'caseness' (defined thresholds as set by IAPT being PHQ-9 ≥ 10 and/or GAD7 ≥ 8) to 'non-caseness' (below the threshold on both measures). At post-treatment (8-week), 46.4% (90/194) of the intervention arm and 16.7% (15/90) control-arm participants recovered. 63.4% (123/194) of the intervention-arm and 34.4% (31/90) control-arm participants showed significant improvement. Reliable

Papers	Study	Intervention	Results
			recovery (both criteria fulfilled) in the intervention-arm was 40.7% (79/194), and 13.3% (12/90) in the control arm – p<0.01 for all between group differences. Palacios 2022b[49] "Of the 241 participants in the intervention arm, 89 participants met the criteria for reliable recovery from depression and anxiety at the post-treatment assessment. Of these 89 eligible cases, 29.2% relapsed within the 9-month period, with 70.8% remaining in remission at 9 months post-treatment. Of those who relapsed, 53.8% experienced a relapse of depression and anxiety; 7.7% experienced a relapse of depression only; and 38.4% experienced a relapse of anxiety only. Younger age, having a long-term condition, and residual symptoms of anxiety at end-of-treatment were all significant predictors of relapse."
Beatty et al, 2022[10]	Not stated	Wysa	**Summary:** Wysa appears acceptable to users and it is possible for users to have a positive therapeutic alliance with the app's conversational agent. **Therapeutic alliance** Assessment 1 (Day 1-5 after installation, n=1,205) mean WAI-SR: 3.64 (SD 0.81) Assessment 2 (3 days after first measure, n=226) mean WAI-SR: 3.75 (SD 0.80) **Acceptability of conversational agent** Qualitative content analysis
Inkster et al, 2018[35]	Not stated	**Wysa**	Over a two-week or more period, high users of Wysa had higher mean improvements in PHQ-2 scores (n=108, mean change 5.84 [SD 6.66]) than low users (n=21, mean change 3.52 [SD 6.15]); Mann-Whitney P=0.03. High users were defined as engaging on the app on 2 screening days when the PHQ-9 surveys were performed and at least once between those days. Amongst those that offered feedback, patient experience responses were generally positive.
Malik et al, 2022[43]	Not stated	**Wysa**	**User feedback** "6700 reviews (6700/7929, 84.50%) giving the app a 5-star rating and 2676 reviews (2676/7929, 33.75%) explicitly terming the app "helpful" or that it "helped." Of 7929 reviews, 251 (3.17%) had a less than 3-star rating and were termed as negative reviews." "The themes of engaging exercises, interactive interface, and artificial intelligence (AI) conversational ability indicated the acceptability of the app, while the non-judgmentality and ease of conversation highlighted its usability. The app's usefulness was portrayed by themes such as improvement in mental health, convenient access, and cognitive restructuring exercises. Themes of privacy and confidentiality underscored users' preference for the integrated aspects of the app."

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Addendum: amendments to the assessment report following external review

Following a factual accuracy check of the report by companies, committee members, specialist committee members (SCMs) and NICE staff the following amendments have been made to the report.

- Further text added around the REEACT RCT throughout the document (pages 8, 9, 37, 41, 42, 59, 60, 109). The changes made were to further clarify details of the study not included in the original report.
- Page 15: amended wording to comparator section to provide clarification on the place of the interventions in the care pathway: 'Guided self-help digital CBT technologies could be a first line treatment prior to more intensive interventions or used as an alternative to standard care for adults with depressive symptoms.'
- Page 21: further considerations in relation to equality and equity have been added: 'People with ADHD and learning difficulties and non-English speakers are also significant groups who may struggle to access dCBT in its current form. In addition, there may be overlap between depression and long-term health conditions such as chronic pain; evidence considering specific physical health conditions has not been considered within this EVA as the scope was limited to depression as the primary diagnosis but could be a topic for future research.'
- Footnote added to table 2 (pages 27 and 35) to clarify that the background of the supporter was not a low-intensity therapist as used in an IAPT setting as this was not a UK-based study.
- Pages 92,110, 122 wording amended to clarify that the advice relating to band of staff delivering digitally enabled therapies was the opinion of one SCM. Another SCM who provided a fact check response disagreed with this comment as in their service these interventions were mainly provided by band 5 psychological

wellbeing practitioner (PWPs). Reference to trainee clinical psychologist as the band 6 staff member has also been removed as band 6 could also be used for a senior PWP. No further amendments were made as band 5 staffing was used in the base case model.

- Page 94 further text added around the use of the health state utilities from the NICE clinical guideline on adults with depression.
- Page 97 table number corrected in text, from table 17 to table 15.
- Page 99 text amended for clarity: 'The major cost components for the interventions are GP costs for follow-up for non-completers who respond to subsequent therapy'.
- Page 117 formatting of table 25 amended.
- Page 43 and 44 information on patient experience data relating to Space from Depression added.
- Page 57 information from one Silvercloud publication on adverse events added.
- Page 85, 86 amendments to table 9 and 10 and associated text to make the table easier to read and an explanation for how to interpret these odds ratios has been added.
- Page 61 added further information in relation to the population included in an economic evaluation.
- Page 39 clarified SCM advice around the stepped care model was from one advisor.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health technology evaluation

Assessment report overview

Digitally enabled therapies for adults with depression

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

Key issues for consideration by the committee are described in section 6, following the brief summaries of the clinical and cost evidence.

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

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional organisations
- Appendix C: Comments from patient and carer organisations
- [Appendix D: Additional analyses carried out by EAG] [delete if no appendix D]

1 The technology

Digitally enabled therapies are a treatment option for adults with depression. They are products that deliver a substantial portion of therapy through its content but are designed to be used with practitioner or therapist support. These therapies are an option for delivering guided self-help and can be delivered online or through apps. Guided self-help may include materials based on structured cognitive behavioural therapy (CBT), problem solving, psychoeducation and behavioural activation delivered face-to-face or by telephone or online. They can be delivered with support from a trained practitioner who facilitates the self-help intervention, encourages completion and reviews progress and outcomes and usually consists of 6 to 8 structured regular sessions. 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.

For this early value assessment (EVA), NICE will consider digitally enabled therapies that:

- are intended for use by adults
- deliver a therapeutic intervention in line with NICE guidelines that can be used in NHS Talking Therapies (previously known as improving access to psychological therapies, IAPT) services with practitioner or therapist support
- deliver a substantial portion of the therapy through the technology rather than being platforms to support teletherapy
- meet the standards within the digital technology assessment criteria (DTAC), including the criteria to have a CE or UKCA mark where required. Products may also be considered if they are actively working towards required CE or UKCA mark and meet all other standards within the DTAC.
- are available for use in the NHS.

Technologies included in this EVA are also expected to complete the NHS Talking Therapies Digitally Enabled Therapies (DET) assessment criteria at an appropriate point. This includes validation of clinical content in line with NICE guidelines and light-touch assessment of clinical effectiveness, to ensure the product meets baseline standards for use in NHS Talking

Therapies. The status of each product against the NHS Talking Therapies DET assessment criteria will be included in the EVA.

In total, 6 digitally enabled therapies for adults with depression are included in the evaluation. One technology was removed from the evaluation (Perspectives) as regulatory approval was not yet being sought. A brief overview of the technologies are summarised below. Detailed descriptions are provided in the scope.

Space from Depression (SilverCloud):

Space from Depression is an online CBT programme for adults with low mood and depression. SilverCloud recommends that all programmes are used with a supporter who regularly reviews progress, provides feedback and unlocks content. Programmes can be accessed at any time using any smartphone, tablet, or computer.

Minddistrict (Minddistrict):

Minddistrict is an online CBT programme intended for treating psychological health conditions, including mild-to-moderate depression. It has a catalogue of modules, diaries, and questionnaires that can be combined and edited to suit the needs of each person. The technology can be accessed via a web browser and there is also a smartphone app.

Beating the Blues (365 Health Solutions Ltd.):

Beating the Blues is an online CBT program for individuals with mild to moderate depression and anxiety. It can be used according to the user's preferences with any computer, laptop, smartphone or tablet with internet access.

Deprexis (Ethypharm Digital Therapy):

Deprexis is a web-based program based on elements from CBT intended to help those with unipolar depression or depressive disorders. The technology is adaptive and adjusts its approach according to the needs and preferences

of the user. It can be used according to the user's preferences with any computer, laptop, smartphone or tablet with internet access.

Wysa (Wysa Ltd.):

Wysa is an artificial intelligence-based app with CBT-based self-help programmes for people with mild to moderate depression and anxiety. Wysa has an AI-guided chatbot that uses natural language processing to encourage self-reflection and help users engage with the mental health tools. In addition to the patient app, Wysa also has a web-based AI-supported e-triage tool that collects data based on questions from the referral form for NHS Talking Therapies services.

Iona Mind (Iona Mind):

Iona Mind is an app-based CBT programme for people with depression or generalised anxiety disorder. It uses machine learning to anticipate and adapt the programme to a person's needs and creates personalised support plans.
Proposed use of the technology

1.1 Disease or condition

Depression is a common mental health problem which can present with a variety of different symptoms. It is characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioural symptoms.

In ICD-11, depression is defined as the presence of depressed mood or diminished interest in activities occurring most of the day, nearly every day, for at least 2 weeks, accompanied by other symptoms such as:

- reduced ability to concentrate and sustain attention or marked indecisiveness
- beliefs of low self-worth or excessive or inappropriate guilt
- hopelessness about the future

- recurrent thoughts of death or suicidal ideation or evidence of attempted suicide
- significantly disrupted sleep or excessive sleep
- significant changes in appetite or weight
- psychomotor agitation or retardation
- reduced energy or fatigue

Depression severity exists along a continuum and is composed of 3 elements:

- symptoms (which may vary in frequency and intensity)
- duration of the disorder
- the impact on personal and social functioning.

Depression has traditionally been grouped in 4 categories: subthreshold, mild, moderate and severe. NICE's clinical guideline on depression in adults: treatment and management has categorised new episodes of depression as less severe or more severe depression, based on the available evidence on the classification. Less severe depression includes subthreshold and mild depression, and more severe depression encompasses moderate and severe depression.

1.2 Patient group

NICE's clinical guideline on depression in adults: treatment and management states that each year 6% of adults in England will experience an episode of depression and more than 15% of people will experience an episode of depression over the course of their lifetime. For many people the episode will not be severe, but for more than 20% the depression will be more severe and have a significant impact on their daily lives. Recurrence rates are high: there is a 50% chance of recurrence after a first episode, rising to 70% and 90% after a second or third episode, respectively.

1.3 Current management

NICE's clinical guideline on depression in adults: treatment and management recommends considering a number of factors when considering treatment including:

- assessment of need
- any physical health problems
- any coexisting mental health problems
- factors that would make the person most likely to engage with treatment
- previous treatment history
- barriers to the delivery of treatments because of any disabilities, language or communication difficulties

It also recommends matching the choice of treatment to meet the needs and preferences of the person with depression and use the least intrusive and most resource efficient treatment that is appropriate for their clinical needs, or one that has worked for them in the past.

For all people with depression having treatment:

- review how well the treatment is working with the person between 2 and 4 weeks after starting treatment
- monitor and evaluate treatment concordance
- monitor for side effects and harms of treatment
- monitor suicidal ideation, particularly in the early weeks of treatment
- consider routine outcome monitoring (using appropriate validated sessional outcome measures, for example PHQ-9) and follow up.

Less severe depression:

The guideline recommends discussing treatment options with people with a new episode of less severe depression and matching their choice of treatment to their clinical needs and preferences. All treatments listed below can be used as first-line treatments, but it is recommended to consider the least intrusive and least resource intensive treatment first (guided self-help):

- Guided self-help
- Group cognitive behavioural therapy (CBT)
- Group behavioural activation (BA)

- Individual CBT
- Individual BA
- Group exercise
- Group mindfulness and meditation
- Interpersonal psychotherapy
- Selective serotonin reuptake inhibitors
- Counselling
- Short-term psychodynamic psychotherapy

The list is arranged in order of the guideline committee's consensus on the average effectiveness and cost effectiveness of the treatments in adults with less severe depression, with the most effective and cost effective listed at the top. Factors which may promote implementation, such as the use of least intrusive treatments first, have also been taken into account. If a less intrusive treatment has not worked then treatment can then be stepped up to offer other treatment options.

More severe depression:

The guideline recommends discussing treatment options with people with a new episode of more severe depression and matching their choice of treatment to their clinical needs and preferences. All treatments listed below can be used as first-line treatments:

- Combination of individual CBT and an antidepressant
- Individual CBT
- Individual BA
- Antidepressant medication
- Individual problem-solving
- Counselling
- Short-term psychodynamic psychotherapy
- Interpersonal psychotherapy
- Guided self-help
- Group exercise

The list is arranged in order of the guideline committee's consensus on the average effectiveness and cost effectiveness of the treatments (as well as consideration of implementation factors) with the most effective and cost effective listed at the top, but the committee agreed that choice of therapy should be a personalised decision and that some people may prefer to use a treatment further down the list and that this is a valid choice.

The guideline committee note that although guided self-help can be a treatment option for people with more severe depression, other treatment choices with more therapist contact should be carefully considered first.

The guideline also states that commissioners and providers of mental health services should consider using models such as stepped care or matched care for organising the delivery of care and treatment of people with depression. The Improving Access to Psychological Therapies (now known as NHS Talking Therapies) programme offers a range of NICE-recommended therapies for depression in line with a stepped-care model, when appropriately indicated. Currently, digitally enabled therapies are primarily used in step 2 of the NHS Talking Therapies programme and are delivered by psychological wellbeing practitioners.

1.4 Proposed management with new technology

NICE's clinical guideline on depression in adults: treatment and management recommends guided self-help as an option for treating both less severe and more severe episodes of depression. Guided self-help includes digital CBT (referred to as digitally enabled therapies for this guidance). Guided self-help should be considered first for most people with less severe depression as it is the least intrusive and least resource intensive treatment for less severe depression. However, guided self-help may not be as appropriate for more severe depression and other treatment choices with more therapist contact should be considered first.

Guided digital therapies are already used in the NHS Talking Therapies setting within the NHS in England. These include the use of Space from

Depression, Minddistrict, Wysa, limited usage of Beating the Blues (although there is wider widespread use in Scotland and Northern Ireland) and piloting the use of Deprexis and Iona Mind.

2 The decision problem

Details of the decision problem are described in the scope. The clinical experts have provided advice to the EAG for some elements of the decision problem, however the EAG made no changes to the decision problem.

3 The evidence

3.1 Summary of evidence of clinical benefit

The EAG identified 46 papers, reporting on 32 studies, that were relevant to the decision problem. These are summarised below. NHS Talking Therapies are reported as IAPT in the evidence sections as the evidence was generated prior to the change of name.

Beating the Blues (12 studies included):

- 4 randomised controlled trials (RCTs;1 done in the UK before IAPT was set up, 1 was a UK-based pragmatic RCT, 2 were on the US version of the technology)
- 6 UK based non-comparative studies (1 naturalistic open trial, 1 real world study, 1 qualitative study, 1 pilot study, 1 implementation study, 1 feasibility study with out of scope comparators)
- 1 non-randomised pilot study done in Scotland

Deprexis (9 studies and 1 meta-analysis included):

- 8 RCTs done in the US, Germany and Switzerland (4 of which were pragmatic)
- 1 meta-analysis of 12 RCTs
- 1 non-comparative observational study done in Germany

There was overlap with the studies included by Twomey et al. (2020) meta-analysis and the 8 included RCTs. However, both were considered as the separate RCTs can provide information on additional outcomes not assessed in the meta-analysis.

Space from Depression (5 studies included):

- 2 RCTs (one pragmatic RCT done in an IAPT setting, 1 RCT with secondary analysis done in Ireland)
- 3 non comparative studies (2 naturalistic studies done in the UK and [redacted])

Wysa (3 studies included):

- 3 non comparative international studies (2 mixed methods studies and 1 qualitative study)

In addition to technology specific studies, 3 meta-analyses on mixed interventions were also considered, although these did not present intervention specific pooled estimates. Further information on these 3 meta-analyses is summarised in table 2 of the assessment report. The EAG did not identify any in scope evidence for Minddistrict or Iona Mind.

Study Design

Of the 32 included studies, there 14 were RCTs on Deprexis, Space from Depression or Beating the Blues included in the evaluation. There were also 4 meta-analyses identified, 1 on Deprexis and 3 on a range of interventions. The remaining studies included 1 non-randomised pilot study comparing Beating the Blues to treatment as usual and 13 non-comparative studies.

Study Setting

Of the included studies, 12 were done in the UK using Beating the Blues or Space from Depression. Of these 12 studies, 3 were RCTs. Two of these RCTs were done in an IAPT setting or involved IAPT services. These 2 RCTs were a pragmatic RCT (REEACT trial; Gilbody et al. 2015, Littlewood et al. 2015) comparing Beating the Blues plus usual GP care with usual GP care alone (usual GP care including access any treatment usually available in primary care including the use of antidepressants, counselling, psychological services such as IAPT, or secondary care mental health services) and a pragmatic RCT comparing Space from Depression (and other out of scope interventions; Palacios et al. 2022, Richards et al. 2015) with waitlist control. The other UK-based RCT used Beating the Blues (Proudfoot et al. 2004,

McCrone et al. 2004) and was done in a primary care setting but was completed prior to the creation of IAPT.

The remaining 9 studies done in a UK setting were non-comparative. Of these 2 were done in an IAPT setting on Space from Depression (Palacios et al, 2022a, Duffy et al. 2020). Some of the other UK studies were done in the time since IAPT was started. However, as IAPT was not explicitly mentioned in the manuscript, the EAG have marked these as 'probable IAPT' within table 2 of the assessment report.

Of the remaining studies, 8 studies using Deprexis were done in Germany or Germany and Switzerland. Seven of these were RCTs (Berger et al. 2011, Moritz et al. 2012, EVIDENT trial [Boschloo et al. 2019, Kaiser et al. 2021, Klein et al. 2016, Klein et al. 2017c, Nolte et al. 2021, Schneider et al. 2018, Schuster et al. 2020], Gräfe et al. 2020, Berger et al. 2018, Meyer et al. 2009, Meyer et al. 2015) and 1 was an observational study (Klein et al. 2020).

For Space from Depression, 2 studies were done in Ireland. This included was one RCT with a waitlist control (Enrique et al. 2019a, Richards et al, 2015b) and [redacted].

Beating the Blues have 2 RCTs which were done in the US, comparing the intervention to usual care (Jonassaint et al. 2017, Rollman et al. 2018). Deprexis also had 1 US-based RCT with a waitlist comparator (Beevers et al. 2017, Mullarkey et al. 2020). The EAG note that the US version of Beating the Blues is structurally different from the UK version which restricts generalisability of US-based studies of this technology.

The studies published on Wysa were done internationally and included 2 mixed methods studies (Beatty et al. 2022, Inkster et al. 2018) and one qualitative study (Malik et al. 2022).

Expert advice to the EAG was that the stepped care model is a concept used in the NHS, so treatment approaches may differ internationally and could be a limitation on the transferability of the evidence.

Population

The EAG concluded that the populations of all included studies were broadly relevant to the decision problem, although the inclusion criteria had to be expanded versus the scope of the assessment to capture sufficient evidence. The EAG notes that in 18 of the 32 included studies (56%) the population was not restricted to depression and included adults with anxiety and other affective disorders. In addition to this, depression severity in the included studies was mostly categorised as mild-to-moderate, although there were some people with greater depression severity included in some studies. These studies did not typically present subgroup results by depression severity meaning the EAG could not conduct clinical subgroup analyses. These results may lead to misalignment to the NICE clinical guideline on depression in adults which categorises treatment options into less or more severe depression, with mild depression being in the less severe category and moderate depression in the more severe category. However, it is acknowledged that change in categorisation was only recently published in a 2022 clinical guideline update. Expert advice was that in terms of population, Scotland (for Beating the Blues) and Germany (for Deprexis) can be considered generally similar to the target English population.

Comparator

Among the 14 RCTs identified by the EAG, 11 used usual care (which can include pharmacological and psychological treatments) or waitlist control as the comparator. The exceptions were Berger et al. (2011) which included unguided Deprexis alongside waitlist control as a comparator, Berger et al. (2018) in which the comparator arm was psychotherapy alone, and Gräfe et al. (2020) which supplemented usual care with an informational brochure on depression.

Outcomes

The scope of the assessment listed a wide range of outcomes. None of the included studies reported on all outcomes included in the scope, but all reported some outcomes of interest.

The most reported outcomes were depression severity and anxiety severity (where the study included a mixed population). The most used outcome measures for depression were the Patient Health Questionnaire-9 (PHQ-9) and the Beck Depression Inventory-II (BDI-II), although other measures were used including BDI-I, Hamilton Rating Scale for Depression (HRSD), Quick Inventory of Depressive Symptoms and Center for Epidemiologic Studies Depression Scale (CES-D). Expert advice to the EAG was that PHQ-9 is the standard depression outcome in IAPT, HRSD is used in the majority of drug trials, BDI was used in the original studies of CBT by Beck, and all three are good rating scales. CES-D was seen as unfamiliar. Quality of life measures, scores on the Work and Social Adjustment Scale and measures of patient experience were also reported by multiple studies. Very limited adverse event or other or other patient safety outcomes were available.

Table 2 below summarises the key studies and outcomes. For further detail of the studies evaluated, see section 9.3 and appendix G of the assessment report.

Table 1: Summary of key studies

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Key Results
Space from Depression				
Palacios et al. 2022b and Richards et al. 2020 Pragmatic RCT ISRCTN91967124	361 people referred to IAPT stage 2 with depression and anxiety Mean baseline PHQ-9: 14.3 (SD 5.0) UK (IAPT setting)	**Intervention:** Space from Depression, Space from Anxiety, Space from Depression and Anxiety (supported by PWPs) (n=241) **Comparator:** Waitlist (n=120)	PHQ-9, GAD-7, WSAS, reliable recovery from depression and anxiety	At 8 weeks significant interaction between time and group (Space from Depression versus waitlist control): **PHQ-9:** b=2.75, p<0.0001 **GAD-7**: b=-2.79, p<0.0001 **WSAS:** b= -2.65, p= 0.075 **Recovery at 8 weeks:** Intervention: 46.4% (90/194) Control: 16.7% (15/90) **Reliable recovery:** Intervention: 40.7% (79/194) Control:13.3% (12/90) p<0.01
Enrique et al. 2019a and Richards et al. 2015b	188 people with BDI-II greater than or equal	**Intervention:** Space from Depression (with support) (n=96)	BDI-II, GAD-7, WSAS, platform usage, reliable change	**BDI-II:** d=0.5, p<0.01

RCT and secondary analysis ISRCTN03704676	to 14 and less than or equal to 29 Ireland	**Comparator:** Waitlist (n=92)		**GAD-7**: d=0.32, p<0.01 **WSAS:** d=0.40, p<0.01 **Reliable recovery:** Intervention: 29.5% (n=28) Control: 7.6% (n=7) p<0.001
Deprexis				
Berger et al. 2011 RCT	128 people with depression (BDI-II greater than 13) Switzerland and Germany	**Intervention:** Deprexis (low-intensity therapist-guided self-help) **Comparator:** Deprexis (unguided), waitlist	BDI-II, general psychopathology, interpersonal problems, quality of life	**BDI-II:** guided versus control: Cohen's d =1.14 unguided versus control: Cohen's d = 0.66 (both p<0.009) No significant difference between unguided and guided groups (p=0.88).
Berger et al. 2018 Pragmatic RCT	98 people with a unipolar affective disorder (BDI-II greater than13)	**Intervention:** Deprexis plus psychotherapy	BDI-II, anxiety symptoms, somatic symptoms, quality of life	**BDI-II:** psychotherapy plus Deprexis versus psychotherapy only d=0.51 (p<0.05)

	Germany	**Comparator:** Psychotherapy		
Boschloo et al. 2019, Kaiser et al. 2021, Klein et al. 2016, Klein et al. 2017, Nolte et al. 2021, Schneider et al. 2018, Schuster et al. 2020 Pragmatic RCT EVIDENT	1013 people with mild-to-moderate depression based on PHQ-9 Germany	**Intervention:** Deprexis (baseline PHQ score of 5 to 9 received unguided therapy, above this they received clinician guidance) **Comparator:** Care as usual	PHQ-9, HDRS-24, QIDS-C16, Questionnaire for the Evaluation of Psychotherapeutic Progress, quality of life, remission rates	**PHQ-9:** Intervention: 2.83 (SD 4.10) Control: 1.22 (SD 4.31) Cohen's d=0.38 (p<0.001)
Gräfe et al. 2020 Pragmatic RCT RKS00003564	3,805 people with PHQ-9 score greater than 4 Germany	**Intervention:** Deprexis plus care as usual **Comparator:** Care as usual plus a brochure with general information about depressive disorders	Depression severity, functional impairment, Work and Social Adjustment Scale, quality of life	**PHQ-9 (post assessment)** Cohen's d=0.37 (p<0.001) Difference reduced in magnitude at 3 and 9 months follow up.
Meyer et al. 2009 RCT ISRCTN64953693	396 adults from internet depression forums Baseline BDI (SD) 26.72 (9.86) in immediate and 27.11	**Intervention:** Deprexis plus treatment as usual **Comparator:** Treatment as usual (delayed access to Deprexis)	Depression (BDI), Work and Social Adjustment Scale, programme acceptability, subjective benefit	**BDI (9 weeks):** d=0.30, 95%CI 0.05-0.55

	(8.98) in delayed treatment groups Germany			
Meyer et al. 2015 RCT	163 people exceeding threshold for severe depression (PHQ-9 greater than 15) Germany	**Intervention:** Deprexis plus usual care **Comparator:** Usual care/waitlist	PHQ-9, GAD-7, PHQ-15, quality of life, treatment satisfaction, alliance/ helpfulness	**PHQ-9 (3 months post treatment)** d = 0.33, 95% CI: - 0.03-0.69 **PHQ-9 (6 months post treatment)** still significantly different (p=0.07) (Both for ITT sample)
Moritz et al. 2012 RCT NCT01401296	210 people with elevated (moderate) depression symptoms Germany	**Intervention:** Deprexis **Comparator:** Waitlist	BDI, Dysfunctional Attitude Scale, Rosenberg Self-Esteem Scale, quality of life, subjective benefit	**BDI score** d = 0.36 (ITT) (p = 0.03)
Twomey et al. 2017, 2020 Meta-analysis (original and update)	12 RCTs on a total of 2901 people with depression International	**Intervention:** Deprexis **Comparator:** Waitlist, delayed access, no treatment, treatment as usual, or active control interventions (computerised or not)	Self-reported or clinician-rated depression measures	Deprexis was more effective than comparators in improving depressive symptoms (g=0.51, 95% CI 0.40-0.62)

Beating the Blues				
Gilbody et al. 2015 Littlewood et al. 2015 Pragmatic RCT REEACT	691 people with PHQ-9 score greater than or equal to 10 (mean PHQ-9 was 17, moderate depression) UK (includes IAPT treatment)	**Intervention:** Usual care from GP plus Beating the Blues; Usual care from GP plus MoodGYM **Comparator:** Usual care from GP	Improvement in depression (PHQ-9), CORE-OM, quality of life, treatment preference, acceptability, user experience, adverse events	No statistically significant improvement in PHQ-9 at four months compared to usual GP care (p= 0.46) or at 12 and 24 month follow up.
McCrone et al. 2004 Proudfoot et al. 2004 RCT	274 people with depression or anxiety (people with mild to severe depression included) UK	**Intervention:** Beating the Blues (results were automatically sent to a health professional after each session) **Comparator:** Usual care	Change in depression level (BDI), Beck Anxiety Inventory, Work and Social Adjustment Scale	**BDI-II:** Intervention: mean (SD): 11.6 (9.6) Control: mean (SD): 16.2 (10.1) p=0.0006
Wysa				
Inkster et al. 2018 Mixed methods	129 users of the Wysa app Mean PHQ-9 for higher users 18.92 and 19.86 for low users International	**Intervention:** Wysa (AI-guided) Higher users: engaging on the app on 2 screening days and at least once in between.	Mood improvement (using the PHQ-2), user experience, user engagement	Mood improvement of high users showed greater improvement than low users Mean (SD) improvement 5.84 (6.66) versus 3.52 (6.15)

		Comparator: none		
Beatty et al. 2022 Mixed methods	1205 people who screened positively for depression or anxiety on PHQ-4 International	**Intervention:** Wysa (AI-guided) **Comparator:** none	Therapeutic alliance, acceptability of conversational agent	**Therapeutic alliance** Assessment 1 (Day 1-5 after installation, n=1,205) mean WAI-SR: 3.64 (SD 0.81) Assessment 2 (3 days after first measure, n=226) mean WAI-SR: 3.75 (SD 0.80)
Abbreviations used: BDI, Beck Depression Inventory; CI, Confidence interval; CORE-OM, Clinical Outcomes in Routine Evaluation - Outcome Measure; GAD, Generalised Anxiety Disorder assessment; GP, General practitioner; IAPT, Improving Access to Psychological Therapies (now known as NHS Talking Therapies); ITT, Intention to treat; PHQ, Patient Health Questionnaire; PWP, psychological wellbeing practitioner; RCT, Randomised Controlled Trial; SD, Standard Deviation; WSAS, Work and Social Adjustment Scale				

Overall, the EAG notes that the largest number of RCTs were available for Deprexis, although these were largely done in Germany. For Space from depression, there was RCT evidence supporting a benefit of Space from Depression in both an IAPT setting and in Ireland. For Beating the Blues, there was an RCT which did not show significant benefit of the technology with usual GP care versus usual GP care alone (usual GP care including access any treatment usually available, including an IAPT referral). However, this trial used Beating the Blue with technical support and encouragement from a trained technician rather than the technology being guided by a psychological therapist. One clinical expert states that there are some similarities to how the technology would be used in practice as psychological wellbeing practitioners (PWPs) would provide encouragement to use the tools but the nature of the support could be different, as patients can receive answers on clinical questions. However, there could be variation in the level of clinical content in the support given by a PWP, dependent on local practices. The trial also reported a low level of engagement in using the digital technology. As this trial was done in 2015, the usability of the technologies has improved since. Evidence from other trials using Beating the Blues did show a beneficial effect on depressive symptoms and quality of life.

For all other scoped interventions (Iona Mind, Wysa and Minddistrict) there was limited or no relevant clinical evidence was available within the population. For Iona Mind, no published clinical outcomes were identified. For Minddistrict, there were papers published on clinical efficacy, but these were in ruminating university students and adolescents and young people (Cook et al. 2019 and Topper et al. 2017). For Wysa, 3 eligible studies were identified (Beatty et al. 2022; Inkster et al. 2018; Malik et al. 2022). However, these were limited by the clinical outcome measures, single arm design and international setting.

Patient experience data was available for Deprexis, Beating the Blues, Wysa and SilverCloud. All reported feedback that was in favour of the use of the digitally enabled therapies.

3.2 Summary of economic evidence

The EAG searches identified 11 publications of direct relevance and 25 publications of indirect relevance to the economic analysis. Of these, 5 economic evaluations alongside clinical trials were identified which provided evidence for Beating the Blues, Space from Depression and Deprexis. Details of these are summarised below. For full details on the published economic evidence, see section 12.1 of the assessment report.

For Space from Depression, 1 UK economic evaluation was done alongside an RCT in an IAPT setting (Richards et al. 2020). The study reported results for people with anxiety and depression combined rather than separately by primary diagnosis. The study concluded that over the 8 weeks of treatment, probability of cost-effectiveness was 46.6% if decision makers are willing to pay £30,000 per quality adjusted life year (QALY; incremental cost effectiveness ratio [ICER] £29,764) when using an estimated intervention cost of £94.63 per person. The probability increases to 91.2% when the control-arm's outcomes and costs were extrapolated over 12-months.

For Deprexis, 2 economic evaluations alongside German RCTs were identified. Both studies found evidence that use of Deprexis had the potential to reduce costs. Gräfe et al. (2020) used data from a 12-week pragmatic RCT (n=3,805) of Deprexis with care as usual compared to care as usual alone. In the intervention group total costs decreased by 32% from €3139 per year at baseline to €2119 in the study year (compared to a mean reduction in total costs of 13% in the control group). Gräfe et al. (2017) used data from a 12-week RCT (n=1,013) comparing Deprexis with usual care compared with usual care. In both groups total direct health care costs decreased during the study period but changes from baseline did not significantly differ between study groups. For both studies, the analysis did not include the license cost for Deprexis.

Two UK economic evaluations alongside RCTs have been reported for Beating the Blues. McCrone et al. (2004) reports the cost-effectiveness of

treatment with Beating the Blues based on data from 274 adults with a diagnosis of depression, mixed depression and anxiety, or anxiety disorders at 12 general practices in England with 8-month follow-up. The improvement in QALYs with Beating the Blues over standard care was 0.032 (3%). The authors acknowledge that this QALY is relatively small, but the follow-up period was also relatively short. At the submitted license cost there was a 99% chance of the intervention being cost-effective at a willingness to pay of £15,000 per QALY and 85% at £5,000 per QALY. The REEACT RCT (n=691; Littlewood et al. 2015, Duarte et al. 2017, Duarte et al. 2014) which included adults with more severe depression (PHQ-9 greater than or equal to 10) assessed the cost-effectiveness of treatment with free (MoodGYM) and commercial (Beating the Blues) programmes for depression in adults as an adjunct to GP care with 2-year follow-up. Neither digital therapy was found to be cost-effective compared with usual GP care alone. The clinical evidence used here found that the digital therapies had negligible impact on patient quality of life in comparison to usual GP care alone. In this trial less than 20% of people given a digital therapy completed the treatment and the digital therapies were supported but not guided. The economic results reported that Beating the Blues was dominated by usual care with a mean difference in QALYs of -0.0435 and a mean difference in costs of £104.24 at a license cost of £50 per patient based on a £250 fee per 5 courses of therapy. At a £20,000 per QALY threshold, usual GP care alone had the highest probability of being cost-effective (0.55) followed by MoodGYM (0.42) and Beating the Blues (0.04). The authors report that the magnitude of the differences in costs and QALYs between all groups appeared minor and not significant.

EAG conceptual modelling

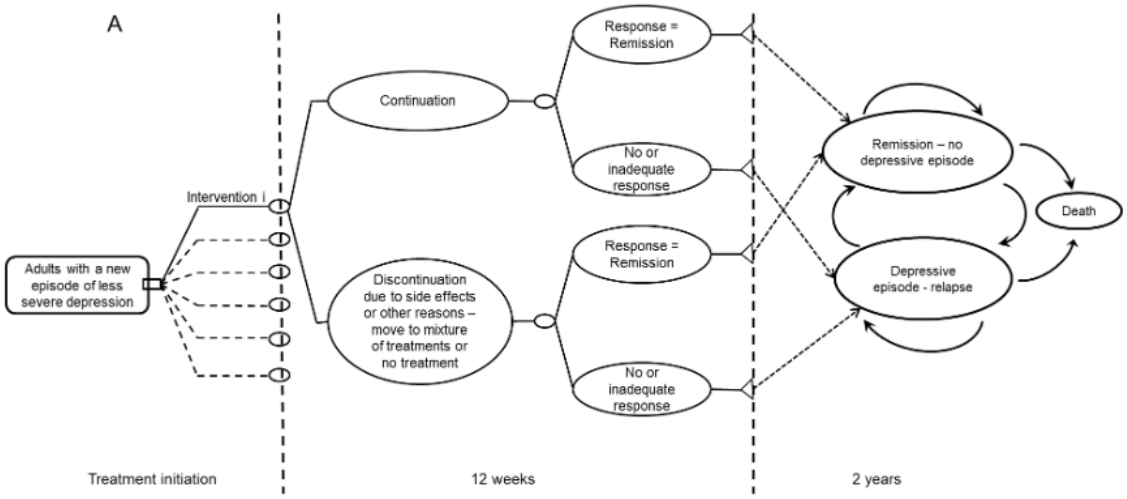
The EAG adapted the economic model from NICE's guideline on depression in adults, with less and more severe depression being modelled separately (Figure 1).

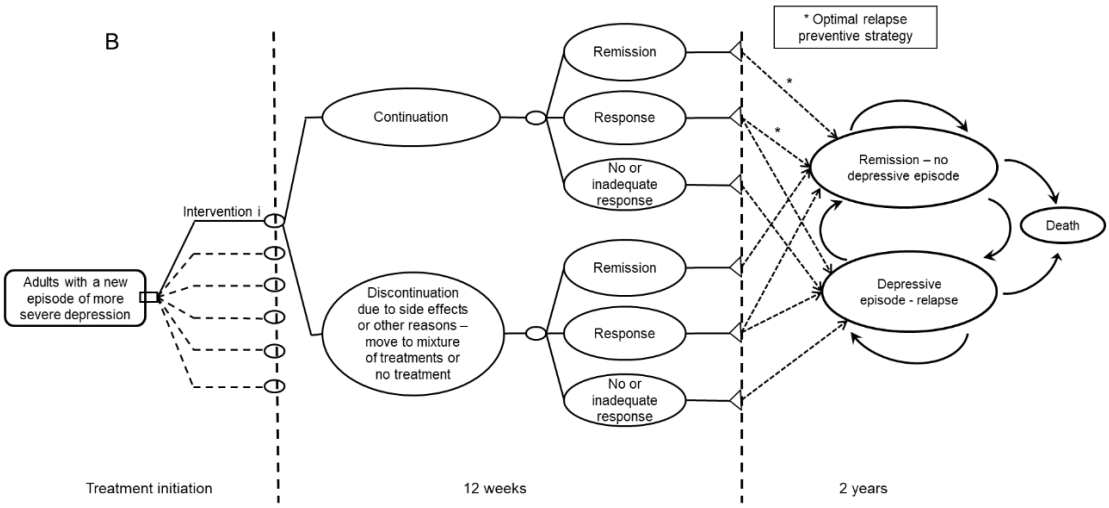
The model comprises a decision tree for the first 12 weeks. Here the model assesses whether treatment is completed at 12 weeks and the treatment response (response defined as a 50% or more improvement from baseline on

any depression scale). For more severe depression response is split into remission (no longer meeting diagnostic criteria) and response. There is then a transition into a Markov model to consider whether or not the patient relapses by 2 years. The Markov model has year cycles with a half-cycle correction applied.

In each model cycle, people entering the Markov component of the model could either remain in the same 'entrance' state, move between the remission and the depressive episode states, or move to the death state (absorbing state). Within the remission and depressive episode states, people entered tunnel states, so that the time they remained in every state (one or two years) could be estimated and a time-dependent probability of relapse or remission, respectively, could be applied.

Figure 1: Schematic diagram of the structure of the economic model of treatments for adults with a new episode of (A) less severe depression and (B) more severe depression





Source: Figure 63, NICE NG222 Evidence Review B

Model parameters

Clinical parameters

For all three interventions with RCT-level evidence more than one key study was identified for inclusion in the economic model. As there was no clear indicator for selecting the most relevant study for any of the interventions, results are presented as a weighted average of each of the included individual studies (according to sample size). Due to the design of the available studies, a waitlist control was added as a relevant comparator, although this was not considered in the NICE clinical guideline on adults with depression. None of the studies included in the evaluation were included in the clinical guideline economic model.

Depression severity and response were measured on either the PHQ-9 or the Becks Depressive Inventory scale (BDI) for all included studies. Response at 12-weeks used log odds ratios, converted from Cohen's D or Hedges' G effect sizes. It was assumed that the effect size in the intention to treat population reported in studies is similar to the effect size in completers. For discontinuation, log odds ratios were calculated by the EAG using the number of participants who discontinued from both the treatment group and the control group in each paper. As the meta-analysis for Deprexis (Twomey et al.

2020) did not present discontinuation data, the EAG calculated a weighted average of 4 included papers for Deprexis. For remission rates, none of the key studies reported this value for people with more severe depression. An assumption is made that the remission rates are the same as those receiving generic computerised CBT in the NICE clinical guideline.

For the response and discontinuation parameters for each relevant study, see table 9 and 10 of the assessment report.

Costs and resource use

The resource use assumptions for each of the technologies are described in table 3 and the unit costs in table 4. The license costs provided are based upon costs supplied by the companies. Some companies use tiered pricing systems and so an average cost has been used in the base case model. There are also differences in the length of the course of treatment and suggested level of support from healthcare practitioners.

As all digitally enabled technologies need access to computing equipment and an internet connection, the cost of a tablet computer and mobile internet connection for the duration of the interventions is included as a resource use item for all interventions. This is a conservative assumption to address equity concerns around digital exclusion. The EAG notes that relative to other parameters in the model, these costs constituted a very small proportion.

Training, set-up and administrative costs for NHS staff were not included in the model and is therefore a limitation.

All other costs, including those associated with comparator therapies, were taken from the NICE clinical guideline on adults with depression (NG222).

Table 2 Resource items and quantities for interventions

	Space from Depression	Beating the Blues	Deprexis	Iona Mind	Minddistrict	Wysa
Duration of intervention	8 weeks	8-10 weeks	8-12 weeks	5-6 weeks	6 weeks	Dependent upon intended use (e-triage or treatment)
Resource items	Tablet computer or smartphone	Tablet computer or smartphone	Tablet computer or smartphone	Tablet computer or smartphone	Tablet computer or smartphone	Tablet computer or smartphone
	Internet connection (8 weeks)	Internet connection (8-10 weeks)	Internet connection (10 weeks)	Requirement for continuous internet access unclear	Internet connection (6 weeks)	Requirement for continuous internet access unclear
	6 sessions of 15 minutes with a PWP	60 minute telephone call with a PWP over 8-10 period	5 minute interaction after 3 weeks, plus a 30 minute initiation and completion therapy calls	Typically 5-6 sessions of 30 minutes with a PWP	6 sessions of 30 mins with a therapist (trained CBT therapist)	Step 2: two review calls 30-45 mins Step 3: weekly/fortnightly calls 30-45 mins with a PWP

Table 3 Unit costs

Item	Cost used in AR model	Source
Licence cost: Space from Depression	£5.13	Mean cost calculated from company submission
Licence cost: Beating the Blues	[redacted]	Mean cost calculated from company submission
Licence cost: Deprexis	£270	Company submission (cost of private purchase of intervention)
Licence cost: Iona Mind	Not provided	Company submission
Licence cost: Minddistrict	[redacted]	Company submission
Licence cost: Wysa	[redacted]	Company submission
Tablet computer or smart phone	£80	Representative cost from large online retailer, January 2023. 10” Android tablet with sim card slot. A basic smart phone is similar cost
Data sim card, per month	£20	Representative cost from price comparison website, January 2023. Unlimited 5G data-only plan, 1m contract
Psychological wellbeing practitioner, Band 5 (cost per hour)	£50	Unit costs 2020 as in the NICE clinical guideline (NG222) economic model

Health state utilities

The EAG used utility values from NICE's clinical guideline of adults with depression. These are summarised in table 15 of the assessment report.

Approach to analysis

The EAG conducted a cost utility analysis reporting net benefit at willingness to pay threshold of £20,000 per QALY gained and analysis of uncertainty. The net monetary benefit is calculated as the incremental benefits multiplied by the willingness to pay threshold (assumed to be £20,000 per QALY), minus incremental costs. Results presented are mean cost, QALYs, net monetary benefit at a willingness to pay threshold of £20,000/QALY and ranking in terms of net monetary benefit. All results are reported for a cohort of 1,000 patients. Probabilistic analyses are presented in all cases, with 100,000 simulations from input distributions.

Results

For less severe depression (Table 5) the results of the probabilistic analysis found generic computerised CBT (as analysed within the clinical guideline on depression) to be in the middle of the ranking with some individual technologies being higher and some being lower. The difference in the net monetary benefit between the most cost-effective and least cost-effective intervention within the overall treatment pathway was less than 5%. This means that there is the plausibility for digitally enabled therapies to be cost-effective in less severe depression. However, there is still uncertainty surrounding the economic case.

Table 4: Base case results, Less Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY	Mean NMB Rank
CBT group	[redacted]	[redacted]	[redacted]	[redacted]
BA group	[redacted]	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]	[redacted]
Sertraline	[redacted]	[redacted]	[redacted]	[redacted]
Space From Depression	[redacted]	[redacted]	[redacted]	[redacted]
MBCT group	[redacted]	[redacted]	[redacted]	[redacted]

Generic computerised CBT	[redacted]	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]	[redacted]
Deprexis	[redacted]	[redacted]	[redacted]	[redacted]
Counselling	[redacted]	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]	[redacted]
Beating the Blues	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BA, behavioural activation; CBT, cognitive behavioural therapy; IPT, Interpersonal psychotherapy; NMB, net monetary benefit; MBCT, Group mindfulness-based cognitive therapy; PDPT, psychodynamic psychotherapy; QALY, quality-adjusted life years.

In more severe depression (Table 6) the results of the probabilistic analysis placed Deprexis (the only treatment with evidence in this subgroup) towards the bottom end of the rankings list. Generic computerised CBT with support resulted in a marginally higher net monetary benefit than Deprexis. The difference in the net monetary between the most cost-effective and least cost-effective option was 9%. Whilst a positive net monetary benefit shows a cost-effective result compared to existing care, digitally enabled therapies are unlikely to be the most cost-effective treatment for more severe depression. This is similar to the results reported in the clinical guideline on depression.

Table 5: Base case results: More Severe Depression (1,000 patients)

	Cost	QALYs	Mean NMB £20,000 per QALY	Mean NMB Rank
Problem solving	[redacted]	[redacted]	[redacted]	[redacted]
CBT individual + escitalopram	[redacted]	[redacted]	[redacted]	[redacted]
Duloxetine	[redacted]	[redacted]	[redacted]	[redacted]
Mirtazapine	[redacted]	[redacted]	[redacted]	[redacted]
Escitalopram	[redacted]	[redacted]	[redacted]	[redacted]
BA individual	[redacted]	[redacted]	[redacted]	[redacted]
Exercise group	[redacted]	[redacted]	[redacted]	[redacted]
Lofepramine	[redacted]	[redacted]	[redacted]	[redacted]
Trazodone	[redacted]	[redacted]	[redacted]	[redacted]
Generic computerised CBT with support	[redacted]	[redacted]	[redacted]	[redacted]
CBT individual	[redacted]	[redacted]	[redacted]	[redacted]

Counselling	[redacted]	[redacted]	[redacted]	[redacted]
Deprexis	[redacted]	[redacted]	[redacted]	[redacted]
Generic computerized CBT without support	[redacted]	[redacted]	[redacted]	[redacted]
Short-term PDPT	[redacted]	[redacted]	[redacted]	[redacted]
IPT	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BA, behavioural activation; CBT, cognitive behavioural therapy; IPT, Interpersonal psychotherapy; NMB, net monetary benefit; PDPT, psychodynamic psychotherapy; QALY, quality-adjusted life years.

The results presented here are based on the 3 of the interventions with enough comparative evidence to be included in the model. For Iona Mind, no cost or effectiveness information was provided. As a result, no evaluation was possible. Although licence costs were provided for Minddistrict and Wysa, there was no in scope effectiveness data or effectiveness data was not provided on a relevant scale. This meant that a cost effectiveness estimate could not be generated.

Additional analyses

To demonstrate the drivers of costs and QALYs associated with the included digitally enabled therapies, the EAG provided cost and QALY breakdowns for representative studies for less severe and more severe depression. This showed that the major cost components for the interventions are GP costs for follow-up for non-completers who respond to subsequent therapy (£821/£1,835, 44.72%), and the cost of a non-remitted episode for those with more severe depression (£1,042/£2,390, 44%).

The costs which directly relate to digitally enabled therapies make up 13% (£239/£1,835) of the costs for less severe depression and 19% (£463/£2,390) of the costs for more severe depression. This demonstrates that the key cost driver relate to effectiveness of the treatment and the next step in the treatment pathway for those in which treatment with a digitally enabled therapy has not improved symptoms.

In response to clinical expert feedback that digitally enabled therapies may be delivered by a band 6 rather than band 5 healthcare professional, scenario

analysis was done. This showed that using a band 6 rather than band 5 staff cost for digitally enabled therapy appointments had minimal impact. A scenario analysis using higher licence costs, to account for technologies that have tiered pricing systems, was also done. This led to a minimal difference in net monetary benefit as the licence fees are not a key driver in the economic analysis.

4 Ongoing research

The companies supplied information on ongoing studies. The EAG did not identify any additional ongoing clinical studies. The relevant ongoing studies are summarised briefly below. For full details on the ongoing studies, see section 13.4 of the assessment report.

Space from Depression

Of the list of ongoing trials provided, the EAG note that 1 is potentially relevant to the scope. This is an RCT on 3360 people looking at adjunctive internet-based cognitive behaviour therapy for treating major depressive disorder among primary care patients in the US (Bossarte et al. 2022). Here the treatment arms are usual care plus guided remote CBT (using Space from Depression), usual care or usual care with unguided remote CBT.

Minddistrict

Of the company provided information, the EAG considered 1 ongoing study could be relevant to the scope. This is an ongoing study (TRENT – testing the depression module in adults) which is expected to complete in February 2023. No further information on this study was provided.

Beating the Blues

The company states that [redacted].

Deprexis

No ongoing trials were noted in the company submission.

Wysa

The company provided a number of under review manuscripts and ongoing grant funded research. However, the EAG did not consider these relevant to the current scope on grounds of population.

Iona Mind

The company submission notes that research in an NHS Talking Therapy setting will be done imminently using a single arm pre-post design at Step 2 in the care pathway.

5 Evidence gap analysis

The EAG presented a summary of the evidence gaps, relating to intermediate and final outcomes from the scope, and those related to the decision modelling, which can be found in table 7. To note, the categorisation of 'patient reported outcomes: patient experience' has changed from red to amber for Space from Depression following company fact check identifying additional studies.

Table 6: Evidence Gap Analysis

Outcomes	Space from Depression	Minddistrict	Beating the Blues	Deprexis	Wysa	Iona Mind
Clinical trials						
Intermediate outcome: Patient choice and preferences	No studies **RED**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**
Intermediate outcome: Treatment satisfaction and engagement	No studies **RED**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**
Intermediate outcome: Intervention adherence and completion	Multiple studies **GREEN**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**	No studies **RED**
Intermediate outcome: Referral to treatment time	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**

Outcomes	Space from Depression	Minddistrict	Beating the Blues	Deprexis	Wysa	Iona Mind
Intermediate outcome: Assessment to treatment time	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**
Intermediate outcome: Intervention-related adverse events	No studies **RED**	No studies **RED**	One RCT **AMBER**	One study **AMBER**	No studies **RED**	No studies **RED**
Intermediate outcome: Inaccessibility to intervention (digital inequalities)	No studies **RED**	No studies **RED**	One study **AMBER**	Multiple studies from one trial **AMBER**	No studies **RED**	No studies **RED**
Intermediate outcome: Rates of attrition (dropouts) and engagement	Multiple studies **GREEN**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**	No studies **RED**
Clinical outcome: Change in depression symptoms	Multiple studies **GREEN**	No studies **RED**	Inconsistent trial evidence **AMBER**	Wide-ranging RCT evidence **GREEN**	One single-arm study **AMBER**	No studies **RED**
Clinical outcome: Change in other psychological symptoms	Multiple studies **GREEN**	No studies **RED**	Inconsistent trial evidence **AMBER**	Wide-ranging RCT evidence **GREEN**	No studies **RED**	No studies **RED**
Clinical outcome: Global functioning and work and social adjustment	Multiple studies **GREEN**	No studies **RED**	One single-arm study **AMBER**	Wide-ranging RCT evidence **GREEN**	No studies **RED**	No studies **RED**
Clinical outcome: Rates of reliable recovery	Multiple studies **GREEN**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**	No studies **RED**

Outcomes	Space from Depression	Minddistrict	Beating the Blues	Deprexis	Wysa	Iona Mind
Clinical outcome: Rates of reliable improvement	Multiple studies **GREEN**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**	No studies **RED**
Clinical outcome: Rates of reliable deterioration	Two single-arm studies **AMBER**	No studies **RED**	One study **AMBER**	Multiple studies **GREEN**	No studies **RED**	No studies **RED**
Clinical outcome: Rates of relapse (including relapse rate and time from remission to relapse)	One study **AMBER**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**	No studies **RED**
Patient reported outcomes: Health-related quality of life	One RCT, no effect **RED**	No studies **RED**	Inconsistent trial evidence **AMBER**	Multiple studies **GREEN**	No studies **RED**	No studies **RED**
Patient reported outcomes: Patient experience	Three studies **AMBER**	No studies **RED**	Multiple studies **GREEN**	Multiple studies **GREEN**	Multiple studies **GREEN**	No studies **RED**
Models and economic outcomes						
Effectiveness evidence: Comparative data	No direct comparisons of effect of the target interventions and either each other, an active control or treatment as usual in an IAPT population. Is one dCBT intervention more effective than another and TAU? **RED**					
Effectiveness evidence: Comparative data	Is one dCBT intervention more effective than another and face to face CBT? **RED**					
Effectiveness evidence: Follow-up times and lengths	Follow-up times vary across the source studies, which are crudely equalized to 12 weeks in the decision model. Common follow up times are required, along with longer term follow-up data (to 2 years). **RED**					

Effectiveness evidence: Impact of stepped care	The optimal treatment pathway following dCBT (repeat session, movement onto high intensity CBT?) and the impact of stepped care on treatment effectiveness are unclear. **AMBER**
Effectiveness evidence: Discontinuations / withdrawals	Withdrawals are currently accounted for a crude assumption of similar relative effectiveness for completers and the ITT population. Future studies should report withdrawal rates, reasons for discontinuation and response in both the ITT population and completers. **AMBER**
Effectiveness evidence: Population	Crude assumptions were required based upon mean or median baseline scores to determine whether patients were classified as having more or less severe depression. There were also fewer papers available considering more severe depression. Reporting by subgroup is required in future studies. **RED**
Effectiveness evidence: Differential wait times	The potential for, and impact of, differential wait times on outcomes for dCBT compared to TAU is unclear. **RED**
Effectiveness evidence: Network meta-analysis	A formal update of the NG222 meta-analysis is suggested once suitable evidence is available for specific treatments. **AMBER**
Effectiveness evidence: NHS Digital data	NHS Digital data could not be used within the current economic analysis as the publicly available data does not provide sufficient granularity and the manner in which patients who discontinue are handled differs from the economic analysis in the NG222 guideline. Ideally such data would be used to supplement future analysis. **AMBER**
Clinical outcome and costs: Qualifications of mental health contact	What type of support worker is required for dCBT treatments (Band 5 or Band 6) and how does this impact on effectiveness? **AMBER**
Clinical outcome and costs: Schedule of mental health contact	The optimal schedule for mental health contact (frequency and duration of contacts) is unknown along with the impact of this on cost-effectiveness. **RED**
Costs: Set up, administration and training costs	The costs associated with system set-up and integration with NHS systems, day to day administration and training of NHS staff to roll out dCBT are unclear. These costs are unrecoverable and could be substantial. **RED**
Costs: Licence costs and patient numbers	Licence costs are currently unknown and are expected to be based upon the volume of usage which is also uncertain. **AMBER**

Costs: Method of provision of access	The method to be used to provided patients who do not have the required hardware and internet connection at home with access is currently unclear. This impacts upon costs and also equality of access. **AMBER**
HRQoL: Caregivers	The impact of treatment on caregiver quality of life has not been included in prior modelling. **AMBER**
HRQoL: Definition of response and benefit	Exploration of broader definitions of response and patient benefit was suggested within the NG222 model following patient commentary that the current definition (50% improvement on any scale) is too narrow and not fully reflective of patient experience. **AMBER**
Abbreviations: dCBT, digital cognitive behavioural therapy (also referred to as digitally enabled therapy within this report); HRQoL, Health-related quality of life; ITT, intention to treat; NG222, NICE's clinical guideline on adults with depression; TAU, treatment as usual	

Summary and conclusions of evidence gap analysis

The EAG identified several evidence gaps. The evidence gaps most relevant to the early value assessment are as follows:

Population

- A minority of clinical studies were done in an IAPT setting
- In over half of included studies, the population was not restricted to depression and included other affective disorders (although expert advice was that co-morbidity of depression and anxiety is high and so may not be a major concern)

Intervention gaps

- There is no or limited relevant evidence on some technologies

Comparator gaps

- Most comparative studies used waitlist or usual care as a control rather than in scope comparators

Outcome gaps

- Published evidence was not available for some outcomes. There was also heterogeneity in how clinical measures are reported, though some key measures (such as PHQ-9 and BDI-II) are frequently reported
- Limited adverse event and safety data were reported

Key areas for evidence generation

The EAG concluded that more randomised controlled trials (RCTs), potentially using pragmatic or clustered designs. These would specifically focus on the scoped interventions compared to the scoped comparators in an IAPT setting with depression severity categorised as per NICE guidelines.

6 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Several potential equality issues have been identified. Key aspects include:

- Depression is more common in women than in men. Women, people from a White British background or in midlife are more likely than others to receive treatment for a common mental health disorder.
- Digitally enabled therapies are delivered through a mobile phone, tablet or computer. People need regular access to a device with internet access to use the technologies. Additional support and resources may therefore be needed for people who are unfamiliar with digital technologies or do not have access to smart devices or the internet.
- People with cognitive impairment, problems with manual dexterity, learning disabilities or who have difficulty reading or understanding health-related information may need additional support to use digitally enabled therapies.
- Digitally enabled therapies should be accessible to people with visual impairments using screen readers, and people with hearing impairments.
- People with English as a second language may have difficulties navigating digitally enabled therapies provided in English. Digitally enabled therapies and mental health services should consider how to translate these interventions or provide additional support as needed.
- People's views of mental health problems or intervention may be influenced by their ethnic, religion and cultural background. People have the right to make informed decisions about their care, including the use of digitally enabled therapies.
- People facing social inequality and disadvantage, discrimination and social exclusion are at higher risk of mental health problems.

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

7 Implementation

The NICE adoption team identified potential factors that could encourage implementation digitally enabled therapies for adults with depression:

- May increase treatments options and allow people to take ownership of their own care.
- Could lead to an increase in practitioner capacity, once they are used to delivering the technology.
- May be a successful treatment option and lead to improved outcomes.
- Greater accessibility for those with long term conditions, busy schedules and those where being open about mental health conditions may be particularly challenging.

Potential barriers include:

- Time is required to attend 1-to-2-day training sessions. A thorough understanding of the digital content is needed to pick the best modules or content for individuals.
- Cost may be a barrier, especially if there isn't a strong evidence base showing that use leads to good outcomes and savings elsewhere e.g., therapist capacity.
- Digital therapies may not be an option for all due to access to technology (e.g., smartphone or computer) and or technology literacy level.

8 Issues for consideration by the committee

Population

- The EAG found that the population in the included studies were broadly relevant to the decision problem. However, in 18 out of the 32 included studies (56%), the population was not restricted to depression and included adults with anxiety and other affective disorders. However, expert opinion is that there is very high comorbidity between anxiety and depression.

Clinical evidence

- The EAG included a total of 32 studies in the evaluation. Of these, 14 were RCTs on Deprexis, Space from Depression or Beating the Blues. There was also 1 meta-analysis on Deprexis summarising evidence from 12 RCTs. Of the included studies, 12 were done in the UK using Beating the Blues or Space from Depression. Two RCTs were done in an IAPT setting or involved IAPT services.

- For the non-UK studies, differences in health system organisation and treatment pathways may limit generalisability of the evidence. For the UK-based studies, a minority were done in an IAPT setting. It is unclear how generalisable the results would be to current clinical practice.

- For 3 other included technologies (Iona Mind, Minddistrict and Wysa) there was no or limited evidence on clinical efficacy for the in scope population.

Cost evidence

- The conceptual modelling showed digitally enabled therapies to be cost effective at the £20,000/QALY willingness to pay threshold in people with less severe depression.

- Although still cost effective, digitally enabled therapies are less likely to be the most cost effective option for people with more severe

depression. This is similar to the results reported in NICE's clinical guideline on adults with depression. The EAG note that the economic evidence in this population is limited by only one technology (Deprexis) reporting clinical outcomes on people with more severe depression.

- In addition to the economic analysis done by the EAG, there are also 5 previous economic evaluations alongside clinical trials for Space from Depression, Deprexis and Beating the Blues which were done in the UK and Germany. These studies generally found treatment with the digitally enabled therapy to be cost-effective compared usual care or waitlist control. The exception was the REEACT study which found Beating the Blues to be dominated by usual care (in line with no significant difference in clinical effectiveness).

- There was not enough clinical evidence on Iona Mind, MindDistrict or Wysa to evaluate the technologies quantitatively in the economic model as efficacy was a key driver of results within the model.

- Overall, the EAG concluded that there is uncertainty in the economic modelling due to the limitations in the clinical evidence base.

Key gap analysis conclusions

- Most evidence was not collected within an NHS Talking Therapies setting and were limited by the use of waitlist or usual care as comparators

- Three of the technologies identified had limited or no evidence on clinical efficacy within the scoped population

- There was heterogeneity in how clinical measures are reported, with published evidence not available for some outcomes such as those relating to safety or adverse events.

9 Authors

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NICE Medical Technologies Evaluation Programme

February 2023

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

Details of assessment report:

- Barnish M et al., Digitally enabled therapies for adults with depression [MTG588] External Assessment Group report, January 2023

  For a list of the organisations that accepted the invitation to participate in this assessment as stakeholders and the Expert Adviser Specialist Committee members, see the published project documents. They were invited to attend the scoping workshop and to comment on the external assessment report.

  Manufacturers and developers of technologies included in the final scope:

  - Beating the Blues
  - Minddistrict
  - Space from Depression
  - Wysa
  - Deprexis
  - Iona Mind

Related NICE guidance

- NICE clinical guideline 222 (2022), Depression in adults: treatment and management. Available from https://www.nice.org.uk/guidance/ng222

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Digitally enabled therapies for adults with depression
Final scope

November 2022

1 Introduction

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

NICE's topic selection oversight panel ratified digitally enabled therapies for depression in adults as potentially suitable for an EVA by the medical technologies evaluation programme (MTEP).

A list of abbreviations is provided in appendix A.

2 Description of the technologies

This section describes the properties of the digital technologies based on information provided to NICE by manufacturers and experts and information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technologies

Depressive disorders are very common and are among the leading causes of disability worldwide. In people aged 18 to 44 years, depression is the leading cause of disability and premature death (NICE clinical knowledge summary, 2022).

Improving and widening services for mental health is a commitment of the NHS (NHS Long Term Plan). The Five Year Forward View for Mental Health and Long Term Plan states that IAPT services need to increase access to support so at least 25% of people (or 1.5 million) with common mental health conditions access services each year and that 75% of people need to access treatment within a 6 week waiting time by 2020/21.

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). This may be for many reasons including IAPT therapies not being suitable for a person's level of risk or impairment. 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 depression. They can be delivered online or through apps and allow people to self-manage their mental health condition with varying levels of practitioner 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.

Digitally enabled therapies may offer greater flexibility, more choice and self-management through remote interventions. They may also help to increase access and reduce waiting lists by improving productivity in care provision. For example, therapist time may be saved as much of the clinical content is presented through digital self-study modules, backed up by weekly remote discussions with the therapist.

2.2 Product properties

NICE's clinical guideline on depression in adults: treatment and management states that guided self-help may include materials based on structured CBT, problem solving, psychoeducation and behavioural activation delivered face-

to-face or by telephone or online. It can be delivered with support from a trained practitioner who facilitates the self-help intervention, encourages completion and reviews progress and outcomes and usually consists of 6 to 8 structured regular sessions.

This scope focuses on digitally enabled therapies for treating and managing depression in adults. Digitally enabled therapies are products that deliver a substantial portion of therapy through its content but are designed to be used with practitioner or therapist support. The draft IAPT assessment criteria for digitally enabled therapies defines this as technology use based on practitioner or therapist review of a patient's progress along with regular (weekly or biweekly) interactions with the patient about their progress. The assistance will also help people deepen their understanding of the intervention materials, support them in setting goals and provide advice on real world assignment.

For this EVA, NICE will consider digitally enabled therapies that:

- are intended for use by adults
- deliver a therapeutic intervention in line with NICE guidelines that can be used in IAPT services with practitioner or therapist support
- deliver a substantial portion of the therapy through the technology rather than being platforms to support teletherapy
- meet the standards within the digital technology assessment criteria (DTAC), including the criteria to have a CE or UKCA mark where required. Products may also be considered if they are actively working towards required CE or UKCA mark and meet all other standards within the DTAC.
- are available for use in the NHS.

Technologies included in this EVA are also expected to complete the IAPT Digitally Enabled Therapies (DET) assessment criteria at an appropriate point. This includes validation of clinical content in line with NICE guidelines and light-touch assessment of clinical effectiveness, to ensure the product meets baseline standards for use in IAPT. The status of each product against the IAPT DET assessment criteria will be included in the EVA.

In total, 6 digitally enabled therapies for adults with depression are included in the scope. The final list of included technologies may be subject to change.

Space from Depression (SilverCloud):

Space from Depression is an online CBT programme for adults with low mood and depression. It aims to teach users skills and strategies to manage depression. The programme comprises of modules that contain quizzes, videos, information, personal stories, interactive activities, homework suggestions and summaries. In addition, the interventions incorporate mindfulness tools and resources, positive psychology, and motivational interviewing techniques. It can be used as a supported or a self-guided programme within IAPT services. Practitioners or therapists can guide people through the programme using built-in messaging within the platform. SilverCloud recommends that all programmes are used with a supporter who regularly reviews progress, provides feedback and unlocks content. Silvercloud has other programmes which can be used for a range of other mental health conditions, including a programme for anxiety and depression combined. However, experts state that the programmes for individual indications are primarily used in IAPT services. SilverCloud has screening tools incorporated into the programme, including the PHQ-9, which can be used to flag risk and send risk alert emails to the user's supporter or relevant members of the care team. Programmes can be accessed at any time using any smartphone, tablet, or computer.

Minddistrict (Minddistrict):

Minddistrict is an online CBT programme intended for treating psychological health conditions, including mild-to-moderate depression. It has a catalogue of modules, diaries, and questionnaires that can be combined and edited to suit the needs of each person. These include modules on mindfulness and self-help short courses that support everyday issues. Minddistrict can be used as a standalone self-help tool or in a therapist-guided model of care, which allows practitioners to use video calling within the platform. The company state that the IAPT depression module has been designed to treat mild-to-

moderate depression in adults. This consists of 7 sessions that are usually completed in 6 weeks. In this IAPT version, the Minimum Data Set is included in the module, with the PHQ-9 questionnaire included to allow services to automatically collect outcomes. The technology can be accessed via a web browser and there is also a smartphone app.

Beating the blues (365 Health Solutions Ltd.):

Beating the Blues is an online CBT program for individuals with mild to moderate depression and anxiety. Each of the 8 sessions comprise 3 or 4 modules each taking 10 to 15 minutes to complete. The sessions contain both reading material and practical hands-on tools and lasts 8 to 12 weeks. It can be used according to the user's preferences with any computer, laptop, smartphone or tablet with internet access.

Deprexis (Ethypharm Digital Therapy):

Deprexis is a web-based program based on elements from CBT intended to help those with unipolar depression or depressive disorders. It is intended to be used as a supplement to care-as-usual. Deprexis integrates 10 modules on topics related to depression. During these modules, the technology adapts its approach according to the needs and preferences of the user. Worksheets, exercises, audio sequences, short texts and illustrations are also available to in order to guide people through the program. It can be used according to the user's preferences with any computer, laptop, smartphone or tablet with internet access. Progress can be tracked using the PHQ-9 questionnaire and moodcheck (to monitor mood). These questionnaires (in addition to progression charts) can then be downloaded to be shared with a healthcare professional.

Wysa (Wysa Ltd.):

Wysa is an artificial intelligence-based app for people with mild to moderate depression and anxiety. It has a collection of CBT-based self-help programmes that are designed to be used with practitioner or therapist support. This includes a web-based therapist companion portal that lets

practitioners and therapists review a person's engagement and recommend programmes. Wysa has an AI-guided chatbot that uses natural language processing to encourage self-reflection and help users engage with the mental health tools. It has built in mental health assessment which collects outcome data such as the PHQ-9 questionnaire. Wysa includes a risk alert system and pathway that provides grounding exercises, a crisis care plan and crisis numbers for emergency support. In addition to the patient app, Wysa also has a web-based AI-supported e-triage tool that collects data based on questions from the referral form for IAPT services.

Iona Mind (Iona Mind):

Iona Mind is an app-based CBT programme for people with depression or generalised anxiety disorder. It is designed to be used alongside therapist support. 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. Progress can be tracked using screening measures such PHQ-9. It also monitors mood and goal progression. The app additionally has functionality to identify crisis events and provide signposting.

Perspectives (Koa Health):

Perspectives is an app-based CBT programme adults with depression. It is designed to be used alongside therapist support. This includes a web-based admin portal that lets practitioners and therapists review a person's progress. The technology has in-app messaging (asynchronous messaging) for people to communicate with their healthcare provider between follow up appointments. Progress can be tracked using screening measures such as PHQ-9.

3 Target conditions

The target population for this assessment is adults with depression.

Depression is a common mental health problem which can present with a variety of different symptoms. It is characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioural symptoms.

In ICD-11, depression is defined as the presence of depressed mood or diminished interest in activities occurring most of the day, nearly every day, for at least 2 weeks, accompanied by other symptoms such as:

- reduced ability to concentrate and sustain attention or marked indecisiveness
- beliefs of low self-worth or excessive or inappropriate guilt
- hopelessness about the future
- recurrent thoughts of death or suicidal ideation or evidence of attempted suicide
- significantly disrupted sleep or excessive sleep
- significant changes in appetite or weight
- psychomotor agitation or retardation
- reduced energy or fatigue

Depression severity exists along a continuum and is composed of 3 elements:

- symptoms (which may vary in frequency and intensity)
- duration of the disorder
- the impact on personal and social functioning.

Depression has traditionally been grouped in 4 categories: subthreshold, mild, moderate and severe. NICE's clinical guideline on depression in adults: treatment and management has categorised new episodes of depression as less severe or more severe depression, based on the available evidence on the classification. Less severe depression includes subthreshold and mild depression, and more severe depression encompasses moderate and severe depression.

NICE's clinical guideline on depression in adults: treatment and management states that each year 6% of adults in England will experience an episode of depression and more than 15% of people will experience an episode of depression over the course of their lifetime. For many people the episode will not be severe, but for more than 20% the depression will be more severe and have a significant impact on their daily lives. Recurrence rates are high: there is a 50% chance of recurrence after a first episode, rising to 70% and 90% after a second or third episode, respectively. Women are between 1.5 and 2.5 times more likely to be diagnosed with depression than men. However, although men are less likely to be diagnosed with depression, they are more likely to die by suicide, have higher levels of substance misuse and are less likely to seek help than women. Depression can have a major detrimental effect on a person's personal, social and work life. This places a heavy burden on the person and their carers and dependents, as well as placing considerable demands on the healthcare system. Depression is the leading cause of suicide, accounting for two-thirds of all deaths by suicide.

3.1 Care pathway

NICE's clinical guideline on depression in adults: treatment and management recommends considering a number of factors when considering treatment including:

- assessment of need
- any physical health problems
- any coexisting mental health problems
- factors that would make the person most likely to engage with treatment
- previous treatment history
- barriers to the delivery of treatments because of any disabilities, language or communication difficulties

It also recommends matching the choice of treatment to meet the needs and preferences of the person with depression and use the least intrusive and

most resource efficient treatment that is appropriate for their clinical needs, or one that has worked for them in the past.

For all people with depression having treatment:

- review how well the treatment is working with the person between 2 and 4 weeks after starting treatment
- monitor and evaluate treatment concordance
- monitor for side effects and harms of treatment
- monitor suicidal ideation, particularly in the early weeks of treatment
- consider routine outcome monitoring (using appropriate validated sessional outcome measures, for example PHQ-9) and follow up.

Less severe depression:

The guideline recommends discussing treatment options with people with a new episode of less severe depression and matching their choice of treatment to their clinical needs and preferences. All treatments listed below can be used as first-line treatments, but it is recommended to consider the least intrusive and least resource intensive treatment first (guided self-help):

- Guided self-help
- Group cognitive behavioural therapy (CBT)
- Group behavioural activation (BA)
- Individual CBT
- Individual BA
- Group exercise
- Group mindfulness and meditation
- Interpersonal psychotherapy
- Selective serotonin reuptake inhibitors
- Counselling
- Short-term psychodynamic psychotherapy

The list is arranged in order of the guideline committee's consensus on the average effectiveness and cost effectiveness of the treatments in adults with

less severe depression, with the most effective and cost effective listed at the top. Factors which may promote implementation, such as the use of least intrusive treatments first, have also been taken into account. If a less intrusive treatment has not worked then treatment can then be stepped up to offer other treatment options.

More severe depression:

The guideline recommends discussing treatment options with people with a new episode of less severe depression and matching their choice of treatment to their clinical needs and preferences. All treatments listed below can be used as first-line treatments:

- Combination of individual CBT and an antidepressant
- Individual CBT
- Individual BA
- Antidepressant medication
- Individual problem-solving
- Counselling
- Short-term psychodynamic psychotherapy
- Interpersonal psychotherapy
- Guided self-help
- Group exercise

The list is arranged in order of the guideline committee's consensus on the average effectiveness and cost effectiveness of the treatments (as well as consideration of implementation factors) with the most effective and cost effective listed at the top, but the committee agreed that choice of therapy should be a personalised decision and that some people may prefer to use a treatment further down the list and that this is a valid choice.

The guideline committee note that although guided self-help can be a treatment option for people with severe depression, other treatment choices with more therapist contact should be carefully considered first.

The guideline also states that commissioners and providers of mental health services should consider using models such as stepped care or matched care for organising the delivery of care and treatment of people with depression. The Improving Access to Psychological Therapies (IAPT) programme offers a range of NICE-recommended therapies for depression in line with a stepped-care model, when appropriately indicated. Currently, digitally enabled therapies are primarily used in step 2 of the IAPT programme and are delivered by psychological wellbeing practitioners.

As guided self-help was not listed as a treatment option for preventing relapse, further-line treatment, chronic depressive symptoms, depression in people with a diagnosis of personality disorder or psychotic depression, these are not discussed in this scope.

Potential place of digitally enabled therapies in the care pathway

NICE's clinical guideline on depression in adults: treatment and management recommends guided self-help as an option for treating both less severe and more severe episodes of depression. It should be considered first for most people with less severe depression as it is the least intrusive and least resource intensive treatment for less severe depression. However, guided self-help may not be as appropriate for more severe depression and other treatment choices with more therapist contact should be considered first. The guideline describes guided self-help as less resource intensive for IAPT services to deliver and is likely to be available for people in a timely fashion without the need for a long time on a waiting list.

The IAPT programme was developed to organise and improve the delivery of, and access to, evidence-based psychological therapies within the NHS. It provides support for adults with depression and anxiety disorders. NICE-recommended therapies are delivered by a single clinician, with or without concurrent pharmacological treatment, which is typically managed by the GP.

Here, digitally enabled therapies being considered in an IAPT setting, after an IAPT assessment. Although anyone with depression can be offered a digitally enabled therapy, depression severity, patient preference and risk need to be

considered. These technologies are more likely to be appropriate for those with sub-threshold to moderate depression.

3.2 Patient issues and preferences

Digitally enabled therapies are delivered via mobile phones, tablets, or computers and can therefore be accessed remotely. As there is an increased demand for treatment for depression, but limited capacity within IAPT services, digitally enabled therapies can be used to increase capacity and support because they tend to require less clinical time than alternatives. Digital CBT provides more treatment options, flexible access, greater privacy and anonymity, and increased convenience. They may be particularly appealing to regular users of digital technologies such as smartphones and tablets. However, not everyone who regularly uses digital technologies may prefer this option. Digitally enabled therapies may also allow people to better self-manage their mental health and be more involved in treatment decisions.

Some people may choose not to use digitally enabled therapies and may prefer clinician led treatment, either face-to-face or teletherapy. There may be some concerns about the level of support provided in a digitally enabled therapy and concerns around data security and quality control. People have the right to make informed decisions about their care, including the use of digitally enabled therapies.

The Ofcom Adults' Media Use and Attitudes report states that 6% of households (around 1.7 million) did not have access to the internet at home in December 2021 (Ofcom report, 2022). The groups more likely not to have internet access at home are those aged 75 and over (26%), those in a lower socioeconomic household classification (DE social grade; 14%) and those who are most financially vulnerable (10%). This digital exclusion was due to having no internet at home or elsewhere, a lack the digital skills or confidence to navigate the online environment safely and knowledgeably and being able to afford access to the internet. Digital exclusion would need to be considered when offering access to digital therapies. In addition to this, 21% of internet users access the internet exclusively via a smartphone (Ofcom report, 2022).

There may be concerns around whether technologies are accessible whilst using a smart phone as this may prevent uptake or retention on this therapy option.

4 Comparator

Digitally enabled therapies would be offered as an alternative to existing psychological interventions in IAPT services. Comparators should be based on the other options offered in IAPT services to adults with depression, according to NICE's clinical guideline on depression in adults: treatment and management.

However, comparators in the evidence may not reflect standard care in IAPT services because studies often use waitlist controls rather than psychological interventions. The evidence review may therefore also need to include studies comparing digitally enabled therapies with waitlist, active or attentional controls to determine efficacy and an absence of harm.

5 Scope of the assessment

Table 1 Scope of the assessment

Populations	Adults with depression who have been referred to IAPT services.
Interventions (proposed technologies)	Digitally enabled therapies for facilitating guided self-help in people with depression. These technologies have been designed to be used with support by healthcare professionals: • Beating the Blues • Minddistrict • Space from Depression • Wysa • Deprexis • Iona Mind • Perspectives
Comparator	Standard care according to NICE's clinical guideline on depression in adults: treatment and management The recommended treatment options for less severe depression include: • Guided self-help

	• Group cognitive behavioural therapy (CBT) • Group behavioural activation (BA) • Individual CBT • Individual BA • Group exercise • Group mindfulness and meditation • Interpersonal psychotherapy • Selective serotonin reuptake inhibitors • Counselling • Short-term psychodynamic psychotherapy For more severe depression include: • Combination of individual CBT and an antidepressant • Individual CBT • Individual BA • Antidepressant medication • Individual problem-solving • Counselling • Short-term psychodynamic psychotherapy • Interpersonal psychotherapy • Guided self-help • Group exercise
Healthcare setting	Improving access to psychological therapies (IAPT) services
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 depression symptoms • 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
	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 depression, adverse events, or complications): o GP or IAPT appointments o Medication o Healthcare professional grade and time
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

Characteristics of digital technologies

- The digital CBT technologies included in the scope are heterogeneous in terms of delivery mode (computer, app). Two of the technologies (Wysa and Iona Mind) use AI in addition to therapist support.

- Technologies included in this EVA will complete the IAPT DET assessment criteria. This includes validation of clinical content in line with NICE guidelines and assessment of clinical effectiveness. Passing this assessment will be a requirement to proceed to evidence generation stage of the EVA.

Population

- Most technologies are for mild to moderate depression. This spans NICE's clinical guideline on depression in adults definition of less (subthreshold and mild) and more severe (moderate and severe) which have different recommendations. This would need to be a consideration during the evidence review.

- People with depression may also have other mental health problems such as anxiety. IAPT services offer disorder-specific treatments based on a person's main presenting problem. For digitally enabled therapies, this would mean offering a person treatment for a depression rather than a combined programme targeting both depression and anxiety.

Evidence

- This assessment will look across a range of evidence types including RCTs, real world evidence and benchmarking against NHS Digital published metrics. Evidence considered will include evidence of clinical effectiveness, comparative outcomes to alternative treatments offered in IAPT for the relevant clinical condition and absence of harm.

- The amount and level of evidence for each of the technologies varies. Many of the identified technologies have RCT data. Some research studies were conducted in an NHS setting while others were done outside of the UK. Comparators also vary but most often include waitlist control. Study populations are also heterogenous and include people with depression or depression and anxiety. It is likely that the different technologies will require different levels of additional evidence.

- This assessment will evaluate the clinical and potential cost effectiveness of digitally enabled therapies as an alternative to standard care in IAPT services. This will include evaluating whether digitally enabled therapies have equal or superior outcomes to alternative treatments offered in IAPT services for adults with depression.

Care pathway

- Digitally enabled therapies can be used at different points in the care pathway depending on their therapeutic content. This should align with NICE guidelines and should be supported or delivered by healthcare professionals who are appropriately trained in delivering the specific therapy. Treatment selection should be guided by healthcare professional assessment, patient risk, and patient choice.

7 Potential equality issues

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

Depression is more common in women than in men. Women, people from a White British background or in midlife are more likely than others to receive treatment for a common mental health disorder. Increasing social deprivation is associated with higher prevalence rates of depressive symptoms.

Digital therapies are delivered through a mobile phone, tablet, or computer. People will need regular access to a device with internet access to use the technologies. Additional support and resources may therefore be needed for people who are unfamiliar with digital technologies, do not have access to smart devices. People with visual, hearing, or cognitive impairment; problems with manual dexterity; a learning disability; or who are unable to read or understand health-related information (including people who cannot read English) may need additional support to use digital therapies. Some people would benefit from digitally enabled therapies in languages other than English. People's ethnic, religious, and cultural background may affect their views of mental health problems and interventions. Healthcare professionals should discuss the language and cultural content of digitally enabled therapies with patients before use.

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

8 Potential implementation issues

Training

Training is required to facilitate these digitally enabled therapies. Technologies offer training for supporters (such as psychological wellbeing practitioners), are mostly in the form of self-directed training. Time needs to be allocated for the completion of training and supporters need a good understanding of the content available in each technology in order to

appropriately offer modules or resources. The language used in some technologies may not match those used in other therapies, so training may be needed to learn the differences in language use.

Cost

Costs may differ between technologies. Smaller service areas may have higher costs per user due to not needing as many licences for the technology. Digitally enabled therapies may be chosen based on the balance between costs and expected outcomes.

Risk of harm

Digitally enabled therapies must be able to identify potential risks for patients. Initial assessment is important to ensure people get the right care at the right level. Some digitally enabled therapies have inbuilt processes to flag the need for more intervention. This is important to consider when choosing digitally enabled therapies.

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Appendix A Abbreviations

AI	Artificial intelligence
EVA	Early value assessment
CBT	Cognitive behavioural therapy
MTEP	Medical technologies evaluation programme
IAPT	Improving access to psychological therapies
PHQ-9	Patient health questionnaire-9
DET	Digitally enabled therapies
DTAC	Digital technology assessment criteria

NICE National Institute for Health and Care Excellence

Adoption report: MT588 Early Value Assessment: Digitally enabled therapies for adults with Depression and MT589 Early Value Assessment: Digitally enabled therapies for adults with anxiety disorders

Summary

Adoption levers identified by contributors

- May increase treatments options.
- Could lead to an increase in practitioner capacity.
- May be a successful treatment option and lead to improved outcomes.
- Greater accessibility for those with long term conditions, busy work/life schedules and those where being open about mental health conditions may be particularly challenging.

Adoption barriers identified by contributors

- Training: time required to attend 1–2-day training sessions and then to gain a thorough understanding of the digital content.
- Cost may be a barrier. Particularly if there isn't a strong evidence base showing that use leads to good outcomes and savings elsewhere e.g., therapist capacity.
- Equity of access- This type of therapy may not be an option for all due to access to technology (e.g., smartphone or computer) and or technology literacy level.

1 Introduction

This adoption report has been developed to support both MT588 Early Value Assessment: Digitally enabled therapies for adults with Depression and MT589 Early Value Assessment: Digitally enabled therapies for adults with anxiety disorders. Although some technologies are being considered for either depression or anxiety disorders only, others are for both. We found that there was significant overlap between the adoption barriers and levers to using digitally enabled therapies for

adults experiencing depression and/or anxiety disorders. We highlight within the report if a barrier is specific to one condition or technology only.

Following the scoping workshop, the adoption team has collated information from healthcare professionals working within NHS organisations with experience of using some of the digitally enabled therapies considered within the scoping documents. All contributors apart from 1 had experience of using one of the therapies either as part of their service or a pilot. The contributors table in section 2 shows the split of contributors across the different technologies. It has been developed for the medical technologies advisory committee (MTAC). This report provides context from current practice and an insight into the potential levers and barriers to adoption and includes adoption considerations for the routine NHS use of the technologies. It does not represent the opinion of NICE or MTAC.

2 Contributors

Details of contributing individuals are listed in the below table.

Job title	Organisation	Current use	Technology	Anxiety/Depression/Both	Therapy stage
GP partner and Clinical Director of Primary Care Warwickshire	Grange Medical Centre and GP Federation in North Warwickshire	Free access as part of a pilot involving 7 GP practices	Deprexis	Depression	Prior to IAPT access
Lead Psychological Wellbeing Practitioner	Telford and Wrekin IAPT	Part of current service provision	Silvercloud	Both	Step 2
Primary Care Therapist	Cwm Taf Morgannwg University Health Board	Part of current service provision	Spring	Anxiety-PTSD	
Primary Care Therapist	Oxford Health NHS Foundation Trust	As part of research trial within IAPT service	iCT-PTSD	Anxiety-SAD	
Step 3 Lead / Cognitive Behavioural Therapist	Telford and Wrekin IAPT	No	Silvercloud	Both	Step 3
Senior Cognitive Behavioural Psychotherapist	Hywel Dda University Health Board	Part of current service provision	Spring	Anxiety-PTSD	
Primary Care Therapist	Cwm Taf Morgannwg University Health Board	Part of current service provision	Spring	Anxiety-PTSD	
Clinical lead of IAPT service & clinician	Hertfordshire Partnerships University NHS Foundation Trust	As part of research trial within IAPT service	iCT-PTSD	Anxiety-PTSD	Step 3

Head of commissioning, mental health and learning disabilities & Therapist	Isle of Wight CCG	Part of current service provision	Silvercloud (previously) & Minddistrict	Both	Step 2
Clinical Services Director	Trent PTS, provides services for regional IAPT	Part of current service provision	Iona Mind Minddistrict SilverCloud	Both	
Clinical lead of IAPT service & clinician	Hertfordshire Partnerships University NHS Foundation Trust	As part of research trial within IAPT service	iCT-PTSD	Anxiety-PTSD	Step 3
GP (non – user)	Birmingham Medical School	N/A		Both	N/A

3 Use of digitally enabled therapies in practice

All the contributors to this report who are currently using digitally enabled technology are doing so following an initial assessment. This assessment identifies the mental health condition to be treated and assesses if the person is likely to be suitable for guided treatment with digitally enabled therapy. Assessment of risk also happens here in addition to throughout treatment. Risk assessment is embedded within all the technologies the contributors to this report are using.

The contributor currently using Iona Mind, has set up a minimum contact pathway. This involves training their psychological wellbeing practitioners (PWPs) to complete short follow up calls with people using the app and only set up longer virtual or face to face (traditional) appointments for those who are not demonstrating an improvement.

One of the contributors using Spring has set up a separate waiting list for those assessed as appropriate for treatment assisted with this technology. This is much shorter than the waiting list for traditional face to face CBT.

One contributor is currently offering Deprexis as part of a pilot within primary care. They are offering this to people prior to accessing IAPT (following supported decision making, an assessment and completion of PHQ9) due to long waiting lists. This contributor provides follow up phone calls/appointments with people as they work through and after completion of the 90-day programme. If, following the assessment, people decide they would prefer face-to-face therapy via IAPT, this service initiates Deprexis for them to use while they await their IAPT appointments. Once IAPT has commence, Deprexis is stopped.

Some contributors have simply integrated the use of digital therapy into the IAPT service as is. No one reported that offering this service has required large service or care pathway redesign.

4 Reported benefits

The potential benefits of adopting digitally enabled therapies, as reported to the adoption team by the healthcare professionals using the technologies are:

- May increase treatment options.
- Could reduce waiting times and allow more people to access treatment due to greater practitioner capacity.
- Could allow people to take ownership of their own care.
- Should lead to greater flexibility for users to access therapy at a time that suits their needs/lifestyle.
- May help with confidentiality as the user can pick a time when other people may not overhear or be able to see any content they add to the digital therapy.
- Continued support post guided therapy.
- Use may lead to improved outcomes and successful treatment.
- Digital enabled therapy may include features which are not possible to achieve through standard therapy, e.g., normalisation of symptoms through insight into other people's journeys.

5 Insights from the NHS

Commissioning

One contributor discussed the fact that it is challenging to pull together a business case for a technology that is not yet proven to work and won't work for all. Different digital therapies are likely to work for different people and so an estimate of how many of each to be purchased is required. This is difficult to forecast.

Some of the companies do not routinely provide reports or feedback to commissioning services on attrition rates which can contribute to this issue.

Selecting a digital therapy needs to be informed by the balance between cost and expected outcomes. One contributor felt that guidance on this would help their decision-making process when the EVA publishes.

One contributor referenced the difficulty experienced when commissioning a new treatment. The multiple levels at which decisions need to be agreed mean that the process is lengthy and cumbersome. This may act as a barrier to the adoption of these therapies other than silvercloud which is already offered in many areas of the country within IAPT services.

Resource impact

Cost was referenced by all contributors as being a potential barrier. Costs of the different products varies. Silvercloud charges a fee for a number of licences. These numbers are high and 2 contributors offering Silvercloud reported that using the amount purchased was not possible resulting in this option being expensive.

One contributor reported that the best price they could get for the various digital therapies offered was similar to the cost of providing traditional face to face therapy. They explained that there would be a capacity saving but only if the digital therapy was effective.

One contributor mentioned that their service was given access to a number of licences for some of the digital therapies detailed in the scope for free by the companies. This was/is so the companies can test their use in NHS services and

begin to collect real world data. However- this contributor reported that to be able to continue with and roll out adoption- a cost/benefit assessment would need to be carried out.

Training

Time required to attend 1–2-day training sessions and then to gain a thorough understanding of the digital content may act as a barrier and lead to variation. All contributors reported that training was provided by the company/research trial team for free, and that time was also needed post initial training to work through and fully understand the content. This may lead to a resource impact especially as there is a high turnover of staff within these services. They also highlighted that as the learning is self-directed motivation of therapists would vary and therefore the knowledge and understanding of the digital therapy and how best to use it, could vary across regions and within a service.

As all the digital therapies allow the therapist to pick specific modules/content to direct a user towards, a good understanding of what's available within each program is required.

All also reported that there was a period of supervision required post training and this varied from once per week (until a person has been supported through use of the whole program/app), to weekly for 1 year.

Two contributors reported that the time invested in working through the programme was time well spent as it served to upskill therapists and therefore improve the quality of all interventions offered to people.

Clinician confidence

Two IAPT clinical service leads using iCT-PTSD as part of a research trial reported that the program has been developed by a highly respected team and has therefore created a trusted brand. They felt that the program mapped onto what would be provided by a face-to-face protocol well and that guided use enhances treatment rather than replicating it or offering a second rate option. These same two

contributors also stated that the quality of the programme is such that it served to upskill them in their ability to work with people with PTSD.

One contributor explained that they are an adopter/implementer of digital therapy but are also cautious about their use. There are so many technologies to choose from and development of them can be easy, so it is important to maintain QA processes and use ones that have demonstrable outcomes.

A clinical service director reported that Practitioners are trained to and enjoy speaking to people to deliver therapy and support them to problem solve. Practitioners may be reluctant to deliver care via a digital platform, though savings in time may incentivise this. This same contributor reported that PWPs have been trained to deliver therapy in a certain way. Changing this and incorporating use of a digital therapy may be difficult.

Practitioner/clinician capacity

One contributor reported that the delivery of guided therapy takes longer to begin with due to limited experience with the app. This gets better with time but is still a consideration for adoption as there is a high turnover of practitioners in IAPT.

Another contributor reported that whilst they found the ability to message clients and receive messages, between sessions, a positive factor, they thought that some clinicians might find this hard to manage / accommodate.

All contributors reported that once practitioners were familiar with using the technologies, capacity was released as less time was needed to deliver the guided element.

Data collection

There is a need to track outcomes whilst using these technologies. One contributor reported that their service uses an EMIS bundle system which tracks outcomes for free.

Two contributors explained the importance of data needing to cover the whole pathway as well as including information on rates and rational for drop out. These

same two contributors reported that they don't currently collect data on re-referrals- i.e., numbers of people going through IAPT and needing help again in the future. This should be included, especially when using digital therapy to see if there is a difference.

As mentioned earlier in the report, some contributors reported that they rely on the company to provide them with access and outcome data. This means that companies are responsible for the data they provide. One contributor talked about the lack of transparency in this data and the limitations of real-world evidence data.

The contributor using Deprexis, explained that the company does not provide feedback on access and attrition rates. As this contributor follows up people referred for Deprexis access, they get the data this way, however this needs to be embedded in electronic patient record systems if wide scale adoption is recommended.

Two contributors using iCT-PTSD reported that outcomes using the program were good and recovery rates high. These same two contributors explained that data collection is embedded within the programme and that it is linked to the service electronic patient record system. This means that outcome data can be processed and analysed in the same way as the rest of the initiatives on offer.

Sustainability

One contributor expressed a concern about the sustainability of some of the companies behind the newer digital therapies supported by a small company team.

One contributor commented that using digitally enabled therapy may be more environmentally friendly as it limits the need for both the therapist and person to travel.

Patient choice

One contributor expressed a concern that offering guided digital therapy may limit patient choice. If a person is assessed as being more suitable for traditional CBT therapy, they should not be offered digitally guided therapy first to see if it works. People should have a discussion with their therapist and make a choice on what they think will be the best therapy type for them.

Patient experience

Iona Mind was referenced by the contributor offering this within their service as being more light touch and therefore easier for people to engage with than others. Some of the digital therapies used by this service required people to read lots of material and complete lots of activities in between sessions.

Both contributors using iCT-PTSD reported that patient feedback has been positive. They stated that the positive elements of the program include; the ability for a person to log onto the programme at any time and watch/interact with content that is engaging, informative, empathic and motivating. For the therapist the ability to see what the person has viewed and the comments they have left were described as positive features. Additionally, the program has the ability to timetable messages to go to people at points relevant to the targets set which provides further support in between sessions.

One of the contributors using i-CT-PTSD reported that the programme includes features which are not possible to achieve through standard therapy, e.g., normalisation of symptoms through insight into other people's journeys (therapy stories and videos). The ability to see how someone else has experienced similar trauma and symptoms and how they have responded to different aspects of therapy was described as being powerful and effective.

The 3 contributors using Spring spoke about the positive feedback they had received on the continued access following discharge. People can access the programme for 3 years following discharge.

One contributor reported that for some people, their difficulties may be such that it is hard for them to face tackling them independently at home and then dealing with the impact on their lives (or feared impact). This should however be picked up at initial assessment and individuals in this category should not be referred for digitally enabled therapy.

6 Comparators

One contributor referenced using Limbic to support the management of referrals, initial assessment and provision of self-help. They referenced the fact that there is a recently available study which demonstrates that use of this app- leads to an improvement in outcomes.