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PROTOCOL

Digital technologies delivering CBT for insomnia for adults

External Assessment Group
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Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Copyright statement

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List of abbreviations

Abbreviation	Definition
CBT-I	Cognitive Behavioural Therapy for insomnia
CSK	Clinical Knowledge Summary
dCBT-I	Digital technologies for the delivery of Cognitive Behavioural Therapy for insomnia
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EAG	External Assessment group
EQ-5D	EuroQol Five Dimensions
GP	General Practitioner
HRQoL	Health Related Quality of Life
HTA	Health technology assessment
IPD	Individual Patient Data
ISI	Insomnia severity index
ML-NMR	Multi-level network meta-regression
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PROMIS GH-10	Patient-Reported Outcomes Measurement Information System Global Health-10
PSQI	Pittsburgh Sleep Quality Index
PSS	Personal and Social Services
PROM	Patient reported outcome measures
QALY	Quality-adjusted life year
QoL	Quality of Life
RCT	Randomised controlled trial
SCI	Sleep Condition Indicator
SF-6D	Short Form 6 Dimensions
TA	Technology Assessment

1 DECISION PROBLEM

The decision question for this assessment is 'Are digital technologies for delivering CBT for insomnia (dCBT-I) offering a cost-effective use of NHS resources?'

Table 1 summarises the decision problem to be addressed in this assessment. Further detail on each element can be found in the published scope for the assessment.

Table 1. Summary table of the decision problem

Item	Description in NICE scope	EAG comments
Assessment type	Routine use	The EAG considers that it is appropriate to assess dCBT-I technologies for routine use.
Population	Adults (aged 18 and over) who have insomnia and for whom CBT-I is suitable.	The presence of insomnia is established either in primary care (or secondary care for those with comorbid conditions), or within a self-referral pathway. Diagnosis of insomnia established in primary care setting is based on the frequency, intensity, distress, and/or impairment of sleep related symptoms, despite opportunity for sleep [NICE CSK].[1] These diagnosis criteria are broadly comparable to those in DSM-5. However, the DSM-5 classication offers further nuance around the definitions of episodic and recurrent insomnia. For individuals self-referring, diagnosis of insomnia is determined by triaging software within a self-referral platform and/or the app delivering dCBT-I. No further information relating to triaging software is available, therefore the accuracy of such software to diagnose insomnia is unknown.
Subgroups	If the evidence allows, the following subgroups may be considered: • People with physical comorbidities • People with mental comorbidities	Other subgroups may also be considered if evidence supportive of differential treatment effectiveness and/or safety conditional on patient characteristics is identified by the evidence review (e.g., by severity and/or persistence of insomnia symptoms, by referral route into the care pathway). Furthermore, subgroups not pre-specified in the scope may be relevant to the cost-effectiveness analysis.
Interventions	Digital technologies delivering CBT-I that have a hybrid delivery (i.e. with an element of human oversight) • Sleepstation • Space for Sleep • This Way Up Digital technologies delivering CBT-I that have an automated delivery (i.e. without any element of human oversight) • Sleepful • Sleepio • Somnio	The interventions may be delivered at different positions in the existing care pathway, depending on referral within primary or secondary care, or self-referral. This assessment will consider alternative positionings of the technologies conditional on feasibility and the clinical relevance of these positions, informed by expert clinical advice.

Comparators	Current NHS practice may be comprised of several treatment options, with proportions varying depending on whether it is short-term or long-term insomnia, and by region. Current NHS practice includes: • Therapist-led CBT-I • No CBT-I available Where no CBT-I is available, current practice may include no NHS treatment being received, sleep hygiene and pharmacological treatments.	The EAG considers the relevant comparators to be: • Therapist-led CBT-I (where available) • No treatment • Sleeping pills (Z drugs)† • Sleep hygiene† • Other pharmalogical treatments (where therapist-led CBT-I is not available) Comparators are also further constrained in accordance with the referal route into the clinical pathway, and the position in the care pathway at which the interventions are being assessed and how persistent insomnia symptoms are (as described further below).
Setting	Primary care (e.g. GP practices, NHS talking therapies), specialist secondary care settings (e.g. sleep clinics), community settings	Clinical opinion received at the scoping workshop suggests that delivery of dCBT-I is unlikely to take place in secondary care settings.
Outcomes eligible for inclusion	**Intermediate outcomes:** • Uptake, adherence and acceptability of dCBT-I interventions • Time to intervention initiation • Change in use of pharmacological treatments **Clinical outcomes:** • Daytime functioning • Adverse events • Insomnia remission **Sleep related outcomes:** • Sleep quality • Sleep quantity • Total sleep time • Sleep efficiency • Reduction in sleep-onset latency • Reduction in wake after sleep onset • Sleep-related satisfaction and QoL • Symptoms of comorbid health conditions (mental and physical) directly impacted by difficulty sleeping **Other patient-reported outcomes:** • Patient satisfaction • HRQoL measures **Costs and resource use:** • dCBT-I costs • Primary care appointments • Secondary care referrals • Prescription of pharmacological treatments • Service productivity, workforce utilisation, and operational efficiency	All outcomes in scope will be considered. Additional relevant outcomes such as insomnia symptoms (e.g. using ISI and SCI) and mortality will also be eligible. Single dimension sleep-related outcomes (e.g., sleep quality and sleep quantity) are unlikely to allow linkage to final economic outcomes (i.e., QALYs). The EAG anticipates that the main linkage mechanism will be established via measures of insomnia symptoms (see Section 3.4). Therefore, as a minimum, outcomes that capture impact on patient reported insomnia symptoms (e.g., ISI and SCI), treatment response/insomnia remission and adherence to dCBT-I interventions will be prioritised for quantitative evidence synthesis (see Section 2.5.2). Other disease specific (e.g., PSQI, etc.) or generic PROMs (e.g. PROMIS GH-10; EQ-5D, etc.) may also be prioritised for quantitative evidence synthesis, conditional on clinical relevance.
Economic analysis	A health economic model will be developed comprising a cost utility or cost-comparison analysis. Costs will be	A short time horizon in the base-case analysis (1 to 3 years) will be modelled, in line with current evidence on durability of treatment

	considered from an NHS and PSS perspective. Sensitivity and scenario analysis should be undertaken to address the relative effect of parameter or structural uncertainty on results. The time horizon should be long enough to reflect all important differences in costs or outcoms between the technologies being compared.	effect and previously published cost effectiveness analysis.[2, 3] Exploratory analysis extending time horizon will also be performed to capture: • alternative treatment effect durability assumptions and/or; • insomnia mortality impacts will be considered (depending on the availability of suitable evidence).

Abbreviations: CBT-I: cognitive behavioural therapy for insomnia; CSK: clinical knowledge summary; dCBT-I: digital technologies for the delivery of cognitive behavioural therapy for insomnia; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; EAG: Evidence Assessment Group; GP: general practitioner; HRQoL: Health Related Quality of Life; ISI: insomnia severity index; NICE: National Institute for Health and Care Excellence; PROMIS GH-10: Patient-Reported Outcomes Measurement Information System Global Health-10; PSQI: Pittsburgh Sleep Quality Index; PROMs; patient reported outcome measures; PSS: Personal and Social Services; QALY: quality-adjusted life year; QoL: quality of life; SCI: sleep condition indicator.
†Z drugs and sleep hygiene are indicated for short-term insomnia (with symptoms persisting for periods shorter than 3 months) but might also be offered as treatments to individuals with long-term insomnia (symptoms ≥3 months) where therapist-led CBT-I is unavailable.

1.1 Position in the care pathway and relevant comparators

The relevance of comparators listed in the final scope is dependent upon:

- availability of therapist-led CBT-I (by area / region)
- the persistence of insomnia for individuals diagnosed in primary (or secondary) care: short term (<3 months) or long-term (≥3 months)
- referral route into the care pathway (primary care, or self-referral)
- proposed position of dCBT-I in the care pathway (see Figure 1 in the published NICE scope)

Comparators listed in the published NICE scope are categorised in Table 2 by position in the care pathway and persistence of insomnia symptoms at which they are relevant comparators.

For individuals diagnosed with insomnia in primary care whose symptoms persist for a period shorter than three months, available evidence may not distinguish between individuals and between the comparator treatments at position 2 and 3 in Table 2. Thus, the Evidence Review and economic analyses may combine these positions in the pathway and/or consider a blended comparator merging together relevant comparators (e.g. as a 'usual care' comparator which may comprise no treatment, sleep hygiene or Z drugs) across closely related positions. Where feasible and appropriate, the EAG will model comparators separately in the economic analysis, but the use of blended comparators will be considered not only where the available evidence does not allow establish a comparison to single treatments, but also where particular comparator treatments may not be routinely available to all patients due to regional constraints. Clinical advice will be sought on the use of the current treatment options for insomnia in NHS practice to accurately define comparator treatments for this assessment. Final decisions on the most appropriate comparator(s), the use of blended comparator and the

composition of blended comparators, at specific pathway positions will be made following discussion with clinical advisers.

Table 2. Relevant comparators of dCBT-I at different positions in the care pathway and by persistence of insomnia symptoms

<table>
<tr><th colspan="2">Position in care pathway and persistence of symptoms</th><th colspan="2">Comparators for dCBT-I</th></tr>
<tr><td>1</td><td>No presentation to primary care (i.e. self-referral route): †</td><td colspan="2">No treatment
Sleep hygiene</td></tr>
<tr><td>2</td><td>Initial assessment in primary care: Short-term insomnia†</td><td colspan="2">No treatment
Sleep hygiene</td></tr>
<tr><td>3</td><td>Initial assessment in primary care: Short-term insomnia† and sleep hygiene advice has not worked</td><td colspan="2">Short course of sleeping pills (Z drugs)</td></tr>
<tr><td rowspan="2">4</td><td rowspan="2">Initial assessment in primary care: Long-term insomnia†</td><td>Therapist-led CBT-I available</td><td>Therapist-led CBT-I unavailable</td></tr>
<tr><td>Therapist-led CBT-I from NHS Talking Therapies (if comorbid with mental health conditions) or another CBT-I provider</td><td>Pharmacological treatments including:
Daridorexant (for people whose daytime functioning is considerably affected)
Prolonged-release melatonin (for people over 55)
Other pharmacological treatments (e.g. antidepressants, Z-drugs) used off label in the NHS to manage long-term insomnia symptoms.
Sleep hygiene</td></tr>
</table>

Abbreviations: CBT-I: cognitive behavioural therapy for insomnia; dCBT-I: digital technologies for the delivery of cognitive behavioural therapy for insomnia; NHS: National Health service; NICE: National Institute for Health and Care Excellence

† In line with the population described in the published NICE scope, dCBT-I is considered suitable for individuals with short-term or long-term insomnia.

1.2 Objectives

The aim of this assessment is to evaluate the clinical and cost-effectiveness of digital technologies for the delivery of cognitive behavioural therapy for insomnia (dCBT-I) for adults with insomnia for routine use in the NHS. To achieve this, the following objectives are proposed:

Clinical effectiveness

- To perform a systematic review, narrative synthesis and, if feasible, a meta-analysis of each dCBT-I technology in scope compared to relevant comparator interventions at different positions in the care pathway for all specified outcomes in people with insomnia.
- If feasible, to compare each dCBT-I technology in scope to relevant comparators and to each other for prioritised outcomes:
    - using meta-analysis if direct evidence is available;
    - using network meta-analysis (NMA) or other forms of indirect treatment comparison in the absence of direct evidence.
- To evaluate and compare dCBT-I technologies in scope within subgroups of people with insomnia (e.g., people with physical or mental health comorbidities).
- To perform a systematic review of a broader evidence base of dCBT-I technologies to bridge anticipated evidence gaps and allow for assessment of potential sources of heterogeneity in clinical effectiveness in quantitative synthesis.

Cost-effectiveness

- To perform a systematic review and critical review of published (and unpublished, if relevant evidence is submitted by companies) cost-effectiveness studies of the six dCBT-I technologies in scope against the relevant comparators and each other in people with insomnia.
- To review cost-effectiveness models assessing (digital or therapist-led) CBT-I in people with insomnia; including out of scope technologies.
- To review cost-effectiveness models used to inform NICE guidance issued by the Technology Appraisal programme for the treatment of insomnia.
- To develop and validate a decision-analytic model to estimate the cost-effectiveness of the dCBT-I technologies in people with insomnia and to populate the model using the most appropriate available evidence. This evidence is likely to be identified from:
    - the quantitative synthesis of effectiveness and safety conducted as part of this assessment
    - routine data sources
    - evidence elicited from relevant clinical experts
    - published and unpublished data provided by companies.

2 EVIDENCE REVIEW METHODS

Two clinical systematic reviews will be conducted following the general principles recommended in CRD's guidance[5] and reported in accordance with the PRISMA statement:[6]

- Main Review: a systematic review of randomised and non-randomised studies of the dCBT-I technologies in scope (main review)
- Supplementary Review: a systematic review of RCTs of a broader evidence base.

Following scoping searches performed by NICE, the EAG anticipates that available evidence restricted to just the dCBT-I technologies in scope will not allow for establishing robust comparisons for all of the dCBT-I technologies against all the relevant comparators at each of the relevant positions in the care pathway (see Section 1.1). Furthermore, studies of dCBT-I technologies in scope only may not provide sufficient evidence to inform formal quantitative exploration of heterogeneity in treatment effects according to, for example, dCBT-I delivery mode (e.g., fully automated vs. hybrid) and patient characteristics (e.g., conditional on referral route: primary care assessment vs. self-referral; short-term vs. long-term insomnia, etc.). Hence, the EAG will conduct a supplementary review to identify a broader clinical evidence base of RCTs on dCBT-I technologies beyond those in scope, to bridge some of the anticipated evidence gaps.

Eligibility criteria

Table 3. Inclusion and exclusion criteria for the systematic reviews

	Review	Inclusion Criteria	Exclusion Criteria
Population	Main and Supplementary review	Adults (aged 18 and over) with insomnia for whom CBT-I is suitable Diagnosis of insomnia, whether made in primary care or via a self-referral platform must be made by DSM-5 criteria, or criteria closely aligning to DSM-5	Adults with insomnia for whom CBT-I is unsuitable, or insomnia diagnosis was made by criteria which do not align with DSM-5
Intervention	Main review	dCBT-I based on the software apps listed in the published NICE scope: Sleepio, Sleepstation, Sleepful, Space for Sleep, Somnio, This Way Up	Other types of dCBT-I not listed in the published NICE scope
	Supplementary review	Any type of multimodal dCBT-I intervention including at least one key cognitive strategy (cognitive restructuring) and one key behavioural strategy (stimulus control or sleep restriction) for a minimum of 4 weeks	Interventions including a single strategy
Comparators	Main and Supplementary review	Comparators referred to in the published NICE scope†, which may be used individually or alongside other comparators: • Therapist-led CBT-I • No treatment • Sleeping tablets (Zdrugs) • Sleep hygiene • Other pharmacological treatments Head-to-head comparisons of dCBT-I interventions will also be included Comparators not listed in the published NICE scope will also be eligible e.g., Placebo or sham versions of dCBT-I, or wait-list control, or education, since they are likely to encompass one or more of the comparators listed above.	None
Outcomes	Main and Supplementary review	As listed in Table 1* Additional relevant outcomes such as insomnia symptoms (e.g. using ISI and SCI) and mortality will also be eligible.	None
Study design	Main Review	RCTs of dCBT-I interventions listed above (alone or as part of a treatment sequence). If no, or limited, RCT evidence is available for eligible dCBT-I interventions, non-RCT evidence will be considered (in preferential order): • Prospective comparative studies • Retrospective comparative studies • Single group studies (prospective or retrospective) with ≥20 patients included • Single group studies with 2 - 19 patients included	Case-reports Systematic reviews
	Supplementary review	Randomised trials of dCBT-I interventions	Non-randomised study designs

Abbreviations: CBT-I: cognitive behavioural therapy for insomnia; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; dCBT-I: digital technologies for the delivery of cognitive behavioural therapy for insomnia; ISI: insomnia severity index; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; RCT: randomised controlled trial; SCI: sleep condition indicator.
†Relevant comparators to dCBT-I will be considered according to referral route, position in the care pathway, duration of insomnia symptoms and regional availability of therapist-led CBT-I (Table 2) and informed by clinical opinion.
*All outcomes listed in the published NICE scope (Table 1) will be included in the clinical systematic reviews, except for cost and resource use outcomes, which will be included in the economic evidence review (Section 3.1).

2.1 Search strategy

The aim of the searches will be to identify both published and unpublished studies of the clinical-effectiveness and cost-effectiveness of dCBT-I technologies.

2.1.1 Main review of dCBT-I technologies in scope

A draft search strategy for Ovid MEDLINE has been developed by the Information Specialist for the project in collaboration with the review team (see Appendix 1). It contains terms for the population, the intervention and the delivery method combined using the Boolean operator AND: insomnia AND CBT AND digital delivery. Subject headings and text word searches of the title, abstract and keyword fields are included for each concept. The names of the six dCBT-I technologies (Sleepio, Sleepstation, Space for Sleep, Sleepful, Somnio and This Way Up) are also included in the search strategy. The search will not be restricted by language or study design. A date limit of 2000 will be applied to capture relevant studies since the introduction of digital technologies for use in insomnia.

The following databases and resources will be searched to capture published, unpublished, and ongoing studies, and relevant guidelines:

- MEDLINE, Embase, PsycINFO, EconLit, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), KSR Evidence, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment database, the NHS Economic Evaluations database (NHS EED), and the International Health Technology Assessment database (INAHTA).
- ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (WHO ICTRP) and PROSPERO, the International prospective register of systematic reviews.
- ECRI Guidelines Trust Database, Guidelines International Network Library, Trip database, National Institute of Health and Clinical Effectiveness website, the Scottish Intercollegiate Guidelines website, and websites of selected HTA agencies.
- MAUDE database and the Medicines and Healthcare products Regulatory Agency website.
- Websites of device companies.

All search results will be imported into EndNote 25 and duplicates removed.

After screening, the reference lists of included studies and relevant systematic reviews will be checked for any further relevant studies. Published and unpublished studies sent from companies and other stakeholders to NICE, will be scrutinised to identify additional relevant studies.

2.1.1.1 Provision of evidence by companies

Companies of dCBT-I technologies that are in scope will be contacted by NICE and asked to supply evidence on their technology. This can comprise published and unpublished studies, conference presentations, additional data and cost information, and original study data. All evidence supplied will be screened for inclusion in accordance with the eligibility criteria described in Table 3.

2.1.2 Supplementary review of a broader evidence base

As described at the start of Section 2, the EAG anticipates that available evidence for the dCBT-I technologies in scope will be limited and therefore a supplementary review of broader RCT evidence including other dCBT-I technologies will be required to bridge evidence gaps.

Search strategies will be developed during the assessment, informed by:

- clinical expert opinion on the use of the current treatment options for insomnia in NHS practice to accurately define comparator treatments at specific pathway positions for this assessment
- published systematic reviews and syntheses of dCBT-I technologies and of comparator interventions for short-term and long-term insomnia

The inclusion and exclusion criteria of the supplementary review may, therefore, need to be updated at the assessment stage to ensure the review is fit for purpose and feasible within the project timelines.

2.1.3 Additional searches

Further pragmatic searches may be required to inform the conceptualisation of the decision model. These may include targeted searches to identify cost-effectiveness models used to assess (digital or therapist-led) CBT-I in people with insomnia or to inform NICE guidance issued by the Technology Appraisal (TA) programme for the treatment of insomnia.

2.2 Study selection

Two reviewers will independently screen all search results for inclusion in the Main Review and the Supplementary Review using EPPI reviewer software, using the machine learning and text mining tool within EPPI reviewer to prioritise titles and abstracts for screening. Full-text studies will be screened independently and in duplicate in EPPI reviewer. Disagreements will be resolved by consensus, or by a third reviewer if required. Studies will be screened in accordance with the eligibility criteria described in Table 3.

The results of the systematic search described in Section 2.1.1, carried out to identify all studies relating to the use of the dCBT-I technologies, will be used to identify any relevant studies on the cost-effectiveness of the technologies compared to alternative care options in people with insomnia. A broad range of studies will be considered in the assessment of cost-effectiveness including economic

evaluations conducted alongside clinical trials, decision-analytic modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature. Studies that report only resource use or cost outcomes will be excluded from the results of the clinical systematic reviews. However, these studies will be summarised in the review of economic evidence (see Section 3.1) and may be considered relevant sources of evidence to inform parameters in the decision-analytic model.

For any additional pragmatic reviews of economic evidence assessing (digital and therapist-led) CBT-I technologies other than the dCBT-I technologies in scope and of previous NICE TAs, studies will be included only if they include a decision-analytic model based full economic evaluation that compares two or more options for the treatment of insomnia and consider both costs and consequences.

2.3 Data extraction

Data extraction forms for the Main Review and the Supplementary Review will be developed and piloted. Study data will be extracted by one researcher and independently checked by another. Disagreements will be resolved via discussion or by a third researcher if necessary. Data will be extracted on population demographics and characteristics, components of dCBT-I, comparator interventions (including components of comparators where applicable), and results data for outcomes.

Within the Main Review (restricted to the dCBT-I technologies in scope), priority for data extraction will be given to RCTs. Data will be extracted from included non-randomised studies for interventions or comparisons where no RCT evidence exists, or where non-randomised studies report outcomes not included in RCTs (see Table 3 for the priority order of non-randomised study designs).

Data from all published and unpublished studies will be requested by NICE from the companies. All published and unpublished material supplied by companies will be checked and data extracted in the same fashion. Any additional data or individual participant data (IPD) supplied from studies will be checked for validity and consistency with published information by one researcher and independently checked by another.

2.4 Quality assessment strategy

For all included studies (regardless of design), applicability of study populations and settings to an NHS context will be evaluated based on input from clinical advisors and examination of study eligibility criteria and prohibited co-intervention lists.

For the Main Review and the Supplementary Review, RCTs will be evaluated using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2).[7]

For the Main Review, comparative, non-randomised studies will be assessed using NICE's cohort studies checklist. Single group studies, if included, will not be assessed against a generic tool. Rather, the applicability of these studies will be assessed as described above, and adherence to the dCBT-I intervention will be assessed.

Quality and applicability assessments will be performed by one researcher and independently checked by another. Disagreements will be resolved via discussion or by a third researcher if necessary.

2.5 Methods of synthesis and analysis

2.5.1 Assessment of clinical heterogeneity and narrative synthesis

Characteristics of included studies will be summarised narratively and in tables, grouped by each dCBT-I technology separately and by baseline population characteristics. It is anticipated that included studies may be heterogeneous with respect to design, included populations, intervention delivery (i.e., fully automated or hybrid) and comparator interventions, including no comparator intervention (i.e. single group studies, if included in the Main Review).

Where clinically homogenous RCT data are available for intermediate, clinical, sleep-related and patient outcomes listed in the published scope, data will be pooled using appropriate evidence synthesis techniques, as described in Section 2.5.2. However, it is anticipated that a narrative approach to synthesis will be required for a subset of the available evidence, including non-randomised study designs.

Within narrative synthesis, numerical and statistical results (e.g., measures of treatment effect and associated measures of precision) will be presented in tables and figures as appropriate, grouped by population and study design for each dCBT-I technology separately.

2.5.2 Quantitative synthesis

Quantitative synthesis of dCBT-I technologies compared to relevant comparators, and dCBT-I technologies compared to each other (if feasible), will be conducted separately at different positions in the care pathway as defined by the route of insomnia identification and persistence of symptoms (see Section 1.1).

Quantitative syntheses will include only RCT evidence. Outcomes that capture impact on insomnia symptoms (e.g., as measured by the insomnia severity index [ISI] and/or the sleep condition index [SCI]), treatment response, insomnia remission and adherence to dCBT-I interventions will be prioritised for quantitative syntheses.

Methods of pairwise meta-analysis and NMA, appropriate for the type of outcome data will be used. All quantitative meta-analyses will be conducted in a Bayesian framework using appropriate packages in R statistical software such as brms,[8] gemtc[9] or multinma.[10]

2.5.2.1 Meta-analysis

Random-effects pairwise meta-analyses will be performed where at least two comparative studies are identified in the Main Review:

- of the same dCBT-I technology in scope versus a relevant comparator
- comparing dCBT-I technologies in scope

Where evidence is sparse, informative priors will be considered to estimate between study-heterogeneity.[11]

2.5.2.2 Network meta-analysis

In the absence of head-to-head RCTs comparing dCBT-I technologies, random-effects NMA will be considered at each position in the care pathway where dCBT-I technologies can be compared indirectly through a shared common comparator.

In the first instance, only the six dCBT-I technologies included in the published NICE scope will be included in the quantitative synthesis (i.e., the Main Review). However, as described at the start of Section 2, the EAG anticipates that available evidence for the dCBT-I technologies in scope will be limited. Therefore, it is likely that broader evidence including other dCBT-I technologies and other comparator interventions outside of the published NICE scope, will need to also be included to allow synthesis versus all relevant comparators at different positions in the care pathway and for a quantitative assessment of heterogeneity of treatment effects (i.e. the Supplementary Review).

'Blended' comparators such as 'treatment as usual' which may include a combination of no intervention, sleep hygiene advice, etc., may be used to construct a network. The EAG anticipates that it may be difficult to construct a connected network to compare dCBT-I technologies to relevant pharmacological treatments in adults with long-term insomnia in regions where therapist-led CBT-I is unavailable; assumptions regarding a shared common comparator (e.g., equivalence of placebo groups) may be required. The clinical plausibility of all assumptions made by the EAG to construct networks will be informed by clinical expert opinion and the EAG will carefully consider the transitivity assumption of NMA when constructing networks.

If IPD are provided by companies of dCBT-I technologies in scope, where appropriate, they will be combined with aggregate data from published and unpublished study reports. Where differences in patient baseline characteristics which may influence treatment effects of health outcomes (i.e.

treatment effect modifiers), IPD may be used to adjust for treatment-effect modifiers in study populations. Multilevel network meta-regression (ML-NMR),[12] which extends a NMA to allow for covariate adjustments, will be considered if feasible.

2.5.2.3 Assessment of heterogeneity and exchangeability of treatment effects

Statistical heterogeneity will be assessed in quantitative synthesis by assessing the magnitude of the estimated between-study heterogeneity standard deviation τ and its 95% credible interval, compared to the estimated relative treatment effects. The presence of inconsistency, that is lack of agreement between direct and indirect evidence in the NMA, will also be assessed using global and loop-specific approaches depending on network structure.

Heterogeneity of treatment effects by intervention (e.g., fully automated vs. hybrid dCBT-I delivery mode), and population characteristics (e.g., subgroups defined in the published NICE scope [see Table 1]) will be assessed using meta-regression and/or network meta-regression or using class effects models,[13] where feasible. Separate meta-analyses and/or NMAs within the subpopulations of interest may also be considered, where constructing networks is feasible.

Quantitative assessments of heterogeneity of treatment effects will be used to inform assessments of the exchangeability of treatment effects between dCBT-I technologies, i.e., interventions with similar or equivalent effects or the existence of class effects (e.g., interventions with fully automated delivery or hybrid delivery). Evidence provided from non-randomised comparative and single group studies of dCBT-I technologies, and wider evidence sources (e.g., published systematic reviews, meta-analyses, network meta-analysis and component network meta-analyses of dCBT-I) may also be used to inform assessments of exchangeability of treatment effects.

Where appropriate and where required (e.g., where only single group [non comparative] evidence, or where no evidence is available for a d-CBT technology in scope), dCBT-I technologies assumed to have similar effectiveness on health outcomes or those exhibiting class effects may be pooled together to allow comparisons with the relevant comparator treatment at the relevant position in the care pathway.

All assumptions regarding exchangeability of treatment effects and class effects between dCBT-I technologies will be informed by clinical expert opinion.

Sensitivity analyses will be performed to test the robustness of results to changes in assumptions, such as random effects and fixed effect models, assumptions on exchangeability or class effects of dCBT-I technologies, and to the risk of bias and applicability of the included studies to the UK NHS setting.

3 METHODS FOR SYNTHESISING EVIDENCE OF COST EFFECTIVENESS

Cost-effectiveness evidence relevant to this assessment will be reviewed and synthesised to inform a cost-effectiveness analysis of the dCBT-I technologies in scope.

The cost-effectiveness analysis of dCBT-I technologies will be in line with the NICE reference case. The perspective of the analysis will be that of the NHS and PSS. Health benefits will be expressed in terms of quality-adjusted life years (QALYs), and both costs and QALYs will be discounted at an annual rate of 3.5%.

In the subsequent sections, we describe the individual components of the synthesis of cost-effectiveness, which include:

1) A systematic review and critical appraisal of relevant cost-effectiveness evidence of the use of the six dCBT-I technologies in scope against the relevant comparators and each other in people with insomnia.
2) Further additional pragmatic searches to support model conceptualisation, and/or identify relevant as input sources.
3) The development and analysis of a *de novo* decision-analytic model, including:
    a) A model conceptualisation exercise, where the structures, inputs and assumptions of the models identified in the reviews (described in Sections 3.1 and 3.2) are considered, together with the clinical expert input, relevant economic evidence submitted by the companies, clinical effectiveness evidence and outputs of the quantitative evidence synthesis from the clinical review.
    b) Model implementation based on the results of the conceptualisation exercise, and a formal cost-effectiveness analysis of the six dCBT-I technologies for the treatment of insomnia, considering use at different positions in the existing care pathway and for different patient subgroups. Comparisons will be established against the alternative insomnia management standard of care, the definition of which is conditional on the treatment pathway position at which dCBT-I is being assessed, persistence of insomnia symptoms and local availability of treatment (see Table 2). The use of blended comparators will be considered where appropriate (see Section 1.1).
    c) Formal assessment of uncertainty using deterministic and probabilistic analyses, as well as scenario analysis.

3.1 Identifying and systematically reviewing published cost-effectiveness studies

The approach taken to identify the relevant published cost-effectiveness evidence in scope has been described in Section 2.1.

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison within the report. In particular, information will be extracted on the perspective of analysis, comparators, study population and setting, main analytic approaches (e.g., patient-level analysis / decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g., deterministic / probabilistic sensitivity analysis).

The appropriateness of existing decision-analytic models to inform the current decision problem will be assessed based on:

- Consistency with the decision problem being considered in this assessment, including relevance to the UK setting.
- Relevance of outputs for decision making (i.e., to capture NHS costs and QALYs based on morbidity [and potentially, mortality] associated with insomnia, over the relevant time horizon).
- Flexibility within the model structure to reflect different patient characteristics for the economic evaluation (e.g., patients with short-term vs. long-term insomnia), potential factors affecting the effectiveness of the care strategies (e.g., adherence to dCBT-I), impacts on the timing of treatment initiation and uptake of subsequent treatments and longer-term indirect impacts of treatment (e.g., potential mortality effects associated with improved sleep).

A study, Darden et al. (2020)[2] has been identified via the NICE scoping searches as potentially relevant in terms of i) the intervention modelled (Sleepio) and ii) its direct comparison to potentially relevant care alternatives; namely, prescription-only pharmacotherapy, therapist-led (group and individual) CBT-I, and no insomnia treatment.

3.2 Additional pragmatic searches and reviews of cost-effectiveness studies

Given the potential limitations of the existing cost-effectiveness literature for the dCBT-I technologies in scope to inform the decision problem, additional reviews of other relevant cost-effectiveness models will be required to assist in the conceptualisation of a *de novo* decision-analytic model for assessing the cost-effectiveness of dCBT-I technologies. Cost-effectiveness modelling studies will be reviewed which evaluate insomnia treatments in the same position(s) in the care pathway as the one(s) proposed for the dCBT-I technologies identified in the searches defined above (Section 2.1), which do not fulfil the inclusion criteria defined by the scope.

These studies will not be subject to a formal assessment. Instead, this review will examine the relevant decision-analytic models to:

- Characterise the modelling/linked evidence approaches used to model the relative treatment effectiveness (and other value components [e.g., delays or reduced need for subsequent treatments], if feasible and appropriate), describing the underlying structural assumptions and identifying relevant data sources in the context of UK decision making.
- Identify main areas of uncertainty and evidence scarcity, and characterise approaches taken to deal with these issues; and
- Identify sources of heterogeneity (e.g., insomnia persistence and/or severity of disease presentation) that may be relevant to characterise the population or treatment outcomes at specific point(s) in the care pathway, as well as approaches taken to handle heterogeneity.
- Linked evidence approaches, and data sources from these models considered appropriate, contemporary and relevant for the current decision problem, will be integrated in the overall development of a *de novo* decision-analytic model for the evaluation of dCBT-I technologies. The appropriateness, for the current decision problem, of the evidence linkage mechanisms and data sources used in these previously developed models will be assessed as specified above for the models identified for the technologies in scope.

Studies will be selected that are considered potentially informative for the model conceptualisation and for the identification of relevant input sources of evidence, with a particular emphasis on those used in UK based or UK generalisable models. Linked evidence approaches, and data sources from these models that are considered appropriate, contemporary and relevant to the current decision problem, will be integrated in the overall development of a *de novo* decision-analytic model for the evaluation of the dCBT-I technologies. The appropriateness for the current decision problem of the evidence linkage mechanisms and data sources used in these previously developed models will be assessed as specified in Section 3.1.

3.3 Evaluation of cost-effectiveness

The cost-effectiveness of dCBT-I for the treatment of insomnia will be assessed, using a newly developed decision-analytic model. In brief, the model will link clinical outcomes associated with insomnia treatment to final health outcomes, where feasible and based on available evidence. Final health outcomes will be evaluated in terms of QALYs. Furthermore, the costs of delivering the dCBT-I technologies and downstream impacts on health care resource use will also be considered in line with the scope. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to their additional cost, in units which permit comparison

with other uses of health service resources. The final specification of the model will be determined during the review and model conceptualisation stage.

The cost-effectiveness of the dCBT-I technologies will be compared to the relevant comparator(s) (i.e., usual care alternatives at a particular position in the care pathway) in people with insomnia. The cost-effectiveness (efficiency) of the different technologies will be considered within a full incremental analysis and supplemented with pairwise comparisons for each technology against the relevant comparators. If evidence does not allow robustly assessing the cost-effectiveness of one or more of the six dCBT-I technologies separately, we will consider the exchangeability of the clinical effectiveness data across technologies and/or class of technologies (e.g., hybrid and fully automated) and any assumptions on class effects will be clearly stated (see Section 2.5.2.3 for details on how exchangeability of treatment effects will be assessed). The range of costs and resource consequences and potential clinical benefits associated with these technologies will be described based on available evidence.

The cost-effectiveness of the dCBT-I technologies will be evaluated based on the NHS and PSS costs and QALYs estimated over the time horizon for the different interventions (or strategies) under comparison. The time horizon of the model will be sufficient to capture the differential outcomes of the interventions, which are expected to be short-term in nature. Longer-term outcomes will be considered in exploratory analysis and conditional on feasibility and robustness of available evidence.

The set of most plausible and relevant inputs and structural assumptions will be applied in the base-case analysis. The cost-effectiveness of the dCBT-I will be expressed in terms of incremental cost per QALY and/or net health (or monetary) benefits at the relevant cost-effectiveness thresholds. Conventional cost-effectiveness rules will be applied to assess whether the use of dCBT-I can be considered an appropriate use of NHS resources.

Handling of uncertainty

Uncertainty in the data used to populate the model will be characterised and translated into decision uncertainty when presenting results to decision makers. To fulfil this purpose, the model will be set up probabilistically. Thus, where possible, uncertainty in inputs will be reflected using appropriate probability distributions, rather than as a fixed parameter input. Using a Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. We will estimate the probability of the alternative strategies being cost-effective at a given cost-effectiveness threshold (expressed as cost per QALY). If appropriate and informative, we will also illustrate decision uncertainty graphically using cost-effectiveness acceptability curves, which show the probability that an intervention is expected to be cost-effective for a given estimate of health opportunity costs (i.e., cost-effectiveness threshold).

The impact of parameter and structural uncertainty on the cost-effectiveness estimates will also be explored via sensitivity, scenario and/or threshold analyses. These will ascertain how sensitive the cost-effectiveness base-case results are to changes in the parameter inputs (e.g., impact of varying treatment compliance), structural assumptions of the model and the time horizon.

Handling of heterogeneity

Where possible and applicable, we will assess the impact of potential sources of heterogeneity on cost-effectiveness, in light of the findings of the clinical effectiveness (see Section 2.5.2.3) and economic evidence reviews (see Section 3.2).

3.4 Model development

Two decision analytic models, Darden et al. (2020)[2] and Briggs et al. (2025)[3] have been identified as potentially relevant. Darden et al. uses a Markov structure to model transitions between insomnia and insomnia remission conditional on care received over a six-month time horizon, while Briggs et al.'s reports a pathway model used to inform NICE TA922[4] (see Section 3.4.1) for details. However, neither of these two models can be directly used to inform the decision problem. Therefore, a *de novo* decision-analytic model will be developed to evaluate the cost-effectiveness of the six dCBT-I technologies for the treatment of insomnia relatively to the relevant comparators at the point(s) in the care pathway at which they are expected to be offered.

The population, interventions and comparator are as set out in Table 1. The model will be developed in accordance with the NICE reference case. The perspective will be that of the NHS and Personal and Social services (PSS), health benefits will be expressed in terms of QALYs, and both costs and QALYs will be discounted at an annual rate of 3.5%.

3.4.1 Model conceptualisation

The model conceptualisation will draw on the outputs of the economic evidence reviews (see Section 3.1 and 3.2) to assist in the development of a new decision-analytic model. For this purpose, the proposed model structure should:

- Account for the direct impacts on costs and health outcomes of dCBT-I (e.g., direct costs of the technology and reduction of insomnia symptoms, achievement of treatment response/insomnia remission and/or prevention of relapse).
- Link the impacts of dCBT-I to short-term costs and HRQoL (e.g., via the impacts on insomnia symptoms and/or treatment response/insomnia remission).
- If feasible and appropriate, link the short-term consequences to potential longer-term costs and consequences (e.g., impact on subsequent insomnia treatment choice and mortality directly or indirectly associated with sleep improvements), using the best available evidence.

The most likely modelling/evidence linkage approach is unknown. The key conceptual issue concerns the type of modelling approach required to link the impact of insomnia treatment on intermediate outcomes (e.g., treatment response measured as a reduction in severity of symptoms or symptoms remission, recurrence, etc.) to final HRQoL and healthcare resource use and costs. It is, however, anticipated that the evidence linkage will be operationalised using multi-domain patient reported outcomes (PROMs)/symptom measures, rather than sleep outcomes (e.g., sleep quality, sleep quantity, total sleep time, sleep efficiency, reduction in sleep-onset latency, reduction in wake after sleep onset, sleep-related satisfaction etc.). This is because, based on the economic evidence identified so far as potentially relevant, sleep outcomes do not provide a link to i) HRQoL and health care cost impacts and ii) clinical choice on whether to stop or modify treatments.

As noted in Section 3.1, preliminary searches undertaken to inform the scope identified two potentially relevant studies, including alternative modelling approaches, which include:

i) The Markov model developed by Darden et al. (2021)[2] to assess the cost-effectiveness of Sleepio in people with insomnia compared to prescription pharmacotherapy, therapist-led CBT-I and no treatment, from the societal perspective in the US. This model defined health states in terms of insomnia remission (defined as achieving a specific ISI [<8 or <11] or SCI [<16] score cut-off) to which utility weights and direct and indirect healthcare costs are associated. Treatment effects are reflected in the probabilities of achieving remission and the time horizon is 6 months (model cycle length is not specified).
ii) The pathway model developed by Briggs et al. (2025)[3] and used to inform NICE TA922,[4] which assessed the cost-effectiveness of daridorexant for long-term insomnia compared to placebo from the NHS and PSS perspective. This model has since become publicly available.[3] The Briggs et al. (2025) model used clinical trial data to estimate the treatment effect of daridorexant and placebo on ISI scores over time, and then linked changes in mean ISI scores over time to health care resource use consumption and changes in HRQoL. The treatment effects are reflected in the trajectory of the ISI score over time, based on a large cross-sectional dataset, the National Health and Wellness Survey, which collected evidence from multiple countries, including the UK. Furthermore, this model also considered (in exploratory analyses using a lifetime model), potential mortality effects from improved sleep, which may be relevant to the current assessment.

This model used clinical trial data to estimate the treatment effect of daridorexant and placebo on ISI scores over time. The model then linked ISI scores to impacts on HRQoL and health care in addition to the linkage approaches used in the two previous models described above to indirectly estimate the impact of dCBT-I on QALYs, this can also be done directly using EQ-5D or SF-6D data collected in RCTs. However, the number of trials reporting these outcomes is likely to be limited. This notwithstanding, there are several other potential approaches to derive QALYs, namely:

- Using external evidence on utility scores based on symptom severity (e.g. presence/absence of insomnia and/or different levels of severity) or response/remission outcomes;
- Mapping between disease specific PROM outcomes and EQ-5D using published algorithms, such as those by Gu et al. (2011)[14] and Chalet et al. (2023)[15] for ISI;
- Mapping between generic (non-preference based) measures and EQ-5D using algorithms such as the one proposed by Stokes et al. (2022)[16] for Patient-Reported Outcomes Measurement Information System Global Health-10 (PROMIS GH-10).

At the protocol stage, ISI scores (either as a continuous or dichotomous outcome) appear to provide the most flexible and, potentially, most appropriate way to inform the linkage between intermediate clinical outcomes and final cost and HRQoL outcomes. The cost-effectiveness evidence review may, however, identify alternative approaches.

Another important conceptual issue concerns the duration of the relevant time horizon. Previous models have considered relatively short-time horizons not exceeding 12 months in their main analyses.[2, 3] The duration of the time horizon in *de novo* decision analytic model is likely to be equally short, given that the expected durability of treatment effect based on evidence for therapist-led CBT-I. Existing evidence suggests that treatment effects of CBT-I on insomnia symptoms are likely to be maintained for one to three years[17, 18] with some studies suggesting durability up to 10 years.[19, 20] Furthermore, the evidence to support the impact of insomnia on mortality (direct or mediated by outcomes with mortality outcomes, as, for example, road traffic accidents) is likely to be scarce and of limited robustness. Nevertheless, we will consider the feasibility and appropriateness of conducting exploratory scenarios using a lifetime horizon to capture the potential impacts of alternative treatment effects durability and/or including insomnia related mortality outcomes will be considered.

The model will also have to explicitly account for different potential positions for the technologies in the care pathway, as these will imply that different (sub)populations will be offered treatment and different comparators. Thus, we will attempt to reflect the characteristics of the populations at each position in the care pathway and compare the dCBT-I technologies against the comparators that define the standard of care at each position. Where feasible and appropriate, we will model comparators separately, but the use of blended comparators will be considered where the available evidence does not allow establish a comparison to single treatments (see Section 1.1) and/or where particular comparators may not be routinely offered to all patients (e.g., due to constraints on the availability of trained therapists) . If blended comparators are included, we will seek clinical opinion on whether dCBT-I is expected to displace all treatments in the blend equally or not. Consideration will also be given to restricting comparators conditional on regional availability, as part of exploratory analyses.

We will consider other components of value for dCBT-I technologies, such as reductions of waiting times for treatment and uptake of subsequent treatments, if feasible and appropriate evidence is available to support the inclusion of these components.

3.4.2 Data sources

The decision-analytic model will be populated using the most appropriate available evidence, as identified in the clinical and cost-effectiveness reviews (Section 2.5 and Section 3.1). In addition, evidence provided by the companies, such as data on the direct resource use (e.g., training requirements if any) and costs of the dCBT-I (e.g., subscription fees) will be used to inform model parameters as appropriate. Clinical opinion will be sought to assess the appropriateness of the data sources and of the structural assumptions in the model, as well as to identify additional data sources (e.g., local trust audits to inform regional variation in clinical practice). Clinical expert opinion may be formally elicited in the absence of empirical evidence on model parameters.

3.4.3 Model implementation and validation

It is anticipated that the model will be developed in Microsoft Excel and/or the statistical programming language R; the appropriate choice of software will be informed by the final conceptualisation of the model.

The validation of the implemented model will comprise:

- The review of individual components of the model by members of the project team with modelling experience and not directly involved in the implementation of these components against the model description in the report.
- Testing the internal validity of the model by using either the TECH-VER[21] or a bespoke model verification checklist.
- Cross-validating results against those from cost-effectiveness models from published literature, if appropriate.

4 HANDLING INFORMATION FROM THE COMPANIES

All data submitted by the companies in evidence and information requests by NICE, or data submitted by other stakeholders, will be considered by the EAG if received by 13th February 2026. Information arriving after this date will be considered if time permits. The EAG may seek clarification or additional information from companies and other stakeholders where necessary. All correspondence between the EAG and companies will happen through NICE.

Any 'commercial in confidence' data provided by a company and specified as such will be highlighted in blue and underlined in the assessment report. Any 'academic in confidence' data provided by a company, and specified as such, will be highlighted in yellow and underlined in the assessment report. If confidential information is included in the economic model, the EAG will provide a copy of the model with 'dummy variable values' for the confidential values (using non-confidential values).

5 COMPETING INTERESTS OF AUTHORS

The authors have no competing interests.

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APPENDIX 1. DRAFT SEARCH STRATEGY

Database: Ovid MEDLINE(R) ALL <1946 to December 12, 2025>
Search Strategy:

1 "Sleep Initiation and Maintenance Disorders"/ (20689)
2 Insomnia, Fatal Familial/ (208)
3 Sleep Wake Disorders/ (31121)
4 Sleep/ (76674)
5 Sleep Quality/ (5039)
6 Sleep Duration/ (1025)
7 Sleepiness/ (1109)
8 Sleep Deprivation/ (12118)
9 Fatigue/ (39415)
10 Wakefulness/ (21666)
11 insomnia$.ti,ab,kf. (37616)
12 hyposomnia$.ti,ab,kf. (45)
13 DIMS.ti,ab,kf. (482)
14 (sleepless$ or wakeful$).ti,ab,kf. (16665)
15 (poor$ adj2 sleep$).ti,ab,kf. (14264)
16 (sleep$ adj2 quality).ti,ab,kf. (38658)
17 ((sleep$ or asleep) adj2 (quantit$ or duration$ or time or short$)).ti,ab,kf. (35472)
18 ((sleep$ or asleep) adj3 (unable or inability)).ti,ab,kf. (293)
19 ((suboptimal$ or sub-optimal$ or insufficien$ or inadequa$ or irregular$ or deficien$ or lack$ or depriv$ or debt$ or shortage$ or deficit$ or loss$ or losing) adj3 sleep$).ti,ab,kf. (21982)
20 ((early or nocturnal or night or nights or nighttime or nightly) adj6 (awake$ or waking$ or wake$ or rise$ or rising$)).ti,ab,kf. (12946)
21 ((lie or lying) adj2 awake$).ti,ab,kf. (46)
22 ((nocturnal or night or nights or nighttime or nightly) adj3 symptom$).ti,ab,kf. (2915)
23 ((difficult$ or dysfunction$ or disorder$ or problem$ or disturb$ or complaint$ or issue$ or struggl$ or interrupt$ or hard or trouble$ or disrupt$ or impair$ or fragment$) adj4 (sleep$ or asleep)).ti,ab,kf. (98056)
24 ((nonrestorative or non-restorative) adj sleep$).ti,ab,kf. (547)
25 ((initiat$ or onset or maintain$ or maintenance) adj3 sleep$).ti,ab,kf. (12730)
26 ((day or days or daytime$) adj5 (sleepy or sleepiness or drowsy or drowsiness or somnolen$ or tired$ or fatigue$ or exhaust$ or energy or irritab$ or concentrat$ or motivat$ or symptom$ or problem$ or impair$ or function$ or dysfunction$)).ti,ab,kf. (120084)
27 ((awake$ or wake$ or waking$) adj5 (sleepy or sleepiness or drowsy or drowsiness or somnolen$ or tired$ or fatigue$ or exhaust$ or energy or irritab$ or concentrat$ or motivat$ or symptom$ or problem$ or impair$ or function$ or dysfunction$)).ti,ab,kf. (7236)
28 or/1-27 (378785)
29 Cognitive Behavioral Therapy/ (34190)
30 Cognitive Restructuring/ (35)
31 ((cogniti$ or behavio$) adj3 (counsel$ or intervention$ or therap$ or psychotherap$ or psychoeducat$ or training or treatment$ or technique$ or restructur$ or refram$ or reconstruct$ or program$ or principle$ or method$ or strategy or strategies)).ti,ab,kf. (171980)
32 CBT.ti,ab,kf. (18497)
33 29 or 30 or 31 or 32 (184321)
34 28 and 33 (10118)
35 (CBT-I or CBTI).ti,ab,kf. (1356)
36 34 or 35 (10172)

37 Digital Health/ (1269)
38 Digital Technology/ (1878)
39 Digital Media/ (45)
40 Mobile Applications/ (16248)
41 exp Internet/ (109620)
42 exp Cell Phone/ (27168)
43 exp Computers, Handheld/ (16634)
44 Medical Informatics Applications/ (2556)
45 Therapy, Computer-Assisted/ (7075)
46 Computer-Assisted Instruction/ (13010)
47 Multimedia/ (2337)
48 Telemedicine/ (47330)
49 Mental Health Teletherapy/ (68)
50 Software/ (135502)
51 Avatar/ (132)
52 (online or web or internet or digital$ or automated or electronic$).ti,ab,kf. (1423688)
53 (computer$ or desktop$ or laptop$ or phone$ or telephone$ or smartphone$ or smart phone$ or cellphone$ or cell phone$ or smartwatch$ or smart watch$ or iOS or android or iPhone$ or iPad$).ti,ab,kf. (558694)
54 (app or apps).ti,ab,kf. (58374)
55 (mobile health or mhealth or m-health or ehealth or e-health or emental or e-mental or etherap$ or e-therap$ or epsych$ or e-psych$).ti,ab,kf. (33453)
56 (mobile$ adj3 (based or application$ or intervention$ or therap$ or device$ or technolog$)).ti,ab,kf. (31272)
57 (telemedicine or tele-medicine or telehealth or tele-health or teletherap$ or tele-therap$ or telepsych$ or tele-psych$ or telemental or tele-mental).ti,ab,kf. (50258)
58 (virtual$ adj3 (coach$ or therapist$ or assitant$ or agent$ or companion$)).ti,ab,kf. (1120)
59 avatar$.ti,ab,kf. (2911)
60 or/37-59 (2088789)
61 36 and 60 (2342)
62 (dCBT or d-CBT or iCBT or i-CBT or cCBT or c-CBT or eCBT or e-CBT).ti,ab,kf. (1972)
63 ((digitis$ or digitiz$ or virtual$) adj3 (cognitive or behavio?r$ or therap$ or CBT)).ti,ab,kf. (3194)
64 62 or 63 (5160)
65 28 and 64 (341)
66 (dCBTI or dCBT-I or iCBTI or i-CBTI or cCBTI or cCBT-I or eCBTI or eCBT-I).ti,ab,kf. (106)
67 ((digitis$ or digitiz$ or virtual$) adj3 (CBT-I or CBTI)).ti,ab,kf. (7)
68 61 or 65 or 66 or 67 (2429)
69 Sleepio$.af. (52)
70 (Sleep station$ or sleepstation$).af. (2)
71 "Space for sleep".af. (33)
72 Sleepful$.af. (4)
73 Somnio$.af. (64)
74 "This way up".af. (397)
75 74 and 28 (3)
76 69 or 70 or 71 or 72 or 73 or 75 (158)
77 68 or 76 (2555)
78 exp animals/ not humans.sh. (5406142)
79 77 not 78 (2488)
80 limit 79 to yr="2000 -Current" (2464)