NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: MT443 Sleepio to treat insomnia symptoms

Supporting documentation – Committee papers

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

1. **EAC assessment report** – an independent report produced by an external assessment centre (EAC) who have reviewed and critiqued the available evidence.
2. **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.
3. **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 company's case for adoption.
4. **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.
5. **Company submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the EAC and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the company's response following a factual accuracy check of the assessment report.
9. **Additional EAC analysis** – the EAC undertook additional work following the initial MTAC discussion. It obtained access to the patient level data

and conducted an independent statistical analysis of it. It also did some additional economic modelling.

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

Document cover sheet

Assessment report: Sleepio

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance
MT443 Sleepio for adults with poor sleep
External Assessment Centre report

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Number of attached appendices: 4

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption 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 provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 3
Medical technologies guidance 3
MT443 Sleepio for adults with poor sleep 3
External Assessment Centre report 3
Executive summary 7
1 Decision problem 10
2 Overview of the technology 15
3 Clinical context 15
4 Clinical evidence selection 17
4.1 Evidence search strategy and study selection 17
4.2 Included and excluded studies 18
5 Clinical evidence review 66
5.1 Overview of methodologies of all included studies 66
5.2 Critical appraisal of studies and review of company's critical appraisal 67
5.3 Results from the evidence base 69
6 Adverse events 81
7 Evidence synthesis and meta-analysis 81
8 Interpretation of the clinical evidence 84
8.1 Integration into the NHS 87
8.2 Ongoing studies 90
9 Economic evidence 94
9.1 Published economic evidence 94
9.2 Company de novo cost analysis 98
9.3 Results from the economic modelling 106
9.4 The EAC's interpretation of the economic evidence 111
10 Conclusions 114
10.1 Conclusions from the clinical evidence 114
10.2 Conclusions from the economic evidence 115
11 Summary of the combined clinical and economic sections 116
12 Implications for research 117
13 References 118
14 Appendices 123
Appendix A 123
Appendix B 126
Appendix C 170
Appendix D 171

Abbreviations

Term	Definition
AI	Artificial Intelligence
BAI	Beck Anxiety Inventory
CBT	Cognitive Behavioural Therapy
CBT-I	Cognitive Behavioural Therapy for Insomnia
CI	Confidence interval
CIS	Coronavirus Impact Scale
DHSC	Department of Health and Social Care
DSM-5	Diagnostic Statistical Manual 5
EAC	External Assessment Centre
GPTS	Green Paranoid Thoughts Scale
iOS	iPhone Operating System
IPD	Individual patient data
IQR	Interquartile range
ISI	Insomnia Severity Index
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSQI	Pittsburgh Sleep Quality Index
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
RR	Rate Ratio
SCI	Sleep Condition Indicator
SD	Standard deviation
SOL	Sleep Onset Latency
SPEQ	Specific Psychotic Experiences Questionnaire
Vs	Versus
WASO	Wake After Sleep Onset

Executive summary

The company included 26 published fulltext studies in their clinical submission (including 12 RCTs and 6 follow-up analyses). The EAC excluded 1 non-randomised study due to the population being under 18 years old (Cliffe et al. 2020). An independent review of evidence found no additional published studies. The fulltext of 2 unpublished real-world retrospective cohort studies (Stott et al. and Studd et al.) was provided by the company and deemed relevant include in the clinical evidence. One abstract (Drake et al. 2019) was included as it described the impact of Sleepio on sleep medication use.

There is an extensive evidence base for Sleepio, including well-designed and reported RCTs. There are 4 UK RCTs (Espie et al. 2012, Freeman et al. 2017, Denis et al. 2020 and Kyle et al. 2020) and 1 multinational RCT including populations from UK, US and Australia (Espie et al. 2019) which may help generalisability to the NHS setting. Populations varied widely, including students with mean age < 25 years, pregnant women, employees from a Fortune 500 company and people who reported symptoms of depression.

Standard care included treatment as usual, waiting list or sleep hygiene education. Various outcomes were measured, such as insomnia, psychological wellbeing, productivity using various indices (such as DSM-5, ISI and SCI [which assesses against DSM-5 criteria] for insomnia).

High study heterogeneity due to differences in population and outcome measurement resulted in diverse effect sizes between studies. Most studies included participants who had self-referred and self-reported outcomes rather than been formally assessed. None of the studies compared Sleepio with face-to-face CBT for insomnia. Clinical experts suggested that Sleepio may be most appropriate for adults over 25 years old with chronic (>3 months) mild to moderate insomnia symptoms and that caution should be urged before referring CBT-I for certain populations such as pregnant women and people under 25 years old to rule out other insomnia mimics. The EAC notes that there is evidence into both populations under 25 (such as Freeman et al. 2017) and in pregnant women (such as Felder et al. 2020) that indicates Sleepio is more effective than control for improving insomnia symptoms.

Despite the variation in effect size, the results from the comparative studies consistently indicate that Sleepio has the potential to have a positive impact for adults with insomnia symptoms compared with standard care or a placebo. One study Luik et al. (2020) provided long-term follow-up data from Espie et al. (2019) indicating that results were maintained at 48 weeks, albeit the positive outcome was observed for a fraction of the participants due to low engagement rates.

There were high rates of loss to follow up, particularly from the Sleepio arm of the RCTs, however 10 studies were analysed as intention to treat (ITT) to account for missing data

[redacted]

The EAC believes that the estimate in the company's economic submission of the proportion of general practice populations that might benefit from Sleepio is a best case scenario. The EAC modified this parameter and applied the estimate of 0.58% based on uptake reported for Buckinghamshire in Sampson et al. (2021). This is lower than 0.94% reported in the 9 general practices from which patient level data were taken, but Sampson et al. (2021) indicates that these practices received additional tailored promotional material. It also seems likely that the GPs in the nine sample practices were highly motivated to refer. Following the change in the uptake parameter to 0.58% Sleepio becomes cost incurring at a cost of £20.09 per patient over one year. The EAC also notes that cost savings in the current model assume that use of Sleepio in future years will be maintained at the same proportion of the adult population as that estimated for the first year. The EAC considers it likely that the proportion of users in subsequent years will not be as high as the proportion recorded in the first year and reported in Sampson et al. (2021). Under a favourable assumption of annual uptake of 0.58% of the population each year, overall costs are positive and grow over time. The EAC believes it is likely that uptake will fall in subsequent years. For these reasons the EAC's cost estimate for the first cohort represents an optimistic assessment of the longer term cost impact of Sleepio. Consequently, the EAC concludes that it is highly likely the Sleepio will be cost incurring at a price per head of £0.90 per year.

The EAC believes that, overall, Sleepio may be clinically beneficial for adults over 25 years old with chronic (> 3 months), mild-to-moderate insomnia compared with treatment as usual or sleep hygiene education. However, at the current EAC estimated base case uptake of 0.58%, Sleepio is cost incurring and therefore the EAC believes the case for adopting the technology is not supported for insomnia in adults. Sensitivity analyses indicate that Sleepio becomes cost neutral when uptake is between 0.6 and 0.7%, therefore adequate uptake is key to recommending the adoption of Sleepio. It is unclear whether engagement at this level is likely in practice. The evidence base would benefit from adequately powered multicentre RCTs comparing long-term effectiveness of Sleepio with face-to-face CBT in targeted populations to address uncertainties. Adequate patient uptake and engagement are crucial to seeing benefits of Sleepio in the health system, therefore, investigating how to optimise patient selection and engagement would be valuable.

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation	EAC comment
Population	Adults with difficulty sleeping	Adults with insomnia symptoms (18 yr plus; no upper age limit)	Addresses insomnia as a specific sleep disorder, addresses effectiveness across entire adult age range	Experts described insomnia as difficulty falling asleep and staying asleep that affects health the following day. They also noted that numerous other conditions can mimic insomnia.
Intervention	*Sleepio*	None	None	None
Comparator(s)	Sleep hygiene Hypnotic drugs Face-to-face CBT for insomnia Digitally-facilitated CBT for insomnia	Omitted digitally-facilitated CBT for insomnia	Lack of comparative studies	The EAC would still include this comparator in the scope if it is a relevant comparator (e.g. to include as part of the search strategy that may need to be repeated later).
Outcomes	Sleep related outcomes • Sleep quality • Sleep quantity	<u>To add:</u> <u>Insomnia related outcomes</u> • Sleep Condition	We include validated clinical scores used in the assessment and management of insomnia	None

	• Sleep-related satisfaction and quality of life • Health related quality of life measures • Symptoms of comorbid health conditions (mental and physical) directly impacted by difficulty sleeping System related outcomes • Access to CBT for insomnia • Waiting time for CBT for insomnia • Number of primary care appointments • Hypnotic drug prescription • Incidence of comorbid health conditions Device related outcomes • Device-related adverse events	Indicator (SCI) • Insomnia Severity Index (ISI)		

Cost analysis	Costs will be considered from an NHS and personal social services perspective. The cost modelling should reflect the business model the company is proposing to use in the NHS, for example if a regional approach is adopted the intervention cost should reflect that rather than the intervention cost when the technology is being purchased per patient. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	None	None	None
Subgroups to be considered	• Pregnant women • People who have not had an insomnia diagnosis • People with short term insomnia (symptoms present for	• People with long term insomnia (symptoms present for 3 months or longer) • People with insomnia and a comorbid mental	The list has been reordered to reflect the likely prevalence of the subgroups. People may have mental or physical health comorbidities so these have been separated. Clarification that there are people	None

	less than 3 months) • People with long term insomnia (symptoms present for 3 months or longer) • People with insomnia and a comorbid condition	health condition • People with insomnia and a comorbid physical health condition • People who have not had a formal insomnia diagnosis • People with short term insomnia (symptoms present for less than 3 months) • Pregnant women with problems sleeping	with insomnia who have no 'formal' diagnosis Clarification that we are referring to pregnant women with problems sleeping	
Functional classification and risk category	N/A	None	None	
Special considerations, including issues related to equality	Patient-facing digital health technologies such as *Sleepio* may be unsuitable for people with visual or cognitive impairment, problems with manual dexterity or learning disabilities. Disability is a protected characteristic under the Equality Act. *Sleepio* is not suitable for those hard of hearing or	None	None	None

	where English is not well understood. Access to internet-enabled devices, access to the internet and user engagement with the technology may be more difficult for the people in deprived communities. Socio-economic status is not a protected characteristic and so is not protected under the Equality Act 2010 but factors affecting access to care delivered using digital devices should be considered. The technology can be used in pregnant women that are contraindicated for hypnotic medication. Pregnancy and maternity are protected characteristics of the equality Act 2010.			

2 Overview of the technology

Sleepio (Big Health) is a self-help sleep improvement programme based on cognitive behavioural therapy for insomnia (CBT-I). It is accessed through a website, with some features available on an app for iOS mobile devices. Sleepio can be used as a standalone treatment and does not require clinical input.

Sleepio consists of six, 15-20 minute sessions that cover a number of topics and techniques for sleep improvement. The company states that the programme uses artificial intelligence (AI) to personalise components of the CBT-I programme for patients. A core component of Sleepio is completion of the sleep diary. It is recommended that patients complete the sleep diary every morning upon waking.

It can link to a compatible wearable fitness tracker to monitor sleep (currently Fitbit and any other device that uses Apple's Healthkit).

The company states that there have been no substantive changes to the CBT-I content since launch.

Sleepio has been CE marked as a class I technology since October 2018.

3 Clinical context

The NICE clinical knowledge summary on insomnia states that good sleep hygiene should be established in all people with insomnia. Hypnotic medication should be avoided, if possible, due to potential for significant adverse effects. CBT-I is recommended for treatment of both short- and long-term insomnia in adults because, unlike medication, benefits associated with CBT-I persist on completion of treatment.

The NICE guidelines on depression in adults with a chronic physical health problem state that advice on good sleep hygiene should be offered if needed.

NICE technology appraisal guidance on zaleplon, zolpidem and zopiclone for the short-term management of insomnia states that the choice of

management strategy depends on the presenting symptoms. Non-pharmacological interventions such as CBT-I have been shown to be effective in managing persistent insomnia. However, in practice, access to many of these therapies is restricted through a combination of a lack of trained providers, cost and a poor understanding of available options.

The company submission describes the current care pathway in primary care (the company notes this is based on NICE guidance) for acute (< 3 months) and chronic (>3 months) insomnia. The company suggests that Sleepio could be prescribed instead of sleep hygiene advice, and prescription of a short course of hypnotics or melatonin in the case of acute insomnia. In cases of chronic insomnia it could be prescribed instead of sleep hygiene advice and either referral to CBT, prescription of hypnotics or other medication, or referral to IAPT if symptoms of depression and anxiety are present.). The company note that in instances where someone may be offered face-to-face CBT for insomnia may currently be rare and there are long waiting times for in-person treatment.

Special considerations, including issues related to equality

The company notes that there is a growing body of evidence that links poor sleep and insomnia with populations with lower socioeconomic status and with racial and ethnic minorities (such as Johnson, et al., 2019). The company claims that providing digital CBT-I would improve access to CBT services, for example, providing a CBT service for insomnia where face-to-face CBT is not available or has long waiting times. Clinical experts noted that long waiting times for face-to-face CBT for insomnia are a significant challenge.

Patient-facing digital health technologies such as Sleepio may be unsuitable for people with visual or cognitive impairment, problems with manual dexterity or learning disabilities. Disability is a protected characteristic under the Equality Act.

Sleepio is not suitable for those hard of hearing or where English is not well understood.

Sleepio can only be used by people who have regular and reliable access to the website, however the company claims that Sleepio has been made available to people without mobile or web devices in community settings through library or practice computers. The Sleepio app is currently only available for iOS mobile devices, however, the company states that it is intending to expand the technology to Android devices.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The EAC reviewed the company's search strategy using the Peer-Review of Electronic Search Strategy (PRESS) and PRISMA-Search guidelines, noting that the search did not contain controlled vocabularies and was limited to a single source (PubMed) without using truncation to cover variations of Sleepio* including SleepioR or SleepioTM. The EAC carried out a new search and expanded the search to include Embase, PubMed, MEDLINE, Cochrane Library databases, EconLit, INAHTA, ClinicalTrials.Gov and WHO ICTRP. The EAC removed the limitation to language and document type (full journal article) to enable the possibility of finding independent studies and ongoing/completed but unpublished studies (registered trial). The results from the clinical evidence search were filtered in EndNote and reviewed separately.

The search revealed 1595 records and following deduplication there were 767 records. The titles and abstracts of these records were evaluated by 2 reviewers and sifted for relevance. Following the first sift, there were 62 records remaining. The full-text versions of the remaining records were sifted against the inclusion and exclusion criteria and following this second sift, 26 studies were included (plus 1 cost-effectiveness analysis – Darden et al. 2020). The fulltext of 2 unpublished UK studies (Stott et al. and Studd et al.) were included in addition to 1 abstract (Drake et al. 2019); these studies were provided by the company. The search strategies and a PRISMA flow diagram is included in Appendix A. The EAC considered the company's inclusion criteria to be appropriate.

The company included 26 published fulltext studies in their clinical submission. The EAC agreed with all but 1 study (Cliffe 2020), that was excluded due to population being out of scope.

The company included 12 studies in their economic submission. Following application of cost and economic filters, the EAC searches retrieved 89 abstracts related to economic evidence. After sifting 3 studies were deemed relevant to scope (see section 9.1).

4.2 *Included and excluded studies*

Table 1: Studies selected by the EAC as the evidence base

RCTs

Table 1.1 Randomised controlled trials

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Espie et al. (2012) UK The software and web development for this study was supported by Sleepio Limited. Lead author is co-founder and shareholder in Big Health (Sleepio) Ltd.	3-arm RCT comparing online web-based CBT (Sleepio), imagery relief therapy (IRT) (placebo) and treatment as usual (TAU). TAU participants comprised, effectively, a wait-list group who completed measures but received no additional help for their insomnia	164 adults (120 women, mean age 49 years (18-78)) with insomnia who had completed the online Great British Sleep Survey (GBSS), and who met proposed DSM-5 criteria for chronic (>3 months) insomnia. Lost to follow-up: Sleepio – 15 IRT – 17 TAU – 4	*Primary outcome - sleep efficiency (SE)* (total time asleep expressed as a percentage of the total time spent in bed): a) Post treatment increase in SE Sleepio - 19.5% (95%CI, 15.3 to 23.7) IRT - 5.7% (95%CI, 2.79 to 8.52)	Assignment to groups was blinded UK study so may be more generalisable to NHS population. Analysed as intention-to-treat. Population with chronic insomnia symptoms. Participants were recruited by online survey and may represent a cohort unusually

	Analysed as intention-to-treat. Participants in all 3 groups were followed up for 8 weeks.		TAU - 6.4% (95%CI, 2.88 to 9.86) in TAU b) 8-weeks post-treatment increase in SE: Sleepio - 20% (95%CI, 15.7 to 23.6) IRT - 7% (95%CI, 4.53 to 10.1) TAU - 9% (95%CI, 4.89 to 13.7) Participants receiving Sleepio experienced a >2-fold improvement in insomnia symptoms (SCI-8), with a large between-group effect compared with TAU (d=1.20) at post-intervention and	interested in addressing sleep problems. The inclusion of healthcare providers in the study design limits the generalisability of the results to the self-referral setting. One expert noted that the primary outcome (SE) may be considered a measure of adherence rather than improvement. Authors acknowledged that selection of SE as the primary endpoint could have unduly favoured CBT because the sleep restriction component of CBT can lead

			follow-up (d=1.11). The equivalent effects for Sleepio compared to placebo were d=0.95 and d=0.77 respectively. 	to improved SE, in the absence of other evidence. The study was designed to have 80% power to detect a medium effect size. EAC confirmed that this study is well powered. Similar numbers lost to follow up in Sleepio and placebo groups.
Pillai et al. (2015) USA. The software and web development for this study	RCT comparing Sleepio with Information Control (IC) comprising weekly 'sleep tips' and general	32 adults (62.5% women, mean age ranged from 44.0 to 53.2 years) with chronic insomnia recruited from previous insomnia research studies. Participants were eligible if they	Sleepio group showed significantly larger reductions in Beck Anxiety Inventory (BAI) scores ($t = 2.6$; $p < .05$; Cohen's $d = 0.8$) and Insomnia Severity Index (ISI)	Small sample size with no power calculation provided. One week follow up is inadequate to assess long-term effectiveness.

was supported by Big Health Limited	sleep hygiene education Per-protocol analysis Participants were followed up for 1 week following treatment. ● ●	met diagnostic criteria for DSM-5 based insomnia and had no history of other sleep disorders. Per DSM-5 diagnostic criteria, participants earned an insomnia diagnosis if they reported experiencing one or more sleep complaints (e.g., 'have you experienced difficulty falling asleep?'; 'have you experienced difficulty staying asleep?') for at least 3 nights a week for a period of three months or longer. Randomised to Sleepio (n = 19, mean age 53.2 years) group or an IC (n = 13, mean age 44 years) group	scores (t = 2.1; p < .05; Cohen's d = .9) at 1 week follow-up than did the IC group. Improvements in sleep onset latency (SOL) from baseline (62.3±44.0 minutes) to follow-up (22.3±14.4 minutes) in the Sleepio group were also significantly greater (t = 2.3; p < .05; Cohen's d = .9) than in the IC group (baseline: 55.0±44.2 minutes; follow-up: 50.±60.2 minutes). ●	

		. Lost to follow-up: Sleepio – 4 Sleep hygiene education control – 2 ●		
Bostock et al. (2016) USA. One author is a cofounder of and shareholder in the company.	RCT comparing Sleepio with waiting list control (WL, no intervention or advice) Intention-to-treat analysis.	270 (180 men: mean age 33.6 years (23 to 56 years)) self-identified insomnia (as per DSM-5 criteria) recruited from a Fortune 500 company. Lost to follow-up:	8 weeks post treatment: Sleep Condition Indicator (SCI) scores were significantly higher for the Sleepio group compared with control (F (1,485) = 15.63, p < 0.0001], representing	Participants self-identified as being poor sleepers; although DSM-5 criteria were used to promote the trial, the participants were not formally evaluated.

	Sleepio group were followed up at 22 weeks after allocation, while the Control Group were followed up at 16 weeks. ● ●	Sleepio 37 at week 8 post-intervention 52 at week 22 Waitlist 19 at week 8 post-intervention 51 at week 16 post-intervention (after receiving Sleepio. ●	Cohen's d of 1.10 following Sleepio (d = 0.34 for WL). Work Productivity and Impairment questionnaire: “presenteeism” demonstrated significant improvements following Sleepio compared with control [F(1,485) = 10.99, P = 0.001: d = 0.64 for dCBT, d = 0.09 for WL]. There was no significant difference between Sleepio and control for “abseenteeism” (p = 0.101). ●	The study presents data from a single company (that did not wish to be identified) and therefore this may affect generalisability. The study was planned with 80% power to detect an effect size = 0.4, thus requiring a minimum sample of 200 (n = 100 per group) at P-value less than 0.05. The EAC confirm that this study is powered to detect an effect size of d = 0.4. The study did not include formal screening of other disorders of sleep, so it is unknown if patients had sleep

				breathing or sleep motor problems. Incentives (aside from the treatment) were used to retain participants in the study.

Barnes et al. (2017) USA. One author is an employee and shareholder in the company.	RCT comparing Sleepio with a waiting list (control - no intervention or advice). Patients in this group completed all major assessments for the trial and were offered Sleepio 10 weeks after the study period. Per-protocol analysis. Analyses were carried out to confirm no significant demographic or focal differences between missing data groups.	223 participants (145 women, mean age 39.95) with self-reported insomnia (per World Sleep Survey and Jenkins' Questionnaire (1988)), recruited online. Randomly assigned to either the treatment (n = 117) or wait-list control condition (n= 106). Lost to follow-up Sleepio: 64 Waitlist control: 38	Significantly greater improvements were found in the Sleepio groups compared with the control: Insomnia: Sleepio $t(51) = -8.15$, $p<0.001$. No significant change in control condition. Mood: Sleepio $t(52) = -3.2$, $p<0.001$. No significant change in control condition. Job satisfaction: Sleepio $t(52) = 1.65$, $p<0.05$. No significant change in control condition. Self-control: Sleepio $t(52) = 6.49$, $p<0.001$. Control $t(67) = 2.31$, $p = 0.024$	However, the analyses were within individuals. Thus, distortions such as response biases that occur at the person-level of analysis were statistically controlled for. No placebo to rule out placebo effect. No measure of insomnia severity. Participants self-referred. No power calculation. No information on funding. No follow-up period reported.

			No significant differences were observed between Sleepio participants and control on measures of organisational citizenship behaviour or interpersonal deviance. Sleep efficiency was improved by 26% and 28% in the Sleepio and control group, respectively.	

McGrath et al. (2017) Ireland. One author is the Clinical and Scientific Director and a shareholder of the company.	RCT comparing Sleepio with standard care (vascular risk factor education) Single-centre, Investigator Blinded Per-protocol analysis. Patients were followed up at 8 weeks (unclear whether this was after starting or finishing treatment). ● ●	134 participants aged 18 years or over with mean blood pressure readings of 130-160/<110mmHg and self-reported sleeping difficulties were randomised 1:1 into 2 groups of 67. 54 participants in Sleepio group, and 67 in control group were included in the analysis. 13 participants in Sleepio group were excluded from the analysis as they did not complete at least 1 session. 6 participants in the Sleepio group and 1 in the control group were lost to follow up.	Mean change in 24 hour ambulatory SBP over 8 weeks was not significantly different between the 2 groups (p=0.95). Participants in the Sleepio group had greater mean improvements in measures of sleep quality: PSQI: 1.1 (p=0.04; 95% CI: 0.1-2.2) ISI: 2.8 (p<0.001; 95% CI: 1.3 - 4.4) SCI: 0.8 (p=0.01; 95% CI: 0.2 – 1.4)	To minimise “contamination” of control participants (i.e., seeking an intervention for sleep), consent forms and information leaflets stated that the trial was evaluating a multicomponent behavioural lifestyle intervention (face-to-face and web-delivered components) without detailing the sleep intervention. In addition, the control group received an educational intervention on cardiovascular risk factor modification. Sample size calculation reported that the study required 62 participants per

		61% female, mean age 59 years. ●	Sleep efficiency: 4.6 (p=0.2; 95% CI: 0.7 – 8.5) Improvement in sleep quality was greatest in a subgroup of participants who completed 3 or more sessions (p<0.001). Antihypertensive drugs were used by 25 (37.3%) of the control group and 19 (28.4%) in the Sleepio group. 50% of the Sleepio group (before exclusions) completed all 6 sessions. ●	group for 80% power, (α = 0.05). Study groups were unbalanced in the analysis and the Sleepio group was underpowered. The EAC calculated that the post-hoc power of this study is just 6%. Baseline characteristics are reported for the 2 groups prior to exclusion of 13 participants

Freeman et al. (2017) UK. Sleepio was provided to all the trial participants at no cost by the company. .	Single blind RCT comparing Sleepio with TAU ("treatment input was likely to be minimal, with prescription of medication for a small proportion") 1:1 randomisation. Follow up at weeks 3, 10, and 22 Intention-to-treat analyses. ●	26 UK universities. 3755 adults who had a positive screen for insomnia, as indicated by a score of 16 or lower on the SCI. 71-72% female, mean age 24.6-24.8 Lost to follow-up Sleepio - 1,158 TAU – 772 ●	Sleep treatment was associated with significant reductions, at all timepoints, in insomnia (SCI-8), paranoia (GPTS), and hallucinations (SPEQ) compared with the control group (all p<0.0001) ●	UK study. Population was primarily students with mean age <25 years. Clinical experts noted that normative delayed sleep phase paterns can still affect people up to the age of 25 and therefore may mimic insomnia symptoms. Based on the SDs observed from a previous study (Freeman et al. 2014) for the GPTS (SD 10.4), a total sample size of 2614 participants (i.e, 1307 per group) would provide 90% power to detect a small effect size in paranoia, with a

				standardised mean difference of 0.15, while accounting for a high amount of expected attrition (40%). The sample size calculation was revised because the dropout rate was greater than expected. The EAC could not confirm whether this study was adequately powered. Bias in the outcome results will have been introduced because of the high dropout rate, especially in the treatment group.

Cheng et al. (2019a) USA. One author is co-founder of the company.	Single blind RCT comparing Sleepio with sleep hygiene (six weekly e-mails based on the National Institutes of Health guide to healthy sleep) Follow up at pre- and post-treatment, with the latter occurring approximately 1 week following the final Sleepio session Per-protocol analysis conducted on 658 participants (Sleepio – 358; Sleep hygiene	1,385 adults with self-reported insomnia as per DSM-5 Participants were randomised to the Sleepio group at a 2:1 ratio due to a higher anticipated attrition rate for an active versus a control condition The follow-up sample included 358 patients for Sleepio and 300 patients in the online sleep education condition. ●	Sleepio was superior to sleep hygiene education at improving insomnia symptoms ($p<0.001$) with the average decrease in ISI in Sleepio (−10.0 points ± 5.7 S.D.) being twice that of the decrease in the sleep education condition (−4.4 ± 4.6). Similarly, insomnia remission was significantly higher for Sleepio compared to sleep hygiene (53.9% vs 14.0%; $p<0.0001$). ●	Depression and insomnia were self-reported and did not use clinician-evaluated diagnosis. Short term follow up. Per-protocol analysis. The majority of individuals had mild depressive symptoms at baseline and therefore, findings may not be generalisable to more severe groups. Power analyses indicated that the final sample size achieved 80% power to detect a small effect size

	education control – 300). ● ●			(0.16) for a three-way interaction.

Espie et al. (2019) UK, USA, Australia. A number of authors are co-founders or have received payment from the company.	RCT comparing Sleepio with sleep hygiene education (website and a downloadable booklet plus treatment as usual) Assessments took place at 0 (baseline), 4 (mid-treatment), 8 (post-treatment), and 24 (follow-up) weeks. Intention to treat analysis.  	1711 adults with self-reported symptoms of insomnia (according to DSM-5) 1329 (77.7%) were female, mean (SD) age was 48.0 (13.8) years Online assessments took place at 0 (baseline), 4 (mid-treatment), 8 (post-treatment), and 24 (follow-up) weeks. Lost to follow-up Sleepio Post-intervention (week 8) - 385 Follow-up (week 24) – 442	Primary outcomes. Sleepio was associated with improved outcomes on the following measures: Functional health (Patient-Reported Outcomes Measurement Information System: Global Health Scale): (Cohen d for week 4, 0.16; week 8, 0.31; and week 24, 0.31) Psychological well-being (Warwick-Edinburgh Mental Well-being Scale): (Cohen d for week 4, 0.13; week 8, 0.35; and week 24, 0.38)	Measures were self-reported. Participants self-referred and were not drawn from patient groups or health care services. There was a substantial dropout from treatment (58% of participants completed ≥4 Sleepio sessions); however, intention-to-treat analyses still identified significant improvements. The authors suggested that the increase in reported adverse events in the Sleepio group may result from the

		413 participants (48.4%) completed all 6 sessions Sleep hygiene education control Post-intervention (week 8) – 341 Follow-up (week 24) – 363 Sleep hygiene education was accessed at least once by 759 of 858 participants (88.5%) ●	Sleep-related quality of life (Glasgow Sleep Impact Index): Cohen d for week 4, –0.69; week 8, –1.38; and week 24, –1.46) Linear mixed-effects models found that results at 8 and 24 weeks were mediated by improvements in insomnia at week 4 and 8, respectively (range mediated, 45.5%-84.0%) Adverse events: There was 1 serious adverse event reported, which was unrelated to the use of Sleepio.	sleep restriction component of the programme. According to the original protocol, a sample size of 433 participants per treatment group was required to detect a standardized effect size of 0.25 with 90% power, assuming a significance level of $p < .01667$ (corrected for 3 primary outcomes), and to detect a large mediation effect with more than 80% power. EAC calculations confirm that this study is sufficiently powered.

			Participants in the Sleepio group reported significantly higher incidents of a number of adverse events. Most significantly fatigue, extreme sleepiness, difficulty concentrating ($p<0.0001$) 	

Denis et al. (2020) UK. One author is co-founder of the company.	Pilot RCT comparing Sleepio with puzzle based attention control. Assessments were performed baseline and then 3-weeks, 6-weeks, and 6-months. Analysed as intention-to-treat. ● ●	199 women: adult university students (mean age 20±5 years) meeting DSM-5 criteria for insomnia (self-reported). Assessments were carried out online at 3 weeks (mid-intervention), 6 weeks (end of intervention), and 6 months after starting the intervention (follow-up). Lost to follow-up Sleepio Post-intervention – 32 6 month follow-up - 52	Sleepio led to significant improvements in insomnia symptoms (per SCI-8) compared with attention control (t (140) = 2.51, p=0.013; d=0.42). The effect was similar when looking only at those who met the threshold requirement for subclinical insomnia at baseline (t (95) = 2.49, p=0.015; d=0.51). Treatment acceptability score was 33.61 (4.82), theoretical range 6–42) at end of intervention. Significantly more people in the control group completed all six weekly sessions (puzzles)	Pilot study into participation rates. Unclear if adequately powered. Only recruited female university students and therefore may not be generalisable to other groups. Clinical experts noted that people under the age of 25 may still experience normative delayed sleep phase pattern which may mimic insomnia.

		Control Post-intervention – 22 6 month follow-up – 38 ●	than in the intervention group; $\chi 2$ (1) > 4.82, p = 0.028 ●	

Felder et al. (2020) USA. One author received voucher codes for Sleepio.	RCT comparing Sleepio with TAU (comprising a range of non-study treatments, including sleep, pain, and antidepressant medications (both prescribed and over-the-counter); alternative therapy or herbal supplements; psychotherapy or counselling; and support groups) Randomised 1:1 to either Sleepio or Standard Care (comprising a range of non-study treatments,	208 pregnant women (up to 28 weeks' gestation) with elevated insomnia symptom severity or who met criteria for insomnia caseness by self-reported questionnaire (met the DSM-5 criteria for insomnia disorder, as determined by the SCI) Mean age 33.6 years, mean gestational age 17.6 weeks. ●	105 patients were randomised to the Sleepio group. 68 women (64.8%) completed all 6 sessions (mean completion time 7.97 weeks). Reduction in ISI: Sleepio: -0.59 Control: -0.23 (Time-by-group interaction, difference = −0.36; 95%CI, −0.48 to −0.23; $\chi 2 = 29.8$; $P < 0.001$; $d = -1.03$). ●	Outcomes are self-reported and subjective. Study statistician remained blinded to condition assignments for all primary analyses. A sample of 208 patients (104 per group) was calculated to be necessary for 80% power and an effect size of d=0.3, α=0.01. EAC calculations confirmed that this study was adequately powered for this effect size. Clinical experts noted that pregnant women can experience conditions which mimic insomnia (such as

	including medications, alternative therapies, psychotherapy and support groups). Participants were followed up for 18 weeks after randomisation Analysed as intention-to-treat. . ● ●			restless legs), and these commonly resolve post-partum.

Kyle et al. (2020) UK. One author is co-founder of the company	Single blind RCT comparing Sleepio with a waiting list control Assessments were carried out online at baseline, and 10 and 24 weeks post-randomisation. Randomised 1:1 Analysed as intention-to-treat. ● ●	410 adults (25 years old +) from the Sleepio online community with insomnia disorder) met DSM-5 criteria for insomnia disorder according to the SCI) and self-reported difficulties with concentration or memory. 87% female, 52.4 years, SD = 11.5; range 26–82) Retention was 82% at 10 weeks and 74% at 24 weeks, and differed by group, with the Sleepio group less likely to provide outcome data than control (at 10 weeks: 76% for dCBT vs. 88% for control; at 24 weeks: 66% for Sleepio vs. 81% in control).	Self-reported cognitive impairment (British Columbia Cognitive Complaints Inventory; BC-CCI). At 10 weeks post-randomization the estimated adjusted mean difference for the BC-CCI was -3.03 (95% CI: -3.60, -2.47; $p < 0.0001$, $d = -0.86$), indicating that participants in the Sleepio group reported less cognitive impairment than the control group. These effects were maintained at 24 weeks ($d = -0.96$) and were mediated, in part, via reductions in	UK study The study was powered at 90% to detect a minimum standardized effect size of 0.42 at post-treatment (week 10) at a 5% level of significance, accounting for 40% attrition from baseline. The EAC confirmed that this study is adequately powered to detect this effect size. The waiting list control arm may slightly inflate effect size differences compared to a minimally active arm (e.g. sleep hygiene education), or behavioural placebo.

			insomnia severity and increased sleep efficiency. Secondary outcome: Insomnia severity (ISI) at 10 weeks (d = −1.57) and 24 weeks (d = −1.60), and for sleep efficiency at 10 weeks (d = 0.91) and 24 weeks (d = 0.72), with the Sleepio group reporting less insomnia symptoms and higher sleep efficiency scores.	Sample was recruited online and may not be representative of treatment-seeking patients in clinical practice. The study required participants to report cognitive complaints to enter the trial, which may have resulted in an over-representation of participants concerned about the effects of sleep disruption on cognitive function. Study sample was over 25 years old (a group that does not tend to experience

				normative delayed sleep phase pattern).

Kalmbach et al. (2020) USA. Unclear if there were conflicts of interest.	RCT comparing Sleepio with sleep hygiene education active control (six weekly emails based on the National Institutes of Health guide to healthy sleep). Assessment before treatment and after treatment during pregnancy, then 6 weeks after childbirth Analysed as intention-to-treat. ●	91 pregnant women (29.03 ± 4.16 years) nearing/entering the third trimester who screened positive for clinical insomnia on the Insomnia Severity Index (ISI) Results were collected before treatment and after treatment during pregnancy, then six weeks after childbirth. ●	From pre-intervention to post-intervention, Sleepio was associated with significant reductions in insomnia severity (ISI, -4.91 points, $t(45) = –5.61$, $p<0.001$, Cohen's d = 0.86), no significant change was observed in the control group. Paired samples t-tests showed that PSQI scores significantly decreased in the Sleepio group by 2.98 points [$t(45) = –6.31$, $p < 0.001$, Cohen's d = 0.93], whereas no significant change in PSQI was observed in the control group.	Power analyses indicated that with an anticipated sample size of n = 90 and anticipating medium-large post-treatment group differences in insomnia outcomes (Cohen's d = 0.65), the study would have 0.86 power to detect effects at a significance level of α = 0.05. The EAC confirmed that this study is adequately powered to detect this effect size. Relatively short-term follow-up and therefore the limited effects on sleep post-partum may be due to lack of stable sleep for the infant.

			Sleepio was associated with increases in sleep duration by 32 minutes (p=0.008). Participants receiving sleep hygiene education did not experience any change. After childbirth, Sleepio participants slept longer by 40 min per night (p = 0.01) relative to controls. 	

Non-RCTs

Table 1.2 Non-randomised studies

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Espie et al. (2014) UK	Follow up analysis of Espie 2012 data to evaluate the impact of Sleepio upon attributions for sleep disturbance (measured with the Sleep Disturbance Questionnaire (SDQ)), night-time thought content (measured with the Glasgow Content of Thoughts Inventory (GCTI)), and stress, depression and anxiety ●	Same as Espie 2012. ●	Sleepio had a greater effect on attribution and cognition than IRT (average *d* = −0.32). Sleepio had a greater effect on attribution and cognition than TAU (*d* = −0.65., moderate to large effect). Treatment effects were observed for all SDQ domains (e.g., Sleepio vs. IRT: relative effect size was d = 0.76 for 'trying too hard'). Similar magnitude of effects were maintained at 8 weeks. Thought content (Glasgow Content of Thoughts Inventory; GCTI).	See Espie 2012.

			CBT was also superior to IRT on the GCTI (e.g., 'rehearsal and planning', d = 0.62; 'sleep and sleeplessness', d = 0.74). CBT vs. TAU comparisons yielded larger effects. ●	
Luik et al. 2017 UK One author is co-founder of the company	Prospective audit (real-world data) Sleepio No comparator ●	98 participants (mean age 44.9 years, SD 15.2, 66% female) who experienced poor sleep in addition to comorbid symptoms of depression or anxiety IAPT service 87 clients (89%) experienced clinical insomnia (ISI > 14) Of the 98 clients included in this evaluation, 72 finished the treatment (73%). Another 15 clients completed between 4	Depression (mean difference-5.7, t(70) = 12.5, p < 0.001) and anxiety [Generalized Anxiety Disorder-7 (GAD-7), Mean difference-4.1, t(70) = 8.0, p < 0.001] were reduced following supported Sleepio for insomnia. This translated into an IAPT recovery rate of 68% for depression and anxiety. Effects on anxiety and depressive symptoms	UK study All clients received six calls from an eTherapy coordinator to support the self-help component. This is not typical of the Sleepio service.

		and 6 sessions and 11 dropped out before session 4. ●	remained significant when accounting for missing data (p<0.001). Significant reductions were also observed in insomnia symptoms (p<0.001). ●	
Elison et al. (2017) UK. One author is co-founder of the company	Before and after design comparing Sleepio with 2 other online therapies -Living Life to the Full Interactive, -Breaking Free Online ●	1068 adult IAPT service users referred for mental health difficulties. 85 (8%) having accessed Sleepio. Engagement time: 29–148 days (4.19–21.08 weeks) with a median of 66.35 days (IQR=39.06) 866 (81%) accessed Living Life to the Full Interactive,	Data indicated baseline differences, with the Breaking Free Online group having higher scores for depression and anxiety than the Living Life to the Full Interactive (depression CI 1.27 to 3.21, p<0.0001; anxiety CI 077 to 1.72, p<0.0001) and Sleepio (depression CI 1.19 to 4.52, p<0.0001; anxiety CI 2.16 to	UK study The sample sizes across the three programmes varied, with the Living Life to the Full Interactive (the most established programme) group being considerably larger than the Sleepio and Breaking Free Online groups.

		engagement time 4–288 days (0.64–41.14 weeks) median of 66.29 days (IQR=43.06) 117 (11%) accessed Breaking Free Online ●	5.23, p<0.0001) groups. Promising improvements in mental health scores were found within all three groups (all p<0.0001), as were significant reductions in numbers of service users reaching clinical threshold scores for mental health difficulties (p<0.0001). Living Life to the Full Interactive mean=11.32, CI. 077 to 1.72, p<0.0001; Sleepio mean=8.49, CI 2.16 to 5.23, p<0.0001). ●	There was no randomisation or control group. There is a lack of follow-up data from participants. Service users engaged with the eTherapy programmes for varying lengths of time, between 4 days and 288 days. Regression analyses indicated that number of days of engagement did not appear to be associated with degree of change in scores for depression, anxiety and social impairment, from baseline to treatment assessment, for the Living Life to the Full

				Interactive and Sleepio users.
Luik et al. (2018) USA and UK. One author is co-founder of the company	Before and after design Sleepio No comparator ●	3551 users (63% female, mean age 44.50 ± 14.78 years), 378 users (10.6%) used a device. 62.9% female, mean age 44.50 ± 14.78. Within-subject, pre-therapy to post-therapy, the Sleep Condition Indicator (SCI, 7 Items) was used to assess insomnia. The post treatment test was completed with a median of 42 days (IQR: 37–54) after the start of session 1.	For all participants, insomnia symptoms significantly improved following Sleepio ($t(3504) = 83.33$, $p < 0.001$; Cohen's $d = 1.45$), as did depression and anxiety symptoms, perceived stress, life satisfaction and work productivity. Those who did not connect a device reported better sleep and less affected work productivity (all $p < .001$) than those who did connect a device at baseline and post-treatment.	Data were from participants who completed Sleepio and therefore, this sample may comprise more motivated individuals. The underlying characteristics of individuals who connected a device may have differed compared to those who did not connect a device.

Espie et al., 2018, USA. A number of the authors are employed by the company.	Before-and-after study Sleepio Sleep tips 	214 employees of a large US company were recruited 90 had insomnia symptoms and were provided with access to Sleepio (mean age 50.8 years; 69% male) with insomnia symptoms. 124 reported good sleep and were given access to sleep tips (mean age 50.0 years; 69% male). 	SCI improved significantly in the sleep tips group (5.36 (3.28) to 6.01 (3.22), t(123) = −3.02, P = 0.003). SCI also improved significantly in the Sleepio group (3.08 (2.24) to 6.03 (2.97); t(89) = −8.40, P < .001). 	The groups are not comparable due to the differences in baseline sleep quality. The population may not be generalisable.

Miller et al., 2018, Australia and New Zealand.	Retrospective cohort study Sleepio No comparator 🟡	96 participants with insomnia (53 with I-NSD, 43 with I-SSD) were recruited from registry data. Mean age 41.4 years, 64% female. 39 participants completed post-treatment ISI assessment (I-NSD, n = 20; I-SSD, n = 19). 🟡	In those who completed post-treatment ISI Assessment, mean ISI was reduced from 17.4 to 10.8 ($p<0.01$). 🟡	Acceptability and tolerability were the primary outcomes in this study but these are considered to be out of scope. Efficacy was reported for a sub-group who completed follow-up.
Cheng et al., 2019b, USA.	1 year follow up analysis of Cheng 2019a. 🟢	From 1358 participants with insomnia, 358 (26.4%, mean age 44.5 years, 78% female) in the dCBT-I group completed 1-year follow up, along with 300 (22.1%, mean age 57.7 years,	Change in ISI differed significantly post-treatment between the groups, shown by a linear mixed model ($t(656) = -13.6$, $p<0.001$). Mean decrease in ISI:	The authors state that no statistical differences were detected at baseline between the patient groups. However, it is unclear if this refers to baseline in the initial trial or for the sub-

		80% female) in Online Sleep Education group. ●	Sleepio: -10 ± 5.7 Control: - 4.4 ± 4.6 Response and Remission rates were higher in the Sleepio group, 65.1% vs 22.3%, respectively (p<0.0001). Demographics (household income, education level, race and sex) did not significantly moderate the efficacy of Sleepio.	groups reported in this analysis. P-values are not reported. This may be important in relation to the demographic outcomes reported. Higher lost to follow-up rates in the Sleepio relative to the control group; however, both statistical and clinical significance were detected using intention-to-treat analysis (the depression rate in the control condition was set to zero (i.e. all individuals lost to follow-up in the control condition were assumed to be non-depressed),

				whereas the depression rate in the Sleepio group was estimated using maximum likelihood via a generalised linear mixed-effects model).
Luik et al., 2020, UK, USA, Australia.	Follow-up analysis of an RCT (Espie 2019). Compared Sleepio to sleep hygiene education (website and a downloadable booklet plus treatment as usual). 	The setting was the same as Espie 2019. From 1,711 participants, 906 participants (52.9%) contributed data at week 24, and 365 participants (21.3%) contributed data at week 48. 	At week 24, ITT analysis showed Sleepio reduced use of prescription (adjusted RR: 0.64, 95% CI: 0.42; 0.97, p = 0.037) and non-prescription sleep medication (adjusted RR: 0.52, 95% CI: 0.37; 0.74, p < 0.0001). At week 48, mean SCI score had increased by 9.80 (95% CI: 9.29, 10.31; Cohen d: 1.54).	ITT Analysis.

Crawford et al., 2020, USA.	Prospective observational cohort study (multiple baseline design). Participants were randomised to receive Sleepio after 2, 4 or 6 weeks of completing baseline sleep diaries.	42 women with chronic migraines and insomnia. Mean age 42.0 years.	35 (83.3%) completed the sessions within 12 weeks. Insomnia severity was reduced at post-treatment (ISI mean = 7.7, SD = 4.1) compared to baseline (ISI mean = 17.6, SD = 4.0, mean difference = −9.9; 95% CI = −11.7; −8).	ITT Analysis.
Cheng et al., 2020a, USA.	Follow-up analysis of Cheng et al. 2019a comparing Sleepio to Sleep Education.	658 participants with insomnia disorder. Sleepio group: n=358, mean age 44.5, 78% female.	The Sleepio group showed greater improvements in post-treatment ISI compared to the SE control group (p<0.001).	Per protocol analysis.

		Sleep Education Group: n=300, mean age 45.7, 80% female).		
Henry et al., 2020, UK, USA, Australia.	Sub-analysis of 2 RCTs (Espie et al. 2019 and Freeman et al. 2017).	3,352 (61.5% of original combined trial sample) participants with probable insomnia disorder and a PHQ-9 Score ≥ 10. Mean age: Sleepio: 29.6 years Control: 29.4 years. Both groups were 76% female. There were no significant differences in insomnia symptoms (p=0.97) or	Adjusted mean difference in insomnia symptoms (SCI-8) at: 8-10 weeks: 5.19 (95% CI 4.63 – 5.75, g=0.76) 22-24 weeks: 5.15 (95% CI 4.47 – 5.83, g=0.69) Intervention effects were not moderated by age, gender, or by baseline insomnia or depressive symptoms	ITT Analysis

		depressive symptoms (p=0.84) at baseline. ●	●	
Cheng et al., 2020b, USA.	Follow-up analysis of Cheng et al. 2019a comparing Sleepio to Sleep Education. ●	From 1358 participants, 102 (7.5%) in the Sleepio group and 106 (7.8%) in the Online Sleep Education Group were included. Mean age; sex: Sleepio: 44.6 years; 72.5%. Control: 44.7 years; 84.0%. ●	67.3% of participants reported direct impact from Covid-19; 26.4% reported living alone. Similar levels of disruption were reported in both groups on the Coronavirus Impact Scale (CIS). Those in the control group reported that the pandemic had a greater impact on their sleep compared to the Sleepio group using the CIS (2.0 vs 1.5, respectively; p=0.009).	Results of this study are unlikely to be generalisable to the wider population during a non-pandemic situation.

			ISI scores were 2.9 points lower in the Sleepio group. 	
Coulson (2016) UK.	Qualitative survey into reasons for using Sleepio online community, and any benefits and issues. 	100 Sleepio users recruited from the Sleepio community. (70/100, 70% female; mean age 51 years, range 26–82 years) 	Analysis revealed 5 initial drivers for engagement: (1) the desire to connect with people facing similar issues, (2) seeking personalised advice, (3) curiosity, (4) being invited by other members, and (5) wanting to use all available sleep improvement tools.	Intervention focusses on one aspect of Sleepio - the online community -, rather than the tool itself. Provides information on engagement.

Drake et al. 2019, USA [Abstract only]	Secondary analysis of RCT comparing Sleepio with online sleep education control in reducing sleep medication use	1232 individuals with insomnia (DSM-5 diagnostic criteria)	Prescription medication use in the control group increased from 16.5% to 18.0% at post-treatment, prescription medication use in the Sleepio group decreased from 17.8% to 14.6%. odds of prescription medication was significantly lower following Sleepio compared to control (OR=0.09, 95%CI[0.02, 0.34])	Abstract only, therefore cannot assess the details of the study. Primary study and patient characteristics unclear.

Abbreviations: BAI: Beck Anxiety Inventory;CI: Confidence Interval; CIS: Coronavirus Impact Scale (CIS); g-value: Hedge's g; I-NSD: Insomnia with Normal Sleep Duration; ISI: Insomnia Severity Index; ISS: Insomnia Symptom Severity; I-SSD: Insomnia with Short-Sleep Duration; PSQI: Pittsburgh Sleep Quality Index; RR: Rate Ratio; SCI: Sleep Condition Indicator; SD: Standard Deviation; SOL: Sleep Onset Latency

Unpublished studies

The EAC was provided access to the fulltext of the following unpublished studies.

Table 2: Unpublished Studies

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Stott (unpublished) UK	[redacted]	[redacted]	[redacted]	[redacted]

Studd (unpublished) UK	[redacted]	[redacted]	[redacted]	[redacted]

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
			[redacted]	

Abbreviations IAPT: Increasing Access to Psychological Therapies ; GAD-7: Generalized Anxiety Disorder 7; PHQ-9: Patient Health Questionnaire-Depression scale; SCI: Sleep Condition Indicator; WSAS: Work and Social Adjustment Scale

Table 3: Studies included by company and excluded by the EAC

Study name and location	Design and intervention(s)	Participants	Outcomes	EAC comments

Cliffe 2020, UK.	Prospective Cohort study. Sleepio No comparator	39 young people aged between 14 and 17 years.	Acceptability of Sleepio. Insomnia severity (ISI). Insomnia symptoms (SCI-8). Anxiety symptoms (Revised Child Anxiety and Depression Scale; RCADS). Depressive symptoms (Mood and Feelings Questionnaire; MFQ).	Population outside of scope.

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

The EAC notes that there is an extensive evidence base for Sleepio. The EAC included 12 RCTs (and 6 secondary analyses), 6 non-randomised studies and 1 abstract. Additionally, the company provided the EAC with 2 unpublished, real-world evidence studies which were relevant to the scope.

There were 4 UK RCTs (Espie et al. 2012, Freeman et al. 2017, Denis et al. 2020 and Kyle et al. 2020) and 1 multinational RCT including populations from UK, US and Australia (Espie et al. 2019) which may help generalisability to the NHS setting. There were 2 UK based non-randomised studies and 3 multinational studies that included UK populations.

[redacted]

The studies were heterogeneous in terms of study design, population and comparator. Study design ranged from pilot studies to adequately powered RCTs (e.g. Espie et al. 2012) and larger more pragmatic real-world effectiveness studies (e.g. Freeman et al. 2017, Luik et al. 2018, [redacted] Follow up times for insomnia symptoms ranged from 1 week (Pillai et al. 2015) to 48 weeks (Luik et al. 2020). Median follow up time for Sleepio in RCTs that reported it was 18 weeks. Cheng et al. 2019b included a follow up time of 1 year for symptoms of depression.

Study participants included people with sleep difficulty with or without medical and mental health comorbidities, pregnant women, and those with differing durations of insomnia symptoms and insomnia diagnoses. There was a lack of formal assessment of insomnia in studies; participants self-reported themselves as being poor sleepers according to different measures, including DSM-5 (e.g. Espie et al. 2012), SCI (e.g. Freeman et al. 2017) and ISI (e.g. Kalmbach et al. 2020). Comparators varied and included standard care (which was non-standardised), placebo and attention control. Standard care

may also vary significantly. It is unclear whether standard care in studies may have included elements of CBT or hypnotic use, and what was included in sleep hygiene education.

The company highlights a key limitation in the body of evidence being that there is a lack of evidence directly comparing Sleepio with individual face-to-face or guided CBT for insomnia because it is not routinely available on the NHS and is not scalable to the UK population. The EAC agrees that this is a key limitation.

5.2 *Critical appraisal of studies and review of company's critical appraisal*

The company's submission did not contain a formal critical appraisal of the evidence. The submission does contain an overall outline of the strengths and limitations (section 9) and for each of the selected studies (within section 5.2 of company submission).

Overall, the EAC agreed with the key strengths and limitations raised in the company's appraisal of individual studies. The EAC would add that missing data has been assumed to be missing at random, which may not be the case given that experts suggest that engagement may be significantly higher in face-to-face CBT programmes compared to online CBT.

Key strengths outlined for individual studies in the company's submission included:

- Most were well-designed RCTs that comprised of Sleepio compared with standard care or a placebo.
- Ten RCTs were analysed as intention-to-treat (ITT) to account for the relatively high number of participants lost to follow up. Two RCTs (Pillai 2015, Cheng 2019a) were analysed as per-protocol (PP). In a secondary analysis, Cheng 2019b analysed the results as ITT to account for the participants who dropped out.

Key limitations outlined for individual studies in the submission included:

- Most studies recruited participants who self-referred online and therefore the cohort may be more interested and motivated to address their sleep problems.

- Potential generalisability of results due to specific study population e.g. Bostock et al. 2016 (people from a single Fortune 500 company), Freeman et al. 2017 and Denis et al. 2020 (UK students), milder comorbid symptoms in Pillai et al. 2015 (anxiety) and Cheng et al. 2019a (depression), [redacted]

- High dropout rate e.g. Freeman et al. 2017 (but noting that most studies were analysed as ITT).

- Length of follow up in some studies being relatively short e.g. Pillai et al. 2015 (1 week), Barnes et al. 2017 (10 weeks from randomisation), McGrath et al. 2017 (8 weeks), Kalmbach et al. 2020 (6 weeks).

The EAC carried out an independent critical appraisal of the RCTs and non-randomised studies. The RCTs were assessed using the Cochrane Risk of Bias 2 (RoB2) tool. Non-randomised studies were assessed using a checklist based on the NICE checklist for cohort studies (see Appendix B). Figures 1a and 1b illustrates the overall judgement of risk for the RCTs analysed as ITT and PP respectively.

Five studies were deemed to have an overall low risk of bias (Espie et al. 2012, Bostock et al. 2016, Freeman et al. 2017, Kyle et al. 2020 and Kalmbach et al. 2020), although some concerns were raised about loss to follow up and differing baseline characteristics between populations in 2 of these studies respectively (Freeman et al. 2017 and Kalmbach et al. 2020). Six studies raised some concerns overall (Barnes et al. 2017, McGrath et al. 2017, Espie et al. 2019, Denis et al. 2020, Felder et al. 2020 and Cheng et al. 2019a). One RCT was deemed to have an overall high risk of bias (Pillai et al. 2015).

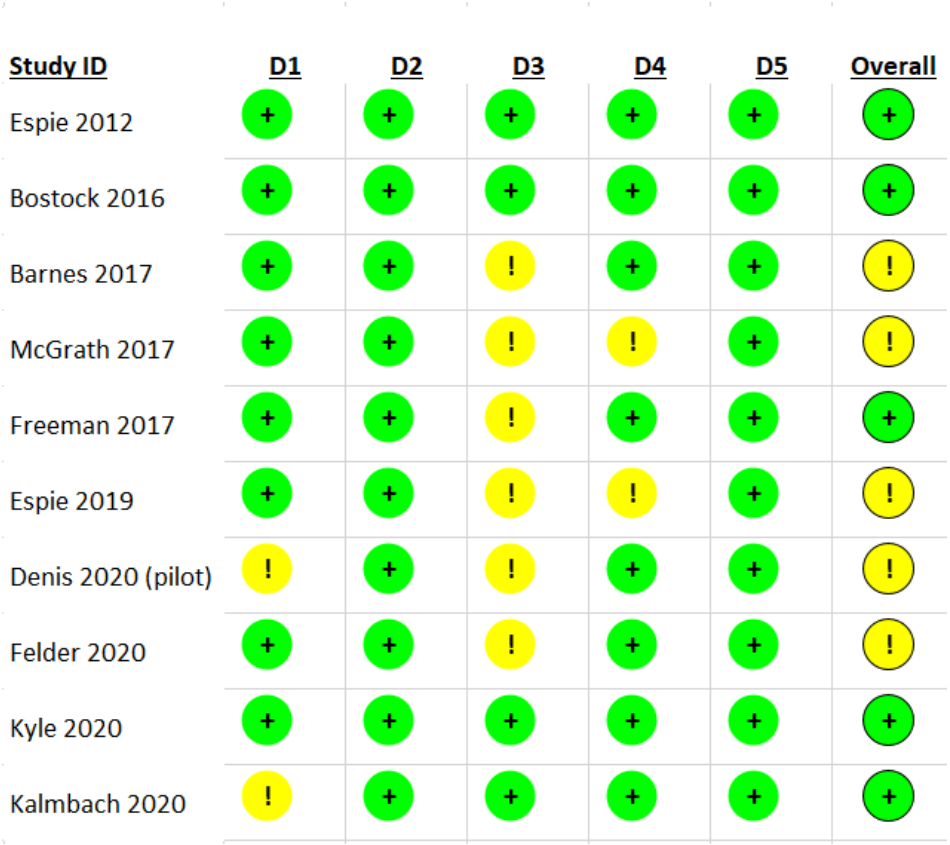


Figure 1a Risk of bias for ITT RCTS. + Low risk; ! Some concerns; - High risk. D1 Randomisation process; D2 Deviations from the intended outcomes; D3 Missing outcome data; D4 Measurement of the outcome, D5 Selection of the reported result.

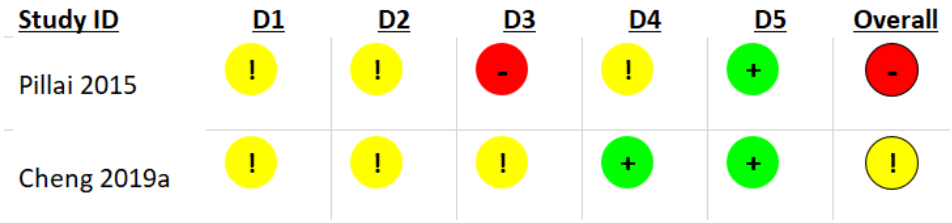


Figure 1b Risk of bias for PP RCTs + Low risk; ! Some concerns; - High risk. D1 Randomisation process; D2 Deviations from the intended outcomes; D3 Missing outcome data; D4 Measurement of the outcome, D5 Selection of the reported result.

5.3 *Results from the evidence base*

Table 4: Results

Study	Sleep Efficiency	ISI	SCI	PSQI	GCTI	Medication Use	Comorbidities
Espie 2012	Post therapy increase: Sleepio - 19.5% (95%CI, 15.3 to 23.7) IRT - 5.7% (95%CI, 2.79 to 8.52) TAU - 6.4% (95%CI, 2.88 to 9.86) in TAU 8-weeks post-treatment: Sleepio - 20% (95%CI, 15.7 to 23.6) IRT - 7% (95%CI, 4.53 to 10.1) TAU - 9% (95%CI, 4.89 to 13.7	NR	Participants receiving Sleepio experienced a >2-fold improvement in insomnia symptoms (SCI-8), with a large between-group effect compared with TAU (d=1.20) at post-intervention and follow-up (d=1.11). The equivalent effects for Sleepio compared to placebo were d=0.95 and d=0.77 respectively.	NR	NR	NR	NR
Espie 2014	NR	NR	SCI improvement was attributed to cognitive factors	NR	Sleepio was superior to IRT, d = 0.62; ‘sleep	NR	NR

			following Sleepio (R^2 = 0.21-0.27).		and sleeplessness', d = 0.74).		
Pillai 2015	NR	Greater reduction in Sleepio group (t = 2.1; p < .05; Cohen's d = .9) at 1 week follow up.	NR	NR	NR	NR	NR
Bostock 2016			8 weeks post treatment: Sleepio group significantly higher compared with control (F (1,485) = 15.63, p < 0.0001], representing Cohen's d of 1.10 following Sleepio (d = 0.34 for WL).				
Barnes 2017	Sleep efficiency was improved by 26% and 28% in the Sleepio	NR	NR	NR	NR	NR	NR

	and control group respectively,						
McGrath 2017	Greater mean increase in Sleepio group by 4.6 (p=0.2; 95% CI: 0.7 – 8.5)	Greater mean increase in Sleepio group by 2.8 (p<0.001; 95% CI: 1.3 - 4.4)	Greater mean improvement in symptoms in Sleepio group by 0.8 (p=0.01; 95% CI: 0.2 – 1.4)	Greater mean increase in Sleepio group by 1.1 (p=0.04; 95% CI: 0.1-2.2)	NR	Antihypertensive drugs were used by 25 (37.3%) of the control group and 19 (28.4%) in the Sleepio group.	NR
Freeman 2017	NR	NR	Sleepio group showed significant reduction in symptoms at all time points.	NR	NR	NR	NR
Cheng 2019a	NR	NR	NR	NR	NR	NR	High comorbidity between insomnia and depression was observed, with approximately half the sample reporting moderate-to-severe depression (QIDS-SR16 ≥ 11) at baseline (dCBT-I: 48.3%, 95% CI [43.1 to

							53.5], control: 48.7%, 95% CI [43.0 to 54.5], p = 0.99).
Espie 2019	NR	NR	NR	NR	Cohen d for week 4, –0.69; week 8, –1.38; and week 24, –1.46)	NR	NR
Denis 2020	NR	NR	Sleepio group improved significantly more (t (140) = 2.51, p=0.013; d=0.42). Sleepio did not offer an advantage in those with subclinical insomnia at baseline (t (95) = 2.49, p=0.015; d=0.51).	NR	NR	NR	NR
Felder 2020	Reduction:	NR	NR	NR	NR	NR	NR

	Sleepio: -0.59 Control: -0.23 Time-by-group interaction, difference = −0.36; 95%CI, −0.48 to −0.23; $\chi 2$ = 29.8; P < 0.001; d = −1.03).						
Kyle 2020	Reductions in Cognitive Impairment were mediated, in part, by increased sleep efficiency.	Reductions in Cognitive Impairment were mediated, in part, by reductions in Insomnia severity.	NR	NR	NR	NR	NR
Kalmbach 2020	NR	From pre-intervention to post-intervention, Sleepio was associated with significant reductions (-4.91 points, t(45) = –5.61, p<0.001,	NR	Significant decreases seen in the Sleepio group by 2.98 points [t(45) = –6.31, p < 0.001, Cohen's d = 0.93], no	NR	NR	NR

		Cohen's d = 0.86), no significant change was observed in the control group.		significant change in the control group.			
Non-RCTs							
Luik 2017	NR	Significant reductions were also observed (p<0.001).	NR	NR	NR	NR	Depression (M difference-5.7, t(70) = 12.5, p < 0.001) and anxiety [Generalized Anxiety Disorder-7 (GAD-7), M difference-4.1, t(70) = 8.0, p < 0.001] were reduced following supported dCBT for insomnia. This translated into an IAPT recovery rate of 68% for depression and anxiety.
Elison 2017	NR	NR	NR	NR	NR	NR	Data indicated baseline differences, with the Breaking Free Online group having higher scores for depression

							and anxiety than the Living Life to the Full Interactive (depression CI 1.27 to 3.21, p<0.0001; anxiety CI 077 to 1.72, p<0.0001) and Sleepio (depression CI 1.19 to 4.52, p<0.0001; anxiety CI 2.16 to 5.23, p<0.0001) groups. Promising improvements in mental health scores were found within all three groups (all p<0.0001), as were significant reductions in numbers of service users reaching clinical threshold scores for mental health difficulties (p<0.0001). Living Life to the Full Interactive mean=11.32, CI. 077 to 1.72, p<0.0001; Sleepio mean=8.49, CI 2.16 to 5.23,

							p<0.0001) (CI unclear, may be reported incorrectly).
Luik 2018	NR	Significant improvements following Sleepio (t(3504) = 83.33, p < 0.001; Cohen's d = 1.45)	NR	NR	NR	NR	Significant improvements following Sleepio in depression and anxiety symptoms (Depression, Z = −26.81, p < 0.001; Anxiety, Z = −29.51, p < 0.001).
Espie 2018	NR	NR	Improvements were seen in the sleep tips group (5.36 (3.28) to 6.01 (3.22), t(123) = −3.02, P = 0.003) and in the Sleepio group (3.08 (2.24) to 6.03 (2.97); t(89) = −8.40, P < .001).	NR	NR	NR	NR

Miller 2018	NR	Mean was reduced from 17.4 to 10.8 ($p<0.01$).	NR	NR	NR	NR	NR
Cheng 2019b	NR	Mean decrease ($p<0.0001$): Sleepio: -10 ± 5.7 Control: - 4.4 ± 4.6.	NR	NR	NR	NR	NR
Luik 2020	NR	NR	At week 48, mean SCI score had increased by 9.80 (95% CI: 9.29, 10.31; Cohen d: 1.54).	NR	NR	At week 24, ITT analysis showed Sleepio reduced use of prescription (adjusted RR: 0.64, 95% CI: 0.42; 0.97, $p = 0.037$) and non-prescription sleep medication (adjusted RR: 0.52, 95% CI: 0.37; 0.74, $p < 0.0001$).	NR
Crawford 2020	NR	Insomnia severity was reduced at post-treatment (ISI mean = 7.7, SD = 4.1) compared to baseline (ISI mean = 17.6, SD = 4.0,	NR	NR	NR	NR	NR

		mean difference = −9.9; 95% CI = −11.7; −8).					
Cheng 2020a	NR	The Sleepio group showed greater improvements in post-treatment ISI compared to the Sleep Education control group (p<0.001).	NR	NR	NR	NR	NR
Henry 2020	NR	NR	Adjusted mean difference in insomnia symptoms (SCI-8) at: 8-10 weeks: 5.19 (95% CI 4.63 – 5.75, g=0.76) 22-24 weeks: 5.15 (95% CI 4.47 – 5.83, g=0.69)	NR	NR	NR	Intervention effects were not moderated by baseline depressive symptoms.
Cheng 2020b	NR	Scores were 2.9 points lower in the Sleepio group,	NR	NR	NR	NR	NR

		compared to Sleep Education.					

Clinical experts noted that the ISI is currently the preferred measure for insomnia symptoms. The SCI (which assesses against DSM-5 criteria) is increasingly used as a measure but it currently does not have the same level of benchmarking evidence as the ISI. The PSQI is often used within industry due to no costs being associated with its use, but experts noted it was not a true measure of insomnia. One expert noted that these measures are primarily used in research and secondary care settings. More subjective information is used in primary care in terms of the impact on people's lives.

6 Adverse events

The EAC searched the MHRA and FDA (MAUDE) databases on the 25th of January 2021, using the search terms ‘Big Health’ and ‘Sleepio’ and found no adverse events associated with the technology.

Espie et al. (2019) reported 1 SAE, however this was unrelated to the intervention. Using a questionnaire of 12 potential adverse symptoms, participants in the Sleepio group reported a significantly higher number of adverse events. The most significant were fatigue, extreme sleepiness, and difficulty concentrating. The authors suggested that this may have been due to the sleep restriction component of the Sleepio programme.

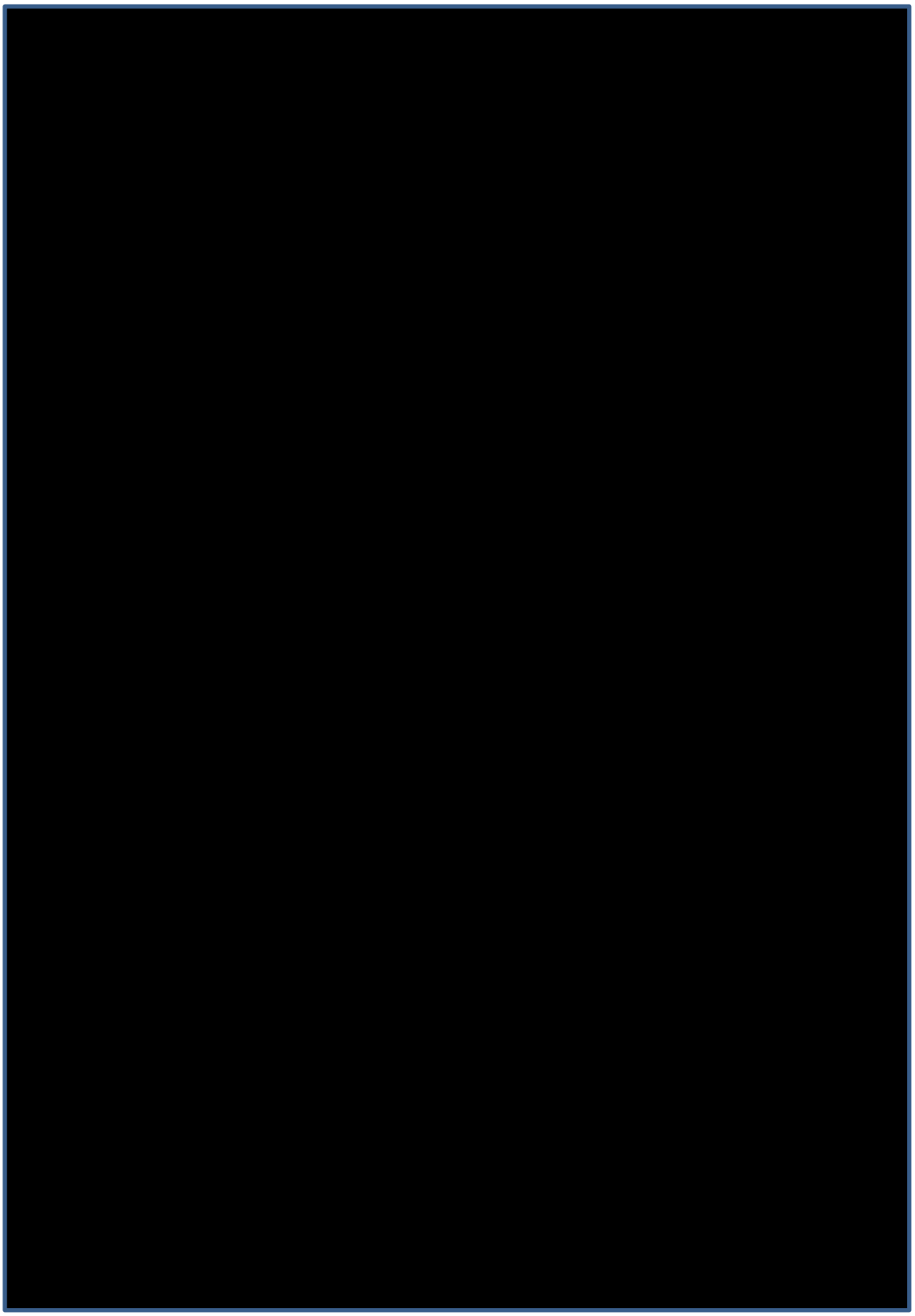
Felder et al. (2020) reported 3 AEs in each group. In the control group, these were 1 stillbirth and 2 miscarriages; the events were determined to be unrelated to study participation. In the Sleepio group, 3 miscarriages were reported. Although it was impossible to rule out a connection between the adverse event and study participation, it is unlikely to be a causal link. One of the participants experienced a miscarriage prior to beginning the programme.

Kyle et al. (2020) reported that there were no statistically significant differences in adverse events between the Sleepio group and the wait list, using the same questionnaire that was used in Espie et al. (2019).

7 Evidence synthesis and meta-analysis

The company described results from an ongoing (unpublished) pre-registered individual participant data (IPD) meta-analysis including 12 RCTs into Sleepio (see table 1.1 in section 4.2). The protocol is available at: PROSPERO 2019 CRD42019105424.

[redacted]



[redacted]

[redacted]

The EAC did not carry out an additional study level meta-analysis as the company has provided results of a meta-analysis at the IPD level (which is a higher standard of analysis than aggregated study level analysis).

[redacted]

8 Interpretation of the clinical evidence

Overall, the EAC believes that there is good quality clinical evidence that Sleepio improves sleep in people with self-reported insomnia symptoms (according to DSM-5, SCI and ISI measures). Most RCTs are relatively small compared with the potential reach of Sleepio, but in general are adequately powered, well-designed and reported. Results consistently indicate that Sleepio is more effective at treating insomnia symptoms than standard care (waiting list, sleep hygiene education) or specific placebos. The EAC believes these results are generalisable to the NHS population. There are 4 UK based RCTs (Espie 2012, Freeman 2017, Denis 2020 (pilot study), Kyle 2020) that all concluded that Sleepio was more effective in reducing insomnia symptoms than treatment as usual/waiting list (Espie et. al 2012, Freeman 2017, Kyle 2020), or a placebo (imagery relief therapy in Espie 2012) or attention control in (Denis 2020). Several US-based RCTs (Pillai 2015, Cheng 2019a, Kalmbach 2020) and 1 multinational RCT (UK, US and Australia in Espie 2019) compared Sleepio with sleep hygiene education. All found that Sleepio was significantly more effective than sleep hygiene education in improving insomnia symptoms (noting that the powering of the studies in Pillai et al. 2015, Barnes et al. 2017 is unclear).

Though the finding is consistent, there is heterogeneity between studies. Studies were carried out in various populations including pregnant women

(Felder et al. 2020, Kalmbach et al. 2020), student populations with mean age < 25 years (Freeman 2017), and people with self-reported depression (Cheng et al. 2019a). Baseline measures of population characteristics varied between studies. For example, sleep efficiency (SE) varied between studies. Patients in Espie (2012) had close to 60% SE at baseline, whereas Bostock (2016) and McGrath (2016) reported baseline SE rates of 76% and 81% respectively.

Some populations may require more caution before referring for treatment with Sleepio. For example, clinical experts felt that pregnant women may not be appropriate for Sleepio (for example, insomnia symptoms may be due to restless legs) and problems may resolve post-partum. In addition, people under the age of 25 years may be still experiencing a normative delayed sleep phase pattern, rather than insomnia, and therefore these insomnia mimics should be ruled out before referral to Sleepio. The EAC notes that in most studies participants were not formally diagnosed with insomnia; populations were self-referred, and measures were self-reported and therefore may not be, for example, a typical population in primary care.

[redacted]

There is a lack of clarity and likely heterogeneity in terms of what the standard care condition included, as treatment as usual and sleep hygiene education are unstandardised. Clinical experts noted that elements of CBT may be incorporated in sleep hygiene education. No studies were found comparing Sleepio with face-to-face CBT. A meta-analysis by Soh et al. (2020) indicated, in an indirect comparison, that face-to-face CBT-I produced greater improvement in ISI compared with digital CBT-I (3.07 (95% CI 1.18 to 4.95, p < 0.001)) but that this was within the non-inferiority interval of 4 points. One clinical expert felt it may be plausible to assume similar results from Sleepio compared with face-to-face CBT on the basis of results in Soh et al. (2020), however noted that this was not the same as having identical effects. Another expert felt that there was not enough head-to-head evidence comparing digital CBT-I with face-to-face CBT-I to assume similar results. Two experts noted

that in their experience, people prefer to have face-to-face sessions compared with online treatment.

Another area of heterogeneity is that various outcomes are measured, such as insomnia, psychological wellbeing, productivity using various indices (such as DSM-5, ISI and SCI [which assesses against DSM-5 criteria] for insomnia). Other specific measures include SE, SOL, WASO etc. Comorbidities were also assessed using anxiety and depression scales. One study also measured blood pressure so physiological outcomes. These were assessed over various follow-up time points from 1 week (Pillai 2015) to 48 weeks Luik et al. (2020). The median fellow-up time was 18 weeks in RCTs. Experts suggested follow up of at least 3 to 6 months after treatment would be needed to assess whether results were maintained. One expert noted that clinical review is usually at 3 months, therefore if results were not maintained at this point then a GP would refer a patient to secondary care. Luik et al. (2020) carried out a long-term analysis on Espie et al. (2019) data indicating that results were maintained at 48 weeks, albeit the positive outcome was observed for a fraction of the participants due to low engagement rates. The results in Luik (2020, based on Espie 2019 data) suggest that if a participant engages with the programme improvements in insomnia symptoms (per SCI) may be maintained in the longer term. Sleepio also led to significant reductions in prescription and non-prescription medication use at 24-weeks, with this effect maintained for non-prescription medication at 48-weeks.

Effect size varied over studies, for example, Espie et al. (2012) reported a 20% improvement in sleep efficiency (SE) from baseline after Sleepio, whereas Bostock et al. (2016) and McGrath et al. (2017) reported an increase in SE of only 10% (noting that experts suggested that SE was more a measure of sleep adherence rather than sleep quality). Effect size for change in SCI varied from d=0.42 in Denis (2020) (compared with attention control) to d=1.2 in Espie 2012 (compared with TAU).

[redacted] This may reflect the difference in populations, measurement tools and time of follow up.

The company suggests that the consistent results in favour of Sleepio indicates the generalisability of its impact. The EAC agrees that this indicates that Sleepio is consistently effective compared with standard care, or sleep hygiene education or certain types of placebo but notes that effect size varies significantly between studies and raises challenges for pooling data in a meta-analysis.

Studies, in general, demonstrated a high loss to follow-up for Sleepio compared with controls. Experts noted that this high dropout is typical for online CBT tools. In addition, Clinical experts noted that it may be a minority of patients that may initially engage (as low as 20%).

[redacted]

The company confirmed that the same version of Sleepio is used in all studies. There have been no modifications content-wise and any modifications are technical, relating to access, for example, linking to a wearable device.

Almost all of the studies include an author who is involved with the company, which may be a source of bias.

8.1 *Integration into the NHS*

Four of the RCTs were done in the UK. All concluded that Sleepio was more effective in reducing insomnia symptoms than treatment as usual/waiting list, or a placebo, or attention control. Participants in the RCTs self-referred and self-reported insomnia or insomnia symptoms, rather than being referred through primary care or an IAPT. The reported outcomes on sleep improvement, psychological wellbeing, improved labour market participation and productivity, and reduced prescribing of hypnotics are all relevant to the NHS care pathway.

Clinical experts highlighted the importance of patient selection and patient choice in increasing engagement and benefits of the Sleepio tool. According to experts, patient eligibility criteria should include people over 25 who present in primary care with chronic (> 3 months) mild to moderate insomnia. Experts noted that caution should be urged before referring CBT-I for certain populations such as pregnant women and people under 25 years old to rule out other insomnia mimics (such as restless legs and normative delayed sleep phase patterns respectively). The EAC notes that there is evidence into both populations under 25 (such as Freeman et al. 2017) and in pregnant women (such as Felder et al. 2020) that indicates Sleepio is more effective that control for improving insomnia symptoms. One expert highlighted that the preferred measure for insomnia is the ISI. Experts highlighted that remission of symptoms in acute insomnia is common, suggesting approximately 50 to 70% of people presenting with acute insomnia experience remission without treatment. Experts also highlighted that patient selection should consider excluding people with high average sleep propensity in daily life (using Epworth sleepiness score), high risk for sleep apnoea (that is untreated) or moderate or severe restless legs. Specific sleep disorders such as narcolepsy and parasomnias may be contra-indicated.

Clinical experts discussed insomnia in people who have co-morbidities such as depression and anxiety. One expert suggested in milder cases of depression, for example, insomnia may be treated first as it may have consequent effects on the symptoms of depression. Another, however, noted that people with depression may be less likely to engage with treatment. One expert noted that treating depression often results in sleep pattern improvement without CBT for insomnia and that medical factors may be addressed first as this may also alleviate insomnia.

Clinical experts suggested that engagement may be predicted by a number of factors, for example whether the patient has self-referred (as a patient may be more motivated to address the condition), or factors such as educational status, health locus of control, access to IT, absence of severe depression, ethnicity, age or poor vision or use of hands. One real-world study into

Sleepio (Coulson et al. 2016) suggested that the following 5 self-reported factors were drivers of engagement 1) the desire to connect with people facing similar issues, 2) seeking personalised advice, 3) curiosity, 4) being invited by other members, and 5) wanting to use all available sleep improvement tools.

The company states that it expects that Sleepio will primarily be used in place of sleep hygiene education and that Sleepio may be used in place of face-to-face CBT for insomnia if the latter is difficult to access. .

The company states that launching Sleepio in a healthcare setting will require clinicians and healthcare providers to attend a 30 minute - 1 hour training session on 1) how to manage poor sleep and insomnia, 2) how Sleepio works and how to describe it to patients and 2) how to prescribe Sleepio through the electronic patient record system. Experts noted that providing feedback to referrers such as GPs on the number of people registered to use Sleepio and those in remission would be helpful for understanding outcomes and inform further referral and training. In general, clinical experts noted that insomnia training in primary care is currently inconsistent. Some basic training in insomnia as a condition may be beneficial, for example, to rule out other sleep conditions that are not insomnia.

8.2 *Ongoing studies*

The EAC identified 10 ongoing studies (see also appendix D).

Table 5 – Ongoing Studies

Study Code, Title & Location	Date Registered	Date of First Enrolment	Date of Expected Final Enrolment	Target Sample Size	Eligibility	Comparator	Study Design	Primary Outcome
ACTRN12619001539123 Online Cognitive and Behavioural Therapy for Insomnia in Australian General Practice: An Implementation Trial Australia	17/11/2019	25/09/2020	01/03/2022	375	Over 18 years.	3 groups based on no medication, a single medication or 2 or more medications at baseline	Non-randomised controlled trial.	Change in number of sleeping pill prescriptions.
ACTRN12620001075976 A pragmatic trial seeking to implement an improved model of care for people with insomnia and obstructive sleep apnoea (OSA) within	19/10/2020	11/01/2021	Not Reported.	650	18 years and over. Sleep Condition Indicator (SCI) questionnaire score of less	TAU.	RCT.	Difference in rate of external medical referrals.

an Australian primary care setting, in order to increase access to evidence-based therapies Australia					than or equal to 16. With Obstructive Sleep Apneoa.			
NCT03109210 Therapist-Directed VS Online Therapy for Insomnia Co-Occuring With Sleep Apnea US	12/04/2017	15/04/2017	14/04/2021	384	21 years and older Diagnosis of OSA with an AHI > 5 on a diagnostic polysomnogram ISI score > 10	Standard Care - This will include routine assessment and adjustment of PAP therapy, and instruction in proper sleep hygiene.	RCT	Insomnia Severity Index (ISI) score change
ISRCTN70652461 Sleep and cognition following digital cognitive behavioral therapy for insomnia (CBTi) - the SCOTIA study UK	08/08/2019	01/04/2018 (Retrospectively registered)	31/12/2020	60	Men and women aged 25 to 65 with poor sleep, who do not currently take medication for their sleep or mental health.	Wait List	RCT	Insomnia severity at the end of treatment (week 10)
NCT03322774	26/10/2017	09/03/2018	30/04/2023	1000	18 years and over, ISI > 14, no major depressive	Sleep hygiene education	RCT	Improvement in Depression and Insomnia severity and

Sleep To Reduce Incident Depression Effectively (STRIDE) US					symptoms at baseline.			Reduction in Rumination.
NCT03688763 A Pilot Study of Digital Cognitive Behavioral Therapy for Veterans USA	28/09/2018`	05/02/2018	Dec 2020	10	18 years and over, with DSM-5 criteria defined insomnia disorder and on a stable dose of prescription medication and have comorbid psychopathology.	None.	Single-group Assignment.	Changes in the Insomnia Severity Index (ISI)
NCT03724305 Reduce Emotional Symptoms of Insomnia With Smart Treatment (RESIST). USA	30/10/2018	01/09/2020	01/12/2023	1100	18 years or over Determination of insomnia (ISI>10) No depression (Patient Health Questionnaire-9)	Sleep Hygiene Education.	RCT	Severity of Insomnia Symptoms - Acute Post Treatment (ISI)
NCT04180709	27/11/2019	30/10/2020	20/11/2022	44	18 years or older.	TAU.	RCT	Change from baseline Work

CBT to Reduce Insomnia and Improve Social Recovery in Early Psychosis (CRISP) UK					SCI-8 ≤ 16 First Episode of Psychosis in past 5 years.			and Social Adjustment Scale (WSAS) score at week 9 of study.
NCT04272892 Improving Sleep in Rehabilitation After Stroke (INSPIRES) UK	17/02/2020	14/02/2020	Jan 2021	86	18 years or older. 3 months post-stroke. In stable health.	Sleep Hygiene Information.	RCT	Change in SCI score
NCT03532282 The RESTING Insomnia Study: Randomized Controlled Study on Effectiveness of Stepped-Care Sleep Therapy (RESTING) US	22/05/2018	01/02/2019	30/06/2023	240	50 years or older. Insomnia disorder.	Stepped-treatment starting with either Sleepio or therapist-led cognitive behavioral therapy for insomnia	Stepped-wedge RCT	Change in the Insomnia Severity Index (ISI).

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

A search for economic evidence was carried out by the company on PubMed. The search strategy was designed to capture economic evidence relating to Sleepio and other comparable dCBT-I interventions using the following terms (Sleep OR Insomnia) AND (digital CBT OR digital CBTI OR dCBT* OR internet CBT OR internet CBTI OR iCBT* OR web CBT OR web CBTI OR Sleepio) AND (econ* OR cost* OR resource* OR productiv* OR workplace* OR "sleep medication use"). This resulted in the selection of 12 papers. The EAC considers the search strategy used by the company to be appropriate, but felt that more databases should have been included in the search. The EAC conducted its own search (see section 4.1 and Appendix A). The EAC included the following databases in its search; Embase, MEDLINE, PubMed, ClinicalTrials, WHO ICTR, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, INAHTA Database, and EconLit. Following the application of cost and economic filters, the EAC confirmed that no economic evidence in addition to the studies submitted by the company was available.

Specific inclusion and exclusion criteria were applied for study selection in the company's search. The inclusion criteria were: adults over the age of 16 with difficulty sleeping; interventions included dCBT-I delivered using Sleepio or dCBT-I delivered using another digital technology; comparators included sleep hygiene, hypnotic drugs, face-to-face CBT for insomnia, usual care, or digitally facilitated CBT for insomnia; and outcomes included health care resource use, (e.g. medication / prescriptions, primary care attendances) or work productivity. Non-English language studies were excluded. The EAC used a similar inclusion and exclusion criteria but excluded all dCBT -I delivered using another digital technology which was not relevant for the evaluation of Sleepio technology.

There were 12 studies (Darden et al., 2020, De Bruin et al, 2016, Thiart et al., 2016, Kjørstad et al., 2020, Shaffer et al, 2020 Behrendt et al, 2020, Blom et

al, 2016, Luik et al, 2020 Moloney et al, 2020, Stott t al. (upublished), Stokes (unpublished), Sampson et al. 2021) identified as relevant to the decision problem by the company, of which 3 were unpublished studies and 9 were published studies. De Bruin et al, 2016 provided evidence generally on online CBT vs group CBT. Only 3 studies (Darden et al., 2020 & Samposon et al 2021, Luik et al 2020) provided economic evidence related to Sleepio technology and were considered by the EAC. Luik et al 2020 did not report costs, but did report resource use (prescribed and non-prescribed medication and health care utilisation (visit to GPs and/or specialist doctors) for Sleepio vs Sleep hygiene.

Of the studies excluded by the EAC: Thiart et al (2016), Shaffer et al. (2020) and Moloney et al. (2020) were for other technologies (Shuti and Get.on Recovery); Kjørstad et al. (2020) reported the impact on presenteeism and absenteeism of digital vs face to face CBT; and Behrendt et al. (2020), Blom et al, (2016) reported impact of digital CBT on insomnia severity scores. [redacted] reported clinical benefits, but not economic outcomes

Published economic evidence review

Darden et al. (2020) simulated a decision Markov model of 100,000 individuals using parameters calibrated from the literature including direct and indirect treatment costs (e.g. insomnia-related healthcare expenditure and lost workplace productivity) to one of 5 arms; dCBT-I (Sleepio), Pharmacotherapy, Individual CBT-I, Group CBT-I, and No treatment. The cohort was partitioned in a decision tree between remission and insomnia at 6 months' time horizon and utility weights were assigned. The study focused on a 6-month time horizon because there is little information on repeated treatment exposure and longer term remission rates. Health utility estimates were converted into quality-adjusted life years (QALYs) and one QALY was valued at $50,000. Direct costs associated with pharmacotherapy was defined as a 100-day course of generic zolpidem, at a cost of $144.10, and the cost of two physician office visits, estimated at $114.40 each. The direct cost of Sleepio

was modelled as a one-time payment of $400 for 12-months access). The cost of 6-months of individual CBT assumed six visits at $174 each (total $1,044). The cost of group CBT was $172.50 per individual using an average (across locations in the US) current procedural terminology (CPT) code rate of $28.75 multiplied by six visits. For each session of face-to-face CBT (individual and group CBT), the authors also included costs of two hours of pay for time spent away from work using the median hourly wage ($27.96) taken from the US Bureau of Labor Statistics. The analysis assumed that most face-to-face sessions are delivered during work time. Individual costs such as travel costs for patients to access face-to-face CBT were not included.

Sleepio was the most cost-effective insomnia treatment followed by group CBT, pharmacotherapy, and individual CBT. Digital CBT was cost beneficial when compared with no insomnia treatment and had a positive net monetary benefit (NMB) of $681.06 (per individual over 6 months). Bootstrap sensitivity analysis demonstrated that the NMB was positive in 94.7% of simulations.

The unpublished Sampson et al. (2021) paper reports a quasi-experimental design, using an interrupted time series to compare the trend in primary care costs before and after the rollout of Sleepio in UK. Primary care costs include general practice contacts and prescriptions. Segmented regression analysis was used to estimate the impact of the introduction of Sleepio on costs and on prescriptions for insomnia. The study was conducted in the Thames Valley region of England, where access to Sleepio was made freely available to all residents between October 2018 and January 2020. Patients were included from 9 practices if they met one of the following four criteria: diagnosis of anxiety or depression; diagnosis of insomnia; prescription of hypnotic or anxiolytic drugs; referral to Sleepio. From a population of 129,865, 10,704 patients were included in the study. The total saving over the 65-week follow-up period was £71,027. This corresponds to £6.64 per person in the sample, or around £70.44 per Sleepio user. Secondary analyses suggest that savings may be driven primarily by reductions in prescriptions. Savings of a similar magnitude were estimated in years 2 and 3 after extrapolating the trend in

costs observed in the observation period. The 2 year savings per user were estimated at £88 and the 3 year savings at £140.

Sensitivity analyses included the impact of the introduction of Sleepio on prescriptions of drugs commonly given for insomnia and a comparison of costs in patient referred to Sleepio with those not referred. The majority of sensitivity analysis confirmed a reduction in resource use following the introduction of Sleepio, but notably, the comparison of patients referred to Sleepio with those not referred found higher costs in referred patients. This sensitivity analysis is not described in detail and the authors dismiss the findings as a product of selection bias. The analysis appears to have been robustly implemented, but the description of the patient cohort is limited. For instance, it is not clear if any restrictions were placed on the duration of time since the trigger entry criteria (such as a diagnosis of insomnia) was recorded.

Luik et al. 2020 reported the use of sleep medication and healthcare use for Sleepio as compared to Sleep hygiene. Intention-to-treat analyses demonstrated that Sleepio reduced use of prescription (adjusted rate ratio [RR]: 0.64, 95% CI: 0.42; 0.97) and non-prescription sleep medication (adjusted RR: 0.52, 95% CI: 0.37; 0.74). Uncontrolled follow-up suggests that these effects were sustained for non-prescribed sleep medication (week 48: rate ratio 0.52, 95% CI: 0.40; 0.67), but not for prescribed medication (week 48: rate ratio 0.78, 95% CI: 0.58; 1.05). No effect of Sleepio on the number of visits to GPs or specialist doctors was observed. The results support the conclusions by Sampson et al. (2021) that savings come from reduced prescription cost, which is around 60% less for Sleepio compared to Sleep Hygiene.

Results from the economic evidence

Darden et al. (2020) reports that Sleepio was the most cost-effective insomnia treatment followed by group CBT, pharmacotherapy, and individual CBT. This is further supported generally by economic literature (De Bruin et al, 2016) which reports that Internet CBT-I is a cost-effective treatment compared to group CBT-I for adolescents. The unpublished Sampson et al. (2021) paper also reports lower primary care costs across nine practices in the UK over one

year following introduction of Sleepio. Secondary analyses suggest that savings were driven primarily by reductions in prescriptions, a result similar to Luik et al 2020. The evidence in Sampson et al. (2021) is derived from a cohort of patients who were identified as having sleep problems and given access to Sleepio. The data does not distinguish costs for patients who accessed Sleepio and those that did not, which weakens attribution of the change in costs to Sleepio use.

9.2 *Company de novo cost analysis*

Economic model structure

The company's economic analysis models a population of adults with insomnia symptoms, which includes people without a formal diagnosis. The model includes a simple one stage decision tree using remission status after treatment initiation (figure 3). However, costs are not a function of remission status and hence the decision tree model plays no role in the analysis of costs. The model compares Sleepio to 2 comparators: treatment as usual, which includes sleep hygiene and sleep medication; and face-to-face CBT for insomnia. The first (and primary) comparator is treatment as usual in England, which is poorly defined, but often involves non-evidence-based treatments. It is most commonly managed by a general practitioner (GP) through verbal advice (100%), sleep hygiene education (89%), and by sleep promoting medication (Everitt et al. 2014). Sleep promoting medication alone as a distinct comparator is not included, since sleep medication is unsafe and generally not recommended for the long-term treatment of insomnia, and there is a lack of evidence comparing Sleepio (or other forms of CBT) to sleep medication. There are clinical trials demonstrating the superiority of Sleepio over sleep hygiene education (Pillai et al, 2015; Cheng et al., 2019, Espie et al, 2019; Henry et al, 2020, Luik et al., 2020, Kalmbach et al., 2020). The second comparator is individual face-to-face CBT for insomnia. This comparator is recommended for the treatment of insomnia, but may have limited availability in parts of the UK.

The company's economic analysis estimates the overall cost of providing access to Sleepio to a large population of patients. Technology costs are a function of the total population size. Access to Sleepio is assumed to reduce primary care costs in patients accessing it. The size of the reduction in annual costs and the proportion of patients accessing Sleepio are based on data from Sampson et al. 2021. Sampson et al. 2021 reports the overall impact on primary care costs of providing access to Sleepio for a cohort of patients identified from records as potentially suffering from insomnia. The study does not differentiate resource use and cost implications according to rates of uptake and engagement, or in relation to remission status. The analysis includes the cost of the technology and comparators and the changes in primary care resource use costs (based on Sampson et al 2021) extrapolated over a 3-year time horizon.

There is some evidence that post-treatment improvements in insomnia and decreases in sleep medication usage are sustained over a 36-month period. These changes were maintained over a three year follow-up period with the use of digital CBT-I in Blom et al. (2016). Luik et al. (2020) found that benefits (improvements in insomnia symptoms as per SCI) were maintained 48-weeks after receiving Sleepio (using Espie 2019 data). The EAC thinks the comparators, outcomes and time-horizon are reasonable for this evaluation. The EAC accepts the structure of the economic analysis presented by the company. This structure is appropriate as Sampson et al. (2021) represents the best available evidence on the cost impact of Sleepio in a UK setting, despite the aggregate nature of the data. The EAC regards the decision tree component submitted by the company to be extraneous. The data on the differential cost of Sleepio users achieving remission is not available, rendering the decision tree redundant.

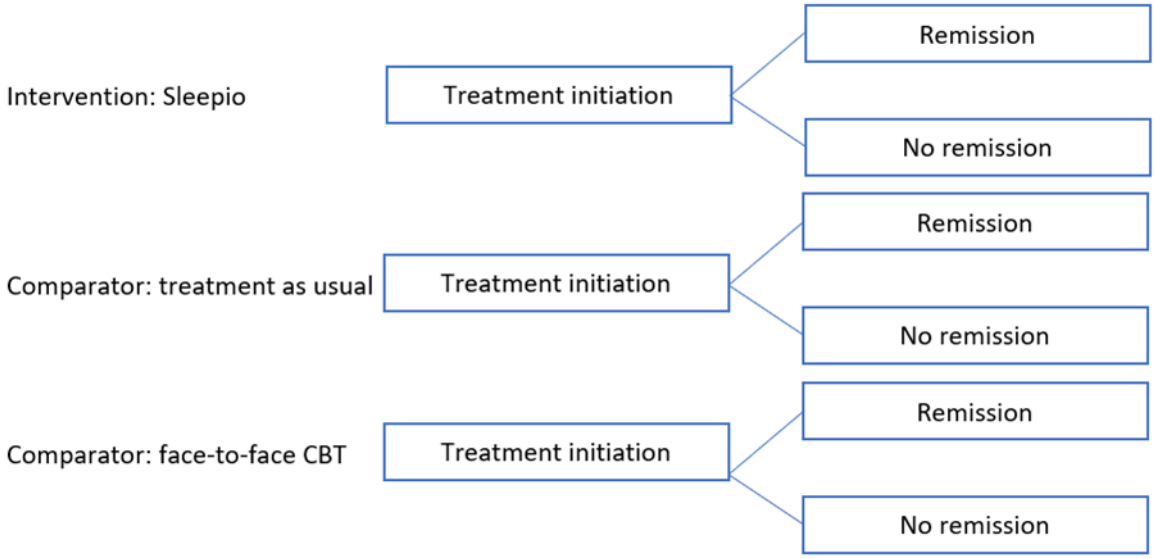


Figure 3 Company model structure

The analysis makes the following assumptions:

- The difference in costs before and after introduction of Sleepio for the cohort identified as having insomnia, reported in Sampson et al. (2021), represents the cost savings in this cohort arising from access to Sleepio. The EAC considers this assumption acceptable.

- The data on resource use observed in the 65 weeks following introduction of Sleepio can be extrapolated over a period of three years and represents the total cost savings for the cohort accessing Sleepio over 3 years. This assumption is concerning. It is possible that cost savings from access to Sleepio will persist for many years after access. However, data over 65 weeks from Sampson is of insufficient duration to be confident of this.

- The analysis implicitly assumes that the cohort accessing Sleepio in Sampson et al. (2021) represents the annual incidence of patients with insomnia. The EAC considers this assumption to be highly optimistic. The cohort in Sampson appears to be a prevalence cohort of patients with insomnia, some of whom have presumably suffered for many

years. The EAC considers it highly unlikely that the cohort observed in Sampson et al. (2021) will be replaced by a similar sized cohort of new users in each subsequent year.

- Sleepio is equivalent to other forms of face-to-face CBT in terms of both remission and its impact on resource use. This is based on a meta-analysis of clinical outcomes by Soh et al. (2020), which supports this assumption for the group of digital CBT technologies for insomnia. [redacted] The EAC could not access the Derose et al. manuscript. The Manber et al. is still in recruitment phase.

- Based on clinical non-inferiority of Sleepio, there is no difference in primary care resource use for patients treated with Sleepio compared to patients treated with face-to-face CBT. The EAC thinks this is an acceptable assumption, due to the lack of data.

Economic model parameters

Clinical parameters and variables

- The company estimates uptake of 24,000 people starting CBT with Sleepio, based on the Thames Valley roll-out. This assumes a 1% uptake amongst adults with access to Sleepio for a population of 2.4m. This parameter has been calculated by first estimating the proportion of patients who commence using Sleepio from the proportion recorded as referred by the GP in the data in Sampson et al. (2021). This figure is then scaled up to account for the estimate that the proportion accessing Sleepio via GP referral is 24.5% of all patients accessing Sleepio (giving 1283 patients or 0.99% of the practice population). The resulting estimate is a little higher than the estimated number of patients from the nine GP practices reported to have accessed Sleepio in Sampson et al. (2021) (1220, 0.94%). Sampson et al. (2021) also report an estimate of Sleepio uptake of 0.58% in Buckinghamshire, and

0.54% in the Thames Valley. Notably, Sampson also indicates the company made significant efforts to promote Sleepio within the nine practices, stating “In Buckinghamshire …the Sleepio team work(ed) closely with the selected general practices to offer Sleepio to patients most likely to benefit.” The company examined a lower bound on uptake of 0.7% in a scenario analysis. The EAC is unclear why the proportion of users required estimation rather than using the figures reported in Sampson et al. (2021). The EAC further believes that the figure used for estimation of GP referrals from the 9 GP practices may be incorrect. The company has used a figure reported in Samson et al. 2021 for the ‘estimated patients based on Sleepio data’ of 1220. The EAC considers this to be the estimate of the overall users of Sleepio in the nine GP practices (0.94% of the practice population). The EAC believes the number of GP referrals on which the company should have based their calculation is given by the data reported as ‘estimated patients based on EMIS data’, which was 1,008. If the latter figure had been used the estimated proportion of Sleepio users is 0.81%.

- Remission from insomnia in the treatment group receiving Sleepio is assumed to be 53.9% in the base case. The source of this estimate is Cheng et al. 2019, which is the only study that reports remission rates for Sleepio across a sample potentially generalisable to the whole treated population. Using the 95% confidence interval, a best case (59.1%) and worst case (48.7%) is also used. The EAC notes that Cheng et al. (2019) includes patients with insomnia and depression. Given that there is no other evidence related to remission, this estimate is considered reasonable by the EAC. **However, the EAC notes that cost savings are not estimated as a function of remission status in the company model**.

- The percentage of patients experiencing post-treatment remission from insomnia for the first comparator (treatment as usual sleep hygiene) is estimated to be 14.0% and used in the base case (Cheng et al. 2019). Using the 95% interval, a best case (17.6%) and worst case (10.4%) is

also used. As above, the EAC notes that Cheng et al. 2019 study includes patients with insomnia and depression. Given that there is no other evidence related to remission, this estimate is considered reasonable by the EAC. **Again, the EAC notes that remission status is not used to estimate costs**.

- Sleepio is considered non-inferior to face-to-face CBT. The percentage of patients experiencing post-treatment remission from insomnia in the comparator (face-to-face CBT) is assumed to be the same as in the intervention group. The company supports this assumption from the literature (Cheng et al. 2019, [redacted]) The EAC could not access the unpublished [redacted] Cheng et al. 2019 includes patients with insomnia and depression, which raises concerns that the populations are not equivalent. Hence, the EAC considers it plausible to assume similar results, but notes weaknesses in the supporting evidence.

Table 6: Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value	Source	EAC value	EAC comment
Cohort size in year one	24000	Sampson et al. 2021	13920	The EAC believes that the figure for Buckinghamshire reported in Sampson is more appropriate than the figure for the nine practices which provided data for the evaluation.
Cohort size in subsequent years	24000	Assumption	13920/4800	The EAC tested an assumption that Sleepio use remained at the initial rate of 0.58% and an assumption that it fell to 0.2%.

- The EAC regards the reported uptake of Sleepio in Sampson et al. 2021 of 0.58% for Buckinghamshire to be a better estimate of uptake in

the first year of access to Sleepio than that calculated by the company, or the figure reported in Sampson et al. (2021) across9 GP practices (0.94%). These 9 GP practices appear to have received bespoke support to provide Sleepio to their practice populations and are likely to have been more highly motivated to prescribe than other practices in Buckinghamshire, which were not providing patient data for the study. Therefore, the EAC amended the company's analysis to use an uptake figure of 0.58% in the first year.

The company's submission implicitly assumes that uptake in subsequent years will remain at the same level as that observed in the first 65 weeks in the study in Sampson et al. (2021). The EAC notes that data were selected on a prevalent cohort of patients meeting criteria for insomnia in Sampson et al. (2021). The duration of symptoms are not reported. However, the EAC considers it highly unlikely that uptake in subsequent years will be maintained at the same rate as the first year. In further analysis, the EAC considered an optimistic scenario in which uptake was maintained at the figure reported in Sampson et al. 2021 for Buckinghamshire (0.58%). In a pessimistic scenario, the EAC assumed that uptake in subsequent years falls to 0.2%. The EAC is unaware of any data upon which to base uptake of Sleepio beyond the first year.

Resource identification, measurement and valuation

- Sleepio is provided to NHS systems in a block funding model, whereby the system pays a fixed price per adult **per year** in their population to cover unlimited access to Sleepio. The pricing table below shows the price per adult charged at different population sizes.

Table 7: Sleepio pricing model

Number of adults in the NHS system population	Price per adult p.a.
0 - 250,000	£1.00
250,001 - 500,000	£0.98
500,001 - 750,000	£0.96
750,001 - 1,000,000	£0.93
1,000,001 +	£0.90

- The company analysis assumes the total population given access to Sleepio is 2,400,000, hence the technology price is £ 0.90 per head per year.

- The cost of face-to-face CBT-I uses the generic cost of CBT (Curtis 2013). Thus, one session of individual in-person CBT-I has an estimated cost to the NHS of £31 - £133. Taking the midpoint of the PSSRU estimate, the cost of six sessions comparable to the Sleepio programme is £82 x 6 = £492. The PSSRU cost uses 2012 prices; after inflation the cost of face-to-face CBT is estimated to be £542 (range £205 and £878).

- There is a reduction in primary care resource use per Sleepio user in year 1 of £49.52 (Sampson et al. 2021), and the estimated cost saving for year 2 and 3 is £45.04 per year. The EAC has some concerns on the validity of extrapolating the data reported in Sampson et al. 2021 over three years, but accepts the values reported in Sampson et al. 2021, in the absence of other evidence.

Table 8: Cost parameters used in the company's model and changes made by the EAC

Parameter	Company value	EAC value	Source
Technology price	£ 0.90 per adult in the population	Same	Company submission
Comparator (Sleep hygiene)	£0	Same	
Comparator (face to face CBT)	£492	£542	Company estimates inflated to current prices
Primary care resource use per user (year 1)	£49.52	Same	Sampson et al. 2021
Primary care resource use per user (year 2)	£43.52	Same	Sampson et al. 2021, discounted at 3.5%
Primary care resource use per user (year 3)	£42.05	Same	Sampson et al. 2021, discounted at 3.5%

Sensitivity analysis

The base case analysis assumes uptake of 1%, based on data reported in Sampson et al. (2021) for the 9 practices providing the cohort. The company has presented a scenario analysis in which uptake is estimated to be 0.7%, and hence the cohort size is reduced to 16000. Sensitivity analyses are conducted on the basis of best- and worst-case scenarios based on confidence intervals for cost savings associated with Sleepio users and the likelihood of remission. The latter sensitivity analysis is redundant as the cost impact of Sleepio in the company's analysis is not a function of remission.

9.3 *Results from the economic modelling*

Base case results

Table 9: Summary of base case results

Comparison with face to face CBT

	Company's results (per patient)			**EAC's results, single cohort analysis (per patient)**		
	Technology	**Comparator (Face to face CBT)**	**Cost saving per patient**	**Technology**	**Comparator (Face to face CBT)**	**Cost saving per patient**
Consumables	£90*	£492	£402	£155.17*	£542	£386.83
Primary care cost savings (Year 1)	-£49.52	-£49.52	£0	-£49.52	-£49.52	£0
Primary care cost savings (Year 2&3)	-£85.56	-£85.56	£0	-£85.56	-£85.56	£0
Total (Year 1)	£40.48	£442.48	£402	£105.65	£492.48	£389.83
Total (3 Years)	**-£45.08**	**£356.92**	**£402**	**£20.09**	**£406.92**	**£386.83**

*Technology cost per person is calculated as the population cost divided by the estimated number of users

Comparison with usual care

	Company's results (per patient)			EAC's results single cohort analysis (per patient)		
	Technology	**Comparator (usual care)**	**Cost saving per patient**	**Technology**	**Comparator (usual care)**	**Cost saving per patient**
Consumables	£90	£0	-£90	£155.17*	£0	-£155.17
Primary care cost savings (Year 1)	-£49.52	£0	£49.52	-£49.52	£0	£49.52
Primary care cost savings (Year 2&3)	-£85.56	£0	£85.56	-£85.56	£0	£85.56
Total (Year 1)	40.48	£0	-£40.48	£105.65	£0	-£105.65
Total (3 Years)	**-£45.08**	**£0**	**£45.08**	**£20.09**	**£0**	**-£20.09**

*Technology cost per person is calculated as the population cost divided by the estimated number of users

Sensitivity analysis results

The company's analysis of best and worst-case scenarios on remission rates show no impact on costs. This is because their analysis does not differentiate costs by remission status. In scenario analysis, the company considered a lower uptake rate of 0.7%. This reduced the patient cohort using Sleepio to 16,800 from 24000. Primary care cost savings, which are estimated per Sleepio user are decreased. The overall cost of Sleepio remains negative, but increases from -£45.08 to -£6.51.

The EAC undertook additional analysis comparing the cost of Sleepio with usual care. This sensitivity analysis examined the proportion of patients accessing Sleepio, the cost of Sleepio and the duration of reductions in primary care resource use following access. Table 10 reports the incremental cost of Sleepio compared to usual care over three years for the first year's cohort as a function of uptake after varying this parameter between 0.5% and 1.0%. Cost savings fall as the proportion of users reduces due to the

associated fall in cost savings. The breakeven rate for the first year's cohort is 0.666%.

Table 10

Sleepio uptake	Sleepio cost per head	Equivalent Sleepio cost per user	Primary care cost savings (three years)	Cost saving per patient
0.5%	£0.90	£180	£135.08	-£44.92
0.6%	£0.90	£150	£135.08	-£14.92
0.7%	£0.90	£128.57	£135.08	£6.51
0.8%	£0.90	£112.50	£135.08	£22.58
0.9%	£0.90	£100	£135.08	£35.08
1.0%	£0.90	£90	£135.08	£45.08

Table 11 reports the incremental cost of Sleepio compared to usual care over 3 years for the first year's cohort as a function of the cost of Sleepio per user and the cost per head of population on an assumptions that 0.58% of the relevant population accesses Sleepio. Sleepio becomes cost saving when the cost saving per head falls to £0.78.

Table 11

Sleepio uptake	Sleepio cost per head	Equivalent Sleepio cost per user	Primary care cost savings (three years)	Cost saving per patient
0.58%	£1.00	£172.41	£135.08	-£37.33
0.58%	£0.90	£155.17	£135.08	-£20.09

0.58%	£0.80	£137.91	£135.08	-£2.83
0.58%	£0.70	£120.69	£135.08	£14.39
0.58%	£0.60	£103.45	£135.08	£31.63
0.58%	£0.50	£86.21	£135.08	£48.87

Table 12 reports the incremental cost of Sleepio compared to usual care for the first year's cohort after varying the duration of cost savings with Sleepio from one year to six years. Sleepio becomes cost saving at a 0.58% uptake if cost savings over 65 weeks observed in Sampson et al. 2021 are maintained for four years in total.

Table 12

Sleepio uptake	Sleepio cost per head	Equivalent Sleepio cost per user	Primary care cost savings (varying years)	Cost saving per patient
0.58%	£0.90	£155.17	£49.52 (one year)	-£105.65
0.58%	£0.90	£155.17	£93.04 (two years)	-£62.13
0.58%	£0.90	£155.17	£135.08 (three years)	-£20.09
0.58%	£0.90	£155.17	£175.71 (four years)	£20.54
0.58%	£0.90	£155.17	£214.96 (five years)	£59.79

0.58%	£0.90	£155.17	£252.88 (six years)	£97.71

Additional results

The company's analysis modelled a single cohort over 3 years based on extrapolation of costs observed over 65 weeks in Sampson et al. (2021). In practice, NHS providers would be expected to pay a fee per capita per annum for ongoing access to Sleepio for their populations. Hence, in practice each subsequent year beyond the first will accrue additional costs for the provision of Sleepio and additional savings. Savings consist of primary care resources reduced for patients accessing Sleepio in that year and also the extrapolated ongoing savings for previous years' cohorts who accessed Sleepio.

The EAC undertook additional analysis to quantify the rolling total costs since inception for 1, 3, 5, 10 and 20 years after commencing provision of Sleepio for a population of 2,400,00. The EAC assumed cost savings over 3 years as in the company's base case submission. The EAC assumed uptake of 0.58% of the population in the first year as for the EAC's single cohort analysis. The EAC compared 2 scenarios for uptake in the years after the first year of provision of Sleepio. In the optimistic analysis the EAC assumed that uptake was maintained at 0.58% of the population (per year). In the pessimistic analysis the EAC assumed that uptake fell to 0.2% of the population for each year beyond the first year of rollout. In both scenarios, the overall cost of provision rises over time.

Optimistic scenario

Years	Sleepio cost	Primary care costs averted	Overall cost saving
1	£2,160,000	£689,318	-£1,420,948
3	£6,263,340	£3,775,110	-£2,404,087

5	£10,093,851	£7,221,208	-£2,775,500
10	£18,592,603	£14,867,063	-£3,599,556
20	£31,773,249	£26,724,958	-£4,877,576

Pessimistic scenario

Years	Sleepio cost	Primary care costs averted	Overall cost saving
1	£2,160,000	£689,318	-£1,420,948
3	£6,263,340	£2,533,712	-£3,603,505
5	£10,093,851	£3,722,022	-£6,156,357
10	£18,592,603	£6,692,681	-£11,497,509
20	£31,773,249	£11,547,712	-£19,541,582

9.4 *The EAC's interpretation of the economic evidence*

The cost impact of Sleepio is based on three components: the cost of access, which is a function of population size; the relevant population with insomnia who might be expected to access Sleepio; and the impact on primary care costs of using Sleepio. The first component is transparently estimated from the company's pricing system. The second component has been estimated by

the company on the basis of data in Sampson et al. 2021. The third component is taken from the Sampson publication results.

The EAC has concerns regarding the estimation that 1% of general practice populations will access Sleepio in the first year and hence reduce their primary care resource use. The EAC believes the figure may have been calculated incorrectly. The EAC further believes that the figures for Sleepio users reported in Sampson et al. (2021) as 'Estimated patients based on Sleepio data' to provide a better estimate of Sleepio users. Finally, the EAC believes that the estimated Sleepio users reported for Buckinghamshre (0.58%) is a better indicator of uptake than the value of 0.94% for the 9 GP practices from which EMIS data were obtained. Sampson et al. (2021) notes that these practices received targeted support and promotional material from the company. The extent of this support is not clearly described. It is also likely that these practices were more highly motivated to recall and refer patients. This appears to have translated into a much higher usage of Sleepio in the 9 practices than the rest of Buckinghamshire.

The company's analysis implicitly assumes that 1% of patients will be referred to Sleepio every year. In the absence of such a pattern, cost savings from Sleepio would quickly fall, whereas the cost of the device is a fixed per annum charge based on population size. The EAC thinks this assumption is highly unlikely to hold. The EAC notes a lack of available data upon which to estimate the fall off in access to Sleepio over time.

The EAC accepts the evidence from Sampson et al. 2021 on the cost savings following the introduction of Sleepio. Notwithstanding, the EAC notes that such an analysis is an unusual basis for a technology appraisal. The study has a number of strengths. The sample is large and is representative of the relevant patient population. The data represent resource use in routine primary care avoiding contamination with artefacts of trial protocols. The analysis appears to be robust. The model specification is transparent and the use of linear trends gives confidence that the results are not an artefact of the model specification.

The application of this evidence to the estimation of the cost impact of Sleepio also highlights limitations. Observations over 65 weeks give some confidence that cost savings are likely beyond the 65 week period, but the EAC believes the data cannot be extrapolated to 3 years with confidence. The possibility remains that other factors rather than Sleepio may have been responsible for the change in the trend of primary care costs. Inference on causation would have been greatly strengthened by the inclusion of control data for the same period. Finally, such designs are susceptible to regression to the mean; it would not be a surprise to find a reduction in prescribing over time in a sample of patients selected on the basis of prescription of short term sleep agents.

The EAC considers the company's model of remission from insomnia to offer no insight into the cost impact of Sleepio, over and above that provided by the Sampson et al. (2021) study. The EAC notes that the company's cost estimates are based on data drawn from Sampson et al. (2021). The EAC accepts this study as the basis of the estimate of the impact on primary care costs of access to Sleepio. However, the EAC believes the proportion of patients likely to use Sleepio is lower than either the base estimate or the value used in sensitivity analysis in the company's submission.

The EAC revised the company's model to consider a base case uptake of 0.58% of the adult population, based on the data from Buckinghamshire reported in Sampson et al. 2021. After this revision the cost savings per Sleepio use, as estimated in Sampson et al. 2021 and extrapolated over 3 years are insufficient to offset the cost of Sleepio. The EAC considers the extrapolation of cost savings from Sampson et al. 2021 to be an optimistic estimate of the long term cost savings derived from the use of Sleepio.

The EAC also notes that cost savings in the current model assume that use of Sleepio in future years will be maintained at the same proportion of the adult population as that estimated for the first year. The EAC considers it likely that the proportion of users in subsequent years will not be as high as the proportion recorded in the first year and reported in Sampson et al. (2021).The EAC undertook additional analysis in which it estimated the cumulative overall cost of the provision of Sleepio over varying time periods

for a population of 2,400,000. This analysis retained the company's original assumptions regarding the cost savings (over 3 years) attributable to the use of Sleepio. Under a favourable assumption of annual uptake of 0.58% of the population *each year*, overall costs are positive and grow over time.

The EAC believes the pessimistic model to offer a more realistic scenario regarding uptake of Sleepio beyond the first year. In this scenario, costs are £1.4m after one year rising to £6.1m for the net present value of the overall costs over five years. On the basis of these projections the EAC concludes that Sleepio is highly unlikely to be cost saving at a price per head of £0.90 per annum per year.

The EAC revised the company's single year comparison of Sleepio with face-to-face CBT. The result was a modest increase in costs for Sleepio users, but Sleepio remained far cheaper than face-to-face CBT. The EAC has not included face-to-face CBT in its multiple year population model. It is plausible that Sleepio will reduce referral for face-to-face CBT. If this were to occur there would be additional cost savings associated with the provision of Sleepio. The EAC notes that existing provision of face-to-face CBT for insomnia is poor in some areas. Consequently, any reduction is unlikely to generate considerable additional savings. On the assumption that referral is capacity constrained, it is possible that no reduction in referral will occur. Hence, the EAC does not consider the exclusion of face-to-face CBT to have significantly impacted its overall cost estimates.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The company included 26 published fulltext studies in their clinical submission (including 12 RCTs and 6 secondary analysis papers). The EAC excluded 1 non-randomised study due the population being under 18 year (Cliffe 2020). The evidence shows that Sleepio is consistently superior to standard care for reducing symptoms of insomnia, however high heterogeneity among studies (in terms of population and outcome measurement) raises challenges pooling

data and providing a definitive conclusion in terms of how effective Sleepio is compared with standard care. There were no studies comparing Sleepio with face-to-face CBT.

The EAC concludes that there is good quality clinical evidence that Sleepio improves sleep. Results favour Sleepio over waiting list, sleep hygiene education or placebo (e.g. Espie 2012 imaginary relief therapy) in people who have self-reported insomnia symptoms. One secondary analysis into longer term outcomes (Luik et al. 2020) found that improvements in insomnia symptoms were maintained at 48 weeks, indicating that improvements due to use of Sleepio may be maintained over the longer term, albeit this was observed for a fraction of the participants due to low engagement rates. The reported outcomes on sleep improvement, psychological wellbeing, improved labour market participation and productivity, and reduced prescribing of hypnotics are all relevant to the NHS care pathway.

There was high loss to follow up in most studies (higher in the Sleepio than the control arm), however most RCTs were analysed as ITT to account for missing data. Clinical experts noted that uptake and engagement is typically low with online CBT for insomnia, leading to high loss to follow up (compared with standard care) and highlighted the importance of appropriate patient selection for using Sleepio.

10.2 *Conclusions from the economic evidence*

The EAC considers the unpublished Sampson et al. (2021) study to provide the most relevant data on the impact of Sleepio on primary care costs. Those data indicate an overall reduction in the first year following access to Sleepio of around £50 for a prevalent cohort with evidence of insomnia and in whom some will have accessed Sleepio. The EAC has reservations regarding the period over which these savings can be extrapolated beyond the 65 week observation window, although it accepts that the trend to lower costs following access to Sleepio was observed over the 65 week follow-up. The EAC believes that the company's estimate of the proportion of general practice populations that might benefit from Sleepio is a best case scenario. The EAC

modified this parameter and applied the estimate of 0.58% based on uptake reported for Buckinghamshire in Sampson et al. 2021. This is lower than the 0.94% reported in the 9 general practices from which patient level data were taken, but Sampson indicates that these practices received additional tailored promotional material. It also seems likely that the GPs in the9 sample practices were highly motivated to refer. Following the change in the uptake parameter to 0.58% Sleepio becomes cost incurring at a cost of £20.09 per patient in a single patient cohort analysis.

This estimate of £20.09 per patient captures the cost of providing Sleepio for 1 year and the projected savings for that cohort over 3 years. Savings lag the ongoing cost of provision of Sleepio. If uptake in subsequent years is the same as the uptake in the first year then the accumulated cost per patient accessing Sleepio will asymptotically approach the cost for the first cohort as the time horizon for the analysis increases. However, the EAC notes that the uptake estimate from Sampson et al. (2021) represents the first year of access for all patients. It seems likely that uptake will fall in subsequent years. In that scenario the cost per patient will asymptotically approach the cost per patient cohort at the estimated steady state uptake rate. For these reasons the EAC's cost estimate for the first cohort represents an optimistic assessment of the longer term cost impact of Sleepio. Consequently, the EAC concludes that it is highly likely the Sleepio will be cost incurring at a price per head of £0.90 per year.

11 Summary of the combined clinical and economic sections

The EAC believes that, overall, Sleepio may be clinically beneficial for adults over 25 years old with chronic (> 3 months), mild-to-moderate insomnia compared with treatment as usual or sleep hygiene education. There is evidence that Sleepio is better than control for improving insomnia symptoms in people under 25 years old and in pregnant women, but clinical experts noted that insomnia mimics in these groups are common and should be ruled

out before referral. The benefits at the health system level are dependent on patients engaging with the programme. The EAC believes that the estimate in the company's economic submission of the proportion of general practice populations that might benefit from Sleepio is a best case scenario. To understand the economic impact, the EAC applied the estimated uptake of 0.58% based on uptake reported for Buckinghamshire in Sampson et al. 2021. This is lower than 0.94% reported in the 9 general practices from which patient level data were taken, as the EAC believes this figure is more realistic. Following the change in the uptake parameter to 0.58% Sleepio becomes cost incurring at a cost of £20.09 per patient over one year. Therefore, at this level of uptake the EAC believes the case for adopting the technology is not supported for insomnia in adults. Sensitivity analyses indicate that Sleepio becomes cost neutral when uptake is between 0.6 and 0.7%, therefore adequate uptake is key to recommending the adoption of Sleepio. It is unclear whether engagement at this level is likely in practice. Adequate uptake and engagement are crucial to seeing benefits of Sleepio in the health system, therefore, investigating how to optimise patient selection, uptake and engagement would be valuable.

12 Implications for research

The evidence base may be further strengthened by addressing the following uncertainties:

- Head-to-head evidence to clarify how Sleepio compares with traditional face-to-face CBT. How does engagement and effectiveness compare in the long term?
- Evidence on patient selection, in terms of who is more likely to engage with Sleepio and who is likely to benefit most, is an important consideration when assessing health system benefits.

- Populations in these studies were self-reporting symptoms. Outcomes may differ in a population with a formal clinical evaluation of insomnia.

- There are currently RCTs that indicate that Sleepio is beneficial in the longer term (at least 3 to 6 months) for insomnia symptoms. Future studies, for example into different population subgroups, would also benefit from including longer term follow up as part of their study design.

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14 Appendices

Use the appendices to describe additional data and information as needed – we've given some examples as a guide.

List the titles of the appendices here.

Appendix A

Clinical data search strategy.

Search date: **11 January 2021**

List of the searches recourses

Cochrane Library including • Cochrane Database of Systematic Reviews • Cochrane Central Register of Controlled Trials (CENTRAL)	384
Embase <1974 to 2021 Week 01> (via Ovid SP)	490
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to January 08, 2021>	286
PubMed	316
ClinicalTrials.Gov	110
WHO ICTRP	9
INAHTA	0
EconLit via Proquest	0

Cochran Library

Date Run: 11/01/2021 17:14:58		
#1	([mh "Sleep Initiation and Maintenance Disorders"] or Insomnia:ti,ab) AND (Sleepio* or (([mh Internet] or [mh "Online Systems"] or [mh Telemedicine] or [mh "Therapy, Computer-Assisted"] or (Digital or Internet or Online or Web):ti,ab) AND ([mh "Cognitive Behavioral Therapy"] or (Cognitive Behavi* Therapy or CBT):ti,ab)))	384

Embase

1 Sleep Disorder/ or Insomnia.ti,ab. (99404)
2 Sleepio*.af. (39)
3 Internet/ or Online System/ or Telemedicine/ or Computer Assisted Therapy/ or (Digital or Internet or Online or Web).ti,ab. (604191)
4 Cognitive Behavioral Therapy/ or (Cognitive Behavi?or* Therapy or CBT).ti,ab. (32499)
5 3 and 4 (3732)
6 2 or 5 (3742)
7 1 and 6 (490)

MEDLINE

1 "Sleep Initiation and Maintenance Disorders"/ or Insomnia.ti,ab. (26474)
2 Sleepio*.af. (15)
3 Internet/ or Online Systems/ or Telemedicine/ or Therapy, Computer-Assisted/ or (Digital or Internet or Online or Web).ti,ab. (453859)
4 Cognitive Behavioral Therapy/ or (Cognitive Behavi?or* Therapy or CBT).ti,ab. (33686)
5 3 and 4 (3555)
6 2 or 5 (3562)
7 1 and 6 (286)

PubMed

("Sleep Initiation and Maintenance Disorders"[MH] OR Insomnia[TIAB]) AND (Sleepio*[ALL] OR ((Internet[MH] OR "Online Systems"[MH] OR Telemedicine[MH] OR "Therapy, Computer-Assisted"[MH] OR Digital[TIAB] OR Internet[TIAB] OR Online[TIAB] OR Web[TIAB]) AND ("Cognitive Behavioral Therapy"[MH] OR Cognitive Behavior Therapy[TIAB] OR Cognitive Behavioral Therapy[TIAB] OR Cognitive Behaviour Therapy[TIAB] OR Cognitive Behavioural Therapy[TIAB] OR CBT[TIAB])))	316

ClinicalTrials.Gov

Advanced Search Condition or disease: Sleep Initiation and Maintenance Disorders OR Insomnia Intervention/treatment: Sleepio OR ((Cognitive OR CBT) AND (Digital OR Internet OR Online OR Web))	110

WHO ICTRP*

Sleepio	9

* Advanced search was inaccessible at search date.

INAHTA

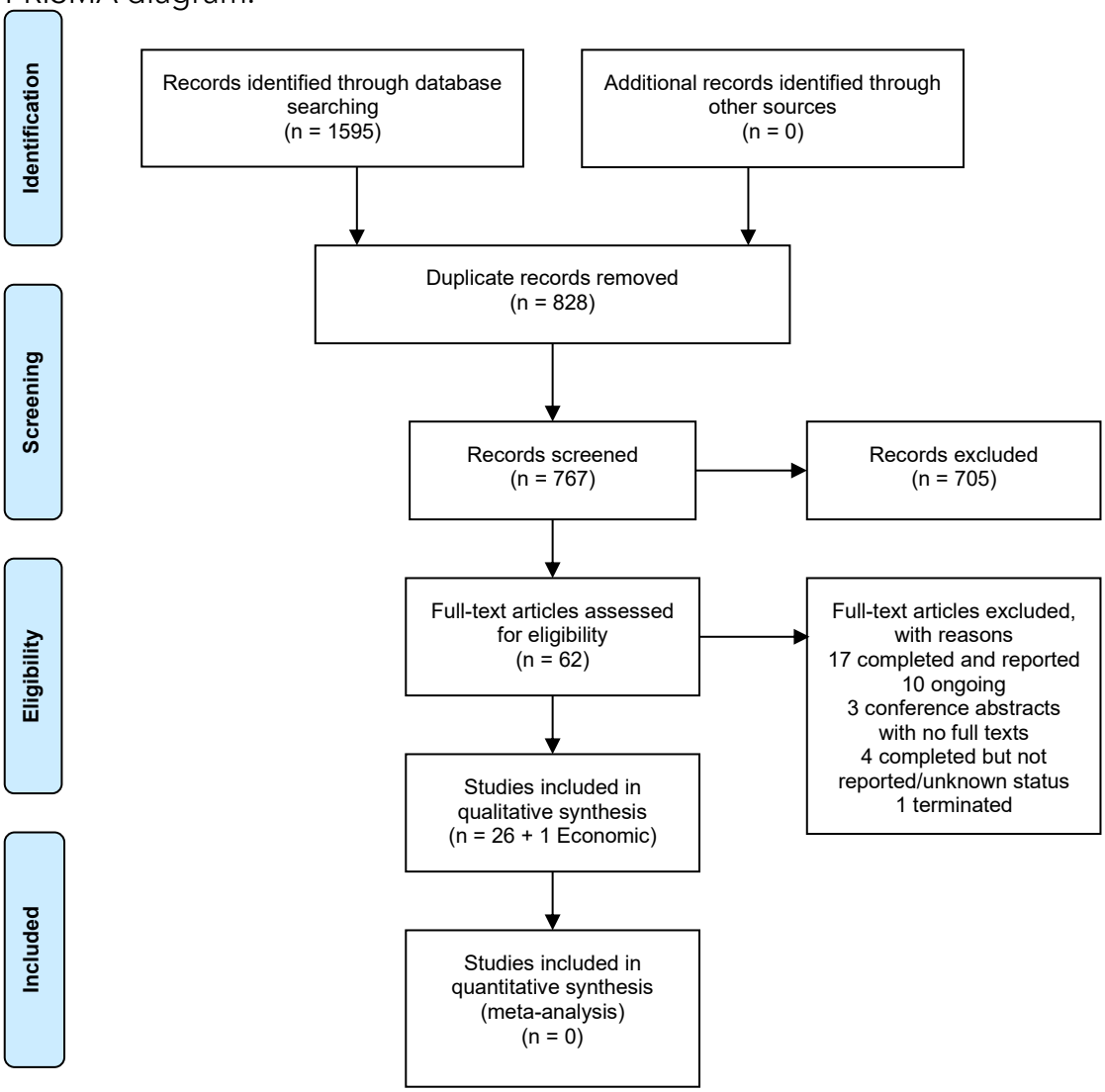
Sleepio	0

EconLit

Sleepio*	0

Critique of company strategy.

PRISMA diagram.



Appendix B

Cochrane Risk of Bias 2 for randomised studies

Intention to treat

Unique ID	A1	**Study ID**	Espie 2012	
Ref or Label	Espie 2012	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Placebo and control	
Outcome	Sleep efficiency	**Results**		

Domain	Signalling question	Response
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN
	Risk of bias judgement	**Low**
Bias due to deviations from	2.1.Were participants aware of their assigned intervention during the trial?	PY

intended interventions	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
	Risk of bias judgement	**Low**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Y
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
	Risk of bias judgement	**Low**
	4.1 Was the method of measuring the outcome inappropriate?	PN

Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Low**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Low**

Unique ID	A3	**Study ID**	Bostock 2016	
Ref or Label	Bostock 2016	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Waiting list	
Outcome	Sleep problem and work productivity	**Results**		

Domain	Signalling question	Response
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN
	Risk of bias judgement	**Low**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
	Risk of bias judgement	**Low**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
	Risk of bias judgement	**Low**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Low**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Low**

Unique ID	A4	**Study ID**	Barnes 2017	
Ref or Label	Barnes 2017	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Waiting list	

Outcome	Insomnia, mood, job satisfaction	**Results**	Waiting list	

Domain	Signalling question	Response
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN
	Risk of bias judgement	**Low**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA

	Risk of bias judgement	**Low**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	
	Risk of bias judgement	**Some concerns**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Low**
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY

Bias in selection of the reported result	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Some concerns**

Unique ID	A5	**Study ID**	McGrath 2017	
Ref or Label	McGrath 2017	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Standard care (vascular risk factor education)	
Outcome	Ambulatory SBP, sleep quality	**Results**		

Domain	**Signalling question**	**Response**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y

	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
	Risk of bias judgement	**Low**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
	Risk of bias judgement	**Low**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PN
	Risk of bias judgement	**Some concerns**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI
	4.3 Were outcome assessors aware of the intervention received by study participants?	N
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Some concerns**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Some concerns**

Unique ID	A6	**Study ID**	Freeman 2017	
Ref or Label	Freeman 2017	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Treatment as usual	
Outcome	insomnia, paranoia, and hallucinations	**Results**		

Domain	Signalling question	Response
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN
	Risk of bias judgement	**Low**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN

	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
	Risk of bias judgement	**Low**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
	Risk of bias judgement	**Some concerns**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN

	4.3 Were outcome assessors aware of the intervention received by study participants?	N
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Low**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Low**

Unique ID	A8	**Study ID**	Espie 2019	
Ref or Label	Espie 2019	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Sleep hygiene education	
Outcome	Functional health, psychological wellbeing, sleep related qol	**Results**		

Domain	**Signalling question**	**Response**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
	Risk of bias judgement	**Low**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA

	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
	Risk of bias judgement	**Low**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PN
	Risk of bias judgement	**Some concerns**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Some concerns**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Some concerns**

Unique ID	A9	**Study ID**	Denis 2020 (pilot)	
Ref or Label	Denis 2020 (pilot study)	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Puzzle based attention control	
Outcome	Acceptability, adherence, insomnia	**Results**		

Domain	Signalling question	Response
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PY
	Risk of bias judgement	**Some concerns**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
	Risk of bias judgement	**Low**

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
	Risk of bias judgement	**Some concerns**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Low**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN

	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Some concerns**

Unique ID	A10	**Study ID**	Felder 2020	
Ref or Label	Felder 2020	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Treatment as usual (comprising a range of non-study treatments)	
Outcome	Insomnia severity, sleep efficiency	**Results**		

Domain	**Signalling question**	**Response**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN

	Risk of bias judgement	**Low**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
	Risk of bias judgement	**Low**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PN

	Risk of bias judgement	Some concerns
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
	4.3 Were outcome assessors aware of the intervention received by study participants?	N
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Low**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Some concerns**

Unique ID	A11	**Study ID**	Kyle 2020	
Ref or Label	Kyle 2020	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Waiting list	
Outcome	Cognitive impairment	**Results**		

Domain	Signalling question	Response
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
	Risk of bias judgement	**Low**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
	Risk of bias judgement	**Low**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
	Risk of bias judgement	**Low**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
	4.3 Were outcome assessors aware of the intervention received by study participants?	N

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Low**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Low**

Unique ID	A12	**Study ID**	Kalmbach 2020	
Ref or Label	Kalmbach 2020	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	
Experimental	Sleepio	**Comparator**	Sleep hygiene education	

Outcome	Insomnia, sleep quality	**Results**		

Domain	Signalling question	Response
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PY
	Risk of bias judgement	**Some concerns**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA

	Risk of bias judgement	**Low**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
	Risk of bias judgement	**Low**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Low**
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY

Bias in selection of the reported result	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Low**

Per protocol

Unique ID	A2	**Study ID**	Pillai 2015	
Ref or Label	Pillai 2015	**Aim**	adhering to intervention (the 'per-protocol' effect)	
Experimental	Sleepio	**Comparator**	Sleep education	
Outcome	Sleep onset latency and anxiety	**Results**		

Domain	Signalling question	Response
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI

	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN
	Risk of bias judgement	**Some concerns**
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	NA
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PY
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	PN
	Risk of bias judgement	**Some concerns**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA

	Risk of bias judgement	**Low**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Some concerns**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Some concerns**

Unique ID	A7	**Study ID**	Cheng 2019a	
Ref or Label	Cheng 2019a	**Aim**	adhering to intervention (the 'per-protocol' effect)	
Experimental	Sleepio	**Comparator**	Sleep hygiene education	
Outcome	Depresssion severity	**Results**		

Domain	Signalling question	Response
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN
	Risk of bias judgement	**Some concerns**
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N

	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	NA
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NI
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	PY
	Risk of bias judgement	**Some concerns**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PN
	Risk of bias judgement	**Some concerns**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
	4.3 Were outcome assessors aware of the intervention received by study participants?	N

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
	Risk of bias judgement	**Low**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
	5.3 ... multiple eligible analyses of the data?	PN
	Risk of bias judgement	**Low**
Overall bias	**Risk of bias judgement**	**Some concerns**

Summary of the strengths and weaknesses (internal and external validity) – non-randomised studies

Luik 2017	Strengths	Weaknesses
Study design	Prospective Service Audit. Provides Real-world data.	Non-comparative. All clients received six support calls from an eTherapy coordinator to support self-help – this is unlikely to be typical of the service in practice, limiting the validity of the results.
Patient selection	UK population.	Inclusion and exclusion criteria are not explicit.
Patient attrition	Reasons for patient withdrawal documented.	None.
Reporting of outcomes	None.	Primary outcomes concern depression and anxiety symptoms, not insomnia. All self-reported.
Statistical analysis	None.	No sample size calculation (as this was an audit).
Study company	Three lead investigators declared no conflict of interest.	Three lead authors are employees of Big Health, while a fourth is a paid consultant for the company.

EXMAPLE 2017	Strengths	Weaknesses
Study design	Prospective Service Audit. Provides Real-world data.	Non-comparative. All clients received six support calls from an eTherapy coordinator to support self-help – this is unlikely to be typical of the service in practice, limiting the validity of the results.
Patient selection		Might not reflect UK population Selection limited to uncomplicated disease Presence and absence of complications not clearly documented. Risk of spectrum bias.
Randomisation	Randomisation performed with adequate concealment of allocation. Low risk of selection bias.	Randomisation lost due to drop-outs post randomisation.
Blinding	Independent and blinded audit controls. Blinded statistical assessment.	Not feasible to blind patients or treating/assessing clinicians. Subjective primary outcome. Moderate to high risk of performance bias.
Patient attrition	Reasons for patient withdrawal documented. Withdrawal low following surgery and evenly spread between arms. Modified ITT analysis appropriate (but weaker evidence).	High withdrawal from prior to surgery led to uneven groups. Low number of eligible patients reporting data at 24 months, so poor confidence in longer term results and risk of bias in results High risk of attrition bias.

Reporting of outcomes	Primary analysis pre-specified in protocol. Outcome X directly related to patient benefit. Extensive reporting of secondary outcomes with appropriate control for multiple comparisons.	Second “primary outcome” may not generalise to NHS care and was not pre-specified in research protocol. Outcomes limited to 24 months (in a small cohort of patients only). Outcome X is subjective primary outcome and could be influenced by participants’ perceptions.
Statistical analysis	Power calculation for sample size for primary outcome performed. Correction for multiple comparisons performed. Low potential for reporting bias.	Sample size requirement for follow-up procedure not clear.
Study company	Three lead investigators declared no conflict of interest.	Study was funded by company. Two lead investigators paid consultants of company.

Elison 2017	Strengths	Weaknesses
Study design	Before-after assessment of Sleepio and 2 other online therapies.	Non-comparative. All clients received six support calls from an eTherapy coordinator to support self-help – this is unlikely to be typical of the service in practice, limiting the validity of the results.
Patient selection		Might not reflect UK population Selection limited to uncomplicated disease Presence and absence of complications not clearly documented. Risk of spectrum bias.
Randomisation	Randomisation performed with adequate concealment of allocation. Low risk of selection bias.	Randomisation lost due to drop-outs post randomisation.
Blinding	Independent and blinded audit controls. Blinded statistical assessment.	Not feasible to blind patients or treating/assessing clinicians. Subjective primary outcome. Moderate to high risk of performance bias.
Patient attrition	Reasons for patient withdrawal documented. Withdrawal low following surgery and evenly spread between arms. Modified ITT analysis appropriate (but weaker evidence).	High withdrawal from prior to surgery led to uneven groups. Low number of eligible patients reporting data at 24 months, so poor confidence in longer term results and risk of bias in results High risk of attrition bias.

Reporting of outcomes	Primary analysis pre-specified in protocol. Outcome X directly related to patient benefit. Extensive reporting of secondary outcomes with appropriate control for multiple comparisons.	Second “primary outcome” may not generalise to NHS care and was not pre-specified in research protocol. Outcomes limited to 24 months (in a small cohort of patients only). Outcome X is subjective primary outcome and could be influenced by participants’ perceptions.
Statistical analysis	Power calculation for sample size for primary outcome performed. Correction for multiple comparisons performed. Low potential for reporting bias.	Sample size requirement for follow-up procedure not clear.
Study company	Three lead investigators declared no conflict of interest.	Study was funded by company. Two lead investigators paid consultants of company.

Luik 2018	Strengths	Weaknesses
Study design	Before-after assessment of Sleepio and 2 other online therapies.	Non-comparative. All clients received six support calls from an eTherapy coordinator to support self-help – this is unlikely to be typical of the service in practice, limiting the validity of the results.
Patient selection		Might not reflect UK population Selection limited to uncomplicated disease Presence and absence of complications not clearly documented. Risk of spectrum bias.
Randomisation	Randomisation performed with adequate concealment of allocation. Low risk of selection bias.	Randomisation lost due to drop-outs post randomisation.
Blinding	Independent and blinded audit controls. Blinded statistical assessment.	Not feasible to blind patients or treating/assessing clinicians. Subjective primary outcome. Moderate to high risk of performance bias.
Patient attrition	Reasons for patient withdrawal documented. Withdrawal low following surgery and evenly spread between arms. Modified ITT analysis appropriate (but weaker evidence).	High withdrawal from prior to surgery led to uneven groups. Low number of eligible patients reporting data at 24 months, so poor confidence in longer term results and risk of bias in results High risk of attrition bias.

Reporting of outcomes	Primary analysis pre-specified in protocol. Outcome X directly related to patient benefit. Extensive reporting of secondary outcomes with appropriate control for multiple comparisons.	Second “primary outcome” may not generalise to NHS care and was not pre-specified in research protocol. Outcomes limited to 24 months (in a small cohort of patients only). Outcome X is subjective primary outcome and could be influenced by participants’ perceptions.
Statistical analysis	Power calculation for sample size for primary outcome performed. Correction for multiple comparisons performed. Low potential for reporting bias.	Sample size requirement for follow-up procedure not clear.
Study company	Three lead investigators declared no conflict of interest.	Study was funded by company. Two lead investigators paid consultants of company.

Espie 2018	Strengths	Weaknesses
Study design	Before-after assessment of Sleepio and 2 other online therapies.	Non-comparative. All clients received six support calls from an eTherapy coordinator to support self-help – this is unlikely to be typical of the service in practice, limiting the validity of the results.
Patient selection		Might not reflect UK population Selection limited to uncomplicated disease Presence and absence of complications not clearly documented. Risk of spectrum bias.
Randomisation	Randomisation performed with adequate concealment of allocation. Low risk of selection bias.	Randomisation lost due to drop-outs post randomisation.
Blinding	Independent and blinded audit controls. Blinded statistical assessment.	Not feasible to blind patients or treating/assessing clinicians. Subjective primary outcome. Moderate to high risk of performance bias.
Patient attrition	Reasons for patient withdrawal documented. Withdrawal low following surgery and evenly spread between arms. Modified ITT analysis appropriate (but weaker evidence).	High withdrawal from prior to surgery led to uneven groups. Low number of eligible patients reporting data at 24 months, so poor confidence in longer term results and risk of bias in results High risk of attrition bias.

Reporting of outcomes	Primary analysis pre-specified in protocol. Outcome X directly related to patient benefit. Extensive reporting of secondary outcomes with appropriate control for multiple comparisons.	Second “primary outcome” may not generalise to NHS care and was not pre-specified in research protocol. Outcomes limited to 24 months (in a small cohort of patients only). Outcome X is subjective primary outcome and could be influenced by participants’ perceptions.
Statistical analysis	Power calculation for sample size for primary outcome performed. Correction for multiple comparisons performed. Low potential for reporting bias.	Sample size requirement for follow-up procedure not clear.
Study company	Three lead investigators declared no conflict of interest.	Study was funded by company. Two lead investigators paid consultants of company.
Miller 2018	Strengths	Weaknesses
Study design	None	Retrospective study. Non-comparative.
Patient selection	Included patients with an objective insomnia subtype through Polysomnography.	Non-UK study and may not reflect UK population or pathway. Retrospective patient identification.
Randomisation	None.	Non-randomised.
Blinding	None.	Not feasible to blind – retrospective.
Patient attrition	No drop-outs.	None.
Reporting of outcomes	None.	Majority of outcomes are outside of scope. All self-reported.

Statistical analysis	None.	No sample size.
Study company	Study not industry funded.	Two lead authors are employees of Big Health and 1 of those is the co-founder.
Crawford 2020	Strengths	Weaknesses
Study design	Before-after assessment of Sleepio and 2 other online therapies.	Non-comparative. All clients received six support calls from an eTherapy coordinator to support self-help – this is unlikely to be typical of the service in practice, limiting the validity of the results.
Patient selection		Might not reflect UK population Selection limited to uncomplicated disease Presence and absence of complications not clearly documented. Risk of spectrum bias.
Randomisation	Randomisation performed with adequate concealment of allocation. Low risk of selection bias.	Randomisation lost due to drop-outs post randomisation.
Blinding	Independent and blinded audit controls. Blinded statistical assessment.	Not feasible to blind patients or treating/assessing clinicians. Subjective primary outcome. Moderate to high risk of performance bias.
Patient attrition	Reasons for patient withdrawal documented. Withdrawal low following surgery and evenly spread between arms. Modified ITT analysis appropriate (but weaker evidence).	High withdrawal from prior to surgery led to uneven groups. Low number of eligible patients reporting data at 24 months, so poor confidence in longer term results and risk of bias in results High risk of attrition bias.

Reporting of outcomes	Primary analysis pre-specified in protocol. Outcome X directly related to patient benefit. Extensive reporting of secondary outcomes with appropriate control for multiple comparisons.	Second “primary outcome” may not generalise to NHS care and was not pre-specified in research protocol. Outcomes limited to 24 months (in a small cohort of patients only). Outcome X is subjective primary outcome and could be influenced by participants’ perceptions.
Statistical analysis	Power calculation for sample size for primary outcome performed. Correction for multiple comparisons performed. Low potential for reporting bias.	Sample size requirement for follow-up procedure not clear.
Study company	Three lead investigators declared no conflict of interest.	Study was funded by company. Two lead investigators paid consultants of company.

Include or attach any competed validated checklists in this section.

Appendix C

Ongoing studies

ACTRN12619001539123. Online Insomnia Treatment in Australian General Practice. https://anzctrorgau/ACTRN12619001539123aspx 2019.

ACTRN12620001075976. A pragmatic trial seeking to implement an improved model of care for people with insomnia and obstructive sleep apnoea (OSA) within an Australian primary care setting, in order to increase access to evidence-based therapies. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ACTRN12620001075976 2020.

Edinger JD, Simmons B, Goelz K, Bostock S, Espie CA. A pilot test of an online cognitive-behavioral insomnia therapy for patients with comorbid insomnia and sleep apnea. Sleep. 2015;38(SUPPL. 1):A236.

ISRCTN70652461. Sleep and cognition following digital cognitive behavioral therapy for insomnia (CBTi) - the SCOTIA study. http://www.who.int/trialsearch/Trial2aspx?TrialID=ISRCTN70652461 2019.

Kyle SD, Madigan C, Begum N, Abel L, Armstrong S, Aveyard P, et al. Primary care treatment of insomnia: study protocol for a pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy to sleep hygiene (the HABIT trial). BMJ Open. 2020;10(3):e036248. [ISRCTN42499563]

NCT03322774. Sleep To Reduce Incident Depression Effectively. https://ClinicalTrialsgov/show/NCT03322774 2018.

NCT03688763. A Pilot Study of Digital Cognitive Behavioral Therapy for Veterans. https://ClinicalTrialsgov/show/NCT03688763 2018.

NCT03724305. Reduce Emotional Symptoms of Insomnia With Smart Treatment. https://ClinicalTrialsgov/show/NCT03724305 2020.

NCT04180709. CBT to Reduce Insomnia and Improve Social Recovery in Early Psychosis. https://ClinicalTrialsgov/show/NCT04180709 2020.

NCT04272892. Improving Sleep in Rehabilitation After Stroke. https://ClinicalTrialsgov/show/NCT04272892 2020.

Terminated study

NCT02571595. A Sleep Program to Improve Sleep Quality in People With HIV. https://ClinicalTrialsgov/show/NCT02571595 2015.

Completed but not reported or unknown status

ISRCTN13837516. The Effects of Sleep Improvement on Emotion Regulation (SLEEPER). http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ISRCTN13837516 2018.

ISRCTN58986139. Sleep Matters Trial. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ISRCTN58986139 2015.

Conference Abstracts with no full text

Espie CA, Gollancz R, Hames P, Espie A, Creanor V, Kyle SD. Integrating social networking into online CBT for insomnia: A descriptive analysis of user behavior and user benefits. Sleep. 2013;36(SUPPL. 1):A209.

Espie CA, Kyle SD, Gollancz R, Hames P. What components of online CBT do people with insomnia use in practice? Sleep. 2013;36(SUPPL. 1):A231.

Sampson C, Cole A, Hampson G, Rose J, Stott R. PMH47 THE IMPACT OF A DIGITAL SLEEP-IMPROVEMENT PROGRAM ON HEALTH CARE COSTS. Value in Health. 2019;22(Supplement 3):S689.

Appendix D

Outcome Measures

- BAI: Beck Anxiety Inventory

- 0 - 21 = Low Anxiety
- 22 - 35 = moderate anxiety
- 36 or more = potentially concerning levels of anxiety

- CIS: Coronavirus Impact Scale (CIS) - Measures degree of change across multiple domains of daily life on a four-point Likert scale
  - 0 = no change
  - 1 = mild
  - 2 = moderate
  - 3 = severe.
- GAD-7: Generalized Anxiety Disorder 7 (action is required for a score of 10 or greater.
  - 5 -9 = Mild
  - 10 - 14 = Moderate
  - 15 + = Severe
- ISI: Insomnia Severity Index
  - 0 – 7 = no clinically significant insomnia
  - 8 – 14 = subthreshold insomnia
  - 15 – 21 = moderate severity clinical insomnia
  - 22 - 28 = severe clinical insomnia
- PSQI: Pittsburgh Sleep Quality Index
  - Ranges from 0 - 21 indicating difficulty sleeping (21 is the most severe difficulty).
- PHQ-9: Patient Health Questionnaire-Depression scale
  - Ranges from 0 - 27 indicating severity of depression (27 is the most severe).
- SCI: Sleep Condition Indicator (correlates inversely with ISI and PSQI)
  - Ranges from 0 – 32 with higher values denoting better sleep.

- WSAS: Work and Social Adjustment Scale
    - Ranges from 0 to 40, higher scores indicate more difficulty in completing day-to-day tasks.
    - A score of 20 or above suggests moderate to severe psychopathology.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

MT443 Sleepio for adults with poor sleep

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) 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 EAC 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 highlighted in [redacted] This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations

1 The technology

Sleepio (Big Health) is a self-help sleep improvement programme based on cognitive behavioural therapy for insomnia (CBT-I). It is accessed through a website or an app for iOS mobile devices, and can link to a compatible wearable fitness tracker to monitor sleep (currently Fitbit and any other device that uses Apple's Healthkit). It is available in the NHS apps library.

The programme is structured around a sleep test, weekly interactive CBT-I sessions, and regular sleep diary entries. The sessions are focussed on identifying thoughts, feelings and behaviours that are contributing to the symptoms of insomnia. Cognitive interventions aim to improve the way a person thinks about sleep and behavioural interventions aim to promote a healthy sleep routine. Although the programme can be completed in 6 weeks users can access the programme for 12 months from registration. They can also access electronic library articles, online tools and the online Sleepio user community. A daily sleep diary helps users track their progress and the programme tailors advice to individuals. Users can fill in the diary manually or the data may be automatically uploaded from a compatible wearable tracking device. The programme does not share the users' data.

Sleepio is accessed via self-referral on the product website or through referral by a health care professional in regions of the NHS where it is commissioned. For patients with mental health conditions managed in routine care, use of Sleepio may benefit from the involvement of a healthcare professional.

2 Proposed use of the technology

2.1 Disease or condition

Around one third of adults in Western countries experience sleep problems at least once a week with 6-10% fulfilling the criteria for insomnia disorder (NICE Insomnia clinical knowledge summary, last updated 2020). Insomnia is diagnosed when symptoms have a negative impact on a person's ability to carry out daily tasks. The International classification of diseases -10 (ICD-10)

defines the criteria for insomnia as being difficulty sleeping three times a week or more for at least 1 month. The Diagnostic and Statistical Manual of mental health disorders-5 (DSM-5) defines insomnia disorder as an unhappiness with the quality and quantity of sleep for 3 times a week or more for at least 3 months. Both diagnoses require that the symptoms of insomnia have an impact on a person's ability to carry out daily tasks.

2.2 Patient group

Sleepio is intended for use by people with symptoms of insomnia or that have been diagnosed with insomnia. Insomnia is characterised by symptoms of difficulty initiating or maintaining sleep, with subsequent daytime functional impairment (e.g. mood, fatigue, cognitive impairment).

The prevalence of people that have symptoms of insomnia in the population varies widely from 5 to 50% depending on the definition used. Short term insomnia typically lasts less than 3 months; long-term insomnia lasts 3 months or longer. Prevalence of insomnia is higher in people with comorbid conditions and around half of all people with diagnosed insomnia have a comorbid psychiatric disorder such as depression or anxiety (Wilson, 2019).

2.3 Current management

Current management of insomnia is described in guidelines published by the British Association of Psychopharmacology published in 2010 and updated in 2019. Current treatment options for adults with poor sleep is dependent on the duration of the symptoms. People that present with symptoms of insomnia are offered advice about sleep hygiene. If sleep hygiene fails and daytime impairment is severe and causing significant distress, a short course (3-7 days) of a non-benzodiazepine hypnotic medication may be prescribed. Hypnotic medication should only be considered if symptoms are likely to resolve soon (for example being because of a short-term stressor). If symptoms are unlikely to resolve soon, face-to-face or digital cognitive behavioural therapy for insomnia (CBT-I) should be offered. A short-term course of hypnotic medication can be offered in addition to CBT-I but should not be offered routinely and only for a short period of time. People should be

offered regular follow up consultations to review the symptoms. Follow up visits should be between every 2 and 4 weeks.

NICE's Insomnia clinical knowledge summary presents a summary of the latest, evidence-based information on the management of insomnia in primary care. Management is summarised according to short term insomnia (< 3 months) and long term insomnia (> 3 months). For both short term and long term insomnia the advice is to consider the need for referral to a sleep clinic or neurology if symptoms of another sleep disorder are present, and to address any triggers or causal factors for insomnia. In addition, advice is to ensure comorbidities (such as anxiety and depression) are optimally managed. The advice regarding sleep hygiene, use of hypnotic medication and use of CBT-I is in line with the recommendations described above by the British Association of Psychopharmacology guideline.

People with insomnia often present with a comorbid psychiatric condition. NICE's clinical guideline for common mental health problems (CG123) recommends that people are assessed using the improving access to psychological therapies (IAPT) screening tools and validated scales. Treatment for common mental health problems is dependent on the severity of their symptoms. This approach is referred to as a stepped-care model. Education and monitoring are recommended for people with mild symptoms, computerised and group CBT are offered to people with moderate symptoms and CBT and medication are offered to people with severe symptoms.

2.4 Proposed management with new technology

Sleepio is primarily intended for use as a first line treatment, in place of sleep hygiene education and may be used in place of face-to-face CBT for insomnia if the latter is difficult to access. People can access Sleepio via self-referral or referral through primary care or through IAPT services.

Where Sleepio is launched in a healthcare setting, the company offer training to clinicians on:

- Management of poor sleep and insomnia

- How Sleepio works and how it should be described to patients
- How to prescribe Sleepio through electronic health records

Clinical experts highlighted the importance of patient selection and patient choice in increasing the adherence to and benefits of Sleepio. Additionally, experts suggested that providing feedback to referrers, such as GPs, about the number of people that registered to use Sleepio and those in remission would be helpful for understanding outcomes and inform further referral and training.

3 Company claimed benefits and the decision problem

These are described in the scope here (link to Appendix E). Table 1 described the company's proposed changes to the decision problem.

Table 1Proposed changes to the decision problem

Decision problem	Variation proposed by company	EAC view of the variation
Population - Adults with difficulty sleeping	Adults with insomnia symptoms (18 yr plus; no upper age limit)	Experts described insomnia as difficulty falling asleep and staying asleep that affects health the following day. They also noted that numerous other conditions can mimic insomnia.
Comparator	Omitted digitally facilitated CBT for insomnia	The EAC would still include this comparator in the scope if it is a relevant comparator (e.g. to include as part of the search strategy that may need to be repeated later)
Outcomes	Wishes to add insomnia related outcomes including sleep condition indicator (SCI) and insomnia severity index (ISI)	The EAC did not comment on this variation
Subgroups – • Pregnant women	The list has been reordered to reflect the likely prevalence of the	The EAC did not comment on this variation

• People who have not had an insomnia diagnosis • People with short term insomnia (symptoms present for less than 3 months) • People with long term insomnia (symptoms present for 3 months or longer) • People with insomnia and a comorbid condition	subgroups and clarification. • People with long term insomnia (symptoms present for 3 months or longer) • People with insomnia and a comorbid mental health condition • People with insomnia and a comorbid physical health condition • People who have not had a formal insomnia diagnosis • People with short term insomnia (symptoms present for less than 3 months) • Pregnant women with problems sleeping	

4 The evidence

4.1 Summary of evidence of clinical benefit

The company identified 26 full text publications from its literature search. The company also included 1 abstract and 2 unpublished reports.

The EAC undertook its own literature search (see section 4.1 of the EAC's assessment report). The EAC agreed with the company's inclusion criteria and excluded only 1 of the studies from the assessment report (Cliffe 2020). The rationale for selection of these studies is in section 4.1 and 4.2 of the EAC assessment report. Of the included studies, 22 studies were comparative (12 RCTs, 7 secondary analyses of RCT data [including 1 abstract], 2 before and after studies and 1 retrospective case controlled study) and 6 were non-comparative (1 retrospective cohort study, 1 before and after study [no comparator arm], 2 real-world evidence studies, 1 prospective observational study and 1 qualitative survey).

Table 2 Studies included and excluded from the assessment

Studies included in the assessment	
Publication and study design	28 studies included by both: • 12 RCTs (Espie et al., 2012; Pillai et al. (2015); Bostock et al. (2016); Barnes et al. (2017); McGrath et al. (2017); Freeman et al. (2017); Cheng et al. (2019a); Espie et al. (2019); Denis et al. (2020); Felder et al. (2020); Kyle et al. (2020); Kalmbach et al. (2020) • 6 secondary analyses - Espie et al. (2014); Cheng et al. (2019b); Luik et al. (2020); Cheng et al. (2020a); Henry et al. (2020); Cheng et al. (2020b); • 3 before and after studies - Elison et al. (2017); Luik et al. 2017; Espie et al. (2018) • 1 prospective observational study - Crawford et al. (2020) • 1 retrospective cohort study - Miller et al. (2018) • 1 prospective real-world audit - Luik et al. 2017; • 1 qualitative survey - Coulson (2016) • 1 abstract - Drake et al. 2019 • 2 unpublished studies (AiC) – Stott (unpublished); Studd (unpublished)
Studies excluded from the assessment	
Publication and study design	• 1 prospective observational – Cliffe (2020) The study was deemed out of scope as it included people aged between 14 and 17 years

The evidence base for Sleepio is extensive and includes a wide range of studies that range in design from RCTs to unpublished real-world evidence. Overall, there is good quality evidence that Sleepio improves sleep in people with self-reported insomnia symptoms (according to DSM-5, SCI and ISI measures). The most robust evidence for Sleepio comprises 12 RCTs, 10 of which used intention to treat analyses to control for high drop rates. The studies are small relative to the potential reach of Sleepio but are adequately powered and well reported.

The UK population is well represented in the evidence base for Sleepio which includes 7 studies that were done in the UK and an additional 4 multinational studies that included UK populations. Four of the studies done in the UK were RCTs (Espie 2012, Freeman 2017, Denis 2020 [pilot study], Kyle 2020); all concluded that Sleepio was more effective in reducing insomnia symptoms

than standard care or waiting list (Espie et. al 2012, Freeman 2017, Kyle 2020), placebo (Espie et al., 2012) or attention control (Denis, 2020). These findings are consistent with RCTs done outside of the UK and indicate that, in general, the evidence base is generalizable to the UK NHS population.

The key limitation of the evidence is that there are no studies directly comparing Sleepio with face-to-face CBT-I. The company acknowledge this limitation and state this is because face-to-face CBT-I for insomnia is not routinely available on the NHS and is not scalable to the UK population. A meta-analysis by Soh et al. (2020) indicated, in an indirect comparison, that face-to-face CBT-I produced greater improvement in ISI compared with digital CBT-I (3.07 (95% CI 1.18 to 4.95, $p < 0.001$)) but that this was within the non-inferiority interval of 4 points. Experts had mixed responses to the relevance of the indirect comparison; one expert felt it was plausible to assume Sleepio results would be similar, whereas another expert felt more head to head comparison data was necessary.

In general, there is notable heterogeneity in design, population, outcome measures and comparators used across the Sleepio evidence base. Study participants included people with sleeping difficulty with or without medical and mental health comorbidities, and those with differing durations of insomnia. Some studies included pregnant women and other studies included adults under the age of 25; experts advised that Sleepio might be less appropriate in these populations as symptoms of insomnia might be due to other causes (restless leg syndrome and normative delayed sleep phase patterns, respectively), however, the evidence shows Sleepio is more effective than control in these populations. The comparator differed between studies and often the description of standard care lacked clarity. It was unclear whether standard care included aspects of CBT-I and/or the prescription of hypnotics and there was little information about what was offered as sleep hygiene education. There is also a high drop-out rate in the studies. Experts noted that this high drop-out is typical for online CBT tools. The EAC also noted most studies were analysed as intention to treat.

The results of an ongoing pre-registered individual participant data (IPD) meta-analysis including 12 RCTs was described by the company. The protocol is available at PROSPERO 2019 CRD42019105424.

[redacted]

Table 3Pivotal studies done in the UK

Study a	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
Pivotal studies done in the UK							
Espie et al. (2012) (Follow up analysis Espie et al. (2014)	164 adults (120 women, mean age 49) who completed the online Great British Sleep Survey and met the proposed DSM-5 criteria for chronic insomnia.	Intervention Sleepio Comparators Imagery relief therapy (IRT [placebo]) Treatment as usual (TAU)	Primary outcome - sleep efficiency (SE) (total time asleep expressed as a percentage of the total time spent in bed) Follow up analysis to evaluate the impact of Sleepio on attributions for sleep disturbance (measured with the Sleep Disturbance Questionnaire	SE post treatment: Sleepio - 19.5% (95%CI, 15.3 to 23.7). IRT - 5.7% (95%CI, 2.79 to 8.52) TAU - 6.4% (95%CI, 2.88 to 9.86)., SE at 8 week post treatment: Sleepio - 20% (95%CI, 15.7 to 23.6) IRT - 7% (95%CI, 4.53 to 10.1)	Lost to follow-up: Sleepio – 15 IRT – 17 TAU – 4	The software and web development for the study was supported by the company	This is a well designed blinded RCT that was done in the UK so may be generalisable to an NHS population. The study was adequately powered to detect a medium effect size. The population is relevant, all patients were randomised and included in the analysis (intention to treat). People were recruited via online surveys which might represent a population of people more interested in addressing sleep problems. The inclusion of healthcare providers in the study may

			(SDQ)), night-time thought content (measured with the Glasgow Content of Thoughts Inventory (GCTI)), and stress, depression and anxiety.	TAU - 9% (95%CI, 4.89 to 13.7) People in the Sleepio group experienced a >2 fold improvement in insomnia symptoms (SCI-8) with a large between-group effect of d=1.20 and 0.95 compared to TAU and placebo, respectively, at post intervention and d=1.11 and d=0.77 at 8 week follow up. 2014 follow up analysis results - Sleepio had a greater effect on attribution and cognition than IRT (average			limit generisability to self-referral cohorts. The use of SE as a primary outcome may unduly favor CBT because the sleep restriction component of CBT can lea d to improved SE. Similarly, an expert noted that SE may be a measure of adherence to CBT rather than improvement.

				d = −0.32). Sleepio had a greater effect on attribution and cognition than TAU (*d* = −0.65., moderate to large effect).			
Espie et al. (2019) Follow up analysis Luik et al., 2020	1,711 adults (77.7% were female, mean age 48 years) with self-reported symptoms of insomnia, s per DSM-5	Intervention: Sleepio Comparator: Sleep hygiene education (website and downloadable booklet plus TAU)	Functional health (Patient-Reported Outcomes Measurement Information System: Global Health Scale), psychological well-being (Warwick-Edinburgh Mental Well-being Scale) and sleep related quality of life (Glasgow Sleep Impact Index) at baseline and weeks 4, 8 and 24.	Sleepio was associated with improved: - functional health (Cohen d for week 4, 0.16; week 8, 0.31; and week 24, 0.31) - psychological wellbeing (Cohen d for week 4, 0.13; week 8, 0.35; and week 24, 0.38) - Sleep-related quality of life Cohen d for week 4, –0.69; week 8, –1.38;	Lost to follow-up. Sleepio - 413 participants (48.4%) completed all 6 sessions. Sleep hygiene education was accessed at least once by 759 of 858 participants (88.5%)		This is a multi-national RCT that includes Sleepio users in the UK, USA and Australia. Analyses were intention to treat. Participants were self-referred and outcome measures were self-reported. The EAC confirmed the study is adequately powered to detect a standardized effect size of 0.25 with 90% power. The authors recognized that there were more adverse events in the Sleepio group and believed this may be related to the sleep restriction component of CBTi.

			Compared Sleepio to sleep hygiene education (website and a downloadable booklet plus treatment as usual).	and week 24, –1.46) Linear mixed-effects models found that results at 8 and 24 weeks were mediated by improvements in insomnia at week 4 and 8, respectively (range mediated, 45.5%-84.0%) Follow up analysis results: At week 24, ITT analysis showed Sleepio reduced use of prescription (adjusted RR: 0.64, 95% CI: 0.42; 0.97, p = 0.037) and non-prescription sleep medication (adjusted RR:			A number of authors expressed conflicts of interest including being co-founders of the company or receiving payment from the company.

				0.52, 95% CI: 0.37; 0.74, p < 0.0001). At week 48, mean SCI score had increased by 9.80 (95% CI: 9.29, 10.31; Cohen d: 1.54).			
Kyle et al. (2020)	410 adults over 25 (87% female, 52.4 years) from Sleepio online community with insomnia disorder (met DSM-5 criteria or insomnia disorder) and self-reported difficulties with concentration or memory	Intervention: Sleepio Comparator: Waiting list control	Self-reported cognitive impairment (British Columbia Cognitive Complaints; BC-CCI) at baseline and 10- and 24-weeks post randomisation	At 10 weeks post-randomization the estimated adjusted mean difference for the BC-CCI was -3.03 (95% CI: -3.60, -2.47; p < 0.0001, d = -0.86), indicating that participants in the Sleepio group reported less cognitive impairment than the control group. These effects were maintained at	Lost to follow up. At 10 weeks: Sleepio retained 76% of participants compared to 88% for control. At 24 weeks Sleepio retained: 66% of participants compared to. 81% in control.		This is a single blind RCT down in the UK. The EAC confirm the study is adequately powered to detect a minimum standardized effect size of 0.42 at post treatment (10 weeks) at a 5% level of significance. The waiting list control arm may slightly inflate effect size compared to a minimally active arm (e.g., sleep hygiene education). The study recruited people online which may not be reflective of people seeking treatment in a clinical setting. The self-reported outcomes patients to report

				24 weeks (d = -0.96) and were mediated, in part, via reductions in insomnia severity and increased sleep efficiency			cognitive complains for inclusion which may have resulted in an over representation of participants concerned about sleep. One author is co-founder of the company
Luik et al. 2017 Prospective audit (real-world data)	98 participants (mean age 44.9 years, SD 15.2, 66% female) who experienced poor sleep in addition to comorbid symptoms of depression or anxiety	Intervention: Sleepio No comparator	Effects on depression and anxiety IAPT recovery rate	Depression (mean difference-5.7, $t(70) = 12.5$, $p < 0.001$) and anxiety [Generalized Anxiety Disorder-7 (GAD-7), Mean difference-4.1, $t(70) = 8.0$, $p < 0.001$] were reduced following supported Sleepio for insomnia. This translated into an IAPT recovery rate of 68% for	Of the 98 clients included in this evaluation, 72 finished the treatment (73%). Another 15 clients completed between 4 and 6 sessions and 11 dropped out before session 4		Prospective UK audit. All clients received six calls from an eTherapy coordinator to support the self-help component. This is not typical of the Sleepio service. One author is co-founder of the company

				depression and anxiety. Effects on anxiety and depressive symptoms remained significant when accounting for missing data (p<0.001). Significant reductions were also observed in insomnia symptoms (p<0.001).			
Studd (unpublished) [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

	[redacted]			[redacted]			

4.2 Summary of economic evidence

The company included 12 studies in their economic submission. The EAC conducted its own search (see section 4.1 of the EAC's assessment report) and found no additional economic evidence. Three studies provided economic evidence related to Sleepio technology and were included by the EAC (Darden et al., 2020; Sampson et al. 2021; Luki et al., 2020). The remaining 9 studies were excluded.

The 3 included studies included 2 full text publications (Darden 2020; Luik, 2020), an unpublished study (Sampson et al., 2021).

Darden 2020 simulated a decision Markov model of 100,000 individuals with a 6-month time horizon. Five arms were compared in the model, dCBT-I (Sleepio), pharmacotherapy, individual CBT-I, group CBT-I and no treatment. cohort were partitioned based on remission or insomnia at 6 months and a health utility weighting was assigned (one QALY was valued at $50,000). Indirect and direct cost parameters were based on the literature. The results of the model reported that Sleepio was the most cost-effective insomnia treatment followed by group CBT-I, pharmacotherapy and individual CBT-I. The study was done in the US.

The unpublished study (Sampson et al., 2021) reports a quasi-experimental design, using an uninterrupted time series to compare the trend in primary care costs before and after the rollout of Sleepio in the UK. Primary care costs include general practitioner contacts and prescription. From 9 practices in the Thames Valley region of England, 10,704 people met the inclusion criteria (diagnosis of anxiety, depression, or insomnia, prescription of hypnotic drugs [or anxiolytic drugs] or referral to Sleepio). The total saving over a 65-week follow up period was £6.64 per person in the sample or £70.44 per Sleepio user.

Luik et al. (2020) reported the impact of using Sleepio on sleep medication and healthcare resource use compared with sleep hygiene. The results

support the conclusions of the unpublished study by Sampson et al. (2021) that savings come from reduced prescription cost, which is around 60% less for Sleepio compared to sleep hygiene education.

De novo analysis

The company's economic analysis models a population of adults with insomnia symptoms. It is a simple one-stage decision tree model using remission status after treatment initiation; however, cost savings are not estimated as a function of remission status and thus remission status has no impact on the model results. The model compares Sleepio to 2 comparators. The first comparator (described by the company as the 'primary' comparator) is treatment as usual (TAU). The second comparator is face to face CBT-I. TAU is poorly defined but includes sleep hygiene and sleep medication and is commonly managed by the GP. The second comparator of face to face CBT-I is recommended for treatment of insomnia in NICE's Insomnia clinical knowledge summary, but availability is limited in the UK.

The company's analysis estimates the overall cost of providing access to Sleepio to a large population. The cost impact and proportion of patients accessing Sleepio are based on data from the unpublished study by Sampson et al., 2021. The EAC accepts the structure of the economic model and thinks the comparators, outcomes and time-horizon are reasonable.

The base case analysis assumes:

- The cost savings reported in Sampson et al (2021) resulted from patient access to Sleepio. The EAC accepted this assumption.
- The data on resource use observed at 65 weeks following the introduction of Sleepio can be extrapolated over a 3-year period. The EAC do not think that 65 weeks is sufficiently long enough to support this assumption.

- The cohort accessing Sleepio in Sampson et al. (2021) is reflective of an annual incidence of patients with insomnia. The EAC felt this was optimistic.

- Sleepio is equivalent to face to face CBT-I in terms of remission and impact on resource use.

- Based on clinical non-inferiority of Sleepio, there is no difference in primary care resource use for patients treated with Sleepio compared to patients treated with face-to-face CBT-I. The EAC thinks this is an acceptable assumption, due to the lack of data.

Model parameters

Clinical parameters

The clinical parameters included in the economic modelling were:

- The estimated uptake of Sleepio as a percentage of the population (the number of people that started session 1 of Sleepio). The company estimates Sleepio is used by 24,000 people from a population of 2.4 million. This assumes an uptake of 1% and is calculated based on the GP referrals across 9 GP practices included in the Thames Valley roll out reported in Sampson et al (2021), in combination with self-referrals and people that were referred through an IAPT service. The EAC noted that Sampson et al. (2021) also reports an uptake of 0.58% and 0.54% in Buckinghamshire and Thames Valley, respectively. The EAC changed the estimated uptake of Sleepio to 13,920 in a population of 2.4 million based on an uptake of 0.58% (Sampson et al., 2021).

- The company's submission assumes that the uptake for subsequent years will remain at the same level as the uptake observed in year 1. The EAC considers this to be unrealistic and used sensitivity analyses to explore the impact of a reduction in uptake in subsequent years.

Costs and resource use

The main costs used in the modelling were the cost of the technology (per adult in the NHS population and per user in year 1, 2 and 3) and the cost of face-to-face CBT-I. The cost of Sleepio per adult varies with the NHS population size as described in table 4. The cost parameters used in the company's model and changes made by the EAC are described in table 5.

Table 4 Company pricing model

Number of adults in the NHS system population	Price per adult p.a.
0 - 250,000	£1.00
250,001 - 500,000	£0.98
500,001 - 750,000	£0.96
750,001 - 1,000,000	£0.93
1,000,001 +	£0.90

Table 5 Cost parameters used in the economic model and EAC changes.

Parameter	Company value	EAC value	Source
Technology price	£ 0.90 per adult in the population The company assumed a population size of 2.4 million, based on company pricing model Sleepio costs £0.90 per adult	Same	Company submission
Comparator (Sleep hygiene)	£0	Same	
Comparator (face to face CBT)	£492 Based on the midpoint of PSSRU costs for individual CBT (£82) multiped by 6 to account for 6 sessions.	£542	Company estimates inflated to current prices

Primary care resource use per user (year 1)	£49.52	Same	Sampson et al. 2021
Primary care resource use per user (year 2)	£43.52	Same	Sampson et al. 2021, discounted at 3.5%
Primary care resource use per user (year 3)	£42.05	Same	Sampson et al. 2021, discounted at 3.5%

Results

The EAC's revised base case shows compared with face-to-face CBT-I using Sleepio results in a cost saving of £386.83 per patient after 3 years. Compared with TAU using Sleepio costs an additional £20.09 per patient after 3 years. These results differ to the company's submission which reported Sleepio to cost saving after 3 years compared with both face-to-face CBT and TAU by £402 and £45.08, respectively.

Table 6 Sleepio compared to face to face CBT-I

Cost category	Company's base-case (per patient)				EAC's base-case (per patient)		
	Device	Comparator (face to face CBT-I)	Cost saving per patient*		Device	Comparator (face to face CBT)	Cost saving per patient*
Consumables	£90	£492	£402		£155.17	£542	£386.83
Primary care cost savings (year 1)	£-49.52	£49.52	£0		-£49.52	-£49.52	£0
Primary care cost savings (year 2 and 3)	£-85.56	£-85.56	£0		-£85.56	-£85.56	£0
Total (year 1)	£40.48	£442.48	£402		£105.65	£492.48	£389.83
Total (3 years)	£-45.08	£356.92	£402		£20.09	£406.92	£386.83
** A minus sign indicates device is more expensive than the comparator in this cost category.*							

Table 7 Sleepio compared to usual care

Cost category	Company's base-case (per patient)				EAC's base-case (per patient)		
	Device	Comparator (treatment as usual)	Cost saving per patient*		Device	Comparator (treatment as usual)	Cost saving per patient*
Consumables	£90	£0	£-90		£155.17	£0	-£155.17
Primary care cost savings (year 1)	-£49.52	£0	£49.52		-£49.52	£0	£49.52
Primary care cost savings (year 2 and 3)	-£85.56	£0	£85.56		-£85.56	£0	£85.56

Total (year 1)	£40.48	£0	-£40.48		£105.65	£0	-£105.65
Total (3 years)	**-£45.08**	**£0**	**£45.08**		**£20.09**	**£0**	**-£20.09**
** A minus sign indicates device is more expensive than the comparator in this cost category.*							

Sensitivity analyses

The company presented best- and worst-case scenario analysis on remission rates, however, these results had no impact on the cost saving results because changing the remission rates in the model does not impact on any of the costs. The company also explored the impact of changing the proportion of the population that start session 1 of Sleepio (percentage uptake) on the results and reported that reducing the uptake percentage to 0.7%, reduced the patient cohort to 16,800 and did not change the direction of the result but reduced the magnitude of the cost-savings.

The EAC undertook additional sensitivity analysis comparing the cost of Sleepio with usual care. The analysis examined uptake rate, the cost of Sleepio and the duration of reductions in resource use. Table 8 shows the impact of percentage uptake on the cost of Sleepio. Cost savings fall as the proportion of users reduces, the breakeven rate for the first year's cohort is 0.666%.

Table 8 Impact percentage uptake on the cost of Sleepio per user, per patient and net cost after 3 years

Sleepio uptake	Sleepio cost per head	Equivalent Sleepio cost per user	Primary care cost savings (three years)	Cost saving per patient
0.5%	£0.90	£180	£135.08	-£44.92
0.6%	£0.90	£150	£135.08	-£14.92
0.7%	£0.90	£128.57	£135.08	£6.51
0.8%	£0.90	£112.50	£135.08	£22.58
0.9%	£0.90	£100	£135.08	£35.08
1.0%	£0.90	£90	£135.08	£45.08

Further analysis reported the impact of varying the initial cost of the technology. The results, reported in full in section 9.3 of the EAC's assessment report, showed that with an uptake of 0.58% Sleepio, compared to TAU, becomes cost saving at a cost of £0.78 per adult per population. At a cost of 0.90 per adult per population, with a percentage uptake of 0.58%, Sleepio becomes cost saving after 4 years, compared to TAU.

The company's analysis modelled a single cohort over 3 years based on extrapolation of costs observed over 65 weeks in Sampson et al. (2021). The EAC undertook additional analyses to quantify the rolling cost of Sleepio considering subsequent cohorts of patients accessing Sleepio. The EAC modelled 2 scenarios. In both scenarios, the overall cost rises over time:

- The uptake of Sleepio was maintained at 0.58% of the population (per year). At year 5, the rolling cost of providing Sleepio is £2,775,500.
- The uptake of Sleepio fell to 0.2% of the population for year beyond the first year of rollout. At year 5, the rolling cost of providing Sleepio is £6,156,357.

The EAC highlighted that the company's model does not offer any further insight into the cost impact of Sleepio over and above that provided by the Sampson et al. (2021) study. It accepts that this study is based on a large sample, representative of the patient population and reflects resource use in routine primary care. The EAC considered that the analysis appears robust, the model specification is transparent and the use of linear trends gives confidence that the results are not an artefact of model specification. However, the EAC does not agree that the 65 weeks follow up data can be extrapolated to 3 years with confidence and there may be other factors affecting the trend of primary care costs after the introduction of Sleepio.

The company considers TAU to be the primary comparator. The EAC concluded that Sleepio may be clinically beneficial to adults over 25 years old with chronic (>3 months), mild to moderate insomnia compared with treatment as usual (including sleep hygiene and medication). The benefits to the health

system are dependent on patient engagement. Compared to TAU, Sleepio becomes cost neutral when the level of uptake is between 0.6% and 0.7%. Compared to face-to-face CBT-I, Sleepio was cost saving by £386.83, however, this assumes that Sleepio is non-inferior to face to face CBT. Currently, there are no direct comparative studies including face to face CBT and Sleepio.

5 Ongoing research

There are 10 ongoing studies, 8 of which are RCTs, 1 is a non-randomised control trial and 1 is a single arm observational study. See section 8.2 of the EAC's assessment report.

6 Issues for consideration by the Committee

Clinical evidence

- Given the heterogeneity within the clinical evidence, are the clinical benefits of Sleepio generalisable?
- Various sleep scales were used to report clinical outcomes. What reflects a clinically meaningful difference in the sleep scale scores?
- In the cost modelling comparison Sleepio is assumed to be equivalent to other forms of face-to-face CBT-I in terms of both remission and its impact on resource use. This assumption is supported by a meta-analysis of clinical outcomes by Soh et al. (2020). Is this assumption reasonable? Are the results of the indirect comparison of digital CBT and face to face CBT (Soh et al., 2020) generalisable to Sleepio?
- Are there any groups of people that shouldn't be offered Sleepio?

Cost evidence

- The company state that treatment as usual (including sleep hygiene education and short course sleep medication) is the primary comparator for this evaluation. NICE's clinical knowledge summary

recommends that people with chronic insomnia should be offered CBT-I. Which comparator is more appropriate?

- The unpublished Sampson et al (2021) reports lower primary care costs across 9 UK GP practices after introducing Sleepio, secondary analysis suggests that savings were related to a reduction in prescriptions. The data does not distinguish between costs for patients that accessed Sleepio and those that did not. Is it a reasonable assumption that the cost-savings were due to the introduction of Sleepio?

- How generalisable are the findings of the unpublished Sampson et al. (2021) study?

- Sleepio requires access to a computer and the internet. What impact will a region's socioeconomic impact have on percentage of the population that are able to access Sleepio? Will the uptake percentage be consistent across all regions of the UK?

- The key cost driver for the cost analysis is the percentage of the population that start using Sleepio (uptake). Sleepio becomes cost-neutral at an uptake of 0.666%, is this an achievable figure?

- The company estimated the cost impact of Sleepio in year 2 and 3 by extrapolating 65 weeks follow up data. Is 65 weeks an adequate follow up period for estimating the cost impact of Sleepio for up to 3 years?

- The company assume that the uptake of Sleepio will be consistent for subsequent cohorts, is this a reasonable assumption?

7 Authors

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Bernice Dillon, HTA adviser NICE Medical Technologies Evaluation Programme

March 2021

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

A Details of assessment report:

- ; Erskine J, Goddard K, et al. Sleepio for adults with poor sleep

B Submissions from the following sponsors:

- Big Health Ltd.

C Related NICE guidance

- Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. NICE technology appraisal guidance 77 (2004). Available from http://www.nice.org.uk/guidance/TA77

D References

Please see EAC assessment report for full list of references.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Kirsty Anderson

Consultant Neurologist and Sleep Specialist,

Newcastle upon Tyne NHS Hospitals Foundation Trust

Dr Tim Cooper

GP Partner, Chineham Medical Practice, Clinical Lead for Mental Health, North Hampshire CCG, Clinical Director, Whitewater Loddon PCN

Professor Jason Ellis

Professor in Psychology at Northumbria University and Director of the Northumbria Centre for Sleep Research

Dr Ari Manuel

Consultant in Sleep and Ventilation, Aintree University Hospital NHS Trust, Oxford

Dr Georgina Ruddle

Acting associate director mental health, maternity and children, and interim transforming care partnerships lead, NHS Wiltshire Clinical

Professor Mike Wang

Emeritus Professor of Clinical Psychology, University of Leicester

Please see the clinical expert statements included in the pack for full details.

Appendix C: Comments from patient organisations

NICE's public involvement programme posted an online survey between December 2020 and February 2021 and received 71 responses. The results of the survey are reported in the Sleepio patient survey report.

The following patient organisations were contacted, and no response was received.

- Anxiety UK
- British Sleep Society
- Mind

Appendix E: decision problem from scope

Population	Adults with difficulty sleeping
Intervention	Sleepio
Comparator(s)	• Sleep hygiene • Hypnotic drugs • Face-to-face CBT for insomnia • Digitally-facilitated CBT for insomnia
Outcomes	The outcome measures to consider include: Sleep related outcomes • Sleep quality • Sleep quantity • Sleep-related satisfaction and quality of life • Health related quality of life measures • Symptoms of comorbid health conditions (mental and physical) directly impacted by difficulty sleeping System related outcomes • Access to CBT for insomnia • Waiting time for CBT for insomnia • Number of primary care appointments • Hypnotic drug prescription • Incidence of comorbid health conditions Device related outcomes • Device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The cost modelling should reflect the business model the company is proposing to use in the NHS, for example if a regional approach is adopted the intervention cost should reflect that rather than the intervention cost when the technology is being purchased per patient. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	• Pregnant women • People who have not had an insomnia diagnosis

	• People with short term insomnia (symptoms present for less than 3 months) • People with long term insomnia (symptoms present for 3 months or longer) • People with insomnia and a comorbid condition	
Special considerations, including those related to equality	Patient-facing digital health technologies such as Sleepio may be unsuitable for people with visual or cognitive impairment, problems with manual dexterity or learning disabilities. Disability is a protected characteristic under the Equality Act. Sleepio is not suitable for those hard of hearing or where English is not well understood. Access to internet-enabled devices, access to the internet and user engagement with the technology may be more difficult for the people in deprived communities. Socio-economic status is not a protected characteristic and so is not protected under the Equality Act 2010 but factors affecting access to care delivered using digital devices should be considered. The technology can be used in pregnant women that are contraindicated for hypnotic medication. Pregnancy and maternity are protected characteristics of the equality Act 2010.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Sleepio for adults with difficulty sleeping.

1 Technology

1.1 Description of the technology

Sleepio (Big Health) is a self-help sleep improvement programme based on cognitive behavioural therapy for insomnia (CBT-I). It is accessed through a website or an app for iOS mobile devices, and can link to a compatible wearable fitness tracker to monitor sleep (currently Fitbit and any other device that uses Apple's Healthkit). It is available in the NHS apps library.

The programme is structured around a sleep test, weekly interactive CBT-I sessions, and regular sleep diary entries. The sessions are focussed on identifying thoughts, feelings and behaviours that are contributing to the symptoms of insomnia. Cognitive interventions aim to improve the way a person thinks about sleep and behavioural interventions aim to promote a healthy sleep routine. Although the programme can be completed in 6 weeks users can access the programme for 12 months from registration. They can also access electronic library articles, online tools and the online Sleepio user community. A daily sleep diary helps users track their progress and the programme tailors advice to individuals. Users can fill in the diary manually or the data may be automatically uploaded from a compatible wearable tracking device. The programme does not share the users' data.

Sleepio is accessed via self-referral on the product website or through referral by a health care professional in regions of the NHS where it is commissioned. For patients with mental health conditions managed in routine care, use of Sleepio may benefit from the involvement of a healthcare professional.

1.2 Relevant diseases and conditions

Sleepio is intended for use by people that have difficulty sleeping or have been diagnosed with insomnia. Insomnia is characterised by symptoms of difficulty initiating or maintaining sleep, with subsequent daytime functional impairment (e.g. mood, fatigue, cognitive impairment).

The prevalence of people that have symptoms of insomnia in the population varies widely from 5 to 50% depending on the definition used. Short term insomnia typically lasts less than 3 months; long-term insomnia lasts 3 months or longer.

Around one third of adults in Western countries experience sleep problems at least once a week with 6-10% fulfilling the criteria for insomnia disorder (NICE Insomnia clinical knowledge summary, last updated 2020). Insomnia is diagnosed when symptoms have a negative impact on a person's ability to carry out daily tasks. The International classification of diseases -10 (ICD-10) defines the criteria for insomnia as being difficulty sleeping three times a week or more for at least 1 month. The Diagnostic and Statistical Manual of mental health disorders-5 (DSM-5) defines insomnia disorder as an unhappiness with the quality and quantity of sleep for 3 times a week or more for at least 3 months. Both diagnoses require that the symptoms of insomnia have an impact on a person's ability to carry out daily tasks.

Prevalence of insomnia is higher in people with comorbid conditions and around half of all people with diagnosed insomnia have a comorbid psychiatric disorder such as depression or anxiety (Wilson, 2019)

1.3 Current management

Current management of insomnia is described in guidelines published by the British Association of Psychopharmacology published in 2010 and updated in 2019. Current treatment options for adults with difficulty sleeping is dependent on the duration of the symptoms. People that present with symptoms of insomnia are offered advice about sleep hygiene. If sleep hygiene fails and daytime impairment is severe and causing significant distress, a short course (3-7 days) of a non-benzodiazepine hypnotic medication may be prescribed.

Hypnotic medication should only be considered if symptoms are likely to resolve soon (for example being because of a short-term stressor). If symptoms are unlikely to resolve soon, face-to-face or digital cognitive behavioural therapy for insomnia (CBT-I) should be offered. A short-term course of hypnotic medication can be offered in addition to CBT-I but should not be offered routinely and only for a short period of time. People should be offered regular follow up consultations to review the symptoms. Follow up visits should be between every 2 and 4 weeks.

NICE's Insomnia clinical knowledge summary presents a summary of the latest, evidence-based information on the management of insomnia in primary care. Management is summarised according to short term insomnia (< 3 months) and long term insomnia (> 3 months). For both short term and long term insomnia the advice is to consider the need for referral to a sleep clinic or neurology if symptoms of another sleep disorder are present, and to address any triggers or causal factors for insomnia. In addition, advice is to ensure comorbidities (such as anxiety and depression) are optimally managed. The advice regarding sleep hygiene, use of hypnotic medication and use of CBT-I is in line with the recommendations described above by the British Association of Psychopharmacology guideline.

People with insomnia often present with a comorbid psychiatric condition. NICE's clinical guideline for common mental health problems (CG123) recommends that people are assessed using the improving access to psychological therapies (IAPT) screening tools and validated scales. A person's treatment is dependent on the severity of their symptoms. This approach is referred to as a stepped-care model. Education and monitoring are recommended for people with mild symptoms, computerised and group CBTi are offered to people with moderate symptoms and CBTi and medication are offered to people with severe symptoms.

1.4 Regulatory status

The Sleepio received a CE mark in October 2018 as a class 1 device for adults with difficulty sleeping or insomnia disorder.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia.
- Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
- Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all.
- Provides CBT for insomnia in a stigma free environment.
- Eliminates waiting time for CBT for insomnia.
- Reduces hypnotic usage and associated risks i.e. dependency, withdrawal, risk of falls and unresolved insomnia.

The benefits to the healthcare system claimed by the company are:

- Reduces primary care appointments.
- Improves quality of care by enabling primary care to meet clinical guidelines.
- Reduces hypnotic drug prescriptions and associated costs.
- Provision of CBT service where face to face CBT is not available or has long waiting times.
- Improves range of treatment options available to primary care prescribers.
- Reduced downstream costs of untreated insomnia.

2 Decision problem

Population	Adults with difficulty sleeping
Intervention	Sleepio
Comparator(s)	• Sleep hygiene • Hypnotic drugs • Face-to-face CBT for insomnia • Digitally-facilitated CBT for insomnia
Outcomes	The outcome measures to consider include:

	Sleep related outcomes • Sleep quality • Sleep quantity • Sleep-related satisfaction and quality of life • Health related quality of life measures • Symptoms of comorbid health conditions (mental and physical) directly impacted by difficulty sleeping System related outcomes • Access to CBT for insomnia • Waiting time for CBT for insomnia • Number of primary care appointments • Hypnotic drug prescription • Incidence of comorbid health conditions Device related outcomes • Device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The cost modelling should reflect the business model the company is proposing to use in the NHS, for example if a regional approach is adopted the intervention cost should reflect that rather than the intervention cost when the technology is being purchased per patient. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	• Pregnant women • People who have not had an insomnia diagnosis • People with short term insomnia (symptoms present for less than 3 months) • People with long term insomnia (symptoms present for 3 months or longer) • People with insomnia and a comorbid condition
Special considerations, including those related to equality	Patient-facing digital health technologies such as Sleepio may be unsuitable for people with visual or cognitive impairment, problems with manual dexterity or learning disabilities. Disability is a protected characteristic under the Equality Act. Sleepio is not suitable for those hard of hearing or where English is not well understood.

	Access to internet-enabled devices, access to the internet and user engagement with the technology may be more difficult for the people in deprived communities. Socio-economic status is not a protected characteristic and so is not protected under the Equality Act 2010 but factors affecting access to care delivered using digital devices should be considered. The technology can be used in pregnant women that are contraindicated for hypnotic medication. Pregnancy and maternity are protected characteristics of the equality Act 2010.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable	

3 Related NICE guidance

Published

- Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia (published 2004, last reviewed 2010) NICE technology appraisal guidance 77.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- British Association of Psychotherapists
- British Neuropsychiatry Association
- British Psychotherapy Foundation
- Faculty of Public Health Medicine
- Institute of Psychiatry

- Royal College of Psychiatrists

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- Anxiety UK
- British Sleep Society
- Mind

Adoption report: MTG Sleepio for adults with poor sleep

Summary

Adoption levers identified by contributors

- There are currently few interventions available to help with poor sleep, Sleepio provides an additional option.
- Potential to reduce NHS resource use (e.g. GP appointments and cost of hypnotics).
- People can be easily directed to Sleepio by a variety of health and care professionals.
- The technology is currently available free of charge for NHS and social care staff for personal use.

Adoption barriers identified by contributors

- Funding arrangements for use in the NHS.
- Uncertainty about NHS cost savings.
- Significant user commitment and motivation is required.
- No clinical awareness of an interface for monitoring.
- Digital self-help programmes may not be suitable for some people.

1 Introduction

The adoption team has collated information from healthcare professionals working within NHS organisations, 6 of whom have experience of recommending people to use Sleepio. This report has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption. It does not represent the opinion of NICE or MTAC.

This adoption report includes some of the considerations for routine NHS use of the technology.

2 Contributors

Details of contributing individuals are listed in Table 1.

Table 1: Contributors and Sleepio usage

Job title	Setting	Referring for Sleepio?	Commissioning model
GP, head of research activities for the GP federation	General Practice Federation (6 GP practices)	Yes	Ongoing company funded pilot started February 2019 in 6 GP practices
GP	General Practice	Previously	3-month company funded trial in 1 practice ended July 2020
GP	General Practice	No	N/A
GP, CCG Clinical Lead for Mental Health	General Practice	Yes	6-month company funded CCG wide trial started October 2020
High Intensity CBT Therapist	IAPT service	No	N/A
Assistant Director Mental Health, Learning Disabilities & Autism	Clinical Commissioning Group	No	N/A
Community navigator	Community long term condition service (Scotland)	Yes	Available since April 2020 to people under the care of the community service
Occupational therapist	Community mental health service (Scotland)	One referral	Company offered one-off free access

3 Current practice in clinical area

NICE has produced a health app briefing on Sleepio which describes the current care pathway. NICE has also produced a clinical knowledge summary on insomnia which provides primary care practitioners with a readily accessible summary of the current evidence base and practical guidance on best practice.

Contributors reported that commonly a person presenting to a GP with poor sleep will undergo assessment to guide next steps. The assessment will include consideration of duration of symptoms, impact of symptoms on activities of daily living and whether the problem is associated with any other conditions. Contributors said it is common for people presenting with poor sleep to have underlying conditions such as anxiety, depression or pain. There was a difference in opinion about the clinical approach to this situation with some adopting a segmented approach to each issue and others a holistic approach addressing everything at the same time.

Contributors noted that there are limited treatment options for poor sleep and these patients often present to primary care services seeking help. Cognitive behavioural therapy for insomnia (CBT I) is not routinely available, therefore GPs will usually offer sleep hygiene advice. If the person is in an acute distressed state, a very short course (1 week) of hypnotic medication (e.g Zopiclone) may be recommended. There was a concern that when GPs are busy, medication may be used as a quick solution but that these have other side effects and can lead to longer term dependence.

When a GP identifies insomnia secondary to an underlying mental health condition such as anxiety and depression they will usually refer the patient to IAPT services where sleep support, either CBT-I (although reported to be not routinely available) or sleep hygiene advice, can be delivered as part of the intervention. This can be face to face or self-help material (posters, slide sets and online programmes).

All people referred to IAPT services are triaged to identify suitable intervention(s) for them. Contributors reported that IAPT services are under pressure with capacity issues, thought to have worsened as a result of the COVID-19 pandemic. They report waiting times of 3 to 12 months with the longest waits for face to face CBT. Negative patient experiences with IAPT services in the past, and a reluctance of people to acknowledge an underlying mental health condition, are barriers to people accessing these services.

Although people presenting with insomnia with no underlying condition was reported to be uncommon, there was an acknowledgement that it might be more common than previously thought. It was reported that poor sleep is an everyday occurrence for many people who may not seek medical help for this as a primary complaint. Poor sleep alone is not a condition treated by IAPT services.

4 Use of Sleepio in practice

The company report that Sleepio is currently available through a sponsored NHS England South East Programme in Oxfordshire, Berkshire and Buckinghamshire. The company have also made the product available to all health and social care staff in England. The Good thinking initiative commissioned Sleepio for all Greater London residents through London Clinical Commissioning Groups (2017 – 2019) but no longer provides access. Table 1 shows use of Sleepio among contributors, most of whom have referred people for Sleepio as part of a company funded trial pilot.

The company report that a laptop or desktop is required to access Sleepio and there is a supplementary app for iOS. Contributors emphasised the interactivity of Sleepio. As part of the programme there is a sleep restriction element in week 3. Users have reported this as challenging, and for some has been the reason they have discontinued the programme.

Contributors said that data tracking usage, completion, and self-assessment results of Sleepio among their patient populations could be used to support the case for adoption locally. People accessing the technology as part of a free trial use a unique project link which allows the company to identify people in the trial. Some usage data was available to pilot sites on an ad hoc basis.

The company report that there is a clinician interface where healthcare professionals can review their patients. Contributors did not refer to this resource during discussions.

5 Reported benefits

The potential benefits of adopting Sleepio, as reported to the adoption team by the healthcare professionals using the technology are:

- Provides an additional tool for a common problem
- Variety of health and care professionals can direct people to Sleepio with no waiting list
- May reduce sleep medication prescribing
- May reduce the number of GP appointments for insomnia and sleep problems

6 Insights from the NHS

Care pathway

Contributors thought Sleepio would be a useful additional resource to support people with poor sleep. Where poor sleep is thought to be secondary to other problems, where it is used in the care pathway is influenced by the clinical approach to addressing underlying problems.

It was suggested that Sleepio could be offered to people whilst they wait to access their recommended IAPT interventions. One contributor said that completing the Sleepio programme could be good preparation for formalised CBT. An IAPT service professional said planning would be required to decide where Sleepio would fit into their service.

Some contributors asked if Sleepio could be completed alongside another treatment, such as another CBT programme. There was some concern that this would increase the required commitment from the user and could reduce the impact of either treatment.

Patient selection

Contributors agreed that the technology is suitable for people with poor sleep.

To select appropriate patients and maximise the benefit contributors suggested:

- Sleepio should not be used when someone is taking sedating medications but can be used alongside medications for mental health problems such as anxiety and depression.
- The programme is challenging, and people need to be motivated to complete it.

- Access to a suitable device, internet connection and IT literacy.
- Evaluation of the person's ability to concentrate for the required time
- Personal learning styles and acceptance. Some people will prefer talking therapy and depending upon personal learning styles the design of Sleepio may not appeal to all users.

The company highlight that the sleep component of the programme may exacerbate underlying pathophysiology and risk in some individuals, for example those with epilepsy, bipolar disorder and at risk of falls. The instructions for use recommend these people speak with their doctor and only use the program under direct medical supervision.

Support and follow up

Although Sleepio is a self-directed programme, contributors varied in the amount of support they provided to users. GPs provided the link to the programme for self-directed completion and did not routinely follow-up. A long-term conditions service offered practical and emotional support to Sleepio users throughout the six-week duration of the programme.

All contributors suggested that it would be useful to be able to access progress data for individuals and provide support to optimise completion and evaluate.

Patient experience

No contributors have routinely collected feedback from patients. However, ad hoc feedback is that the programme helped and was easy to use and access.

One contributor thought the app would be more accessible and easier to use than a desktop programme if there was enhanced functionality.

Clinician confidence/acceptance

In general, there was positive clinician opinion of Sleepio as an additional option for helping people with poor sleep. There was agreement that it is safe and low risk with some evidence to support its use. One contributor suggested that evidence of

outcomes vs CBT-I would help convince clinicians further of its efficacy and support adoption.

It was acknowledged that online programmes are not suitable for everyone and there was scepticism from one contributor on the value of self-help programmes, although this is not specific to Sleepio.

Commissioning and procurement

Access to Sleepio is provided through a free access code developed for a pilot, a research site or commissioned area. The company's intended procurement model for the NHS is for locality or regional commissioning on an annual basis.

All contributors agreed that funding Sleepio in the current NHS climate was a major barrier to its use. While poor sleep can have significant impact on quality of life for individuals, it is not considered a priority area in local or national health policy. CCGs were identified as the likely providers of funding, however contributors were concerned that the financial savings of using Sleepio in reducing hypnotic medications and GP appointments were not likely to be significant enough for CCGs to justify commissioning it, which would be a barrier to adoption.

Clinician familiarisation

All contributors who had experience of referring people for Sleepio had received a minimum 1-hour familiarisation session delivered by the company with an optional follow-up question and answer session after 6 weeks. The company have advised that training is provided free of charge to staff at pilot and research sites and commissioned areas. Training now includes information to help clinicians explain the benefits of the sleep restriction which people find challenging at week 3.

Contributors agreed this is useful to assess an individual's suitability, prepare the person about what to expect and offer support during the programme if required. They believed these steps would increase patient compliance and completion of the programme.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT443 Sleepio for adults with poor sleep

Company evidence submission

Part 1: Decision problem, clinical evidence and outline of economic evidence

Company name	Big Health Ltd.
Submission date	11 December, 2020
Regulatory documents attached	Please list regulatory documents submitted (e.g. CE certificate, instructions for use, etc.) • CE Declaration of Conformity • Instructions for use • Quality systems (ISO 13485) certificate
Contains confidential information	No

Contents

1 Decision problem 4
2 The technology 7
2.1 Overview of the technology 7
2.2 Claimed benefits of the technology 14
2.3 Other considerations 19
3 Clinical context 25
3.1 Clinical care pathways 25
3.2 Validation of pathways 27
3.3 System changes 28
3.4 Reducing health inequalities and improving access 29
4 Evidence search 30
5 Clinical evidence 31
5.1 List of relevant clinical studies 31
5.2 Details of relevant clinical studies 51
5.3 Results of relevant clinical studies 95
6 Ongoing use and data collection 110
7 Adverse events 111
8 Evidence synthesis and meta-analysis 111
8.1 Quantitative review 111
8.2 Qualitative review 115
9 Summary and interpretation of clinical evidence 116
10 Outline of economic evidence 123
10.1 Population benefiting 123
10.2 List price of technology 124
10.3 Value of patient and system benefits 124
10.4 Training and pathway costs 127
10.5 Other annual NHS costs and savings 128
10.6 Total costs and savings 129
10.7 Economic evidence 131
11 References 133

12 Appendices 140
Appendix A: Study identification for clinical and economic evidence 140
Appendix B: Search strategy for adverse events 150
Appendix C: Checklist of confidential information 152

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	Adults with difficulty sleeping	Adults with insomnia symptoms (18 yr plus; no upper age limit)	Addresses insomnia as a specific sleep disorder; addresses effectiveness across entire adult age range
Intervention	*Sleepio*	None	None
Comparator(s)	Sleep hygiene Hypnotic drugs Face-to-face CBT for insomnia Digitally-facilitated CBT for insomnia	Omitted digitally-facilitated CBT for insomnia	Lack of comparative studies
Outcomes	Sleep related outcomes • Sleep quality • Sleep quantity • Sleep-related satisfaction and quality of life • Health related quality of life measures • Symptoms of comorbid health conditions (mental and physical) directly impacted by difficulty sleeping System related outcomes • Access to CBT for insomnia	To add: Insomnia related outcomes • Sleep Condition Indicator (SCI) • Insomnia Severity Index (ISI)	We include validated clinical scores used in the assessment and management of insomnia

	• Waiting time for CBT for insomnia • Number of primary care appointments • Hypnotic drug prescription • Incidence of comorbid health conditions Device related outcomes • Device-related adverse events		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The cost modelling should reflect the business model the company is proposing to use in the NHS, for example if a regional approach is adopted the intervention cost should reflect that rather than the intervention cost when the technology is being purchased per patient. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared.	None	None

	Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		
Subgroups to be considered	• Pregnant women • People who have not had an insomnia diagnosis • People with short term insomnia (symptoms present for less than 3 months) • People with long term insomnia (symptoms present for 3 months or longer) • People with insomnia and a comorbid condition	• People with long term insomnia (symptoms present for 3 months or longer) • People with insomnia and a comorbid mental health condition • People with insomnia and a comorbid physical health condition • People who have not had a formal insomnia diagnosis • People with short term insomnia (symptoms present for less than 3 months) • Pregnant women with problems sleeping	The list has been reordered to reflect the likely prevalence of the subgroups. People may have mental or physical health comorbidities so these have been separated. Clarification that there are people with insomnia who have no 'formal' diagnosis Clarification that we are referring to pregnant women with problems sleeping
Functional classification and risk category	N/A	None	None
Special considerations, including issues related to equality	Patient-facing digital health technologies such as *Sleepio* may be unsuitable for people with visual or cognitive impairment,	None	None

	problems with manual dexterity or learning disabilities. Disability is a protected characteristic under the Equality Act. *Sleepio* is not suitable for those hard of hearing or where English is not well understood. Access to internet-enabled devices, access to the internet and user engagement with the technology may be more difficult for the people in deprived communities. Socio-economic status is not a protected characteristic and so is not protected under the Equality Act 2010 but factors affecting access to care delivered using digital devices should be considered. The technology can be used in pregnant women that are contraindicated for hypnotic medication. Pregnancy and maternity are protected characteristics of the equality Act 2010.		

2 The technology

2.1 Overview of the technology

Give the brand name, approved name and details of any different versions of the same technology (including future versions in development and due to launch within 12 months). Please also provide links to (or send copies of) the instructions for use for each version of the technology.

Brand name	*Sleepio*
Approved name	*Sleepio*
CE mark class and date of authorisation	Class I CE Mark – 1 October 2018
Main function	Digital CBT for insomnia software
Development stage	In market
Current availability in the UK	Available to residents in Buckinghamshire, Oxfordshire, Berkshire and North Hampshire. Available to health and social care staff in NHS England, NHS Scotland and Social Care staff in Wales.

Version(s)	**Launched**	**Features**
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, functionality, integration with other systems, any innovative features, and if the technology must be used alongside another treatment or technology. Include diagrams if appropriate.

Sleepio is a fully automated, personalised digital sleep improvement program delivering cognitive behavioural therapy for insomnia (CBT-I). *Sleepio* can be used as a standalone treatment for insomnia and does not require clinical input. *Sleepio* is a highly interactive programme that uses artificial intelligence (AI) to personalise components of the CBT-I programme for patients.

While typically triggered by a stressful life event, insomnia is maintained by unhelpful behaviours and thoughts. Over the course of six sessions, a virtual sleep expert - 'The Prof - teaches evidence-based cognitive and behavioural interventions, sleep hygiene education, and relaxation exercises to target these unhelpful behaviours and thoughts. Reducing these unhelpful behaviours and thoughts leads to a reduction in insomnia symptoms.

Common behaviours maintaining insomnia include spending an excessive amount of time awake in bed, sleeping in on the weekends, taking daytime naps, and drinking excessive caffeine. Sleep restriction (i.e., establishing a regular sleep window based on the actual amount of time spent asleep), stimulus control (i.e., reducing the amount of time awake in bed to reassociate the bed with sleep), and sleep hygiene (i.e., education about behaviours that interfere with sleep) are introduced in *Sleepio* to target unhelpful behaviours.

Common thoughts maintaining insomnia include excessive worries about sleep, dysfunctional beliefs about sleep, and bed-related tension and anxiety. *Sleepio* identifies, challenges, and addresses thoughts and worries that contribute to difficulty sleeping using cognitive therapy such as cognitive restructuring (i.e., identifying and challenging unhelpful thoughts) and paradoxical intention (i.e., instead of focusing on trying to sleep, focus on trying to stay awake). Relaxation techniques such as progressive muscle relaxation are also introduced to help reduce bed-related anxiety and tension.

The *Sleepio* course

Sleepio consists of six, 15-20 minute sessions. After completion of a session, the next session is made available one week later. It is recommended that patients complete one session per week but they can spend as much time as they need between sessions and can repeat sessions as required.

During the *Sleepio* sessions, The Prof will teach scientifically backed tools (see below for a detailed breakdown of each session) to reduce insomnia symptoms. It is recommended that patients incorporate these tools into their daily routines as instructed. Research shows that putting in the work between sessions leads to better outcomes.

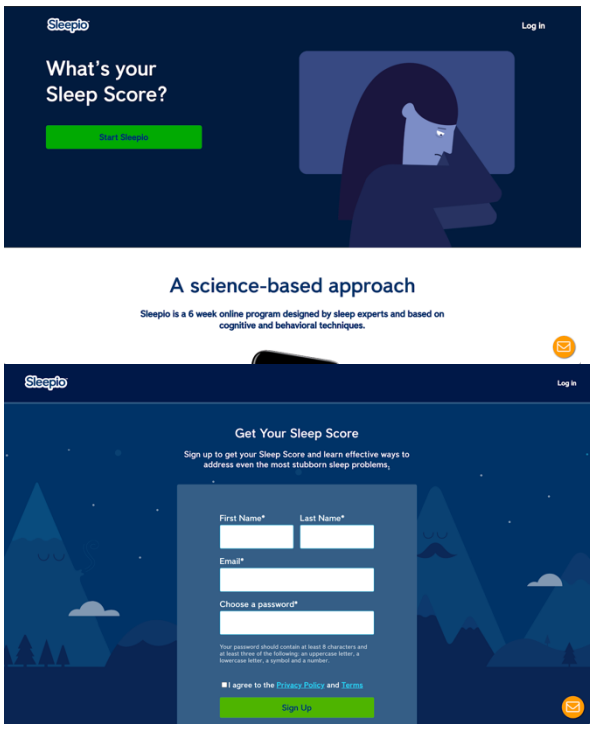
A core component of *Sleepio* is completion of the sleep diary. It is recommended that patients complete the sleep diary every morning upon waking. The diary can be completed within the *Sleepio* program. A paper copy can be downloaded and printed should patients prefer a non-digital option.

Many *Sleepio* patients start seeing improvements in their sleep by session 2 or 3, however, to get the full benefit of the program it is recommended that they complete all six sessions and practice the skills between sessions.

Onboarding

People sign up using a link provided by their healthcare provider, after signing up they will be asked a series of questions to generate their Sleep Score, after which they can start

the first session of CBT. A series of Sleep Guides supporting a range of issues e.g. shift work and pregnancy, are provided to download before starting the session.



Weekly CBT sessions

Structure of a Session

Each *Sleepio* session covers a number of topics and techniques for sleep improvement. The specific topics in each session are listed during the first few minutes of the session. Topics must be covered in order and cannot be skipped. At the end of each session there is a 5-question quiz to test comprehension. The quiz must be completed to finish the session.

Throughout each session there are interactive elements such as asking questions and completing exercises that engage the patient. The more a patient engages the better the outcomes

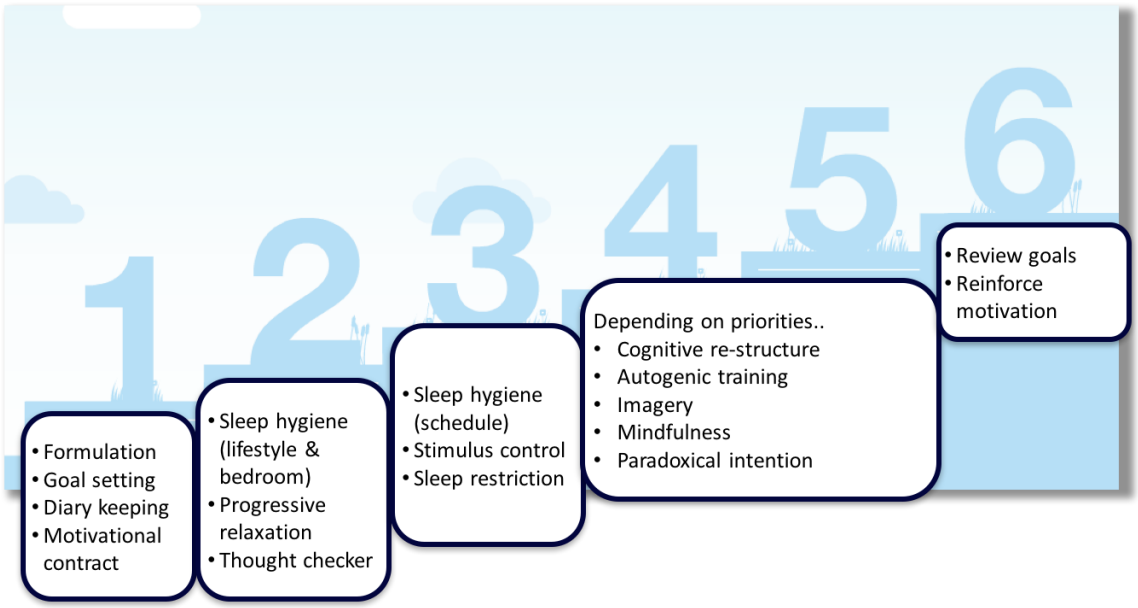
From Session 2, sessions will begin with a summary of progress, starting with how the patient slept based on Sleep Diaries. Then, they will answer a few questions about their week to track your goals and overall progress. From Session 4, they may also receive feedback on how to adjust sleep schedules.

As each session is completed patients receive an email summary for that session and new content is added to their *Sleepio* Case File and Library.

Session content

1. Identify the cause of poor sleep and set goals for the programme.
2. Learn to optimise the daytime for sleep.
3. Boost the connection between bed and sleep.
4. Learn a range of techniques that help clear the mind for sleep.

5. Grow the toolkit with final techniques tailored to the patient.
6. Assess progress, revisit material, and post questions to the team of Sleep Experts.

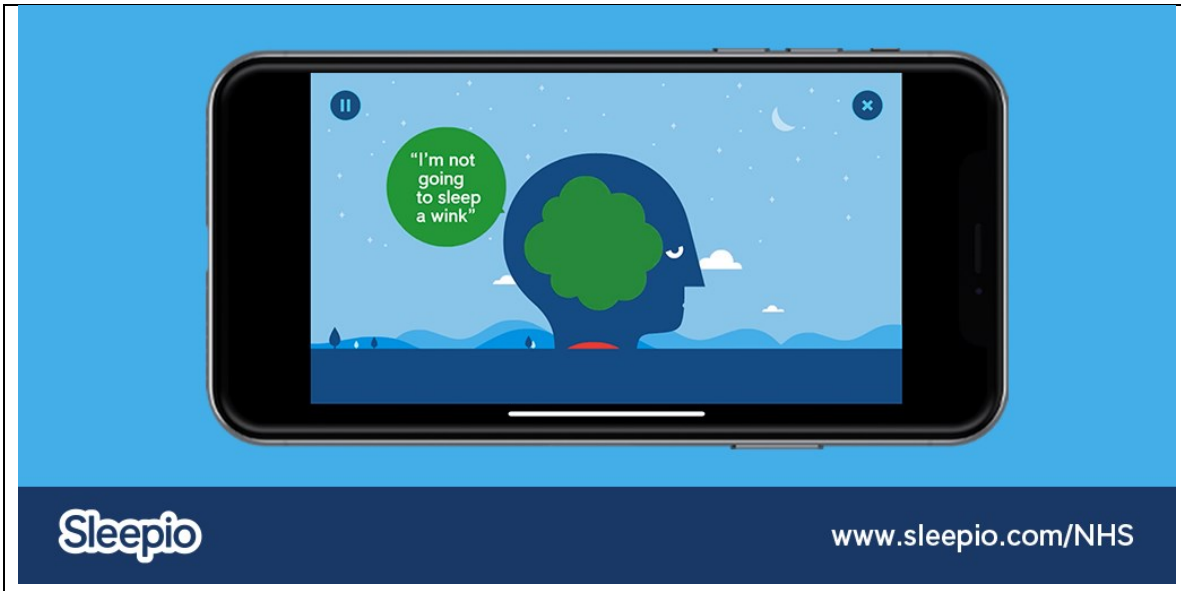


Desktop features:

- Onboarding sleep test,
- *Sleepio* programme,
- Sleep diary,
- *Sleepio* community,
- Case file and library of Sleep guides,
- Add tracking devices to import sleep data, *Sleepio* is compatible with FitBit and iOS Health Kit
- *Sleepio* clinic (for clinicians only)

App features (iOS only):

- *Sleepio* programme,
- Sleep diary,
- Help getting to sleep now



2.2 Claimed benefits of the technology

What are the claimed benefits for patients and the NHS of using the technology for the decision problem described in Section 1?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia.	All papers cited are either fully published or included as structured abstracts in appendix A. Espie et al., (2012) Espie et al., (2014) Pillai et al., (2015) Barnes et al., (2016) Bostock et al., (2016) Luik et al., (2017) Elison et al., (2017) Freeman et al., (2017) Miller et al., (2018) Cheng et al., (2019a) Espie et al., (2019) Denis et al., (2020) Felder et al., (2020) Luik et al., (2020) Crawford et al., (2020) Cliffe et al., (2020) Kyle et al., (2020) Kalmbach et al., (2020) Cheng et al., (2020a) Henry et al., (2020) Stott et al., (2020 abstract) Studd et al., (2020 abstract) Kanady et al., (2020) Derose et al., (in review) Manber et al., (in progress)	*Sleepio* is superior to placebo, to active comparators and to treatment as usual at improving insomnia symptoms and is effective in people with sub-threshold symptoms and pregnant women. *Sleepio* is safe and accepted, and led to significant improvements in insomnia symptoms in 14-17 year olds. Patients who had used *Sleepio* experienced reduced risk of insomnia relapse and depressive symptoms during the coronavirus pandemic.

Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.	Espie et al., (2014) Pillai et al., (2015) Bostock et al., (2016) Luik et al., (2017) Elison et al., (2017) Freeman et al., (2017) Miller et al., (2018) Cheng et al., (2019a) Espie et al., (2019) Denis et al., (2020) Felder et al., (2020) Luik et al., (2020) Crawford et al., (2020) Cliffe et al., (2020) Kyle et al., (2020) Kalmbach et al., (2020) Cheng et al., (2020a) Stott et al., (2020) Henry et al., (2020) Studd et al., (2020 abstract) Kanady et al., (2020) Manber et al., (in progress)	*Sleepio* is effective in improving symptoms of depression and anxiety, as well as other mental health symptoms including paranoia. *Sleepio* is also effective in reducing fatigue, improving wellbeing, functional health status and QoL. Studies show the above sets of improvements are attributable to *Sleepio* improving users' sleep. *Sleepio* has been shown to be effective in improving insomnia symptoms in patients with cancer, cardiometabolic, and neurological conditions. Patients who have used *Sleepio* experienced reduced risk of insomnia relapse and depressive symptoms during the coronavirus pandemic.
Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all.	Luik et al., (2017) Elison et al., (2017) Luik et al., (2020) Cliffe et al., (2020) Stott et al., (2020 abstract) Studd et al., (2020 abstract) Derose et al., (in review) Manber et al., (in progress)	*Sleepio* improved IAPT recovery rates and provided access to CBT-I for patients who otherwise would not have had their insomnia treated.

Provides CBT for insomnia in a stigma free environment.	Coulson et al., (2016) Luik et al., (2017) Cliffe et al., (2020) Stott et al., (2020 abstract) Studd et al., (2020 abstract) Derose et al., (in review)	Non-judgmental interactions were cited as one of the positive drivers for engagement with the *Sleepio* community
Eliminates waiting time for CBT for insomnia	Stott et al., (2020 abstract) Studd et al., (2020 abstract) Derose et al., (in review)	Real world evaluations of *Sleepio* demonstrate that the programme was accessible with no waiting times to large populations. In the Thames Valley *Sleepio* was accessed by over 20,000 people and those who had completed at least 2 sessions achieved a 58% remission rate for insomnia.
Reduces hypnotic usage and associated risks i.e. dependency, withdrawal, risk of falls and unresolved insomnia.	Luik et al., (2020) Drake et al., (2020)	*Sleepio* provides CBT-I with no waiting times at point of care allowing GPs to provide psychological care instead of medications. *Sleepio* led to significant reductions in prescription and non-prescription medication use at 24-weeks, with this effect maintained for non-prescription medication at 48-weeks. Populations using *Sleepio* were likely to have lower prescription medication use. Reduction in

		prescription medication was greatest for antidepressants followed by hypnotics.
System benefits		
Reduces primary care appointments	Sampson et al., (2020) Derose et al., (in review)	*Sleepio* may reduce people's need to engage with primary care services. Evidence from England suggests that *Sleepio* rollout within a population is associated with reduced primary care resource use, including prescriptions and GP attendances. *Sleepio* was non-inferior to face-to-face group CBT-I, therefore, if implemented at scale, could be cost effective and reduce primary care psychological resources.
Improves quality of care by enabling primary care to meet clinical guidelines	Stott et al., (2020 abstract) Studd et al., (2020 abstract) Derose et al., (in review)	When implemented at scale in the Thames Valley, *Sleepio* was available immediately at point of care, allowing GPs to prescribe CBT-I for chronic insomnia, instead of medications.
Provision of CBT service where face to face CBT is not available or has long waiting times	Stott et al., (2020 abstract) Studd et al., (2020 abstract)	As above, before *Sleepio* the Thames Valley did not have a CBT-I service.

Improves range of treatment options available to primary care prescribers	Cliffe et al., (2020) Stott et al., (2020 abstract) Studd et al., (2020 abstract)	As above, *Sleepio* enables GPs to prescribe CBT-I at point of care, therefore, adding choice to the currently limited treatment options (sleep medications) in primary care.
Cost benefits		
Reduced downstream costs of untreated insomnia	Hafner et al., (2017) Cheng et al., (2019a)	By reducing the incidence of insomnia and its symptoms, *Sleepio* can prevent direct and indirect costs associated with insomnia.
Reduces hypnotic drug prescriptions and associated costs	Sampson et al., (2020) Darden et al., (2020)	*Sleepio* is an effective and less costly substitute for hypnotics.
Reduces primary care resource costs	Sampson et al., (2020) Derose et al., (in review)	*Sleepio* may reduce people's need to engage with primary care services. Evidence from England suggests that *Sleepio* rollout within a population is associated with reduced primary care resource use, including prescriptions and GP attendances. *Sleepio* was non-inferior to face-to-face group CBT-I, therefore, if implemented at scale, could be cost effective and reduce primary care psychological resources.

Sustainability benefits		
Reduced emissions and use of non-renewable resources due to reduced travelling	Common knowledge	*Sleepio* avoids the need to travel to hospital once a referral has been made to CBT-I services.

2.3 Other considerations

Describe any training (for healthcare professionals and patients or their carers) that would be needed if the NHS were to adopt the technology (no more than 500 words).

Staff training is offered by Big Health at no additional cost.

Primary care training

Prescribing *Sleepio* to your patients (30 mins - 1 hour)

- All training is delivered by a Big Health engagement manager and a Big Health clinical psychologist/ specialist in Sleep Medicine.
- A group of GP practices, or primary care networks can be trained at the same time either face to face or through a webinar.
- Training covers:
    - Managing insomnia disorder
    - Introduction to *Sleepio*
    - How to prescribe *Sleepio*: patient selection, referral links, and how to support patients through session 3 sleep restriction, FAQs
    - Patient feedback and outcomes reporting
- Follow up materials and a dedicated webpage for training resources are set up for practice staff to access.

Technical training and set up

- *Sleepio* can be prescribed through EMIS, SystemOne, AccuRx, MJOG, and other primary care messaging platforms.
- A Big Health engagement manager provides guides, messaging and walks clinicians through the digital prescription process at setup.

Briefly describe the environmental impact of adopting the technology across the NHS, including for example the impact of the manufacturing process and waste disposal process, and any sustainability considerations (no more than 500 words).

Sleepio avoids the need to travel to appointments once a referral has been made to CBT-I services. *Sleepio* is intended to be a standalone solution that delivers CBT-I to patients at a time and place most convenient to them. This model reduces the need for healthcare premises to host CBT-I services, therefore reducing the reliance on non-renewable energy and resources.

If the technology provides any health information, such as advice to users, briefly describe how this is aligned with best available sources such as NICE guidance or guidance from other relevant professional organisations or bodies. Describe how this is kept up to date and accurate (no more than 500 words).

Sleepio provides six sessions of CBT-I and has been included in the British Association of Psychopharmacology (BAP) (Wilson et al., 2019) guidelines as an effective web/mobile-based solution for insomnia.

The core principles and techniques in CBT-I such as sleep restriction and stimulus control have remained consistent across the decades. There have been minor changes in adding relaxation and shortening CBT-I to focus on behavioural interventions only (BBTI), *Sleepio* focuses on behavioural interventions. To date there have been no significant updates to *Sleepio* content which include sleep restriction, stimulus control and relaxation (see above for session content). *Sleepio* is currently undergoing improvements and it is anticipated that in the near future the programme will be able to support iterations on the content. All content in *Sleepio* is monitored and designed by internal and external clinical psychologists specialising in sleep medicine and evaluated using internal product design testing and clinical trials.

Summary of guidelines

Three guidelines are relevant to insomnia, the National Institute of Health and Care Excellence (NICE) guideline for insomnia (Clinical Knowledge Summary Insomnia, 2020), the British Association of Psychopharmacology (BAP) (Wilson et al., 2019) guidelines and the European Guideline Summary Recommendation (Riemann et al., 2017).

All three guidelines recommend CBT-I as first-line treatment for chronic insomnia. Sleep medications e.g. hypnotics or melatonin are indicated in acute insomnia that is likely to resolve. Sleep medications are limited to a short (3-7 day course) and are not indicated for pregnant women. Melatonin is recommended for those aged 55 years and over.

BAP guidelines assert the importance of treating all types of insomnia. Insomnia is also associated with increased risk of poor physical health and conditions that are expensive to treat and include cardiometabolic and mental health difficulties (Taylor, et al., 2003; Javaheri, et al., 2017; Lin, et al., 2018; Hertenstein, et al., 2019; Li, et al., 2020).

However insomnia often remains undiagnosed and untreated despite its high prevalence, and CBT-I can improve symptoms of insomnia and associated sleep difficulty, quality of life, and daytime functioning (Wilson et al., 2019; Riemann et al., 2017).

If peer-support or other similar communication functions are available within the technology please describe what safeguarding measures are in place to ensure the safety of users, for example user agreements or moderation. Describe who has access to the platform and their roles and why these people are suitable and qualified to have access (no more than 500 words).

Big Health has a clinical governance process that is compliant with rigorous medical device risk management standards (e.g., ISO 13485, ISO 14971 and IEC 62304). This process involves both (1) setting user expectations before starting *Sleepio* (by providing information about suitability and safety during sign-up and asking users to confirm understanding of suitability) and (2) managing risks during program use.

During program use, users receive customised guidance embedded within *Sleepio*. For example, if a user indicates that they have existing health difficulties (i.e., if they respond to the statement, "in general, would you say your health is…" with the options of "poor" or "very poor"), if they endorse falling asleep or struggling to stay awake during the day or they completed fewer than 6 our of 14 diary entries during the first two weeks, their recommended sleep window for sleep restriction is less constricted (i.e., the sleep window minimum is increased from 5 to 6 hours). Additionally, individuals who endorse difficulty staying awake during the day, stopping breathing during their sleep, or snoring are provided with additional information in their sleep report about sleep apnoea.

Within the program, an email icon on the bottom right corner of the screen allows the user to email the User Happiness team for technical support. The User Happiness team are the Big Health customer service team who have undergone training to manage the community, respond to posts or emails and manage issues. Email communications are responded to within 24 hours and are subject to manual monitoring for indications of risk by the User Happiness team. Posts on the *Sleepio* community board are monitored by the User Happiness team, as well as by other community members, for inappropriate and/or risk-related content. Additionally, a list of risk-related and inappropriate words are automatically flagged for the User Happiness team to review. User free text entry responses to the question, "What else would you like your *Sleepio* expert to know?" are also monitored for risk-related words every month through a combination of automated and manual processes.

If a concerning email, post, or entry is identified, the User Happiness and Clinical Safety Officer (CSO) review the content, log the incident, and create a response plan. Responses do not include direct medical advice, but remind users that the program is self-help only and to speak to a doctor or local emergency services if they feel their health or wellbeing is at risk. Emailed replies to concerns of risk come from (or under the directive of) the User Happiness Manager, after conferring with the Clinical team, which is made up of clinical researchers, clinical psychologists, and specialists in sleep medicine.

Does the technology use recognised behaviour change techniques or frameworks? If yes, please provide details of these and provide academic references supporting the use of these techniques or frameworks. Please state how the principles of these techniques or frameworks have been incorporated into the technology and how the

technology will be updated/aligned with best practice going forward (no more than 1,000 words).

CBT-I is established in clinical guidelines as recommended treatment for non-resolvable acute insomnia and chronic insomnia. This is stated in NICE guidelines for the management of insomnia (NICE, 2020) and *Sleepio* is included in the British Association of Psychopharmacology guidelines (Wilson et al., 2019).

Wilson et al., summarises three rationales for recommending CBT-I.

1. insomnia is regarded as a psycho-physiological disorder in which mental and behavioural factors play a predisposing, precipitating, and perpetuating role,
2. CBT-I directly addresses these factors by combining sleep restriction, stimulus control with cognitive restructuring,
3. there is significant evidence for the safety, efficacy and effectiveness of CBT-I, whether delivered individually, in a group or through web/mobile intervention.

Sleepio technology delivers CBT-I and is based on cognitive behavioural theory and practice. Principles of classical and operant conditioning, social modelling, social learning and reinforcement are integral, as is the use of stimulus control and behavioural shaping. Cognitive principles derived from recognised sources include the selective attention, attentional training, attribution theory, cognitive restructuring, paradoxical intention and articulatory suppression. *Sleepio* sets attainable goals using SMART principles, with programmatic prompting, nudging, reminders, and rewards. Goals are in keeping with a shared formulation based on hypotheses. Progress is quantified, visualised and feedback to the individual. Motivational models and behavioural contracting encourage successive steps to shape behaviours towards desired outcomes. A social community helps users on their journey, with 'graduates' acting as support. *Sleepio* experts answer questions raised by users. The programme is structured over 6 weeks and delivered by an animated personal therapist The Prof and his dog, Pavlov.

As above (pg. 21), the core techniques in CBT-I have remained consistent and *Sleepio* is aligned with current CBT-I practice.

Does the effectiveness of the technology rely on the use of artificial intelligence (AI)? If yes, please describe how AI is embedded into the technology, the type(s) of AI used and how the technology will be updated/aligned with best practice going forward (no more than 1,000 words). Provide any relevant references.

Sleepio displays personalized content generated by the *Sleepio* Algorithm during the course of the program to ensure that it is relevant to the user and delivered in the most suitable order for the user. Before the user can begin the *Sleepio* treatment sessions, they must complete the Long Sleep Test (LST). The *Sleepio* Algorithm utilizes the initial information gathered during the LST as well as the information collected during the course of the treatment to personalize content. This approach to therapy personalization allows *Sleepio* to maintain its safety and efficacy profile by adjusting the treatment regimen according to individual needs (e.g., sleep complaints, health status, other treatments). The *Sleepio* treatment is personalized to each user in three different ways: content addition, content ordering, and content modification.

Content Addition:

The user will be introduced to additional relevant session content depending on their responses within the LST. This approach allows for *Sleepio* to provide additional support to users that may need it based upon their lifestyle choices or relevant medication regimen. For example, if the user indicates drinking alcohol, using nicotine, and/or taking sleeping pills in the LST, additional information about the alerting and sedating properties of these behaviors is discussed during the lifestyle section of *Sleepio*. Understanding the impact of alcohol, nicotine, and sleeping pills on sleep is an important component of sleep hygiene for individuals engaging in these behaviors.

Content Ordering:

Therapy personalization is also achieved by introducing certain interventions in order from most relevant to least relevant for the specific user. More specifically, the six standard, evidence-based cognitive interventions (Beck, 2011) introduced in sessions 4 and 5 are sequenced according to how users respond to questions about sleep-interfering thoughts during the LST. Notably, users are introduced to all six cognitive techniques, regardless of how they answer LST questions. Rather, the ordering of the techniques is unique and is based on relevance for the user. This allows users to apply the techniques that are going to be most effective for them sooner.

Content Modification:

Finally, the *Sleepio* algorithm is used to modify therapy content. There are many examples of content modification within the *Sleepio* program. One of the most important examples is the calculation of the sleep restriction window.

Sleep restriction is an intervention that reduces time in bed to the amount of time spent asleep. The *Sleepio* Algorithm calculates the initial sleep restriction window, introduced during session 3, from the user's average total sleep time from the previous two weeks of sleep diaries (e.g., if the user slept for 6 hours per night on average, their sleep window is set at 6 hours). By default, the minimum sleep restriction window allowed is 5 hours. Five hours is the standard minimum sleep restriction window (Espie, 2006; Manber et al., 2014) and has been safely applied across thousands of participants in CBT-I clinical trials (Trauer et al., 2015), including trials using *Sleepio* (Espie et al., 2012; Pillai et al., 2015; Bostock et al., 2016; Barnes et al., 2017; McGrath et al., 2017; Freeman et al., 2017; Cheng et al., 2019; Espie et al., 2019; Denis et al., 2020; Felder et al., 2020; Kyle et al., 2020; Kalmbach et al., 2020). As a precaution, this minimum is raised to 6 hours for individuals who indicate having "poor" or "very poor" health, excessive daytime sleepiness, and/or who completed fewer than 6 of 14 diary entries during the first two weeks. This modification ensures safely applying sleep restriction in individuals who may be more sensitive to sleep loss. The sleep restriction window is then adjusted from week to week

based on the previous week of sleep diaries and answers to the weekly check in questions. More specifically, if the user achieves 90% sleep efficiency (total sleep time / time in bed), a sleep efficiency increase of 20% or greater, or if the user indicates "struggling" or "feeling like quitting", the user is allowed the option to increase the sleep window by 15 minutes. If the user doesn't satisfy any of those conditions, the sleep window stays the same. This approach is very similar to applied sleep restriction via in-person CBT-I and personalizing the sleep window in this way is important for ensuring efficacy, safety, and retention.

Another example of content modification is the introduction of the "challenging negative thoughts" intervention. The Prof models how to apply this skill by communicating with a virtual character with sleep problems. The content of the conversation is modified based on users' answers to LST questions to make this intervention more relevant and applicable for each individual user.

Other examples of content modification include different emphases on diet and exercise in the lifestyle section of session 2 depending on users' LST answers; demonstrating the progressive muscle relaxation intervention depending on whether the user indicated an interest in learning this exercise during the session; and the personalized program progress that is reviewed at the beginning of each session.

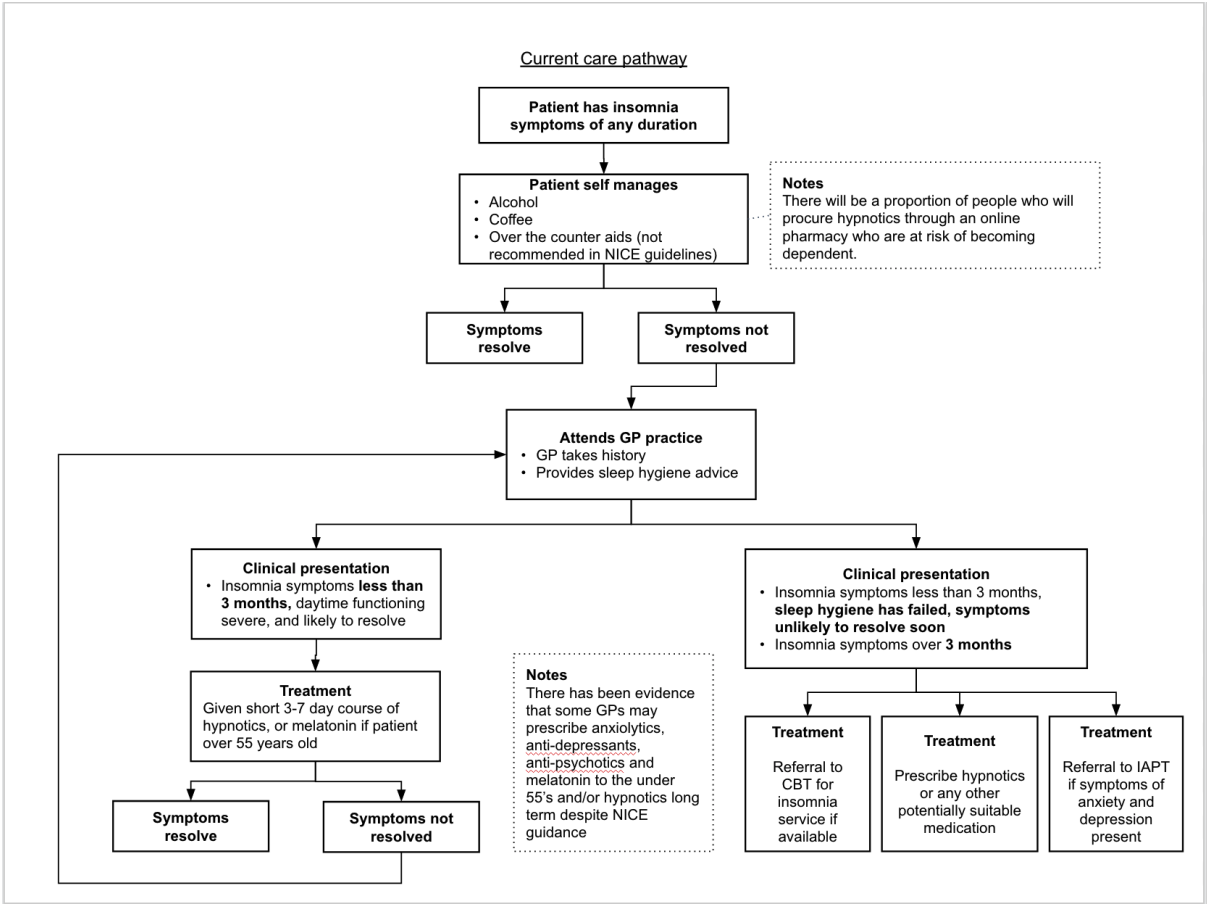
Updating the *Sleepio* Algorithm Going Forward

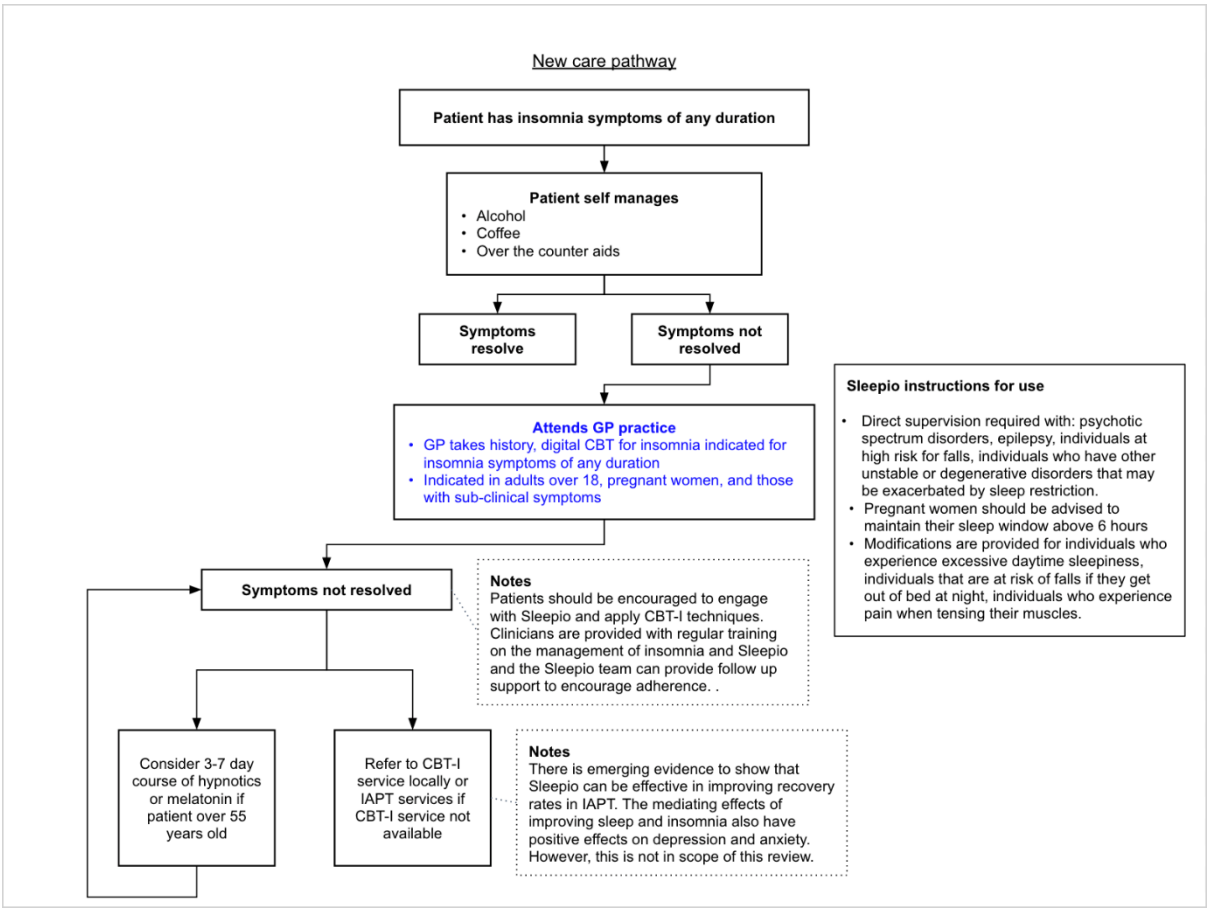
To date, we make *Sleepio* algorithm changes with the help of Big Health engineers. We are currently in the process of migrating *Sleepio* to a new platform. Once on the new platform, the *Sleepio* product team (without the assistance of engineers) will be able to make quick updates to the program in an effort to further increase program effectiveness and safety and align with best practices. Any changes to the *Sleepio* program are informed by internal and external experts in the behavioral sleep medicine field and/or internal experimentation.

3 Clinical context

3.1 Clinical care pathways

Describe the existing clinical care pathway(s) and the new clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. If there are multiple options for new care pathways all should be detailed below.





3.2 Validation of pathways

Provide information for new pathways to demonstrate that UK health/social care professionals have been involved in the design/development/testing and/or sign-off of the technology, and that the technology has been successfully piloted or implemented within the NHS (no more than 500 words).

Delivery of *Sleepio* at scale has been comprehensively tested in a population level rollout (n = 21,004 registrations) alongside NHS partners across the Thames Valley (Berkshire, Buckinghamshire and Oxfordshire) between 2018 - 2020. Development of models of referral pathways was done in partnership with the local Oxford AHSN and Clinical Commissioning Groups, as well as with partners in a local Improving Access to Psychological Therapies (IAPT) service and local primary care teams.

The principal delivery models tested in this project were 1) self-referral, 2) referral through IAPT services, and 3) referrals through primary care. The self-referral route did not require the patient to report any difficulties with sleep or to have a diagnosis of insomnia disorder to register on *Sleepio*. This route encompassed a broad range of channels that included employer launches, local broadcasting, public health messaging and digital advertising. The IAPT route involved training Psychological Wellbeing Practitioners to use a sleep protocol that introduced *Sleepio* if symptoms of insomnia were indicated in new patient screening using the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001). The primary care referral route was developed in partnership with fifteen local GP practices across two waves of implementation (wave 1; n = 9; wave 2; n = 5), at which an induction session on insomnia and *Sleepio* was delivered prior to opening the pathway. These practices were provided with additional engagement material including posters, leaflets and a silent video for practice waiting rooms. Additionally, electronic 'prescribing' was enabled in these practices through installation of alerts on the practice's electronic patient record system, such that GPs were prompted to suggest *Sleepio* if, for instance, a prescription for a hypnotic medication was being considered. Outcome reporting was provided to both IAPT and primary care partners on a quarterly basis to provide feedback on uptake and clinical outcomes. During regular meetings with these NHS partners, refinement of the pathways was made. As patients were able to identify their referral pathway when registering for *Sleepio*, it was possible to compare uptake and outcomes across these respective pathways. Of the three routes, the self-referral pathway resulted in the highest uptake, however clinical channels showed better conversion rates from registration to starting the treatment. Remission rates for insomnia symptoms were broadly similar across all referral routes. The next iteration of population rollouts continue in both North Hampshire, with 15 GP practices (across six different primary care networks) and in the Western Isles of Scotland, with nine GP practices and in partnership with three groups of social prescribers.

NHS clinicians specifically involved in the development and validation of the proposed care pathways include:
Dr Dimitri Gavriloff, Senior Clinical Psychologist, Non-Respiratory Sleep Disorders Service, Oxford University Hospitals NHS FT and Clinical Course Tutor in Sleep Medicine, University of Oxford
Dr Ian Wood, GP, Clinical Director at EMIS and National First Five Chair and Honorary Treasurer at the Royal College of General Practitioners

Dr Michael Mulholland, GP Partner and Vice Chair of the Royal College of General Practitioners
Dr John Pimm, Consultant Clinical Psychologist and Clinical Lead, Healthy Minds IAPT service
Dr Richard Stott, Clinical Psychologist and Clinical Senior Lecturer, King's College London
Dr Tim Cooper, GP, Clinical Lead for Mental Health, North Hampshire CCG
Professor Colin Espie, Professor of Sleep Medicine, University of Oxford

(The underlined names include links to biographies.)

3.3 System changes

Describe any system changes (for example staff changes, IT infrastructure and changes to clinical protocols) that would be needed if the NHS were to adopt the technology (no more than 500 words).

Sleepio is intended to be used as a first line treatment for patients presenting with insomnia symptoms. In the new pathway, medications are indicated for those with severe daytime functioning only and where symptoms have not resolved after using *Sleepio*, patients should be referred to IAPT services.

No additional staff or IT resources are required to prescribe *Sleepio*. Where, in the unlikely situation that a GP practice is not digitally enabled, the *Sleepio* link can be distributed via a leaflet.

Local clinical protocols for the appropriate use of hypnotics in the management of sleep will need to change in light of this guidance and *Sleepio* inclusion. Education of how to manage insomnia will need to be included in local clinical training sessions.

Wider system changes to improve the awareness of insomnia management and to formalise the treatment of insomnia in primary care will be required. A recent report by the Mental Health Foundation sets out a number of recommendations:

- The importance and benefits of sleep for both mental and physical health should be highlighted in national and local public health campaigns, including in schools and workplaces. New and easily accessible resources should be made available advising people on what they can do themselves to improve their sleep.
- The Royal College of GPs should provide up to date, evidence-based training and information for its members on the importance and benefits of sleep for physical and mental health. GPs should also have access to a diagnostic tool for use in recognising sleep problems in primary care settings.
- The new Public Health Outcomes Framework should include a specific outcome on reducing sleep problems across the whole population. Sleep should also be reflected in new national mental health outcome indicators, including improving sleep for people who experience significant sleep problems requiring specialist help.
- The National Institute of Health and Clinical Excellence (NICE) should develop guidance for the management of insomnia using non-pharmacological therapies, to complement existing guidance on using pharmacological therapies.
- People with sleep problems should be recognised within the Improving Access to Psychological Therapies (IAPT) programme, especially regarding access to Cognitive Behavioural Therapy (CBT). IAPT staff should be suitably trained on sleep issues.
- Further research should be carried out to establish the effectiveness of low cost, non-intrusive CBT based interventions for sleep problems, such as self-help books and online courses.

3.4 Reducing health inequalities and improving access

Describe any contribution the technology makes to improving health inequalities in the UK health and social care system, or improving access to care among hard-to-reach populations (no more than 500 words).

Sleep is fundamental to life, and the relationship between insomnia and poor mental health is established. Poor mental health has a two-way relationship with socioeconomic status, which can be associated with race. There is a growing body of evidence that links poor sleep and insomnia with populations with lower socioeconomic status and with racial and ethnic minorities (Patel, et al, 2010; Grandner, et al., 2016; Johnson, et al., 2019). Significant health disparities are associated with certain races, ethnicities and lower socioeconomic groups, including higher rates of cardiovascular disease, poor mental health and increased morbidity and mortality compared with the general population (Williams, et al., 2016). Certain ethnic groups and lower socioeconomic groups are more likely to work night shifts – increasing the risk of poor sleep, and due to societal factors, may experience increased stress from racism, occupational hazards, unsafe neighbourhoods, and financial difficulty. Given the primacy of sleep to overall health, the increased rates of sleep disturbance could explain the higher rates of poor physical health in these populations. **The lack of CBT-I provision only increases the health inequality gap**. In the UK, CBT-I provision is limited to a few acute Trusts and private clinics. Evidence shows that there is an inverse relationship between socioeconomic status and health seeking behaviour (Pampel, et al., 2010). Certain racial groups e.g. black and minority ethnic, perceive significant barriers to mental health services- relating to stigma, cultural identity and social norms that lead to poor use of mental health services in the NHS (Memon, et al., 2016). *Sleepio* is efficacious across a broad range of populations, mean indices of multiple deprivation (IMD) was 16.7 (SD 11.8) (Espie, et al., 2012). In Cheng, et al., 2019 there were no differences in treatment effects or attrition between white or black groups, but there were differences observed with attrition related to socioeconomic status. When *Sleepio* is deployed, patients are provided with immediate access, in a destigmatised environment to effective digital CBT-I. *Sleepio's* digital nature enables it to be downloaded and used at a scale that face-to-face therapy cannot support. In community settings, *Sleepio* has been made available to people without mobile or web devices through library or practice computers. Qualitative studies show that people have a positive experience with *Sleepio's* community, ranging from experiencing acts of altruism, feeling part of a non-judgmental community to feeling less isolated and being encouraged by others (Coulson, et al., 2016).

4 Evidence search

Undertake a systematic literature search to identify clinical and economic evidence on the technology. Also present any unpublished evidence.

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search and study identification strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		26
Number of **clinical** studies identified as being relevant to the decision problem.		26
Number of **economic** studies identified as being relevant to the decision problem[1].		3
Of the relevant **clinical** studies identified:	Number of published **clinical** studies (included in table 1).	26
	Number of **clinical** abstracts, unpublished clinical studies or other clinical data sources (included in table 2).	6
	Number of **clinical** ongoing studies (included in table 3).	6
Of the relevant **economic** studies identified:	Number of published **economic** studies (to be included in company submission part 2).	2
	Number of **economic** abstracts, unpublished **economic** reports (to be included in company submission part 2).	1
	Number of economic ongoing studies (to be included in company submission part 2).	0

5 Clinical evidence

5.1 List of relevant clinical studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published clinical studies in table 1.
- Summarise details of clinical abstracts, unpublished clinical studies and other clinical data sources in table 2.
- Summarise details of ongoing clinical studies in table 3.
- List the results of all clinical studies and data sources (from tables 1, 2 and 3) in table 4

Economic studies will be presented in part 2 of the submission. An overview of economic evidence is required in Section 10.

[1] Further detail about economic studies is required in Section 10

For any unpublished clinical studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published clinical studies

Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention (and version(s))	Comparator(s)	Main outcomes
Espie et al., 2012, UK.	Randomised controlled trial.	164 adults with insomnia disorder recruited online. Analysed as intention-to-treat. Lost to follow-up: Sleepio – 15 Placebo – 17 Treatment as usual - 4	*Sleepio.*	Treatment as usual and imagery relief therapy placebo.	Sleep diary parameters: sleep efficiency (SE), sleep onset latency (SOL), wake after sleep onset (WASO), total wake time (TWT), total sleep time (TST) and sleep quality. Insomnia symptoms (8-item sleep condition indicator; SCI-8). Two items assessing daytime functioning.
Espie et al., 2014, UK.	Secondary analysis of randomised controlled trial data.	164 adults with insomnia disorder recruited online. Analysed as intention-to-treat.	*Sleepio.*	Treatment as usual and imagery relief therapy placebo.	Attribution of sleep difficulties (Sleep disturbance questionnaire; SDQ). Thought content (Glasgow Content of Thoughts Inventory; GCTI). Psychopathology (Depression, Anxiety

					and Stress Scale; DASS-21).
Pillai et al., 2015, USA.	Randomised controlled trial.	22 adults with insomnia disorder recruited from previous insomnia research studies. Per-protocol analysis. Lost to follow-up: Sleepio – 4 Sleep hygiene education control - 2	*Sleepio.*	Sleep hygiene education active control.	Sleep diary SOL and TST. Anxiety symptoms (Beck Anxiety Inventory; BAI). Insomnia severity (Insomnia Severity Index; ISI). Sleepiness (Epworth Sleepiness Scale; ESS).
Coulson et al., 2016, UK.	Qualitative study.	100 Sleepio users recruited from the Sleepio community.	*Sleepio.*	Uncontrolled.	N/A
Bostock et al., 2016, USA.	Randomised controlled trial.	270 self-identified poor sleepers recruited from a Fortune 500 company. Intention-to-treat analysis. Lost to follow-up: Sleepio	*Sleepio.*	Wait-list control.	Insomnia symptoms (SCI-8). Workplace presenteeism and absenteeism (Workplace Productivity and Activity Impairment Index; WPAI). Anxiety symptoms (2-item Generalized Anxiety Disorder questionnaire; GAD-

		37 at week 8 post-intervention 52 at week 22 Waitlist 19 at week 8 post-intervention 51 at week 16 post-intervention (after receiving *Sleepio*.			2). Depressive symptoms (2-item Patient Health Questionnaire; PHQ-2).
Luik et al., 2017, UK.	Cohort study.	98 adults self-reporting poor sleep in addition to symptoms of anxiety or depression within IAPT.	*Sleepio.*	Uncontrolled.	Anxiety symptoms (GAD-7). Depressive symptoms (PHQ-9). Insomnia symptoms (ISI).
Barnes et al., 2017, USA.	Randomised controlled trial.	223 participants recruited online who expressed interest in taking part in a sleep improvement study. Lost to follow-up *Sleepio*: 64 Waitlist control: 38	*Sleepio.*	Wait-list control.	Insomnia severity (Four questions adapted from the Sleep Questionnaire). Negative affect (5 negative affect items from the Positive and Negative Affect Scale). Job Satisfaction (5 items from the Index of Job Satisfaction). State

					self-control (5 items from the State Self-Control Capacity Scale). Organisational citizenship assessed using 8-items. Interpersonal deviance was assessed using 7-items.
McGrath et al., 2017, Ireland.	Randomised controlled trial.	134 adults with mild sleep impairment and blood pressure between 130 and 160/<110 mmHg. Participants were recruited from community screening events and media advertisements. Analysed as intention-to-treat. Lost to follow-up: *Sleepio* – 6 Standard care - 1	*Sleepio.*	Standard care.	Difference in mean change in 24-hour ambulatory systolic blood pressure, mean change in 24-hour ambulatory diastolic blood pressure, diurnal and nocturnal peak and mean systolic and diastolic blood pressure. Insomnia severity (ISI) and symptoms (SCI-8). Sleep quality (Pittsburgh Sleep Quality Index; PSQI). Depressive symptoms (Beck

					Depression Inventory; BDI). Anxiety symptoms (BAI).
Elison et al., 2017, UK.	Cohort study.	1,068 IAPT service users referred for mental health difficulties. Of these, 85 accessed *Sleepio*.	*Sleepio.*	Uncontrolled.	Depressive symptoms (PHQ-9). Anxiety symptoms (GAD-7). Functioning (Work and Social Adjustment Scale; WASAS).
Freeman et al., 2017, UK.	Randomised controlled trial.	3,755 university students with insomnia. Analysed as intention-to-treat. Lost to follow-up *Sleepio* - 1,158 Usual care - 772	*Sleepio.*	Usual care waitlist control.	Insomnia symptoms (SCI-8). Paranoia (Green et al Paranoid Thought Scales; GPTS). Hallucinations (Specific Psychotic Experiences Questionnaire-Hallucinations subscale; SPEQ).
Luik et al. 2018, USA and UK.	Case-control study.	3,551 *Sleepio* users.	*Sleepio.*	Uncontrolled.	Insomnia symptoms (SCI-8). Depressive symptoms (PHQ-2). Anxiety symptoms (GAD-2). Stress using a single item from the Perceived Stress Scale (PSS).

					Life satisfaction using a single item, and workplace productivity using a single item based on the WPAI. Engagement with Sleepio assessed by the number of sleep diaries completed, posts in the community and views of library material.
Espie et al., 2018, USA.	Cohort study.	214 employees from Goodyear Tire and Rubber.	*Sleepio.*	Uncontrolled.	Insomnia symptoms (SCI-2). Workplace absenteeism and presenteeism (2 items from the WPAI). Stress (PSS).
Miller et al., 2018, Australia.	Cohort study.	96 adults with insomnia.	Self-selected into CBT for insomnia treatment modalities including *Sleepio*, in-person CBT, and Sleep Restriction Therapy (single CBT component), either individually or in combinations.	Uncontrolled.	Acceptability was assessed by the number of participants starting treatment. Tolerability assessed by the proportion completing treatment. Insomnia severity (ISI).

Cheng et al. 2019a, USA.	Randomised controlled trial.	1,385 adults with insomnia disorder were randomised. Per-protocol analysis conducted on 658 (*Sleepio* – 358; Sleep hygiene education control – 300).	*Sleepio.*	Sleep hygiene education active control.	Insomnia severity (ISI). Depression severity (Quick Inventory of Depressive Symptomatology; QIDS).
Espie et al., 2019, UK, USA, Australia.	Randomised controlled trial.	1,711 adults with insomnia disorder. Analysed as intention-to-treat. Lost to follow-up *Sleepio* Post-intervention (week 8) - 385 Follow-up (week 24) - 442 Sleep hygiene education control Post-intervention (week 8) - 341 Follow-up (week 24) - 363	*Sleepio.*	Sleep hygiene education active control.	Physical health (Patient-Reported Outcomes Measurement Information System: Global Health Scale; PROMIS-10). Wellbeing (Warwick-Edinburgh Mental Wellbeing Scale; WEMWBS). Sleep-related quality of life and impairments (Glasgow Sleep Impact Index; GSII).

Cheng et al., 2019b, USA.	1-year follow-up data from a randomised controlled trial (Cheng et al., 2019a).	658 adults with insomnia disorder.	*Sleepio.*	Sleep hygiene education active control.	Depression (QIDS). Clinically significant depression was determined using validated cut-offs on the QIDS. Insomnia severity (ISI).
Denis et al., 2020, UK.	Randomised controlled trial.	199 women. Analysed as intention-to-treat. Lost to follow-up *Sleepio* Post-intervention – 32 6 month follow-up - 52 Control Post-intervention – 22 6 month follow-up - 38	*Sleepio.*	Puzzle-based attention control.	Treatment acceptability assessed using the Treatment Acceptability Questionnaire (TAQ). Insomnia symptoms (SCI-8).
Felder et al., 2020, USA.	Randomised controlled trial.	208 pregnant women with insomnia disorder. Analysed as intention-to-treat.	*Sleepio.*	Standard care / treatment as usual.	Insomnia severity (ISI). Sleep efficiency assessed using daily

		Lost to follow-up: *Sleepio* Post-intervention – 14 Follow-up – 16 Standard care Post-intervention – 9 Follow-up – 12			self-reported sleep diaries.
Luik et al., 2020, UK, USA, Australia.	Long-term follow-up from a randomised controlled trial (Espie et al., 2019).	1,711 adults with insomnia disorder. Analysed as intention-to-treat.	*Sleepio.*	Sleep hygiene education active control.	Physical health (PROMIS-10). Wellbeing (WEMWBS). Sleep-related quality of life and impairments (GSII).
Crawford et al., 2020, USA.	Single-case experimental design study.	42 women with chronic migraine and insomnia symptoms.	*Sleepio.*	Uncontrolled.	Patient satisfaction (Patient Satisfaction Questionnaire Short Form; PSQSF). Insomnia severity (ISI). Self-reported sleep diary outcomes. Migraine impairment (Migraine Disability

					Assessment; MIDAS). Feasibility and acceptability, defined as completing all 6 sessions in 12 weeks, and completion of a single acceptability item respectively.
Cliffe et al., 2020, UK.	Cohort study.	39 adolescents (14-17 years old) with insomnia.	*Sleepio.*	Uncontrolled.	Acceptability of Sleepio. Insomnia severity (ISI). Insomnia symptoms (SCI-8). Anxiety symptoms (Revised Child Anxiety and Depression Scale; RCADS). Depressive symptoms (Mood and Feelings Questionnaire; MFQ).
Kyle et al., 2020, UK.	Randomised controlled trial.	410 adults (25 years old +) with insomnia disorder and self-reported difficulties with concentration or memory. Analysed as intention-to-treat.	*Sleepio.*	Waitlist control.	Self-reported cognitive impairment (British Columbia Cognitive Complaints Inventory; BC-CCI).

		Lost to follow-up *Sleepio* Post-intervention: 47 Follow-up: 69 Waitlist control Post-intervention: 24 Follow-up: 39			
Kalmbach et al., 2020, USA.	Randomised controlled trial.	91 pregnant women (near or entering the third trimester) with insomnia disorder. Analysed as intention-to-treat. Lost to follow-up *Sleepio* Post-intervention: 0 Follow-up / postnatal: 2 Sleep hygiene education control	*Sleepio.*	Sleep hygiene education active control.	Insomnia severity (ISI).

		Post-intervention: 1 Follow-up / postnatal: 3			
Cheng et al., 2020a, USA.	Secondary analysis of data from a randomised controlled trial (Cheng et al., 2019a).	658 adults with insomnia disorder.	*Sleepio.*	Sleep hygiene education active control.	Insomnia severity (ISI). Depression (QIDS). Rumination (Perseverative Thinking Questionnaire; PTQ).
Henry et al., 2020, UK, USA, Australia.	Combined sub-analysis of data from two randomised controlled trials (Espie et al., 2019 and Freeman et al., 2017)	3,352 adults with insomnia disorder and clinically significant depressive symptoms. Analysed as intention-to-treat.	*Sleepio.*	Sleep hygiene education active control and waitlist control.	Insomnia symptoms (SCI-8). Depressive symptoms (PHQ-9).
Cheng et al., 2020b, USA.	Secondary analysis of data from a randomised controlled trial (Cheng et al., 2019a).	208 adults with a previous history of insomnia disorder.	*Sleepio*	Sleep hygiene education active control.	Insomnia severity (ISI). Depression (QIDS). General stress and COVID related stress (Impact of Events Scale COVID-19). Global health (Global-10).

Table 2 Summary of all relevant clinical abstracts, unpublished clinical studies or other clinical data sources

Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention (and version(s))	Comparator(s)	Main outcomes
Stott et al., (2020), UK.	Retrospective observational clinical case-control cohort study.	552 Thames Valley IAPT service patients who used *Sleepio* in the UK. 88 lost to follow-up.	*Sleepio.*	Treatment as usual.	IAPT collected depression (PHQ-9) & anxiety (GAD-7) questionnaire outcomes.
Studd et al., (2020), UK.	Retrospective observational clinical cohort study.	21,004 *Sleepio* users from the Thames Valley region of the UK.	*Sleepio.*	Uncontrolled / treatment as usual.	Feasibility, defined by uptake and enrolment evaluated by referral pathway (self-, primary care-, or IAPT- referral).
Drake et al., (2019), USA.	Secondary analysis of a randomised controlled trial.	1,232 individuals with insomnia, from Henry Ford Healthcare System, USA.	*Sleepio*	Online sleep education control.	Use of medications for sleep (prescription and non-prescription).
Kanady et al (2020), UK, USA, Australia.	Combined sub-analysis of data from two randomised controlled trials (Espie et al., 2019 and Freeman et al., 2017).	2,172 individuals with insomnia and clinically significant anxiety symptoms. Analysed as intention-to-treat.	*Sleepio*	Sleep hygiene education active control and waitlist control.	Insomnia symptoms (SCI-8). Anxiety symptoms (GAD-7).
Derose et al., (in review), USA.	A pragmatic hybrid randomised controlled trial.	133,402 adult Kaiser health plan members with insomnia (a	*Sleepio*	In-person group CBT for insomnia.	Dispensed insomnia medications and

		diagnosis or insomnia medication dispensation or at high-risk of insomnia (a diagnosis of depression or anxiety).			provider encounters. Sleep parameters.
Smejka et al., (in review), UK.	A qualitative examination of the feasibility of Sleepio in stroke survivors.	11 community-dwelling chronic stroke survivors	*Sleepio*	Uncontrolled	Feasibility and accessibility of Sleepio reported qualitatively in semi-structured interviews.

Table 3 Summary of all relevant ongoing clinical studies

Principal investigator, and location [ClinicalTrials Identifier where appropriate]	Year (expected completion date)	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention (and version(s))	Comparator(s)	Outcomes
Rachel Manber, Stanford, CA, USA. Clinicaltrials.gov: NCT03532282.	2024	Randomised controlled trial.	Older adults (aged 50+) with insomnia disorder recruited from General Practice.	*Sleepio*.	Therapist led cognitive behavioral therapy for insomnia.	Insomnia symptom severity measured by the insomnia severity Index; Patient-Reported Outcomes Measurement Information System (PROMIS) - sleep related impairment questionnaire; The 4 Item Patient Health Questionnaire For Anxiety and Depression.
Heidi Johansen-Berg, UK. ClinicalTrials.gov Identifier: NCT04272	March 2021	Randomised controlled trial	Chronic community dwelling stroke survivors with sleep difficulty	*Sleepio.*	Sleep diary waitlist control.	Sleep Condition Indicator, sleep parameters, anxiety, depression,

						stroke specific quality of life, cost effectiveness
Jack D Edinger, USA. ClinicalTrials.gov Identifier: NCT03109210	April 2023	Randomised controlled trial.	384 participants with insomnia and comorbid obstructive sleep apnoea.	*Sleepio.*	Therapist-directed cognitive behavioural therapy and standard clinical care.	Insomnia Severity Index, Quebec Sleep Questionnaire, sleep parameters, Positive Airway Pressure (PAP) Therapy Adherence.
Lesley Fellows, Canada. ClinicalTrials.gov Identifier: NCT02571595	March 2021	Randomised controlled trial.	27 participants with Insomnia Disorder and Human Immunodeficiency Virus aged 35 and above.	*Sleepio.*	Waitlist control.	Insomnia, sleep, cognitive performance, Anxiety and Depression, quality of life.
Shannon McCaslin, USA. ClinicalTrials.gov Identifier: NCT03688763	December 2020	Single Group Assignment.	10 participants with Insomnia Disorder and Comorbid Psychopathology recruited from Palo Alto Veterans Institute for Research.	*Sleepio.*	None (Open Label).	Insomnia, Sleep parameters, Participant Perception of the Acceptability, Perceived Value, and Feasibility of using a Digital Modality to Treat Insomnia Symptoms, Posttraumatic

						Stress Disorder, Depression, Anxiety, and Psychosocial Functioning.
Peter B Jones, UK. ClinicalTrials.gov Identifier: NCT04180709	November 2022	Randomised controlled trial.	44 participants with Insomnia Disorder and First Episode of Psychosis recruited from CAMEO Early Intervention services.	*Sleepio.*	Treatment as usual.	Work and Social Adjustment, Time Use Survey, Depression, Cognitive functioning.

5.2 Details of relevant clinical studies

Please give details of all relevant clinical studies (all studies in tables 1, 2 and 3). Copy and paste a new table into the document for each study. Please use 1 table per study.

A Randomized, Placebo-Controlled Trial of Online Cognitive Behavioral Therapy for Chronic Insomnia Disorder Delivered via an Automated Media-Rich Web Application – Espie et al., 2012	
How are the findings relevant to the decision problem?	This study reports a randomised controlled trial of *Sleepio* compared to treatment-as-usual and an imagery relief therapy placebo control in adults with DSM-5 insomnia disorder (3 months or longer). *Sleepio* was superior to both placebo and treatment-as-usual conditions for improvements to self-reported sleep diary outcomes including sleep efficiency, sleep onset latency, wake after sleep onset, total sleep time, and also insomnia symptoms and daytime functioning.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • This study has a rigorous placebo control condition in addition to a treatment as usual control. • Data were analysed using intention-to-treat. • Documents improvements in standardised measures of sleep and self-reported sleep diary outcomes. Limitations • Participants were recruited online and therefore may be more interested and motivated to address their sleep problems. • Individuals with poor or very poor physical or mental health were excluded.
How was the study funded?	None reported.

Attribution, cognition, and psychopathology in persistent Insomnia Disorder: outcome and mediation analysis from a randomized placebo-controlled trial of online Cognitive Behavioral Therapy – Espie et al., 2014	
How are the findings relevant to the decision problem?	This study reports a secondary analysis of data from the above trial. Findings demonstrate that *Sleepio* was superior to both placebo and TAU at improving attributions for poor sleep, dysfunctional beliefs about sleep and depression, stress and anxiety symptoms. These factors are thought to maintain insomnia. Improvement in insomnia symptoms was partially explained by improvement in attributions and beliefs about sleep.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia and Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • This study has a rigorous placebo control condition in addition to a treatment as usual control. • Evaluates improvements in factors that maintain insomnia disorder. Limitations • Participants were recruited online and therefore may be more interested and motivated to address their sleep problems. • Individuals with poor or very poor physical or mental health were excluded.
How was the study funded?	None reported.

The anxiolytic effects of cognitive behavior therapy for insomnia: Preliminary results from a web-delivered protocol – Pillai et al., 2015	
How are the findings relevant to the decision problem?	This study showed that, in adults with DSM-5 insomnia disorder (3 months or more), *Sleepio* was associated with benefits to insomnia severity, self-reported sleep onset latency and anxiety symptoms compared to sleep hygiene control.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • An active control condition was used (Sleep Hygiene Education). Limitations • Baseline anxiety was mild and therefore results may not generalise to individuals with more severe anxiety.
How was the study funded?	None reported.

The Pros and Cons of getting engaged in an Online Social Community Embedded Within Digital Cognitive Behavioral Therapy for Insomnia: Survey Among Users – Coulson et al., 2016	
How are the findings relevant to the decision problem?	This study documented the advantages and disadvantages of using the *Sleepio* community within real-world *Sleepio* users. Participants commented that the *Sleepio* community provided continuous support, reduced feelings of isolation, allowed them to be part of a non judgemental community and helped encourage them to keep going. Some disadvantages that were highlighted included design and navigation issues, uncertain quality of user-generated content, negative comparisons with others, time commitments and data privacy concerns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides CBT for insomnia in a stigma free environment.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Lived experience of Sleepio community use in patients with sleep difficulty. Limitations • Participants may have had a more positive experience than others who did not participate.
How was the study funded?	None reported.

Sleep and productivity benefits of digital Cognitive Behavioral Therapy for Insomnia: a randomized controlled trial conducted in the workplace environment – Bostock et al., 2016	
How are the findings relevant to the decision problem?	This randomised controlled trial shows that compared to waitlist control, *Sleepio* results in benefits to insomnia symptoms, sleepiness and presenteeism in adults who self-identified as experiencing poor sleep.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • This study is a randomised controlled trial, examining benefits to workplace outcomes in individuals recruited from a Fortune 500 company. • There was no minimum threshold of sleep difficulties required for inclusion. Limitations • Sleep diary outcomes were uncontrolled as this was only collected for *Sleepio* participants. • No formal screening of other sleep disorders. • As this trial was conducted within employees from a single company, results may not be generalisable.
How was the study funded?	None reported.

Treating depression and anxiety with digital Cognitive Behavioural Therapy for insomnia: a real world NHS evaluation using standardized outcome measures – Luik et al., 2017	
How are the findings relevant to the decision problem?	This cohort study demonstrates the benefits *Sleepio* confers on depression, anxiety and insomnia symptoms in adults who had complaints of poor sleep and comorbid symptoms of depression and/or anxiety and were eligible for referral to IAPT services within England.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides CBT for insomnia in a stigma free environment and improves range of treatment options available to primary care prescribers. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would have not received any treatment at all.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • This study was a service evaluation within an IAPT service in Manchester, thereby providing a real-world evaluation of *Sleepio* and therefore, has high ecological validity. • Compares results of *Sleepio* to standard IAPT targets. • Recovery and reliable recovery rates for *Sleepio* were above IAPT targets. Limitations • Uncontrolled study. • Individuals with higher baseline scores of depression and anxiety did not complete treatment.

Treating depression and anxiety with digital Cognitive Behavioural Therapy for insomnia: a real world NHS evaluation using standardized outcome measures – Luik et al., 2017	
How was the study funded?	None reported.

Helping employees sleep well: effects of cognitive behavioral therapy for insomnia on work outcomes – Barnes et al., 2017	
How are the findings relevant to the decision problem?	In this randomised controlled trial comparing *Sleepio* to waitlist control, *Sleepio* led to significant benefits in insomnia symptoms and workplace outcomes including: negative affect, job satisfaction and self-control in adults who self-identified as poor sleepers.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • This study was a randomised controlled trial using employees recruited from a real-world setting. Limitations • The study had a waitlist control group. • Short-term follow-up (10 weeks from randomisation).
How was the study funded?	None reported.

Sleep to lower elevated blood pressure: a randomized controlled trial (SLEPT) – McGrath et al., 2017	
How are the findings relevant to the decision problem?	Findings from this randomised controlled trial demonstrate that, compared to standard care, *Sleepio* led to improvements in insomnia severity and symptoms, sleep quality and self-reported sleep efficiency in adults with hypertension (130-160/<110m, Hg) who self-reported sleep difficulties in the previous 3 months. Significant improvements were also observed in anxiety and depressive symptoms for *Sleepio* participants compared to controls.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • This study was a randomised controlled trial comparing *Sleepio* to standard care. Limitations • The short-term follow-up did not permit evaluation of the effects of *Sleepio* on long-term outcomes. • Sample had mild hypertension and therefore may have reduced the likelihood to detect changes in blood pressure associated with improved sleep.
How was the study funded?	None reported.

Feasibility of a UK community-based, eTherapy mental health service in Greater Manchester: repeated-measures and between-groups study of 'Living life to the Full Interactive', 'Sleepio' and 'Breaking Free Online' at "Self Help Services' – Elison et al., 2017	
How are the findings relevant to the decision problem?	This study reports a service evaluation of feasibility and outcomes of adults referred either by a healthcare provider or self-referred to an eTherapy mental health service within IAPT. Participants receiving *Sleepio* experienced significant improvements in anxiety and depressive symptoms and work and social functioning.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would have not received any treatment at all. • Provides CBT for insomnia in a stigma free environment. • Improves range of treatment options available to primary care prescribers.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Study was conducted within IAPT services, therefore has high ecological validity. Limitations • No control group. • No long-term follow-up data.
How was the study funded?	None reported.

The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis – Freeman et al., 2017	
How are the findings relevant to the decision problem?	Findings from this randomised controlled trial indicate that, compared to a treatment as usual control, *Sleepio* leads to benefits in insomnia severity and mental health including paranoia and hallucinations in university students with DSM-5 insomnia disorder (assessed using the SCI-8). Improvements in sleep at mid-intervention significantly mediated improvements in paranoia and hallucinations at post-intervention. Compared to treatment as usual, *Sleepio* also led to benefits in secondary mental health outcomes.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Large randomised controlled trial of 3,755 university students. • Used causal mediation analyses. • Improvements in paranoia, and hallucinations were causally mediated by improvements in sleep. Limitations • The study had minimal inclusion criteria and therefore may have resulted in a high degree of self-selection. • Findings may have limited generalisability as the sample comprised university students. • Outcomes were assessed using self-report measures. • High dropout rate, however the results were robust in sensitivity analyses.
How was the study funded?	The study was funded by the Wellcome Trust.

Delivering digital cognitive behavioral therapy for insomnia at scale: does using a wearable device to estimate sleep influence therapy? – Luik et al., 2018	
How are the findings relevant to the decision problem?	These findings demonstrate that, in real world individuals, the effects of *Sleepio* on insomnia symptoms and other outcomes including anxiety and depressive symptoms, stress, life satisfaction and work productivity, do not differ between those connect a wearable device to *Sleepio* and those who do not.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Examines the effects of *Sleepio* in a large (N=3,551) sample of real-world users. • *Sleepio* leads to benefits in insomnia symptoms and mental health symptoms which are equivalent for those who manually enter sleep diary data and those who use a wearable device. Limitations • No randomisation. • No control group of users who do not receive *Sleepio*. • Data were from participants who completed *Sleepio* and therefore, these sample may comprise more motivated individuals. • Due to the limited measures, individuals who connected a device may have differed compared to those who did not connect a device on certain characteristics.
How was the study funded?	None reported.

Insomnia symptoms and their association with workplace productivity: cross-sectional and pre-post intervention analyses from a large multinational manufacturing company – Espie et al., 2018	
How are the findings relevant to the decision problem?	These findings demonstrate that *Sleepio* led to significant improvements in insomnia symptoms and presenteeism in a real-world employee population who self-selected to use *Sleepio.* These individuals, therefore, did not require
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Examines the effects of *Sleepio* in a real-world environment in a group of self-selected individuals – no eligibility criteria were used. • Documents benefits to workplace functioning. Limitations • No randomisation. • Data were analysed from individuals who provided pre- and post-intervention data. • Few measures collected to control for confounders.
How was the study funded?	None reported

Acceptability, tolerability, and potential efficacy of cognitive behavioural therapy for Insomnia Disorder subtypes defined by polysomnography: A retrospective cohort study – Miller et al., 2018	
How are the findings relevant to the decision problem?	In this cohort study, *Sleepio* was shown to be feasible, acceptable and efficacious at improving insomnia severity in individuals with a clinician diagnosis of insomnia disorder with normal or short sleep duration.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Examines the effects of *Sleepio* in two insomnia disorder subtypes. Limitations • No randomisation. • Unable to examine reasons for attrition or non-completion of therapy. • Not all participants received *Sleepio*.
How was the study funded?	National Health and Medical Research Council (NHMRC, Australia) Centre for Integrated Research Understanding of Sleep (CIRUS), NeuroSleep, 1060992 and the Cooperative Research Centre for Alertness, Safety and Productivity, Australian Commonwealth Government.

Efficacy of digital CBT for insomnia to reduce depression across demographic groups: a randomized controlled trial – Cheng et al., 2019a	
How are the findings relevant to the decision problem?	This randomised controlled trial compared the effects of *Sleepio* on insomnia severity and depressive symptoms compared with sleep hygiene education in adults with DSM-5 insomnia disorder (3 months minimum). Participants receiving *Sleepio* experienced significantly greater reductions in insomnia severity and depressive symptoms compared to sleep hygiene education. Depression remission rates were also significantly greater for *Sleepio* compared to sleep hygiene. Importantly, treatment effects were not moderated by race, gender, age or socio-economic status. These results show that *Sleepio* can address both insomnia and depression across different socio-demographic groups.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Randomised controlled trial comparing *Sleepio* to an active control (sleep hygiene education). • Large and diverse sample recruited (n=658). • Examined moderators of treatment effects. Limitations • Per-protocol analysis. • The majority of individuals had mild depressive symptoms at baseline and therefore, findings may not be generalisable to more severe groups.
How was the study funded?	This trial was funded by the Robert Wood Johnson Foundation, the National Institute of Mental Health and the National Heart, Lung and Blood Institute.

Effect of Digital Cognitive Behavioral Therapy for Insomnia on Health, Psychological Well-being and Sleep-Related Quality of Life: A Randomized Clinical Trial – Espie et al., 2019	
How are the findings relevant to the decision problem?	This randomised controlled trial documents that, compared to sleep hygiene education, *Sleepio* leads to significant improvements in physical health, psychological wellbeing and sleep-related quality of life in addition to insomnia symptoms in adults with DSM-5 insomnia disorder (assessed using SCI-8, 3 months or more), many of whom had comorbidities. Insomnia appears to be a therapeutic target by which to improve these outcomes as reductions in insomnia symptoms mediated improvements in physical health, psychological wellbeing and sleep-related quality of life.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Randomised controlled trial comparing *Sleepio* to an active control (sleep hygiene education). • Very large sample (N=1,711). • Examined the mediating role of sleep improvement on primary outcomes. • Individuals had a range of comorbidities. Limitations • Participants were recruited online and therefore may not be directly reflective of the general population.
How was the study funded?	This trial was funded by Big Health Ltd.

Depression prevention via digital cognitive behavioral therapy for insomnia: a randomized controlled trial – Cheng et al., 2019b	
How are the findings relevant to the decision problem?	This study provided 1-year follow-up data to Cheng et al., 2019a. Participants receiving *Sleepio* experienced significantly lower depression severity relative to sleep hygiene education control at 1-year. Rates of depression remission were 51% higher in for *Sleepio* participants compared to participants receiving sleep hygiene. There was a significantly lower incidence rate of moderate-to-severe depression in the *Sleepio* group compared to the sleep hygiene education control group.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Long-term follow-up of the effects of *Sleepio* on depression outcomes • Large sample analysed (n=658). Limitations • Self-reported measure of depression. • Per-protocol analysis. • Did not examine long-term effects on insomnia. • Participants were recruited online and therefore may not be directly reflective of the general population. • The majority of individuals had mild depressive symptoms at baseline and therefore, findings may not be generalisable to more severe groups.
How was the study funded?	This trial was funded by the Robert Wood Johnson Foundation, the National Institute of Mental Health and the National Heart, Lung and Blood Institute.

Is digital cognitive behavioural therapy for insomnia effective in treating sub-threshold insomnia: a pilot RCT – Denis et al., 2020.	
How are the findings relevant to the decision problem?	This randomised controlled trial examines the benefits of *Sleepio* in female adults recruited from universities. There was no specific inclusion criterion for sleep. Findings demonstrated that compared to an attention control, participants receiving *Sleepio* experienced significant benefits to insomnia symptoms and in secondary mental health outcomes (e.g., anxiety paranoia, perceived stress). Improvements in insomnia symptoms experienced by individuals with sub-threshold insomnia were equivalent to the whole sample. Improvements in insomnia symptoms were mediated by changes in beliefs about sleep and pre-sleep somatic arousal. This study, therefore, shows that *Sleepio* can improve sleep in individuals with sub-threshold insomnia symptoms.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Minimal inclusion criteria to examine the effects of *Sleepio* who do not have an insomnia diagnosis and have sub-threshold symptoms. • Used an attention-matched control. Limitations • Only recruited female university students and therefore may not be generalisable to other groups.
How was the study funded?	This trial was funded by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

Efficacy of Digital Cognitive Behavioral Therapy for the Treatment of Insomnia Symptoms Among Pregnant Women: A Randomized Clinical Trial – Felder et al., 2020	
How are the findings relevant to the decision problem?	This randomised controlled trial compared the effects of *Sleepio* to usual care in pregnant women who have had insomnia symptoms for at least 1 month. Compared to usual care, participants receiving *Sleepio* experienced significantly greater improvements in insomnia severity, sleep efficiency and sleep quality. Significant improvements were also observed in measures of anxiety and depressive symptoms. Those receiving *Sleepio* had significantly lower rates of insomnia caseness compared to control.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Minimal inclusion criteria to examine the effects of *Sleepio* who do not have an insomnia diagnosis and have sub-threshold symptoms. Limitations • Remission outcomes were based on self-reported measures rather than a clinical diagnostic interview. • Sample was predominantly white, wealthy and highly educated.
How was the study funded?	This trial was supported by the University of California, San Francisco Preterm Birth Initiative, Bill and Melinda Gates Foundation, a donation from Marc and Lynne Benioff, the National Centre for Advancing Translational Sciences, National Center for Complementary and Integrative Health and the National Heart, Lung and Blood Institute.

Long-term benefits of digital cognitive behavioural therapy for insomnia: Follow-up report from a randomized clinical trial – Luik et al., 2020	
How are the findings relevant to the decision problem?	This study reported long-term follow-up data from Espie et al., 2019. Findings demonstrated that benefits to physical health, wellbeing and sleep-related quality of life were maintained 48-weeks after receiving *Sleepio*. *Sleepio* also led to significant reductions in prescription and non-prescription medication use at 24-weeks, with this effect maintained for non-prescription medication at 48-weeks.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Reduces hypnotic usage and associated risks i.e. dependency, withdrawal, risks of falls and unresolved insomnia.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Long-term outcome data from a randomised controlled trial comparing *Sleepio* to sleep hygiene education. Limitations • The week 48 assessment was uncontrolled.
How was the study funded?	This trial was funded by Big Health Ltd.

Digital Cognitive Behavioral Therapy for Insomnia in Women with Chronic Migraines – Crawford et al., 2020	
How are the findings relevant to the decision problem?	This findings of this study demonstrate the feasibility, acceptability and preliminary efficacy of *Sleepio* to improve insomnia severity in individuals with chronic migraines and insomnia symptoms. Participants also experienced significant reductions in migraine frequency and migraine-related disability.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Provides proof of concept for the use of *Sleepio* to treat insomnia in individuals with chronic migraine and insomnia symptoms. • Used a rigorous multiple baseline design which allows assessment of changes in outcome when a treatment is introduced. Limitations • Treatment acceptability was assessed using a single item. • Only recruited individuals with chronic migraine, therefore may not be generalisable to other headache disorder groups. • Sample comprised entirely of females.
How was the study funded?	This trial was funded an award from the American Sleep Medicine Foundation.

Digital Cognitive Behavioral Therapy for Insomnia for Adolescents With Mental Health Problems: Feasibility Open Trial – Cliffe et al., 2020	
How are the findings relevant to the decision problem?	This study evaluated the feasibility of adding *Sleepio* to usual care for young adults aged 14-17 years with mental health problems and comorbid insomnia symptoms who attend CAMHS services. *Sleepio* was found to be feasible, acceptable and safe. In addition, *Sleepio* led to significant improvements in insomnia symptoms and severity, and measures of anxiety and depressive symptoms.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would have not received any treatment at all. • Provides CBT for insomnia in a stigma free environment. • Improves range of treatment options available to primary care prescribers.
Is any information from this study likely to be used in the economic model?	No

Digital Cognitive Behavioral Therapy for Insomnia for Adolescents With Mental Health Problems: Feasibility Open Trial – Cliffe et al., 2020	
What are the strengths and limitations of this evidence?	Strengths • *Sleepio* was found to be feasible, acceptable and safe within this young adult age group. • Provides valuable feasibility data for *Sleepio* within a young adult sample. • *Sleepio* can be integrated into CAMHS services. Limitations • No control group. • Cannot infer whether improvements were due to *Sleepio* or the face-to-face intervention participants received. • Support phone calls may have confounded the results. • Self-selected sample and participants may have been highly motivated.
How was the study funded?	This trial was funded by Wiltshire CAMHS commissioning group.

The effects of digital cognitive behavioral therapy for insomnia on cognitive function: A randomized controlled trial – Kyle et al., 2020	
How are the findings relevant to the decision problem?	This randomised controlled trial evaluated the effects of *Sleepio* compared to waitlist control on cognitive functioning in adults with DSM-5 insomnia disorder (SCI-8) and self-reported memory difficulties. At post-intervention and follow-up, participants receiving *Sleepio* experienced significantly less self-reported cognitive impairment than control participants. *Sleepio* also demonstrated superiority at improving sleep quality, insomnia severity, fatigue, sleepiness, cognitive failures, and anxiety and depressive symptoms compared to waitlist control. Improvements in self-reported cognitive impairment was mediated by improvements in sleep.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • The sample comprised of individuals with a range of physical and mental health comorbidities. Limitations • Use of a waitlist control arm. • The sample was recruited entirely online and therefore may be a more motivated sample.
How was the study funded?	This study was supported by the NIHR Oxford Biomedical Research Centre.

A randomized controlled trial of digital cognitive behavioral therapy for insomnia in pregnant women – Kalmbach et al., 2020	
How are the findings relevant to the decision problem?	This randomised controlled trial examined the effects of *Sleepio* compared to sleep hygiene education in pregnant women with insomnia during the third trimester. Compared to sleep hygiene education, *Sleepio* led to significant reductions in insomnia severity and significant improvements in sleep quality and sleep duration. Significant improvements were maintained for sleep duration post-partum.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Examined the effects of *Sleepio* during the third trimester and after birth. Limitations • Use of a waitlist control arm. • Relatively short-term follow-up and therefore the limited effects on sleep post-partum may be due to lack of stable sleep for the infant.
How was the study funded?	This study was funded by the American Academy of Sleep Medicine.

Depression prevention in digital cognitive behavioral therapy for insomnia: Is rumination a mediator? – Cheng et al., 2020a	
How are the findings relevant to the decision problem?	This study was a further follow-up analysis of data from Cheng et al., 2019a and examined the role of rumination as a mediator of improvement in insomnia and depression following *Sleepio*. Results showed that participants in the *Sleepio* group experienced significantly greater reductions in rumination than the sleep hygiene education group. Reductions in rumination significantly mediated improvements in insomnia severity and depression severity after *Sleepio*. Reductions in rumination also medicated the prevention of clinically significant depression.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Highlighted the role of rumination as a potential mechanism underlying both insomnia and depression improvement following *Sleepio*. Limitations • Depression was assessed using a self-report measure.
How was the study funded?	This study was supported by the Robert Wood Johnson Foundation and the National Institutes of Health.

Insomnia as a mediating therapeutic target for depression symptoms: A sub-analysis of participant data from two large randomized controlled trials of a digital sleep intervention – Henry et al., 2020	
How are the findings relevant to the decision problem?	This study was a combined subanalysis using data from Freeman et al., 2017 and Espie et al., 2019. Individuals were included in this sub-analysis if they had DSM-5 insomnia disorder (assessed using SCI-8) and clinically significant depressive symptoms (PHQ-9>=10) at baseline. *Sleepio* led to significant improvements in insomnia and depressive symptoms compared to control (waitlist or sleep hygiene education). *Sleepio* also significantly reduced the odds of having clinically significant depressive symptoms. Reductions in insomnia symptoms mediated improvements in depressive symptoms.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Very large sample size (N=3,552) • Examined effects of *Sleepio* on insomnia and depressive symptoms in individuals with insomnia disorder and clinically significant depressive symptoms. • Assessed insomnia symptom improvement as a mediator of depression improvement. Limitations • Samples were recruited as part of two RCTs and, based on the original samples, may not be entirely generalisable. • Depression was assessed using a self-report measure rather than a clinician assessment.

Insomnia as a mediating therapeutic target for depression symptoms: A sub-analysis of participant data from two large randomized controlled trials of a digital sleep intervention – Henry et al., 2020	
How was the study funded?	This study was funded by Big Health Ltd.

Digital Cognitive Behavioral Therapy for Insomnia Promotes Later Health Resilience During the Coronavirus Disease 19 (COVID-19) Pandemic – Cheng et al., 2020b	
How are the findings relevant to the decision problem?	This study was a further follow-up analysis of data from Cheng et al., 2019a and examined the effect of prior use of *Sleepio* compared to sleep hygiene education control on health resilience during the COVID-19 pandemic. Previous use of *Sleepio* was associated with significantly less severe insomnia symptoms during the pandemic compared to those who previously used sleep hygiene. Risk of resurgent moderate-to-severe insomnia was lower in those who previously received *Sleepio* compared to sleep hygiene. Those who received *Sleepio* had significantly lower depressive symptoms, lower odds of moderate-to-severe depressive symptoms, better physical health and fewer COVID-related cognitive intrusions.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Demonstrates that *Sleepio* increases health resilience and may prevent development of future insomnia and mental health difficulties. • Direct impact of COVID-19 was equivalent across both groups. • Shows long-term benefits conferred by *Sleepio*. Limitations • Outcomes were assessed using self-reported measures.
How was the study funded?	This study was supported by the National Institutes of Health.

Adjunctive digital sleep intervention within routine mental health treatment in IAPT – Stott et al., 2020	
How are the findings relevant to the decision problem?	This study shows that Sleepio can be used adjunctively to help with sleep difficulty in those attending IAPTs psychological services for outcomes of depression and anxiety.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all. • Eliminates waiting time for CBT for insomnia. • Provides CBT in a stigma free environment. • Provision of CBT service where face to face CBT is not available or has long waiting times. • Improves range of treatment options available to primary care prescribers. • Improves quality of care by enabling primary care to meet clinical guidelines
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Real-world clinical sample in secondary care settings • Matched control comparison to similar patients from two clinical cohorts • Data collected from IAPT services Limitations • Observational long-term follow-up.
How was the study funded?	Innovate UK funding as part of the Thames Valley project.

Evaluation of fully-automated digital CBT (*Sleepio*) for insomnia at scale in the UK: A retrospective cohort study – Studd et al., 2020	
How are the findings relevant to the decision problem?	This paper evaluates the implementation of *Sleepio* at scale in the Thames Valley in the UK through three referral pathways: self-referral, IAPT referral and primary care referral.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all. • Eliminates waiting time for CBT for insomnia. • Provides CBT in a stigma free environment. • Provision of CBT service where face to face CBT is not available or has long waiting times. • Improves range of treatment options available to primary care prescribers. • Improves quality of care by enabling primary care to meet clinical guidelines

Evaluation of fully-automated digital CBT (*Sleepio*) for insomnia at scale in the UK: A retrospective cohort study – Studd et al., 2020	
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Real-world evaluation of the implementation of *Sleepio* using three referral pathways. • Increases access to and provision of guideline treatment for insomnia. Limitations • Limited capture of socio-economic variables and ethnicity data, therefore it is hard to infer whether implementation in this manner provides access to underserved groups.
How was the study funded?	This study was funded by Innovate UK.

Changes in use of sleep aids following digital cognitive behavioral therapy for insomnia – Drake et al., 2019	
How are the findings relevant to the decision problem?	This study shows that compared to sleep hygiene education, *Sleepio* increased the odds of lower prescription medication use. Reduction in prescription medication was greatest for antidepressants followed by hypnotics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Reduces hypnotic usage and associated risks i.e. dependency, withdrawal, risk of falls and unresolved insomnia.
Is any information from this study likely to be used in the economic model?	Yes
What are the strengths and limitations of this evidence?	Strengths • Provides evidences that a fully-automated digital CBT intervention without a medication reduction component can lead to a reduction in use of prescription sleep medication. Limitations • The observed reductions in medication were small.
How was the study funded?	This study was funded by the National Institute of Mental Health.

Insomnia as a mediating therapeutic target for anxiety symptoms: A sub-analysis of participant data from two large randomized controlled trials of a digital sleep intervention – Kanady et al., 2020	
How are the findings relevant to the decision problem?	This study was a combined subanalysis using data from Freeman et al., 2017 and Espie et al., 2019. Individuals were included in this sub-analysis if they had DSM-5 insomnia disorder (assessed using SCI-8) and clinically significant anxiety symptoms (GAD-7>=10) at baseline. *Sleepio* led to significant improvements in insomnia and anxiety symptoms compared to control (waitlist or sleep hygiene education). *Sleepio* also significantly reduced the odds of having clinically significant anxiety symptoms. Reductions in insomnia symptoms mediated improvements in anxiety symptoms. Reductions in insomnia symptoms at post-treatment and follow-up were moderated by insomnia severity at baseline, with lower baseline SCI-8 scores associated with greater improvements in sleep.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.
Is any information from this study likely to be used in the economic model?	No

Insomnia as a mediating therapeutic target for anxiety symptoms: A sub-analysis of participant data from two large randomized controlled trials of a digital sleep intervention – Kanady et al., 2020	
What are the strengths and limitations of this evidence?	Strengths • Very large sample size (N=2,172) • Examined effects of *Sleepio* on insomnia and anxiety symptoms in individuals with insomnia disorder and clinically significant anxiety symptoms. • Assessed insomnia symptom improvement as a mediator of anxiety improvement. Limitations • Samples were recruited as part of two RCTs and, based on the original samples, may not be entirely generalisable. • Anxiety was assessed using self-report rather than a clinical assessment.
How was the study funded?	This study was funded by Big Health Ltd.

A Population Health Approach to Insomnia Using Internet-Based Cognitive Behavioral Therapy for Insomnia – Derose et al., in review	
How are the findings relevant to the decision problem?	This study shows that compared to in person delivered group CBT for insomnia, *Sleepio* was non-inferior for system related outcomes of dispensed insomnia medications and provider healthcare encounters over 12 months. The *Sleepio* group also demonstrated pre-to-post improvements in sleep-related outcomes.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Eliminates waiting time for CBT for insomnia • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all. • Provides CBT for insomnia in a stigma free environment. • Improves quality of care by enabling primary care to meet clinical guidelines. • Improves range of treatment options available to primary care prescribers.
Is any information from this study likely to be used in the economic model?	Yes

A Population Health Approach to Insomnia Using Internet-Based Cognitive Behavioral Therapy for Insomnia – Derose et al., in review	
What are the strengths and limitations of this evidence?	Strengths • Large population real world implementation study to evaluate the effects of Sleepio in comparison to an active in-person group-based version of CBT for insomnia. • Outcomes consisted of real-world system related outcomes. Limitations • A real-world randomised controlled trial included very large numbers and required a pragmatic hybrid study design to evaluate between group outcomes. This included a matched control group to examine between group effects at post treatment.
How was the study funded?	This study was funded by Kaiser Permanente.

A qualitative examination of the usability of a digital cognitive behavioural therapy for insomnia programme in chronic stroke survivors – Smejka et al., in review	
How are the findings relevant to the decision problem?	This study examined the feasibility and usability of *Sleepio* within adults chronic stroke survivors who had an interest in improving their sleep.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • *Sleepio* was found to be feasible, however, chronic stroke survivors may require support. Limitations • There was no minimum required threshold for sleep difficulties, therefore participants may not have felt the CBT techniques within *Sleepio* were necessary to improve their sleep.
How was the study funded?	This study was funded by the Wellcome Trust

The RESTING Insomnia study: Randomized Controlled study on Effectiveness of Stepped-Care Therapy – Manber et al. in progress	
How are the findings relevant to the decision problem?	This study is comparing the effectiveness of two different approaches to treating insomnia in middle aged and older adults with insomnia disorder in primary care. Specifically, *Sleepio* alone will be compared to stepped care for insomnia (In-person CBT only or Sleepio only, followed by in-person CBT in non-responders).
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all. • Improves range of treatment options available to primary care prescribers.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Examines *Sleepio* compared to and in the context of stepped care. Limitations • Participants are middle-to-older age and therefore the findings may not be generalisable to younger individuals.
How was the study funded?	This study is funded by the National Institutes of Health.

An Investigation into the Efficacy of Online Cognitive Behaviour Therapy for Insomnia ("Sleepio") for Stroke Survivors – Johansen-Berg et al., in progress	
How are the findings relevant to the decision problem?	This study is examining the effectiveness of *Sleepio* compared to sleep monitoring waitlist control in chronic community dwelling adult stroke survivors who self-report sleep difficulties.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Evaluates *Sleepio* in a comorbid sample of chronic stroke survivors. Limitations • Waitlist control.
How was the study funded?	This study is funded by the Wellcome Trust

Therapist-Directed vs Online Therapy for Insomnia Co-Occurring with Sleep Apnea – Edinger et al., in progress	
How are the findings relevant to the decision problem?	This study will compare *Sleepio* with therapist-delivered CBT and usual care in individuals with insomnia disorder and comorbid sleep apnea.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Evaluates the effects of *Sleepio* in a comorbid sleep apnea sample. • Evaluates *Sleepio* in the context of stepped care. Limitations •
How was the study funded?	This study is funded by the National Institutes of Health.

A Sleep Program to Improve Sleep Quality in People with HIV – Fellows et al., in progress	
How are the findings relevant to the decision problem?	This study is examining the effects of *Sleepio* on sleep efficiency insomnia severity, anxiety and depression symptoms and quality of life in adults with HIV compared to a waitlist control.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Examines *Sleepio* in individuals with HIV. Limitations •
How was the study funded?	This study is funded by the Canadian Institute of Health Research.

A pilot study of Digital Cognitive Behavioral Therapy for Veterans – McCaslin et al. in progress	
How are the findings relevant to the decision problem?	This single-case experimental design study is examining the effects of *Sleepio* on insomnia severity in veterans with DSM-5 insomnia disorder with comorbid mental health difficulties (e.g. PTSD symptoms, anxiety or depression).
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Examines *Sleepio* in a sample with comorbid mental health difficulties. Limitations • Small sample size.
How was the study funded?	This study is funded by Big Health Ltd.

CBT to Reduce Insomnia and Improve Social Recovery in Early Psychosis – Jones et al., in progress	
How are the findings relevant to the decision problem?	This randomised controlled trial will examine the effects of *Sleepio* compared to treatment as usual at improving sleep and social recovery in adults with psychosis and insomnia disorder (SCI-8) attending early intervention psychosis services.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. • Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. • Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all.
Is any information from this study likely to be used in the economic model?	No
What are the strengths and limitations of this evidence?	Strengths • Examines *Sleepio* in the context of current secondary mental health services. Limitations •
How was the study funded?	This study is supported in part by Cambridgeshire Peterborough NHS Foundation Trust.

5.3 Results of relevant clinical studies

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Please provide results of all relevant studies in a table format. Example tables are presented below and can be adapted.

Study	Results summary	Company

<table>
<tr>
<td>Espie et al. 2012</td>
<td>At post-intervention and follow-up Sleepio led to significant increases in sleep efficiency compared to both placebo and treatment-as-usual (p<0.0001).

Significant reductions were also observed in sleep onset latency (SOL; p<0.001) and wake after sleep onset (WASO; p<0.0001) at post-intervention and follow-up for Sleepio participants compared to placebo and TAU. Significant reductions were also observed in total time spent awake during the night for Sleepio participants compared with placebo and TAU (p<0.001) at post-intervention and follow-up. Similarly, significant increases in total sleep time (p=0.026) and sleep quality (p=0.003) were observed for Sleepio participants compared to placebo and TAU at post-intervention and follow-up. Beyond improvements in sleep, Sleepio led to improvements in daytime and social functioning (both p<0.0001) in adults with insomnia disorder, and that improvements are superior to both placebo control and treatment-as-usual.

Table 1. Between group effect sizes (Cohen’s d) for each treatment group comparison (CBT = Sleepio; IRT = Placebo; TAU = Treatment as usual) at post-treatment and follow-up.

<table>
<tr><th></th><th colspan="3">Relative effect size (d)
Pre-treatment to post-treatment</th><th colspan="3">Relative effect size (d)
Pre-treatment to 8-wk Follow-up</th></tr>
<tr><th>Variable</th><th>CBT-TAU</th><th>IRT-TAU</th><th>CBT-IRT</th><th>CBT-TAU</th><th>IRT-TAU</th><th>CBT-IRT</th></tr>
<tr><td>Sleep Efficiency, %</td><td>0.95</td><td>-0.06</td><td>1.06</td><td>0.69</td><td>0.15</td><td>1.00</td></tr>
<tr><td>Sleep Onset Latency, min</td><td>-0.45</td><td>0.30</td><td>-0.86</td><td>0.34</td><td>-0.27</td><td>0.86</td></tr>
<tr><td>Wake Time After Sleep Onset, min</td><td>-1.03</td><td>-0.41</td><td>-0.71</td><td>-0.77</td><td>-0.41</td><td>-0.67</td></tr>
<tr><td>Total Wake Time, min</td><td>-0.96</td><td>0.05</td><td>-1.03</td><td>-0.81</td><td>-0.21</td><td>-0.98</td></tr>
<tr><td>Total Sleep Time, h</td><td>0.00</td><td>-0.24</td><td>0.26</td><td>0.32</td><td>-0.26</td><td>0.73</td></tr>
<tr><td>Sleep quality, 0–100 rating</td><td>0.71</td><td>0.33</td><td>0.37</td><td>0.70</td><td>0.32</td><td>0.41</td></tr>
<tr><td>Sleep Condition Indicator</td><td>1.20</td><td>0.33</td><td>0.95</td><td>1.11</td><td>0.34</td><td>0.77</td></tr>
<tr><td>Impact on social functioning, 0-4 rating</td><td>-0.44</td><td>-0.10</td><td>-0.37</td><td>-0.78</td><td>-0.53</td><td>-0.24</td></tr>
<tr><td>Impact on daytime performance, 0-4 rating</td><td>-0.72</td><td>-0.40</td><td>-0.32</td><td>-0.85</td><td>-0.72</td><td>-0.23</td></tr>
</table>

Participants receiving Sleepio experienced a >2-fold improvement in insomnia symptoms (SCI-8), with a large between-group effect compared with TAU (d=1.20) at post-intervention and follow-up (d=1.11). The equivalent effects for Sleepio compared to placebo were d=0.95 and d=0.77 respectively.

At post-intervention 76% of participants in the Sleepio group were no longer classified as having poor sleep (achieved sleep efficiency >80%) which was significantly higher than IRT and TAU (p< 0.001). Similarly, 55% of Sleepio participants achieved a sleep efficiency of 85% (p<0.001), and approaching 40% achieved sleep efficiency ≥ 90% (p=0.001).These benefits were largely maintained during follow-up.</td>
<td>This trial used a rigorous placebo control arm in addition to a treatment as usual control. Significant improvements were observed in self-reported sleep diary outcomes, insomnia symptoms and measures of daytime and social functioning at post-intervention. These effects were maintained at 8-week follow-up.</td>
</tr>
</table>

Espie et al. 2014	*Sleepio* led to treatment effects for all sleep disturbance questionnaire (SDQ) domains (e.g., *Sleepio* vs. placebo: *d* = 0.76 for 'trying too hard'). *Sleepio* was also superior to placebo on the GCTI (e.g., 'rehearsal and planning', d = 0.62; 'sleep and sleeplessness', d = 0.74). CBT vs. TAU comparisons yielded larger effects, whereas placebo effects (IRT vs. TAU) were small to moderate. Hierarchical regression demonstrated partial mediation of SCI improvement by attributional and cognitive factors (R2 = 21–27%) following CBT.	The outcomes examined in this secondary analysis are proposed maintaining factors of insomnia disorder.
Pillai et al., 2015	*Sleepio* led to significantly greater reductions in anxiety ($p<0.05$; $d = 0.8$) and insomnia severity ($p<0.05$; $d = 0.9$) than the sleep hygiene education control group, Similarly, *Sleepio* significantly reduced sleep onset latency compared to control ($p<0.05$; $d = 0.09$). No significant differences were observed in sleepiness or total sleep time (both $p>0.05$).	This study demonstrates that, compared to sleep hygiene education, *Sleepio* has significantly greater reductions in anxiety symptoms and insomnia severity in addition to other sleep outcomes.
Coulson et al., 2016	100 *Sleepio* users completed the online survey. Thematic analysis of responses to open-ended questions revealed five drivers for engagement with the *Sleepio* community: (1) the desire to connect with people facing similar issues; (2) seeking personalised advice, (3) curiosity; (4) being invited by other members; and (5) wanting to use all available sleep improvement tools. Participants described advantages to engaging with the community which included having continued support; feeling less isolated; being part of a nonjudgemental community; receiving personalised advice; having positive comparisons with others; receiving encouragement from others to persist with *Sleepio*; and altruism. A number of disadvantages were highlighted too including: issues with design and navigation; uncertainty of the quality of user-generated content; negative comparisons with others; significant time commitments; and data privacy concerns. Participants attributed their community experiences to engagement with *Sleepio,* indicating that the community supported their efforts to improve their sleep and continue to persist with *Sleepio*. Despite the disadvantages, participants felt that the *Sleepio* community was a valuable resource.	This study comprised 100 real-world *Sleepio* users and describes their perceptions and experience of the *Sleepio* community – a feature of the *Sleepio* platform whereby individuals can engage in discussions with other users.

Bostock et al., 2016	At post-intervention, participants using *Sleepio* experienced significantly lower insomnia symptoms (higher SCI-8 scores) compared to participants in the waitlist control group (p<0.0001), with a large within-group effect size for *Sleepio* (d=1.10) and a small effect size for control (d=0.34). Similarly, *Sleepio* participants had greater improvements in presenteeism at post-intervention compared to control (p=0.001). There were no significant differences in absenteeism between *Sleepio* and control.	This study was conducted in a real-world sample of working individuals. *Sleepio* led to benefits in insomnia symptoms and workplace presenteeism.
Luik et al., 2017	*Sleepio* was provided to 98 adults in an IAPT service who experienced poor sleep in addition to comorbid symptoms of depression or anxiety. Of the 98 adults, 72 (73%) completed *Sleepio*. Significant reductions were observed in anxiety symptoms (p<0.001) and depressive symptoms (p<0.001), in those who completed post-intervention assessments. Effects on anxiety and depressive symptoms remained significant when accounting for missing data (p<0.001). Significant reductions were also observed in insomnia symptoms (p<0.001). 48 of 71 individuals (68%) who scored above caseness thresholds on either the PHQ-9 or GAD-7 at baseline moved to recovery when the last observation was carried forward. 59% of participants (42 / 71) met criteria for IAPT reliable recovery. These proportions are above the IAPT target recovery rate of ≥50% and reliable recovery rate of 43%.	This study documents the effects of *Sleepio* in individuals with poor sleep and comorbid anxiety and/or depressive symptoms in IAPT services. This real-world evaluation demonstrates that *Sleepio* can be implemented successfully and lead to improvements above IAPT averages.

Barnes et al., 2017	*Sleepio* was associated with improvements in insomnia symptoms (p<0.001) and a number of benefits in work outcomes including reduced negative affect, increased job satisfaction and self control. No significant differences were observed between *Sleepio* participants and control on measures of organizational citizenship behaviour or interpersonal deviance.	Results from this study show that *Sleepio* leads to benefits in aspects of workplace functioning in addition to sleep in working individuals.
McGrath et al., 2017	Treatment with *Sleepio* led to significant improvements in sleep efficiency (p=0.02), sleep quality (p=0.04), insomnia severity (p<0.001), insomnia symptoms (p=0.01), depressive (p=0.02) and anxiety symptoms (p=0.0047) compared to control. There were, however, no significant differences in measures of blood pressure between *Sleepio* and standard care.	Results from this study show that *Sleepio* is associated with benefits to sleep and mental health in individuals with sleep difficulties and hypertension.
Elison et al., 2017	Participants using *Sleepio* engaged for a median of 66.35 days. Significant reductions were observed in anxiety and depressive symptoms (both p<0.0001) and improvements were observed in work and social functioning (p<0.0001) from pre-to-post,	In a real-world sample within IAPT, *Sleepio* led to significant improvements in mental health and functioning.

Freeman et al., 2017	In this large randomised controlled trial of 3,755 participants, *Sleepio* was superior to usual care control at improving insomnia severity (*d*=1.11; *p*<0.0001), paranoia (*d*=0.19; *p*<0.0001), and hallucinations (*d*=0.24; *p*<0.0001). Effects were maintained at 22 weeks for these outcomes [insomnia severity (*d*=1.12; *p*<0.0001), paranoia (*d*=0.24; *p*<0.0001), and hallucinations (*d*=0.23; *p*<0.0001)]. Improvements in insomnia at mid-intervention (week 3) significantly mediated reductions in paranoia at post-intervention (week 10) by 29.5%, and change in insomnia over 10 weeks mediated 57.8% of reductions in paranoia. Improvements in insomnia also significantly mediated reductions in hallucinations, with these figures 20.7% and 38.6% for mid-intervention and post-intervention change in sleep respectively.	We believe this to be one of the largest trials ever conducted of CBT for insomnia. Significant improvements were observed in insomnia and a number of areas of mental health at both post-intervention (week 10) and follow-up (week 22). Improvements in sleep resulting from *Sleepio* causally explained reductions in paranoia and hallucinations.

Luik et al., 2018	Users who did not connect a wearable device to estimate their sleep with *Sleepio* had a significantly better sleep and less sleep affected work productivity than device users both at baseline ($p < 0.001$) and at posttherapy (both $p < 0.001$). Those who did not connect a device had less depressive symptoms at post-therapy than those who connected a device ($p < 0.001$). Similar to all users, therapy effects were significant for all variables (insomnia symptoms, depressive symptoms, anxiety symptoms, perceived stress, life satisfaction and work productivity) for both those who connected a device and those who did not connect a device (all $p \leq 0.001$). Further analyses of change scores, i.e. post-treatment scores minus baseline scores, demonstrated that the therapy effect did not differ for change in insomnia between those who connected a device and those who did not.	Users have the option of connecting a wearable device to *Sleepio*. This study shows that treatment effects do not differ between those who connect a device to estimate their sleep and those who do not.
Espie et al., 2018	Data from 214 participants who completed pre and post assessments were analysed. Of these, 124 individuals had relatively good sleep and were provided access to sleep tips. Those with more insomnia symptoms accessed *Sleepio*. Those who accessed *Sleepio* experienced significant improvements in insomnia symptoms (SCI-8; $p<0.001$), and a reduction in sleep's negative impact upon productivity loss (26.6% to 15.6%, $p<0.001$). No significant change was observed in absenteeism.	This study reported data from real-world employees who used *Sleepio*.
Miller et al., 2018	CBT was acceptable to 63% of participants (normal-sleep = 31, short sleep = 29), with 28 completing therapy (tolerability: normal-sleep = 11, short-sleep = 17). For potential efficacy, 39 (normal-sleep = 20, short-sleep = 19) out of 96 participants (41%) completed a follow-up ISI assessment. In this reduced sample, mean (SD) ISI scores decreased across both groups (normal-sleep: 18.0 (4.0) to 10.7 (4.6); short-sleep: 16.5 (5.5) to 11.0 (6.3); both P < 0.01). Those with normal-sleep were more likely to respond (≥6-point ISI reduction) to CBT compared to short-sleep (70%, n = 14/20 vs. 37%, n = 7/19 respectively, P = 0.038). In this cohort, 60 (63%) of participants attempted CBT and of those 28 (47%) completed therapy.	In this study *Sleepio* was either delivered alone or combined with other psychological interventions for insomnia (e.g. face-to-face CBT for insomnia, or SRT).

Cheng et al., 2019a	Sleepio was superior to sleep hygiene education at improving insomnia symptoms (p<0.001) with the average decrease in ISI in *Sleepio* (−10.0 points ± 5.7 S.D.) being twice that of the decrease in the sleep education condition (−4.4 ± 4.6). Significantly more participants in the *Sleepio* group experienced a clinically significant treatment response compared to control (65.1% vs 22.3%; p<0.0001). Similarly, insomnia remission was significantly higher for *Sleepio* compared to sleep hygiene (53.9% vs 14.0%; p<0.0001). Secondary outcomes of depressive symptoms also showed improvement such that *Sleepio* participants had significantly lower depressive symptoms than those in the sleep hygiene education control group. The average decrease in depressive symptoms for *Sleepio* (−4.1 ± 4.7 s.d.) was 2.5 times greater than that of the sleep education condition (−1.6 points ± 3.7). This equated to an effect size of g=0.64. Importantly, the effects of Sleepio on insomnia symptoms and depressive symptoms did not differ between different demographic and socio-economic groups, highlighting its generalizability.	*Sleepio* was associated with significant benefits to insomnia symptoms and depressive symptoms. Importantly, effects were equivalent across different demographic and socio-economic groups, highlighting its generalizability to improve these clinical outcomes.
Espie et al., 2019	Relative to sleep hygiene education, *Sleepio* led to significant improvements in functional health (PROMIS-10) at post-intervention (d=0.31, p<0.001) and follow-up (d=0.31, p<0.001). Significant improvements were also observed in psychological well-being (WEMWBS) for *Sleepio* compared to sleep hygiene education post-intervention (d=0.35, p<0.001) and follow-up (d=0.38, p<0.001). Significant reductions in the negative impact of sleep on quality of life (GSII; improvements in sleep-related quality of life) were observed for *Sleepio* compared to sleep hygiene education on individuals' highest ranked complaint at post-intervention (d=-1.38, p<0.001) and follow-up (d=-1.46, p<0.001). Improvements in insomnia at mid-intervention (week 4) significantly mediated improvements in physical health at post-intervention (week 8) by 50.5%, and change in insomnia over 8 weeks mediated 83.8% of reductions in paranoia at follow-up (week 24). The respective % mediated for psychological well-being was 47.0% and 74.9% respectively, and for sleep-related quality of life was 45.9% and 65.9% respectively.	This randomised controlled trial comprised a very large sample (N=1,711) of adults with insomnia disorder, many of whom had comorbid physical and mental health conditions.
Cheng et al., 2019b	At 1-year follow-up, participants who received *Sleepio* had significantly lower depression severity compared to those who received sleep hygiene education (p<0.001). Incidence of depression was also significantly higher in sleep hygiene participants compared to *Sleepio* participants (18,8% vs 9.6%; OR = 0.51, 95% CI [0.26 to 0.81], p <0.01).	This study shows that *Sleepio* may prevent incident depression at 1 year follow-up.

Denis et al., 2020	Sleepio led to significant improvements in insomnia symptoms compared with attention control (*p*=0.013; *d*=0.42). The effect was similar when looking only at those who met the threshold requirement for subclinical insomnia at baseline (*p*=0.015; *d*=0.51). The effect was smaller for those who met insomnia caseness at baseline. Changes in insomnia were explained by changes in thoughts and worries about sleep and physical arousal.	Results from this RCT show that *Sleepio* leads to benefits in sleep in individuals with subthreshold insomnia symptoms.
Felder et al., 2020	Participants receiving Sleepio experienced significantly greater reductions in insomnia severity than those in the standard care group (p<0.001; d=-1.03). Those receiving *Sleepio* had significantly greater insomnia remission (ISI >=7; 44.0% vs 22.3%; *p*=0.002). Significant improvements were observed in other sleep outcomes including sleep efficiency (*p*=0.001; *d*=-0.51), sleep quality (*p*<0.001; *d*=1.04) and in depression (*p*<0.001; *d*=-0.39) and anxiety symptoms (*p*<0.001; *d*=-0.42). No significant differences were observed ins sleep duration. These effects were consistent at 6-month follow-up.	This study shows that compared to standard care, *Sleepio* is superior at reducing insomnia severity and improving other sleep and mental health outcomes in pregnant women with insomnia.

Luik et al., 2020	This study provided 48 week long-term follow-up data for Espie et al., 2019. Participants who initially received sleep hygiene education were provided access to *Sleepio* at week 25 and therefore analyses at 48 weeks were uncontrolled. *Sleepio* led to improvements in physical health (*d*=0.50, *p*<0.001), psychological wellbeing (*d*=0.55, *p*<0.001) and sleep-related quality of life (*d*=-1.44, *p*<0.001) at 48 weeks compared to baseline. Significant improvements from baseline were also observed for secondary outcomes of anxiety (*d*=-0.44, *p*<0.001) and depressive symptoms (*d*=-0.75, *p*<0.001), insomnia symptoms (*d*=1.54, *p*<0.001), sleepiness (*d*=-0.28, *p*<0.001), fatigue (*d*=-1.04, *p*<0.001), relationship satisfaction (*d*=-0.23, *p*<0.001), cognitive functioning (*d*=-0.37, *p*<0.001), presenteeism (*d*=-0.72, *p*<0.001), absenteeism (*d*=-0.13, *p*=0.008), and life satisfaction (*d*=0.13, *p*<0.001). No significant improvements were observed in job satisfaction. At week 24, *Sleepio* was associated with reductions in use of prescription (adjusted rate ratio [RR}: 0.64, 95%CI: 0.42; 0.97, *p*=0.037) and non-prescription sleep medication (adjusted rate ratio [RR}: 0.52, 95%CI: 0.37; 0.74, *p*<0.0001). Uncontrolled data at 48 weeks showed that effects were sustained for non-prescription medication (*p*<0.001) but not for use of prescription medication (*p*=0.10). No significant changes were observed for healthcare utilisation.	This study examined 48-week follow-up data from a previous RCT of *Sleepio*. Importantly, effects were maintained for all primary outcomes. Results also indicated that *Sleepio* was associated with reductions in the use of both prescription and non prescription sleep medication
Crawford et al., 2020	*Sleepio* was found to be feasible in individuals with chronic migraine and insomnia. Of 42 participants who were randomized to receive *Sleepio,* 35 (83.3%) completed all six sessions within 12 weeks. The majority of completers (33; 94.3%) found *Sleepio* to be acceptable. Of the 35 who completed *Sleepio*, 23 (65.7%) demonstrated a clinically meaningful difference on the ISI (>7 change from baseline). 16 (45.7%) were classified as being in remission (ISI score <8). In addition, 34% of completers reverted from chronic migraine to episodic migraine.	The results of this study show that *Sleepio* is feasible, acceptable and demonstrates efficacy to improve insomnia and migraines.

Cliffe et al., 2020	*Sleepio* led to significant improvements in self-reported sleep efficiency (p=0.005) and sleep quality (p=0.001). Significant reductions were also observed for insomnia severity (p<0.001), insomnia symptoms (p<0.001), depressive symptoms (p=0.03) and anxiety (p=0.005).	This study was conducted in a real-world CAMHS service in Oxfordshire. Results indicate that *Sleepio* is feasible,
Kyle et al., 2020	Compared to waitlist control, *Sleepio* led to significantly less cognitive impairment at 10 weeks post-intervention (d=-0.86, p<0.0001). These effects were maintained at 24 weeks (d=-0.96) and were significantly mediated by reductions in insomnia severity (60.4%) and increased sleep efficiency (29.5%) at 10 weeks. Significant treatment effects for *Sleepio* were observed at both 10 and 24 weeks for insomnia severity, sleep efficiency, cognitive failures, fatigue, sleepiness, depressive symptoms and anxiety symptoms (all p<0.0001). There were no significant between-group effects on objective measures of cognitive functioning.	*Sleepio* led to significant improvements in cognitive functioning in addition to insomnia symptoms in individuals with insomnia and cognitive complaints.

Kalmbach et al., 2020	From pre-intervention to post-intervention, *Sleepio* was associated with significant reductions in insomnia severity (p<0.001), improvements in sleep quality (p<0.001) and increases in sleep duration by 32 minutes (p=0.008). Participants receiving sleep hygiene education did not experience any change. Effects were maintained for sleep duration after birth, with those who used *Sleepio* sleeping for 40 minutes longer than controls. There were no significant effects on depression or cognitive arousal before or after birth.	Findings from this study show that *Sleepio* improves sleep both during and after pregnancy.

Cheng et al., 2020a	Reductions in rumination significantly mediated the improvement in post-treatment insomnia severity (proportional effect = 11%) and post-treatment depression severity (proportional effect = 19%) associated with the dCBT-I condition. Finally, reductions in rumination also significantly mediated the prevention of clinically significant depression via dCBT-I (proportional effect = 42%).	This study shows that improvements in insomnia severity and depression severity are explained by reductions in rumination
Henry et al., 2020	Compared to control, *Sleepio* significantly improved insomnia (p<.001; g=0.76) and depressive symptoms (p<.001; g=0.48) at post-intervention (weeks 8–10), and increased the odds (OR = 2.9; 95% CI = 2.34, 3.65) of clinically significant improvement in depressive symptoms (PHQ-9 <10). Improvements in insomnia symptoms at mid-intervention mediated 87% of the effects on depressive symptoms at post-intervention. No variables moderated effectiveness outcomes on either insomnia or depressive symptoms.	This study was a subanalysis of data from two large effectiveness RCTs. Participants were included if they had probable insomnia disorder (an eligibility requirement for the two original trials) and had clinically significant depressive symptoms defined by a baseline PHQ-9 score ≥10. This led to a final included sample of (N=3,352)

Cheng et al. 2020b	Previous use of Sleepio was associated with less severe insomnia symptoms during the pandemic (b=-2.9 ± 0.8 SE, *p*=0.001 [B = -0.41]). Odds of resurgent moderate-to-severe insomnia (ISI>=15) in those who reported symptom resolution (ISI<8) at 1-year follow-up was 51% lower in those who received Sleepio relative to control (OR = 0.49, 95% CI [0.25, 0.96], *p*<0.001).	This study showed that previous use of *Sleepio* was associated with better less insomnia symptoms and better mental health during the COVID-19 pandemic.

6 Ongoing use and data collection

Briefly describe any ongoing or planned data collection which is aimed at demonstrating the effectiveness of the technology. Provide details of the patients included and the setting where these data are collected and the planned duration. Provide details of any NHS partners involved in the data collection.

Briefly describe if data is collected on an ongoing basis to demonstrate usage of the technology in the target population and improvement in user outcomes or user satisfaction with the technology, where applicable. Provide details of the patients included and the setting where these data are collected and comment on whether ongoing usage data reflects usage required to achieve outcomes reported in the clinical evidence (no more than 1000 words).

Real-world data collection with *Sleepio* is currently ongoing in England, Scotland and the United States. It is anticipated that we will publish future real-world implementation evidence reports of *Sleepio* at scale in the academic literature. These reports will be similar to our current report concerning uptake in the Thames Valley which is in preparation for submission to a journal. It is anticipated that future research will report on clinical effects for outcomes of insomnia, sleep and health outcomes for patients with sub-threshold and full insomnia disorder.

Real-world data are currently being collected from the following locations:

- In England, *Sleepio* is currently available to all residents of the Thames Valley (2.3 million covered lives) and North Hampshire (230,000 covered lives)
- In Scotland, *Sleepio* is available to all residents in the Western Isles (25,000 covered lives) and can be accessed through Social Prescribers (MPower Team) who respond to members of the population who enquire about *Sleepio* from online adverts/news articles.
- In the United States, *Sleepio* is further available to employees through employer-based health plans and employers include large Fortune 500 corporations.

7 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please describe the search in appendix B and provide links and references.

A search was conducted in the FDA MAUDE database on November 24th 2020 with search dates from 23 November 2011 to 23 November 2020 using the device category "Software for Diagnosis/Treatment", manufacturer as "Big Health" and brand name as "Sleepio". No adverse events associated with the technology were found.

Describe any adverse events and outcomes associated with the technology in the clinical and data usage evidence.

Across the 12 RCTs no serious adverse events have been reported related to *Sleepio*. One serious adverse event has been reported (Espie et al., 2019), however this was unrelated to *Sleepio.* In another study, 6 adverse events were reported, three within the control group and three within the *Sleepio* group (Felder et al., 2020) and were similar (miscarriages and stillbirths). The investigators of this study state it is likely that these were caused by factors other than study participation. Adverse effects, captured in a pre-specified questionnaire of 12 potential unwanted symptoms, have been documented in two trials of *Sleepio*. Espie et al., (2019) find that those who received *Sleepio* reported higher occurrence of symptoms including headache, fatigue and difficulty with concentration. Using the same questionnaire, Kyle et al., (2020), found similar rates of adverse effects for those in both *Sleepio* and waitlist control groups and were not statistically different between groups.

8 Evidence synthesis and meta-analysis

If a quantitative evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

8.1 Quantitative review

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

We set out to evaluate the effects of an automated digital cognitive behavioural therapy program (*Sleepio*) for the treatment of self-reported insomnia symptoms, sleep-related outcomes (including sleep quality, quantity, and satisfaction), symptoms of comorbid health conditions, system-related outcomes (including hypnotic drug prescription and incidence of comorbid health conditions), and device-related adverse effects.

The systematic review and meta-analysis were based on an ongoing (unpublished) pre-registered individual participant data meta-analysis including all 12 randomised controlled trials of *Sleepio*. Registered as: PROSPERO 2019 CRD42019105424.

For our systematic search, we searched from 2012 onwards, 2012 was the year of the first published *Sleepio* trial, and we first identified all publications authored by the review team members from Big Health and review collaborators external to Big Health. We then re-conducted and updated a previous systematic search of digital cognitive behavioural therapy for insomnia published by Zachariae et al., (2016). We searched PubMed for the clinical evidence, included all types of trials that specifically evaluated the use of *Sleepio* in both uncontrolled observational and controlled studies. We included studies that evaluated effects on the above outcomes for participants reporting either insomnia disorder (assessed by any recognised diagnostic criteria or self-reported symptoms captured by a validated questionnaire) or subthreshold insomnia symptoms of insomnia disorder at study entry.

We did not limit our methods to specific patient populations and specifically included those studies, which examined the effects of *Sleepio* in pregnant women, people without a diagnosis of insomnia and those with acute and chronic insomnia disorder, and those with insomnia and a comorbid health conditions.

Report all relevant results, including diagrams if appropriate.

The 12 trials used a range of comparators including waitlist control (Bostock et al., 2016; Barnes et al., 2017; Kyle et al., 2020); usual care / treatment as usual (Espie et al., 2012; Felder et al., 2020; Freeman et al., 2017; McGrath et al., 2017), placebo control (Espie et al., 2012); attention control (Denis et al., 2020); sleep hygiene education active control (Cheng et al., 2019a; Espie et al., 2020; Kalmbach et al., 2020; Pillai et al., 2020).

For measures of symptoms of insomnia and sleep difficulty (Insomnia Severity Index, Sleep Condition Indicator), *Sleepio* demonstrated an overall large and statistically significant between group effect size (Cohen's *d*) of 1.05 when compared with control conditions (waitlist, treatment as usual, active sleep hygiene education control, psychological placebo control, attention control) at post treatment (8-12 weeks after randomization) This overall effect size estimation increased to 1.14 at follow-up (22-24 weeks after randomisation) and remained statistically significant.

For measures of symptoms of depression (Patient Health Questionnaire, Beck Depression Inventory), *Sleepio* demonstrated an overall small and statistically significant between group effect size of 0.28 when compared with control conditions at post treatment. This overall effect size estimation increased to 0.45 at follow-up and remained statistically significant.

For measures of symptoms of anxiety (Generalized Anxiety Disorder 7-item questionnaire, Beck Anxiety Inventory), *Sleepio* demonstrated an overall small and statistically significant between group effect size of 0.31 when compared with control conditions at post treatment. This overall effect size estimation decreased very slightly to 0.30 at follow-up but remained statistically significant.

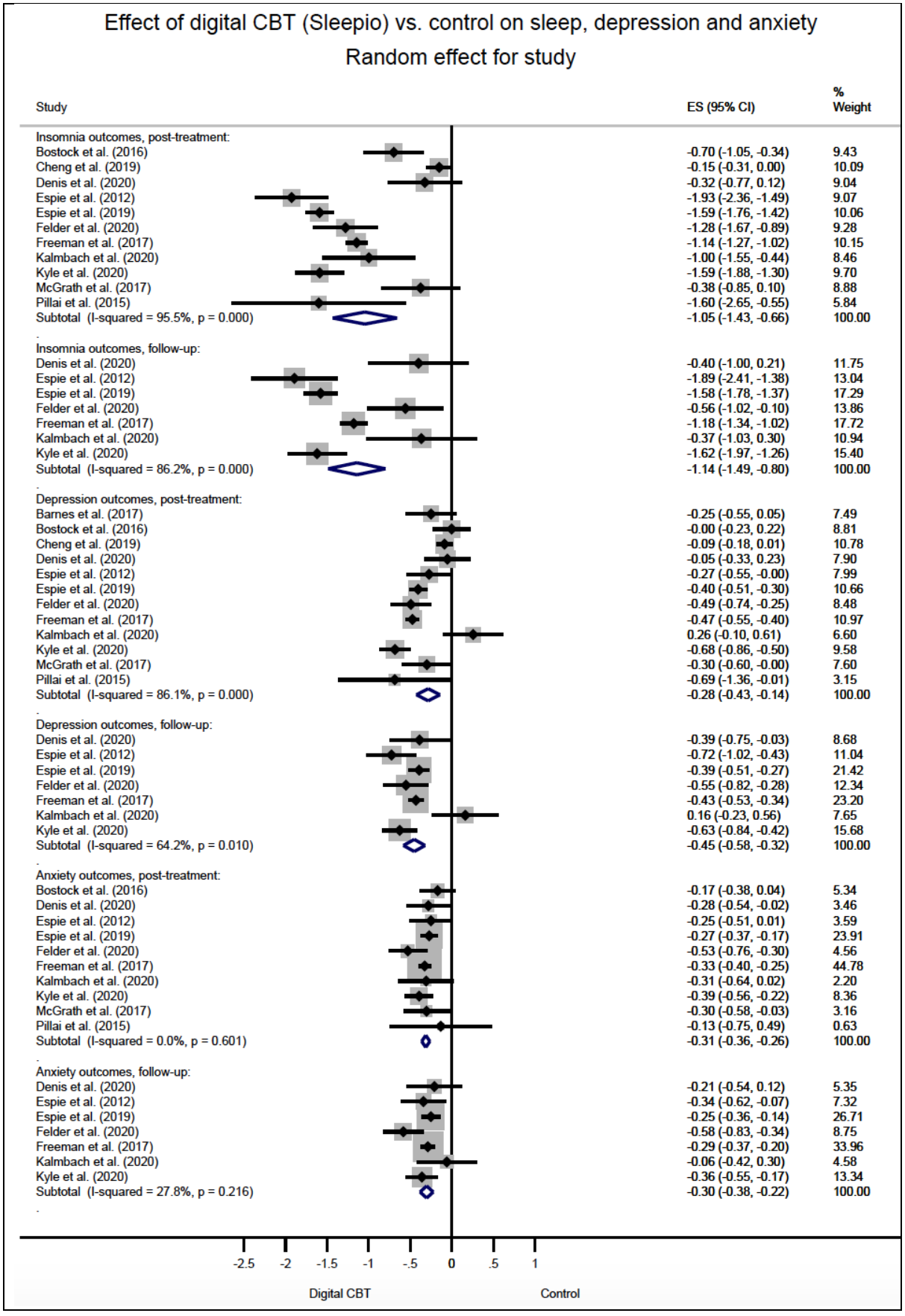


Figure note: P-values for the subtotal-specific overall effects (testing null hypothesis that each overall effect is zero): sleep outcomes post-treatment (z=5.31, p<.001), sleep outcomes follow-up (z=6.50, p<.001), depression outcome post-treatment (z=3.92, p<.001), depression outcome follow-up (z=6.80, p<.001), anxiety outcomes post-treatment (z=12.49, p<.001), anxiety outcomes follow-up (z=7.44, p<.001).

Explain the main findings and conclusions drawn from the quantitative evidence synthesis.

To date, *Sleepio* has been examined in 12 published gold standard randomised controlled trials. An individual participant data meta-analysis, which included 7,845 participants from all 12 trials, demonstrated that *Sleepio* robustly improves outcomes relating to insomnia symptom severity (Insomnia Severity Index) and problems relating to sleep difficulty due to insomnia (Sleep Condition Indicator). Large and clinically meaningful effects were observed at post treatment (at least 8 weeks from randomisation) relative to a range of control conditions. Control conditions included waitlist, treatment as usual, active sleep hygiene education control, and a psychological placebo control (Espie et al., 2012). Effects on measures of insomnia symptom severity and sleep difficulty were sustained at follow-up (at least 22 weeks from randomisation).

Further secondary outcomes relating to comorbid conditions, highly associated with insomnia also demonstrate clinically meaningful and statically significant improvements for outcomes of depression and anxiety at both post treatment and follow-up assessments in comparison with control conditions. Patient populations have included those with insomnia disorder (insomnia duration longer than 3 months: Cheng et al., 2019a; Espie et al., 2012; Espie et al., 2019), shorter than 3 months (Felder et al., 2020), difficulty sleeping with no insomnia diagnosis (Bostock et al., 2016; McGrath et al., 2017; Freeman et al., 2017; Denis et al., 2020), and those with further mental health and physical health comorbidities (Freeman et al., 2017; Espie et al., 2019; McGrath et al., 2017) and pregnant women with sleep difficulty (Felder et al., 2020; Kalmbach et al., 2020).

8.2 Qualitative review

Please only complete this section if a quantitative evidence synthesis for all relevant outcomes is not appropriate.

Explain why a quantitative review is not appropriate for all relevant outcomes.

n/a

Provide a qualitative review for outcomes where a quantitative review is not appropriate. This review should summarise the overall results of the individual studies with reference to the information in Section 5.

Coulson and colleagues (2016), evaluated the use of an online community within *Sleepio*, which includes weekly discussions with experts in sleep medicine, peer discussion forums, and personal message walls. The aim of this qualitative study was to explore the reasons for why participants engaged with the community, uncover potential benefits and identify any issues with the community. In total 100 *Sleepio* participants responded to the survey. Thematic analysis revealed five drivers for engagement (including: connecting with people who face similar issues, personalised advice, curiosity, being invited by others, and wanting to use all of the tools). Advantages included continuous support, reduced sense of isolation, being part of a community, individual advice and encouragement. Disadvantages included design and navigation issues, uncertain quality of user-generated content, negative comparisons with others, excessive time commitments, and data privacy concerns. Many participants stated the community had supported their efforts to improve their sleep and adhere to the program. Despite some concerns, participants overall valued the use of the community.

9 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefits and any risks relating to adverse events from the technology.

Since 2012, 12 randomised controlled trials including 7,845 participants have established *Sleepio* to be safe, efficacious and effective in improving insomnia symptoms for adults. In addition, *Sleepio* improves symptoms related to poor sleep and insomnia such as stress, sleep related wellbeing, workplace productivity and mediates mental health symptoms correlated with insomnia such as depression and anxiety. *Sleepio* has been shown to be effective in improving insomnia symptoms in a broad range of patients with co-morbid conditions including cancer, cardiometabolic, and neurological disorders. *Sleepio* offers a treatment solution for insomnia for pregnant women where sleep medications are contraindicated.

Trial data has been reflected in real world outcomes. *Sleepio* has scaled to 2.3 million people in the Thames Valley where over 20,000 patients received *Sleepio* and those that had completed at least two sessions had a 58% recovery rate for insomnia. Patients experienced no waiting times, and could access CBT-I in their own time in a de-stigmatised environment. *Sleepio* has been shown to be non-inferior to group facilitated CBT-I, raising the potential for *Sleepio* to be cost effective and more accessible than traditionally delivered CBT-I.

Sleepio also leads to reduced usage of sleep medication, and observed real world cost data in the Thames Valley showed reduced primary care costs. When extrapolated to England, *Sleepio* has the potential to save £49m net over 3 years for the NHS.

Sleepio is effective for all types of insomnia

Sleepio has been found to be beneficial for those with a formal insomnia disorder diagnosis and for those with self-reported sleep difficulty. Effects from 12 gold standard randomised controlled trials (RCTs) including 7,845 participants show clinical improvements for outcomes of insomnia symptom severity, associated sleep parameters, and symptoms of further mental health conditions including depression and anxiety. *Sleepio* is superior in comparison with a range of different control conditions including a placebo control, wait-list, treatment as usual (sleep hygiene education, sleep medication, and no insomnia treatment), minimally effective sleep hygiene education, and non-inferior when compared with in-person group CBT-I (Derose et al., in review). Overall clinical effects have been found to persist at longer term follow-ups (Cheng et al., 2020b), with reductions to self-reported use of over the counter and prescription medications for sleep (Luik et al., 2020).

Sleepio mediates mental health symptoms as a cause of insomnia

Sleepio prevents future incidence of depression (Cheng et al., 2019), and causally mediates improvements to depression, anxiety, paranoia and hallucinations by way of improvement to insomnia (Espie et al., 2019; Freeman et al., 2017; Henry et al., 2020; Kanady et al., 2020).

Sleepio is effective in a broad population of patients

In large and pragmatic effectiveness trials, *Sleepio* is clinically effective and safe in 'real-world' populations, and this includes younger and older age groups (feasible in 14-16 year olds, effective in 18 year old university students to older aged adults aged 80+), those with subclinical, and clinically significant comorbid mental health (depression and anxiety disorders) and long term physical health conditions (cancer, neurological, cardiovascular and metabolic disorders). Effectiveness trials further demonstrate *Sleepio* improves outcomes of insomnia symptom severity and sleep difficulty, global measures of functional health and wellbeing, and patient-specific measures of sleep-related quality

of life including diverse demographic groups (Cheng et al., 2018), those at risk of hypertension (McGrath et al., 2017), those who suffer from migraines (Crawford et al., 2020), adolescents with significant mental health problems (Cliffe et al., 2020), and in participants with pre-existing medical and mental health conditions (Espie et al., 2019; Freeman et al., 2017).

Sleepio is effective in real world settings

Sleepio is a fully automated and standardised treatment, and reduces the need for in-person visits, which helps save NHS money when implemented in primary care (Sampson et al., 2020). Real-world clinical service and implementation evaluations have demonstrated *Sleepio* to be acceptable, usable and effective at different levels of care for both insomnia symptoms (Studd et al., 2020) and IAPT rates (Stott et al., 2020). *Sleepio* enables destigmatized access to a mental health treatment has been integrated successfully to both IAPT (Luik et al., 2017; Elison et al., 2017) and Child and Adolescent Mental Health Services in the NHS in England (Cliffe et al., 2020). When asked in qualitative feedback reports, patients are keen to engage with many aspects of the *Sleepio* programme (Coulson et al., 2016).

Given these benefits, *Sleepio* is an effective, used and safe intervention, which provides a scalable first line treatment option for the management of Insomnia Disorder and sleep difficulties at population scale.

Briefly discuss the relevance of the evidence base to the decision problem. This should focus on the claimed benefits proposed by the company and the quality and quantity of the studies in the evidence base.

Quantitative evidence synthesis and meta-analysis
In an individual participant data meta-analysis of 12 gold standard randomised controlled trials including 7,845 participants, *Sleepio* demonstrates large and clinically significant improvements in sleep difficulty and symptoms of anxiety and depression. This means *Sleepio* robustly improves sleep-related and other salient mental health (e.g., anxiety and depressive symptoms) outcomes in the best possible evaluation of clinical evidence. These findings show that *Sleepio* outperforms a range of comparators including waitlist, placebo and attention controls, treatment as usual (e.g., sleep hygiene, medication, no treatment) and sleep hygiene education active control.

Subgroups
A wide range of diverse demographic groups and patient populations have been included in these trials including those with comorbid medical and mental health conditions, pregnant women, people varying degrees of sleep difficulty including those without an insomnia diagnosis and those with different lengths of insomnia duration.

Claimed benefits

The findings of our individual participant data meta-analysis and those of our non-RCT studies show convincing and strong effects on sleep-related outcomes including sleep quality, sleep quantity, insomnia severity and insomnia symptoms, demonstrating *Sleepio* provides **effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia** in broad populations such as pregnant women, younger people, older adults and for those with underlying chronic conditions.

Studies demonstrate that *Sleepio* **improves other salient outcomes, particularly to mental health, wellbeing and to quality of life,** including anxiety (Pillai et al., 2015) and depression in both individuals with insomnia (Cheng et al., 2019; 2020a; 2020b) and insomnia disorder alongside clinically significant depressive symptoms (Henry et al., 2020). These benefits to anxiety and depression have been observed in patients attending IAPT services (Luik et al., 2017), and *Sleepio* improved recovery rates to above IAPT targets (Stott et al., 2020). A large effectiveness study in 3,755 university students showed reductions in paranoia and hallucinations following *Sleepio*, with these reductions mediated by improvements in sleep (Freeman et al., 2017). Another large effectiveness study showed that, compared to sleep hygiene education, *Sleepio* leads to improvements in wellbeing, physical health and sleep-related quality of life. Reductions in insomnia symptoms mediated improvements in these outcomes (Espie et al., 2019).

As discussed above, *Sleepio's* efficacy has translated to the real world where over 20,000 people in the Thames Valley have had immediate access to CBT-I, **eliminating waiting times for CBT-I and providing a CBT-I service where previously unavailable.** These people would **otherwise have been provided with minimally effective sleep hygiene education, non-indicated pharmacotherapy or who would have not received any treatment at all.** Implementation in primary care in the Thames Valley meant that GPs had **increased treatment options for insomnia** beyond sleep

hygiene and medications. By prescribing *Sleepio*, GPs could **improve quality of care by enabling primary care to meet clinical guidelines.**

Qualitative data from Coulson, et al. shows patients feel they benefit from the *Sleepio* community and that support and advice were provided in a non-judgmental space, therefore, *Sleepio* **provides CBT-I in a stigma free environment.**

***Sleepio* reduces hypnotic usage, and by association, reduction in associated risks.** Long-term follow-up data from Espie et al. 2019 show reductions in the use of both over-the-counter sleep aids and prescription sleep medication (Luik et al., 2020). Significant reductions in the use of prescription medication use for sleep was also observed in a secondary analysis of RCT data following *Sleepio* (Drake et al., 2019). The greatest reductions were for antidepressants followed by hypnotics. *Sleepio's* Markov model (Darden, et al., 2020) modelled a significant **reduction in downstream costs related to insomnia** which has been observed in the real world. **Reductions in sleep medication costs and primary care resource costs** has been documented in real world data taken from nine GP practices as part of a health economic study in the Thames Valley (Sampson et al., 2020).

Identify any factors which might be different between the patients in the presented evidence and patients having routine care in the NHS in England.

Clinical trials of *Sleepio* span the clinical trial pathway, from efficacy trials, similar to Phase II testing (e.g. Espie et al., 2012), through to very large pragmatic effectiveness trials, equivalent to Phase III testing (e.g. Espie et al., 2019; Freeman et al., 2017) and naturalistic real-world studies (e.g. Luik et al., 2017; Cliffe et al., 2020). Indeed, the two latter studies have been conducted within NHS care pathways for mental health, IAPT and CAMHS, and therefore are representative of real-world patients who would access *Sleepio*. Recently, *Sleepio* has been evaluated as part of an implementation project within Thames Valley whereby access was provided through three referral pathways: self-referral, IAPT referral and GP referral. This project had 21,004 individuals register to use *Sleepio* and is the largest examination of the implementation of *Sleepio* and digital CBT-I in the UK to date. These data are currently in the process of being analysed and written-up for submission to a peer-reviewed journal.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

Sleepio is intended for use by people with insomnia. This includes those with sub-clinical symptoms as well as patients with chronic insomnia disorder (ICD-10-CM: F51.01). Criteria for the diagnosis of chronic insomnia disorder according to the International Classification of Sleep Disorders (3rd Edition; ICSD-3) are:

1. Difficulty initiating sleep, maintaining sleep or waking earlier than desired
2. Associated impairment in daytime function (e.g. fatigue, cognitive impairment, mood disturbance, daytime sleepiness, dissatisfaction with sleep, impaired social, family, occupational or academic performance, reduced motivation)
3. Reported complaint is not due to inadequate opportunity or circumstances for sleep
4. The sleep disturbance and associated daytime symptoms occur at least three times a week
5. The sleep disturbance and associated daytime symptoms have been present for at least three months
6. The sleep disturbance is not better explained by another sleep disorder

However, recent published research and implementation studies in the NHS provide greater confidence in the extension of use to certain insomnia population sub-groups.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

Strengths

A robust clinical evidence-base across different types of clinical trials from an individual participant meta-analysis of 12 randomized controlled trials. Trials include early stage efficacy evaluations leading to larger more pragmatic real-world effectiveness studies. A range of comparators have been evaluated in trials and these include sham-placebo control, wait-list control and treatment as usual (non-limited access to sleep medication, sleep hygiene control) control conditions. A diverse range of diverse patient populations have been included in these trials which included those from subgroups with sleep difficulty and medical and mental health comorbidities, pregnant women, and those with differing durations of insomnia symptoms and insomnia diagnoses. In a further 14 observational non randomised controlled trials are reflective of how *Sleepio* will be prescribed as a Primary Care treatment in a real-world setting. Studies were also initiated in both the UK and US by investigators external to Big Health Ltd. and without funding from Big Health Ltd., limiting potential conflicts of interest.

Limitations

Observational studies lacked randomisation in certain settings. A number of trials were conducted outside of the UK and in locations where CBT-I is considered the first line recommended treatment option for sleep difficulty. There are no studies directly

comparing *Sleepio* to sleep promoting medication because sleep medication is unsafe and not recommended for longer term insomnia treatment. There is a lack of trials more generally which randomise participants to either CBT-I (any modality) or sleep medication because of safety concerns and a lack of efficacy for medications.

There is a lack of evidence directly comparing *Sleepio* with individual face-to-face or guided CBT-I because it is not routinely available on the NHS and is not scalable to the UK population.

10 Outline of economic evidence

10.1 Population benefiting

Provide an estimate of the numbers of people likely to benefit from use of the technology in year 1 and how uptake will change over time to year 5. Explain assumptions and evidence sources informing your estimate.

Sleepio is accessible free at the point of care if a local NHS system (e.g. CCG, ICS, STP) has funded access for their patient population.

The estimates below are split into two categories:

1. **The number of people with access to *Sleepio*** – this is based on existing contracts held with NHS systems, contracts in negotiation for 2021, and realistic commercial assumptions on future interest leading to additional contracts (and therefore greater numbers of people having access to *Sleepio*).
2. **The number of people starting CBT with *Sleepio*** – this represents anticipated uptake of the CBT portion of the *Sleepio* programme among those populations whose NHS system has funded access (see point 1). Anticipated uptake is estimated based on current rollouts of *Sleepio*.

The estimates below refer to England only and assume that Year 1 is Calendar Year 2021.

	# people with access to Sleepio	# people starting CBT with Sleepio	Assumption
Year 1 (2021)	3,100,000	31,000	n/a
Year 2 (2022)	8,300,000	83,000	4 ICSs procure *Sleepio*
Year 3 (2023)	16,100,000	160,000	6 ICSs procure *Sleepio*
Year 4 (2024)	26,500,000	260,000	8 ICSs procure *Sleepio*
Year 5 (2025)	56,000,000	500,000	National reimbursement agreed with NHSE/I

The estimates above are based on the following assumptions:

- Average size of an NHS Integrated Care System (ICS) = England population / number of ICSs = c. 56m / 44 = c. 1.3m
  Sources: population size: Office for National Statistics; ICS development: NHSE/I, King's Fund)

10.2 List price of technology

Provide the unit list price(s) for the technology, including all related charges such as licence fees and subscription charges (all charges excluding VAT). The cost of the technology used in the base case of the economic modelling must be publicly available. Companies can present additional economic analyses using other technology costs to support their case for adoption. Please highlight any confidential information as explained at the start of the user guide.

The unit list price for *Sleepio* is a treatment tariff of £70 per patient who begins the CBT portion of the programme. This price is designed to deliver cost savings to NHS systems based on the health economic evidence behind *Sleepio*. Discounts on list price may be available if systems wish to procure *Sleepio* at significant scale.

NHS systems have two options when procuring *Sleepio*:

1. Purchase a discrete number of *Sleepio* licenses to cover anticipated treatment volumes
2. Take a 'block funding' approach, whereby they pay a fixed price per person in their population to cover unlimited access to *Sleepio*.

10.3 Value of patient and system benefits

Section 2.2 describes the patient and system benefits. Where possible, provide an estimate of the impact of these changes on NHS annual costs. Explain assumptions and evidence sources informing your estimate. If no financial estimate is possible, describe the anticipated resource savings and related supporting evidence.

Primary care resource use: primary care appointments and medications

Having access to *Sleepio* creates an opportunity for patients to substitute digital CBT-I for more resource-intensive health service use, including primary care contacts and medications.

An unpublished study by Sampson et al (2020) investigated the impact of a population-wide rollout of *Sleepio* in terms of primary care costs in the NHS in England. Costs of GP contacts and relevant prescriptions were assessed for a sample of 10,704 people from nine general practices in Buckinghamshire. Inclusion criteria were used to identify people more likely to use *Sleepio*: a diagnosis of insomnia, depression, or anxiety; any prescription of anxiolytics or hypnotics; or referral to *Sleepio* by a general practitioner. Over a 65-week follow up period, cost savings were estimated to be £3.50 per person, or a total of £37,505 across the nine practices. Extrapolated to the population of England, this implies a potential reduction in primary care costs of around £16 million.

The table below presents projections for the estimates of average cost savings for different populations over different durations. The projections assume that, beyond the period of observation (65 weeks), the trend in primary care costs returns to the trend observed before *Sleepio* rollout.

We note that the table below represents cost savings only. It does not factor in the price of providing *Sleepio* access. See Section 10.2 for pricing and Section 10.6 for net cost savings.

Sample	1 year	65 weeks	2 years	3 years
Per person (95% confidence interval)	£2.36 (-£0.20 – £4.92)	£3.50 (-£0.01 – £7.02)	£7.24 (£0.70 – £13.78)	£12.22 (£1.64 – £22.80)
Nine practices	£25,273	£37,505	£77,493	£130,811
Buckinghamshire	£105,099	£155,969	£322,264	£543,992
Thames Valley	£447,596	£664,240	£1,372,458	£2,316,749
England	£10,894,090	£16,167,022	£33,404,436	£56,387,655

Estimate of downstream cost savings

There is strong evidence that insomnia has a significant negative impact on mental and physical health, including increased risk of anxiety, depression, and cardiometabolic disease (Taylor, et al., 2003; Javaheri, et al., 2017; Lin, et al., 2018; Hertenstein, et al., 2019; Li, et al., 2020).

It is reasonable to assume that providing patients with access to safe and effective treatment for insomnia (such as *Sleepio*) would reduce NHS costs associated with these conditions in those instances where they are caused or exacerbated by untreated insomnia. However, few studies have quantified the health economic impact of insomnia on the NHS.

Darden et al recently reported a model-based cost-effectiveness analysis from a US perspective. The study evaluated the use of *Sleepio* compared with pharmacotherapy and face-to-fact CBT, with outcomes driven by the achievement of remission from insomnia.

This study adopted a broader perspective than health and social care services, incorporating productivity losses. Nevertheless, the researchers reported that *Sleepio* was cost-saving in part due to reductions in health care use associated with lower direct costs of treatment and remission from insomnia. Digital CBT was estimated to dominate all other interventions with the net monetary benefit of $681.06 per patient over six months compared with no treatment.

Cost of delivering face-to-face CBT-I

There is currently a severe lack of therapists trained in CBT-I in England (Thomas, et al., 2016), with only a handful of NHS sleep services offering this treatment.

Building and maintaining a sufficiently large-scale CBT-I service to meet the level of need across the country is unfeasible in terms of cost and available workforce. However, the cost required to deliver in-person CBT-I can serve as a reference point when assessing the economic evidence for *Sleepio*.

One session of in-person CBT-I has an estimated cost to the NHS of £102-173 (Griffiths et al., 2013). Taking the midpoint of this estimate, the cost of six sessions comparable to the *Sleepio* programme is £137.50 x 6 = £825. By comparison, the list price of *Sleepio* is £70 (see 10.2). A meta-analysis of *Sleepio* suggests digital CBT-I is non-inferior to in person CBT (Soh, et al., 2020)

10.4 Training and pathway costs

Section 2.3 describes training requirements, section 3 describes the changes in the clinical pathway(s) and section 3.3 other system changes associated with the technology. Where possible provide an estimate of the impact of these changes on NHS annual costs. Explain assumptions and evidence sources informing this estimate. If no financial estimate is possible, describe the anticipated resource changes that will cause costs to increase. Please provide supporting evidence for any anticipated changes to resource use.

As noted in Section 2.3, launches of *Sleepio* in a healthcare setting will require clinicians and HCPs to attend a 30 minute - 1 hour training session to recap on 1) how to manage poor sleep and insomnia, and 2) how to prescribe *Sleepio* through their electronic patient record system, and 3) how *Sleepio* works and how to describe it for their patients.

In previous launches with the NHS, training sessions have been delivered remotely in existing meeting forums (e.g. Primary Care Network meetings) or over lunch. This avoids any cost associated with reduced time to see patients.

As noted in Section 3, *Sleepio* can integrate with the existing clinical pathway in a way that does not increase workload for NHS staff. Staff can refer patients to *Sleepio* by providing a URL and the programme is fully automated, without the need for ongoing interaction. This avoids cost to the system.

As noted in Section 3.3, other system changes associated with *Sleepio* are negligible. The Big Health team will support with changes to systems (e.g. installing EMIS toaster alerts), while other changes such as adding *Sleepio* to primary care practice websites form part of regular activity for NHS services. Therefore there is no additional cost estimated.

10.5 Other annual NHS costs and savings

Are there any other material costs or savings which have not been described earlier? If so, where possible, provide an estimate the impact of these changes on NHS annual costs. Explain assumptions and evidence sources informing the estimate. If no financial estimate is possible, describe the anticipated resource changes which will cause costs to change. Please provide supporting evidence for any anticipated changes to resource use.

N/A

10.6 Total costs and savings

Given the responses to section 10.2 to 10.5, where possible estimate the annual total costs to implement and operate the technology and the associated annual savings to the NHS. If the total costs and savings will change over time, describe the expected changes. Conclude with a sentence summarising the expected net lifetime savings (that is after all costs have been deducted) to the NHS from using this technology. If no financial estimate is possible please describe the anticipated net lifetime savings and related supporting evidence.

This response should be the consistent with that used in Section 2.2 'Cost benefits'.

It is possible to estimate annual total costs to implement and operate *Sleepio*, along with associated annual savings to the NHS, using the three-year health economic profile outlined in Section 10.3. This represents cost savings associated with *Sleepio* in primary care.

We note that *Sleepio* is likely to be associated with significant additional cost savings to those shown below. These fall into two categories:

1. Downstream cost savings - i.e. those associated with comorbid conditions outlined in Section 10.3
2. Cost savings beyond three years - the health economic modelling conducted by the Office of Health Economics is able to forecast up to a three-year time horizon but this does not mean no cost savings are realisable beyond this. It is likely that treating insomnia will continue to be associated with reduce health costs over time

For this submission, we consider only those cost savings backed by health economic evidence. To do this, we model a three-year contract to align with Section 10.3 and scale to the total population of England to estimate annual savings to the NHS. Savings are shown over a five-year period to capture total savings for each year's cohort of *Sleepio* patients.

	Year 1	Year 2	Year 3	Year 4	Year 5	**TOTAL**
Anticipated # people starting CBT with Sleepio	500,000	500,000	500,000	-	-	**1,500,000**
Cost of unlimited access to Sleepio	£35,000,000	£35,000,000	£35,000,000	-	-	**£105,000,000**
Cost savings (Year 1 cohort)	-£9,929,922	-£20,533,058	-£20,953,818	-	-	**-£51,416,797**
Cost savings (Year 2 cohort)	n/a	-£9,929,922	-£20,533,058	-£20,953,818	-	**-£51,416,797**
Cost savings (Year 3 cohort)	n/a	n/a	-£9,929,922	-£20,533,058	-£20,953,818	**-£51,416,797**
Total cost savings	-£9,929,922	-£30,462,980	-£51,416,797	-£41,486,876	-£20,953,818	**-£154,250,392**

Net cost	**£25,070,078**	**£4,537,020**	**-£16,416,797**	**-£41,486,876**	**-£20,953,818**	**-£49,250,392**

Therefore the expected total net savings to the NHS of a three-year implementation of *Sleepio* are c. £49,250,392.

10.7 Economic evidence

Summarise any existing economic evidence.

Several studies have evaluated the impact of digital CBT-I in terms of costs and economic outcomes. However, these studies have tended to focus on a societal or employer cost perspective (Natsky et al., 2019; De Bruin, van Steensel and Meijer, 2016; Thiart et al., 2016), rather than a health service perspective, and have used data from outside the UK (Darden et al., 2020). It is possible that the majority of the cost savings to society associated with the use of *Sleepio* would arise from savings outside of the health service. In part, this is because *Sleepio* is most likely to be used by patients receiving either no treatment (e.g. where face-to-face CBT-I is unavailable) or receiving low-cost pharmacotherapy that does not correspond with clinical guidance. Nevertheless, these studies suggest that digital CBT-I may be cost-effective from an NHS perspective.

One unpublished study (Sampson, Bell and Cole, 2020) has investigated the impact of *Sleepio* in a population-wide rollout in a region of England, focussing on the impact on primary care costs. *Sleepio* rollout was associated with a change in the trend of primary care costs, such that costs were estimated to be £37,509 lower across nine practices over 65 weeks. Extrapolated to the population of England, the estimates imply a potential reduction in primary care costs of around £16million. The expected impact on primary care costs in any particular setting will depend on the prevalence of the patient characteristics identified above and the uptake of *Sleepio.*

Numerous studies have estimated the excess health care expenditure due to insomnia in Australia (Hillman, Murphy and Pezzullo, 2006; AlGhanim et al., 2008), Canada (Daley, 2009), France (Leger, Levy and Paillard, 1999), and the US (Ozminkowski, Wang and Walsh, 2007). However, few studies from the UK can inform estimates of health care costs attributable to insomnia, with most evidence focussed on productivity and societal costs (Hafner et al., 2017).

Summarise the planned economic analysis detailing likely model structure, relevance to clinical pathway, decision problem and time horizon.

The planned economic analysis will involve development of a cost consequence model, using a decision tree structure, to identify the relative costs and consequences of *Sleepio* as compared to sleep hygiene; hypnotic drugs; and face-to-face CBT (individual and group).

The decision problem will incorporate treatment choice; uptake levels; and treatment adherence. A sub analysis for individuals with anxiety and depression may also be incorporated, if the available evidence allows for it. The time horizon will extend to five years, with sensitivity analysis varying the time point at which individual's primary care resource usage is assumed to return to pre-*Sleepio* levels.

Though the focus of our model, and the primary analysis, will adopt an NHS cost perspective, we will also report societal costs and economic outcomes, such as productivity and absenteeism.

Describe the main parameters in the planned economic analysis and the key sources of uncertainty.

Parameters for the model will be identified through a separate systematic review (to be described in the Economic Evidence Submission). The main parameters in the planned economic analysis will be uptake of and adherence to treatment; cost of delivering treatment, remission from insomnia; and changes in primary care resource use. Key sources of uncertainty are the rates of uptake and adherence, and time horizon over which trends in primary care resource usage are believed to continue post treatment.

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Please include all references below using NICE's standard referencing style.

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12 Appendices

Appendix A: Study identification for clinical and economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	25th November 2020
Date span of search:	1st January 2012 - 25th November 2020
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
A search was performed in PubMed from 1st January 2012 until 25th November 2020 using the following search terms: (Sleep OR Insomnia) AND (digital CBT OR internet CBT OR web CBT OR Sleepio)	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
As investigators must contact Big Health Ltd. to use Sleepio for research, we had a database of 26 published studies that had used Sleepio. These were included within the systematic review and any duplicates sourced as part of the PubMed search were removed.	
Inclusion and exclusion criteria:	
1. Using Sleepio 2. Any study design was permitted 3. Articles written in English 4. Full published articles	
Data abstraction strategy:	
The results of the PubMed literature search were downloaded as a csv file in excel. Details of the 26 published studies of Sleepio were added to those sourced from the PubMed search. After this, duplicates were highlighted and removed. Titles and abstracts were then reviewed for each paper and those not meeting the above inclusion criteria were excluded at that point if eligibility could be determined from either the title or abstract.	

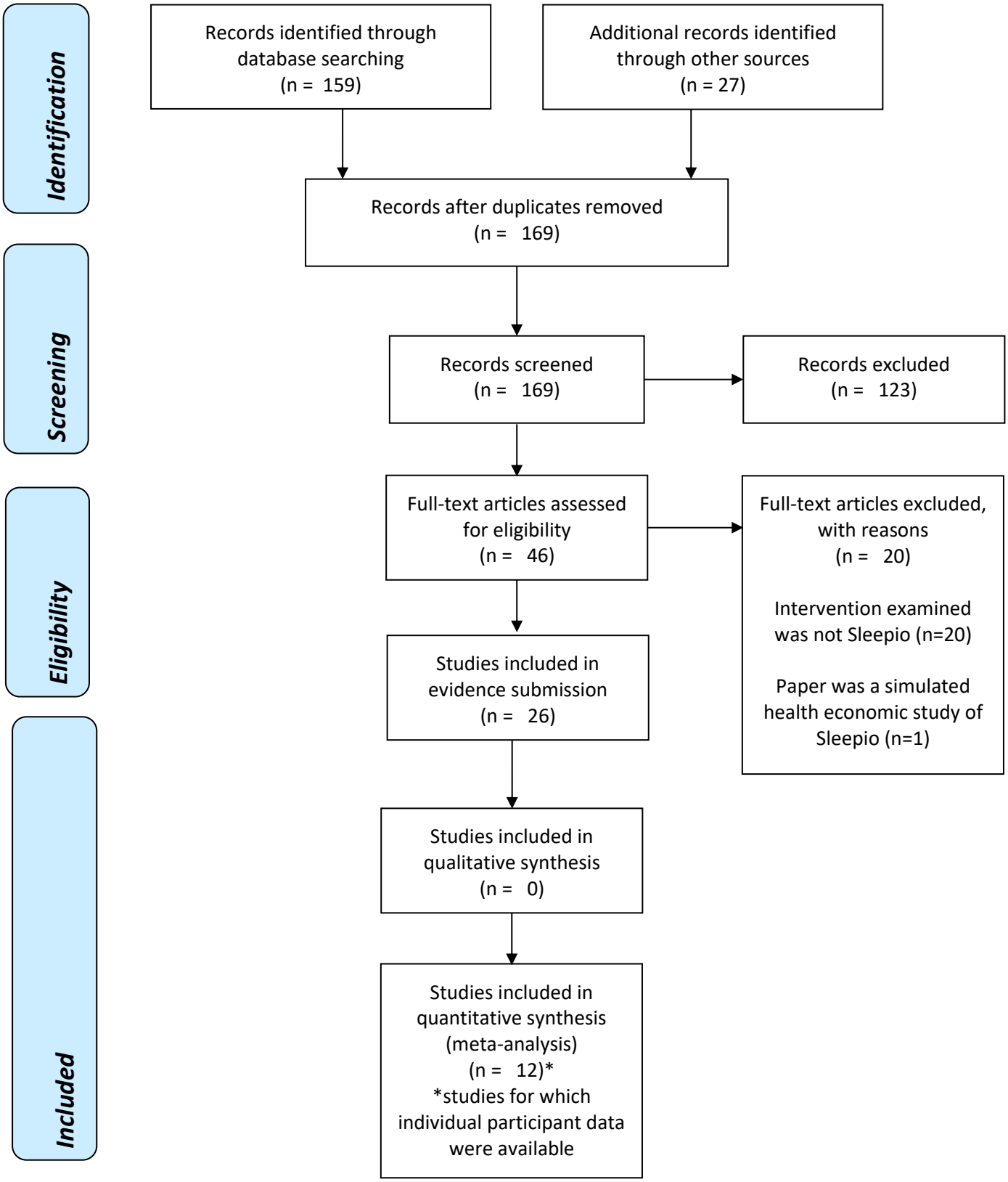
The full text manuscripts were then reviewed for all remaining papers and those that were not eligible were then removed at this stage.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Text	**Text**	**Text**	**Text**
Text	**Text**	**Text**	**Text**
Text	**Text**	**Text**	**Text**
Text	**Text**	**Text**	**Text**
Text	**Text**	**Text**	**Text**
Text	**Text**	**Text**	**Text**
Text	**Text**	**Text**	**Text**

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Structured abstracts for unpublished clinical studies

Changes in use of sleep aids following digital cognitive behavioral therapy for insomnia – Drake et al., (2019), USA.
Cognitive behavioral therapy for insomnia is now recommended as first-line treatment for chronic insomnia, and can be delivered digitally (dCBT-I) for increased access. Furthermore, dCBT-I confers an advantage of reduced adverse events relative to pharmacologic interventions (e.g., hypnotics and other sleep aids).
This study examined if treatment with dCBT-I can also reduce use of sleep aids compared to an online sleep education control.
1232 individuals with insomnia (DSM-5 diagnostic criteria) were randomized into two conditions: dCBT-I (N=639), or an online sleep education control (N=593). Use of medications for sleep (prescription and non-prescription) were assessed pre-treatment and post-treatment. Responses were categorized into general classes of medications (i.e. benzodiazepine, hypnotic, antihistamine, etc.), and compared across time points between the two conditions.
Results from a repeated-measures mixed-effects logistic regression indicated that the odds of prescription medication was significantly lower following dCBT-I compared to control (OR=0.09, 95%CI[0.02, 0.34]). Specifically, whereas prescription medication use in the control group increased from 16.5% to 18.0% at post-treatment, prescription medication use in the dCBT-I group decreased from 17.8% to 14.6%. Change in prescription medication use was more pronounced for antidepressants, followed by hypnotics. No differences were found in use of non-prescription medications.
This study provides preliminary evidence that use of prescription sleep aids may decrease following completion of dCBT-I. Together, this suggests that a minimally resource intensive intervention may have a small effect in reducing reliance on prescription sleep aids.
Published conference abstract. Drake, Christopher L; Cheng, Philip; Tallent, Gabriel; Atkinson, Rachel; Cuamatzi, Andrea S; et al. *Sleep*, suppl. 1; Westchester Vol. 42, (Apr 2019): A149. DOI:10.1093/sleep/zsz067.365

A qualitative examination of the feasibility of a digital cognitive behavioral therapy for insomnia program in chronic stroke survivors – Smejka et al., in review.
Sleep is commonly impaired after stroke. Current primary treatment for sleep difficulty is Cognitive Behavioural Therapy for Insomnia (CBT-I). Digital CBT-I offers a novel way to deliver this treatment at scale. "*Sleepio*" is effective in insomnia cohorts but has not yet been tested specifically in stroke survivors.
Before testing the efficacy of Sleepio in this population, we first wanted to explore its feasibility.
Participants were given access to the digital CBT-I program, Sleepio. Self-reported sleep measures were recorded at baseline, in addition to participant demographics. Participants discussed their experiences with the program during a semi-structured interview following completion. Thematic analysis was used to find common themes within the interview responses.
Five themes emerged from the interviews: (1) positive experiences led to increased engagement with the program, (2) motivation to follow the program was related to perceived severity of sleep problem, (3) impractical advice for stroke survivors, (4) negative experiences led to reduced engagement with the program and (5) difficulty operating the program.
In its current form, *Sleepio* is feasible for most stroke survivors to use. However, stroke survivors with certain disabilities highlighted issues with some aspects of the program indicating that not all suggestions were practical for everyone. We therefore suggest possible adaptations which may make the program more easily usable and engaging for a stroke survivors with varying impairments.
Manuscript under review at a Neuropsychological Rehabilitation.

Adjunctive digital sleep intervention within routine mental health treatment in IAPT. – Stott et al., 2020.
Insomnia is widely recognized as having a bidirectional relationship with broader mental health functioning, including anxiety and depression. Yet, poor sleep has historically been neglected as a specific treatment target in mental health programmes (Freeman et al, 2020).
To evaluate the impact on mental health outcomes of routinely introducing an adjunctive digital sleep intervention into real world care within an English IAPT service.
All patients over a 12 month period entering the IAPT service endorsing a 'poor sleep' questionnaire item at intake assessment, were offered a self-guided digital sleep intervention, Sleepio, in addition to their routine care. Propensity score matching established a non-Sleepio control group matched on demographic and baseline measures. Routine IAPT metrics (PHQ-9, GAD-7) were analyzed to compare standardized outcomes and recovery rates, as well as the total durations of clinical input.
Patients who signed up to Sleepio (n=552) achieved significantly better final outcomes on PHQ-9 and GAD-7 than the matched controls. At discharge from IAPT, recovery rates rose to 64.7%, significantly higher than the 58% in the control group. Overall duration of clinical contact time was marginally elevated in the Sleepio group but the difference amounted to less than one hour.
This study demonstrated, in a real-world setting, the clinical benefit of a specific focus on an evidence-based sleep intervention alongside other mental health interventions for depression and anxiety. The digital and self-guided nature of Sleepio enabled widespread deployment with immediate availability, and minimal additional clinical time or staff training requirements. It is argued this approach provides a feasible and highly scalable model for improving mental health outcomes in clinical services.
Manuscript in preparation for submission to a journal.

Treatment of insomnia with digital cognitive behavioral therapy (dCBT) reduces anxiety symptoms: A sub-analysis of participant data from two large randomized controlled trials. – Kanady et al., 2020.
Insomnia and anxiety are closely related and exhibit a bidirectional association. Worry and anxiety often precipitate and perpetuate sleep problems and poorer sleep exacerbates subsequent anxiety symptoms. Previous research suggests that treatment of insomnia with cognitive behavioral therapy for insomnia (CBT-I) reduces anxiety symptoms.
Here we examine whether a fully automated digital CBT-I intervention (Sleepio) reduces anxiety and insomnia symptoms. We also examine the mediating role of sleep improvement on anxiety symptoms and explore possible moderators of treatment effects.
Participants from two previously published randomized controlled trials were included in the analyses. All participants met criteria for probable insomnia disorder and had clinically significant anxiety symptoms (GAD-7≥ 10, N= 2,172). Participants were randomized to digital CBT-I or a control condition and treatment effects were assessed at post-treatment (weeks 8 and 10) and follow-up (weeks 22 and 24) assessments.
Compared to the control condition, digital CBT-I significantly reduced anxiety and insomnia symptoms at post-treatment (GAD-7: p< 0.01, g= 0.44; SCI-8: p< 0.01, g= 0.81) and follow-up (GAD-7: p< 0.01, g= 0.39; SCI-8: p< 0.01, g= 0.77) and increased the odds of reliable remission from anxiety symptoms (post-treatment: OR= 2.24, 95% CI= 1.73, 2.89, p< 0.01; follow-up: OR= 2.03, 95% CI= 1.54, 2.68, p< 0.01). Reductions in insomnia symptoms mediated 84% of the effects on anxiety symptoms at post-treatment. Reductions in insomnia symptoms at post-treatment and follow-up were moderated by insomnia severity at baseline, with lower baseline SCI-8 scores associated with greater improvements in sleep.
Our findings suggest that a fully automated digital CBT-I intervention is effective for the treatment of insomnia and anxiety symptoms. These findings further underscore the idea that insomnia may be an important therapeutic target to help manage anxiety symptoms.
Manuscript in preparation for submission to a journal.

A Population Health Approach to Insomnia Using Internet-Based Cognitive Behavioral Therapy for Insomnia – Derose et al., in review.
Chronic insomnia is common and contributes to both mental and physical health problems, and internet-based cognitive behavioural therapy for insomnia has shown to be an effective treatment. This study evaluated a population health approach to insomnia using internet-based cognitive behavioural therapy.
To determine if a population health approach to insomnia using internet based cognitive behavioral therapy for insomnia (ICBT-I) effects dispensed medications and provider encounters compared to usual care.
A pragmatic hybrid study design was used to evaluate both the implementation strategy and the long-term effects of ICBT-I on health care utilization in an integrated health system. Adult members with insomnia (a diagnosis or insomnia medication dispensation) or at high-risk of insomnia (a diagnosis of depression or anxiety) were randomized to receive information on either an ICBT-I program (intervention arm) or in-person classes on insomnia (usual care arm). Outcomes included dispensed insomnia medications and provider encounters over 12 months. The effectiveness of our implementation of ICBT-I on the target population was determined by an intention-to-treat analysis and by regression models comparing those who engaged in ICBT-I to matched usual care arm controls.
136,630 subjects were randomized. 638 (0.96%) accessed the ICBT-I program while 431 (0.66%) attended one or more usual care insomnia classes. Dispensed insomnia medications and provider encounters were no different in the ICBT-I arm vs the usual care arm (intention-to-treat) or among those who engaged in ICBT-I vs matched usual care arm controls.
Since ICBT-I program engagement was low, additional strategies to improve engagement should be explored. ICBT-I did not result in a reduction in key measures of health care utilization compared to in-person insomnia classes; nevertheless, it offers an alternative and accessible approach to managing population insomnia.
Manuscript under review at a Journal of Clinical Sleep Medicine.

Evaluation of fully-automated digital CBT (Sleepio) for insomnia at scale in the UK: A retrospective cohort study – Studd et al., 2020.
Cognitive Behavioural Therapy (CBT) for insomnia is the first-line recommended treatment for insomnia. Barriers, however, prevent widespread access to and provision of CBT at a national level.
Here we report the uptake and clinical results of a UK-based large-scale implementation project of a fully automated digital Cognitive Behavioral Therapy (CBT) intervention for insomnia, Sleepio.
Digital CBT for insomnia (Sleepio) was made available in the Thames Valley (2.7 million citizens). Individuals could access Sleepio through three referral pathways: (i) self-referral, (ii) Improving Access to Psychological Therapies (IAPT) service referral, and (iii) primary care referral. Uptake was examined across and by referral pathways. Improvements in insomnia symptoms were evaluated before and after Sleepio in those who demonstrated clinically significant insomnia (measured by the 2-item version of the Sleep Condition Indicator: SCI-2) at entry and started treatment (completed session 2).
21,004 participants registered for Sleepio (13,650 from self-referral, 2,387 from IAPT and 4,967 from primary care). For clinical effects, 15,615 (74%) scored ≤2.5 on the SCI, indicating clinical insomnia symptoms, and of these, 2,723 (17%) completed session 2, and 2,148 completed session 3 (14%). Of those who were in the clinical range at baseline and completed session 2, 1,578 (58%) moved out of the clinical range after Sleepio.
Digital CBT for insomnia (Sleepio) can be effectively delivered at scale through self-referral, IAPT and primary care pathways. Distribution through existing clinical pathways and self-referral can provide access to a wider population and may help overcome barriers to accessing evidence-based digital CBT for insomnia
Manuscript in preparation for submission to a journal.

Appendix B: Search strategy for adverse events

Date search conducted:	23 November 2020
Date span of search:	23 November 2011 to 23 November 2020
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Search conducted on FDA Manufacturer and User Facility Device Experience (MAUDE) from 23 November 2011 to 23 November 2020.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Enter text.	
Inclusion and exclusion criteria:	
Device: Software for Diagnosis/Treatment Manufacturer: Big Health Brand Name: Sleepio	
Data abstraction strategy:	
No record of adverse events were found in the FDA database: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/results.cfm	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
Espie et al., 2019	Randomised controlled trial	One serious adverse event reported and deemed unrelated to Sleepio.	Rates of adverse effects (captured by the pre-specified questionnaire) were

		Adverse effects were also captured by a pre-specified questionnaire of 12 potential unwanted symptoms and included headache, fatigue and difficulty with concentration	higher in the Sleepio group than the control group.
Felder et al., 2020	Randomised controlled trial	Six adverse events reported, three within the control group and three within the Sleepio group.	The investigators of this study state that it is likely that these were caused by a factor other than study participation.
Kyle et al., 2020	Randomised controlled trial	Adverse effects captured by a pre-specified questionnaire of 12 potential unwanted symptoms and included headache, fatigue and difficulty with concentration	Rates of adverse effects for those in the *Sleepio* and waitlist groups were not statistically different between groups.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

See PRISMA flow diagram above.

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for information about identifying confidential information and instructions on how to complete this section. As stated there it is the company's responsibility to highlight any commercial- or academic-in-confidence data clearly and correctly:

- information that is commercial in confidence should be underlined and highlighted in blue
- information that is academic in confidence should be underlined and highlighted in yellow.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*:

** Must be Medical Director or equivalent*

Date: 11 December 2020

Print: Professor Colin Espie

Role / organisation: Chief Medical Officer and co-founder, Big Health

Contact email: colin@bighealth.com

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Digital Health Technology (DHT) Pilot

MT443 Sleepio for adults with poor sleep

Company evidence submission

Part 2: Economic evidence

Company name	Big Health Ltd
Submission date	12 January 2021
Contains confidential information	No

November 2019 v1.0

Contents

1 4

1.1 4

1.2 4

1.3 18

2 37

2.1 37

2.2 38

2.3 47

2.4 47

3 51

3.1 51

3.2 51

3.3 53

3.4 62

3.5 63

3.6 64

4 67

4.1 67

4.2 69

4.3 69

4.4 70

4.5 72

4.6 73

4.7 73

5 75

6 79

6.1 79

6.2 79

6.3 79

7 81

\8 86

Appendix A: Structured abstracts 27
Appendix B: Model structure 28
Appendix C: Search strategy for resource use 29
Appendix D: Checklist of confidential information 30

1 Published and unpublished economic evidence

1.1 Identification and selection of economic studies

Complete the following information about the number of economic studies identified.

Number of economic studies identified as being relevant to the decision problem (as per Part 1 submission, Section 4).		12
Of the relevant economic studies identified:	Number of published economic studies.	9
	Number of economic abstracts.	0
	Number of ongoing economic studies.	3

1.2 List of relevant economic studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix D.

Table 1 Summary of all relevant economic studies (published and unpublished)

Author, year, location and published (P) or unpublished (U)	Patient population and setting	Intervention [version(s)] and comparator	Results	Sensitivity analysis and conclusion
Darden et al., 2020, United States, P	Simulated, 100,000 individuals seeking treatment for insomnia	Sleepio (dCBT), pharmacotherapy, individual CBT, group CBT, none.	Digital CBT was cost-beneficial when compared with no insomnia treatment and had a positive net monetary benefit of $681.06 (per individual over 6-months).	Bootstrap sensitivity analysis demonstrated that the net monetary benefit was positive in 94.7% of simulations. Relative to other insomnia treatments, digital CBT was the most cost-effective treatment because it generated the smallest incremental cost-effectiveness ratio (-$3,124.73). Digital CBT was the most cost-effective insomnia treatment followed by group CBT,

				pharmacotherapy, and individual CBT. It is financially prudent and beneficial from a societal perspective to utilize automated digital CBT to treat insomnia at a population scale.
De Bruin et al, 2016, Amsterdam, P	Participants were aged 12-19 years. Online and mental health care centre setting.	Internet-delivered CBT vs in person group CBT	Primary analysis showed costs over 1 y were higher for face to face group therapy (GT) but effects were similar for internet delivered (IT) and GT. Bootstrapped ICERs demonstrated there is a high probability of IT being cost-effective compared to GT. Secondary analyses confirmed robustness of results.	No sensitivity analyses were reported. Internet CBTI is a cost-effective treatment compared to group CBTI for adolescents, although effects were largely similar for both formats. Further studies in a clinical setting are warranted.
Thiart et al., 2016, Germany, P	128 adult school teachers, online	ICBT-I compared to waitlist control group	Assuming intervention costs of €200 ($245),	Two sensitivity analyses of intervention costs were conducted in order to

			cost-effectiveness analyses showed that at a willingness-to-pay of €0 for each positive treatment response, there is an 87% probability that the intervention is more cost effective than treatment as usual alone. Cost-benefit analyses led to a net benefit of €418 (95% confidence interval: −593.03 to 1,488.70) ($512) per participant and a return on investment of 208% (95% confidence interval: −296.52 to 744.35). The	assess the robustness of the findings. In the main analysis, the authors used intervention costs of €200. However, there exists uncertainty concerning these costs, as prices may differ once the intervention is integrated into occupational health care. Therefore, all analyses were repeated assuming two additional conditions of 50% (€100) and 150% (€300) intervention costs. Sensitivity analyses led to similar results, confirming the robustness of these results. Focusing on sleep improvement using iCBT-I may be a cost-effective strategy in

			reduction in costs was mainly driven by the effects of the intervention on presenteeism and to a lesser degree by reduced absenteeism.	occupational health care.
Kjørstad et al., 2020, St Olavs University Hospital, Department of Psychiatry, Trondheim, Norway, P	Outpatient sleep clinic, 101 patients	Digital vs face to face CBT	Study participants showed significant improvements in presenteeism ($p = .001$; Cohen's $d = 0.46$), total work impairment ($p < .001$; $d = 0.48$), and activity ($p < .001$; $d = 0.66$), but not absenteeism ($p = .51$; $d = 0.084$) between baseline and follow-up assessment. Individuals meeting criteria for remission showed significantly greater improvement in	The authors do not report any sensitivity analysis. This study suggests that the benefits of CBT-I extend beyond improvement in sleep to encompass moderate-to-large improvements in work productivity and activity levels particularly for individuals who achieve remission from insomnia.

			presenteeism (p = .002), total work impairment (p < .001), and activity (p = .006), but not absenteeism (p = .064).	
Shaffer et al, 2020, USA, P	Online, recruitment via a study website	Internet Delivered CBT-I compared to patient education (PE)	Participants randomized to SHUTi were about 50% less likely than those in the PE condition to report any absenteeism, total impairment, or activity impairment at post-assessment; however, differences were not detected at 6- or 12-month follow-ups. SHUTi participants also reported lower overall levels of presenteeism, total impairment , and activity impairment at post assessment relative to PE participants. Differences were	The authors do not report any sensitivity analyses. Findings suggest that Internet-based CBT-I may help accelerate improvement in work-related and daily activity impairment corroborating prior research, but did not find that CBT-I has persistent, long-term benefits in productivity relative to basic insomnia education.

			sustained at 6-month follow-up for presenteeism. No differences were detected by 12-month follow-up.	
Behrendt et al, 2020, German health insurance company, P	177 workers, online	Web-based self-help iCBT-I compared routine occupational health care	Participants who received iCBT-I reported significantly lower insomnia severity scores at post intervention (between-group mean difference −4.36; 95% CI −5.59 to − 3.03; Cohen d=0.97) and at 6-month follow-up (between-group difference: −3.64; 95% CI −4.89 to	The robustness of the assumption regarding missing outcome data was examined in a series of sensitivity analyses (missing data patterns and inclusion of sample characteristics associated with having missing outcomes, eg, number of completed modules). In conclusion, the results of this study give further indications that an internet-delivered self-help CBT-I adapted for workers has stable

			−2.39; Cohen d=0.86).	effects up to 6 months after the training began.
Blom et al, 2016, Internet Psychiatry Clinic, Stockholm, Sweden, P	148 media recruited nondepressed adults with insomnia	Guided internet-based cognitive behavioral therapy for insomnia (ICBT-i) or active control treatment (ICBT-ctrl).	The large pretreatment to posttreatment improvements in insomnia severity of the ICBT-i group were maintained during follow-up. ICBT-ctrl exhibited significantly less improvement posttreatment (between-Cohen d = 0.85), but after 12 and 36 months, there was no longer a significant difference. The within-group effect sizes from pretreatment to the 36-months follow-up were 1.6 (ICBT-i) and 1.7 (ICBT-ctrl), and 74% of the interviewed participants no longer had insomnia diagnosis after 36 mo.	A sensitivity analysis was conducted including only hypnotic medication such as zolpidem, zopiclone and propiomazine which did not change the result in a significant way (P=0.015). The large improvements in the ICBT-i group were maintained after 36 months, corroborating that CBT for insomnia has long-term effects. After 36 months, the groups did not differ in insomnia severity, but ICBT-ctrl had used more sleep medication and undergone more

			ICBT-ctrl used significantly more sleep medication (P = 0.017) and underwent significantly more other insomnia treatments (P < 0.001) during the follow-up period.	other additional insomnia treatments during the follow-up period.
Luik et al, 2020, UK, USA, Australia, P	1711 adults, online	Sleepio compared to sleep hygiene education (SHE)	dCBT improved functional health (difference: 2.45, 95% confidence interval [CI]: 2.03; 2.88, Cohen's d: 0.50, p < .001), psychological well-being (difference: 4.34, 95% CI: 3.70; 4.98, Cohen's d: 0.55, p < .001) and sleep-related QoL (difference: −44.61,	No sensitivity analyses were reported. In conclusion, this study suggests that dCBT results in sustained benefits to insomnia and its daytime outcomes.

			95%CI: −47.17; −42.05, Cohen's d: −1.44, p < .001) at week 48 compared to baseline. At week 24 dCBT, compared to SHE, also reduced use of prescription and non-prescription sleep medication up to week 24 (adjusted rate ratio [RR]: 0.64, 95% CI: 0.42; 0.97, p = .037 and adjusted RR: 0.52, 95% CI: 0.37; 0.74, p < .0001, respectively), but not healthcare utilization. Uncontrolled follow-	

			up suggests that these effects were sustained for non-prescribed sleep medication (RR: 0.52, 95% CI: 0.40; 0.67, p < .001).	
Moloney et al, 2020, Appalachian Kentucky, USA, P	46 women, online	Pre and post SHUT-i intervention	Positive and statistically significant (p < .01) improvements were observed on mean scores for the Insomnia Severity Index (15.1 to 6.5), the Pittsburgh Sleep Quality Index (12.1 to 8.5), the Perceived Stress Scale (20 to 14.6), and the Center for Epidemiologic Studies Depression Scale Revised (9.8 to 5.2). The odds of reporting sleep	No sensitivity analyses were reported Internet-based CBT-I may be a useful, non-pharmacologic treatment that reduces insomnia severity, perceived stress, depression symptoms, and sleep aid use in middle-aged Appalachian women.

			medication use post-intervention were significantly lower than pre-intervention (OR 0.28 [95% CI 0.11–0.74]). Interviews highlighted most and least helpful intervention components and suggested that participants benefitted from SHUTi.	
Stott, R et al, forthcoming, Buckinghamshire, UK, U	510 participants, mental health clinical setting	Participants in an Increasing Access to Psychological Therapies (IAPT) programme offered Sleepio compared to a non-Sleepio control group, matched on demographic and baseline clinical measures via propensity score matching.	Patients who signed up to Sleepio (n=510) achieved significantly better outcomes on core clinical metrics (PHQ-9, GAD-7, WSAS) than controls. Recovery rates rose to 64.7%, versus 58% in the control group. Duration of clinical contact time was marginally elevated overall in the Sleepio	No sensitivity analyses were reported Significant clinical benefit was associated with the introduction of an evidence-based digital sleep intervention alongside other mental health interventions for depression and anxiety. Widespread deployment was achieved with immediate availability,

			group but by less than one hour.	minimal additional clinical time or staff training. This approach provides a feasible and highly scalable model for improving mental health outcomes in clinical services.
Stokes, E, forthcoming, UK, U	n=743, trial setting	Additional analysis of trial data, mapping from PROMIS to EQ-5D	EQ-5D scores were significantly ($p<0.05$) greater in Sleepio participants at week 4 (mean difference [95%CI] = 0.020 [0.005, 0.036]), week 8 = 0.043 [0.026, 0.060]), and week 24 = 0.035 [0.018, 0.052]. The mean difference for QALYs gained was 0.018 [0.010, 0.025] higher ($p<0.05$) in Sleepio participants than controls.	Sleepio was associated with more QALYs than the control at 8-, 24-, and 48-week follow-up. Multiple imputation was used to handle missing values in a sensitivity analysis and found similar results.

Sampson, C et al (2021), England, U	n=10,704. Primary care, relevant diagnoses and prescriptions	Sleepio (population rollout): before-and-after	The absolute difference in mean weekly costs per person, associated with Sleepio rollout, is a saving of £6.64 per person over the 65-week follow-up period, including the initial rollout period. Sleepio rollout reduced primary care costs by £71,027.	Several models were used as sensitivity analysis of alternative specifications, testing assumptions about seasonal adjustment and assuming fixed effects for different diagnoses. Findings were robust. In conclusion, the rollout of Sleepio in the Thames Valley resulted in lower primary care costs across nine practices.

1.3 Details of relevant economic studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Cost-effectiveness of digital DBT (Sleepio) for insomnia: A Markov Simulation model in the United States, Darden et al., 2020	
What are main differences in resource use and clinical outcomes between the technologies?	The authors considered both direct costs to payers and indirect costs to society - additional healthcare utilisation, loss of work productivity and risk of workplace accidents. The authors find that digital CBT generates the lowest overall cost by assumption, followed by group CBT, no treatment, pharmacotherapy, and then individual CBT. The study did not report on clinical outcomes but estimated QALYs for each comparator, based on insomnia status. All treatments were effective compared with no treatment. dCBT-I and individual CBT-I were associated with the highest number of QALYs, while pharmacotherapy was the least effective treatment.
How are the findings relevant to the decision problem?	The authors compared Sleepio with sleep medication and face to face CBT.
Does this evidence support any of the claimed benefits for the technology? If so, which?	● Reduces hypnotic usage and associated risks i.e. dependency, withdrawal, risk of falls and unresolved insomnia. ● Reduces hypnotic drug prescriptions and associated costs. ● Reduced downstream costs of untreated insomnia.
Will any information from this study be used in the economic model?	This study does not report any primary data collection or novel observational evidence. Therefore, its use in our modelling is only as a methodological guide.
What cost analysis was done in the study? Please explain the results.	The study examines the cost-effectiveness and potential net monetary benefit of Sleepio for the treatment of insomnia, compared with no insomnia treatment, in the United States. The authors employ a simulated Markov model of 100,000 individuals using parameters calibrated from the literature including direct costs (treatment) and indirect costs (e.g. insomnia-related health care expenditure and lost workplace productivity). Health utility estimates were converted into quality-adjusted life years (QALYs) and one QALY was assumed to be worth $50,000.

	100,000 simulated individuals were randomised equally to one of 5 arms: 1. dCBT-I 2. Pharmacotherapy 3. Individual CBT-I 4. Group CBT-I 5. No treatment All costs and benefits were summed over a 6-month period. **Results** Direct costs associated with pharmacotherapy was defined as an 100-day course of generic zolpidem, at a cost of $144.10, and the mean cost of two physician office visits, estimated at $114.40 each. The direct cost of digital CBT (Sleepio) was modelled as a one-time payment of $400 for 12-months access (healthcare provider expenditure as not available direct-to-consumers). The cost of 6-months of individual CBT assumed six visits at $174/visit and was estimated at $1,044. The cost of group CBT was $172.50 per individual using an average (across locations in the US) non-facility rate of $28.75 multiplied by six visits. For each session of clinician delivered CBT (individual and group CBT), the authors also included costs of two hours of pay for time spent away from work using the median hourly wage ($27.96) in the US from the Bureau of Labor Statistics. This cost is experienced because the majority of clinician-delivered sessions are delivered during work time. Individual costs such as travel costs for patients to access clinician-delivered CBT were not included. The lower direct costs of Sleepio compared with the other treatments were due to a reduction in pharmacotherapy costs, CBT appointment costs and costs associated with productivity loss. Indirect costs associated with insomnia were also considered. Health expenditures related to insomnia are higher than for individuals without insomnia. The authors also consider the indirect cost associated with the risk of workplace accidents. (Shahly et al., 2012) found an additional one percentage point chance of a workplace accident costs more than $500 for those with insomnia relative to those that do not. In addition, the cost of accidents associated with insomnia was found to be more than $6,000 more expensive compared to those that were not attributed to insomnia.
What are the strengths and limitations of this evidence?	The findings of this study are similar to previous work, which found both guided digital-CBT and clinician-delivered CBT to be cost-effective. The analysis includes indirect costs from a

	societal perspective, which are highly relevant in this context, including reductions in health care expenditure, workplace accident risk, and improvements to workplace productivity. As the sample was constructed of homogenous individuals, the authors were not able to explore heterogeneity in cost-effectiveness. The assumed parameters may not reflect the heterogeneity in individual health backgrounds and responsiveness to treatment. The use of dichotomous end states of insomnia vs. remission is a simplification of clinical states. The model also does not account for selection into treatment, combination of multiple treatments, or the impact of insomnia recurrence.
How was the study funded?	Big Health

Cost Effectiveness of Group and Internet Cognitive Behavioral Therapy for Insomnia in Adolescents: Results from a Randomized Controlled Trial, De Bruin et al (2016)	
What are main differences in resource use and clinical outcomes between the technologies?	Total healthcare costs over 12 months were reduced by €146.83 per adolescent for internet therapy compared with group therapy. Clinical outcomes were comparable between groups.
How are the findings relevant to the decision problem?	This study provides comparison between different modes of CBT-I delivery. However, it focuses on a subset of the population of interest and includes children. The inclusion of a range of cost-related outcomes are relevant to our decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	● Reduces hypnotic drug prescriptions and associated costs. ● Reduced downstream costs of untreated insomnia.
Will any information from this study be used in the economic model?	Provides further evidence of the potential cost-savings associated with Internet-based CBT. However, the estimates will not be used as parameters in our modelling.
What cost analysis was done in the study? Please explain the results.	The aim of the study was to investigate the cost-effectiveness of CBT-I delivered through the Internet (non-Sleepio) compared to face-to-face group CBT-I for adolescents in the Netherlands. Cost-effectiveness is estimated from a societal perspective with a time horizon of 1 year.

	Costs and effects data up to 1-year follow-up were obtained from a randomized controlled trial comparing Internet CBT-I to face-to-face group CBT-I. Sixty-two participants meeting DSM-IV criteria for insomnia were randomized to face-to-face group CBT-I (n = 31, age = 15.6 y ± 1.8, 71.0% girls) or individual Internet CBT-I (n = 31, age = 15.4 y ± 1.5, 83.9% girls). The intervention consisted of six weekly sessions and a 2-month follow-up booster-session of CBT-I, consisting of psychoeducation, sleep hygiene, restriction of time in bed, stimulus control, cognitive therapy, and relaxation techniques. Group therapy sessions were held in groups of six to eight adolescents guided by two trained sleep therapists. Internet therapy consisted of individual therapy with pre-programmed content similar to the group therapy, and guided by trained sleep therapists. For comparisons of cost effectiveness, the authors conducted a primary analysis and several secondary analyses to test robustness of the outcomes from the primary analysis. Measures were obtained at baseline, at post-treatment after the 6 weeks of treatment were completed but before the booster session (i.e. approximately 15 weeks after baseline), and at 1-year follow-up (i.e., approximately 37 w after posttreatment). Outcome measures were subjective sleep efficiency (SE) ≥ 85%, and quality-adjusted life-years (QALY). At each measurement occasion, parents filled out retrospective cost questionnaires that reported on resource usage over the past 2 months (e.g., doctors' visits, use of medication, mental health care visits, additional help at school/home, etc.). A family perspective was used, meaning all costs related to the adolescent were taken into account, including direct and indirect costs for health care usage such as doctor visits and medication use, and direct and indirect non-health care costs such as informal care, parents' loss of (non)paid work, traveling expenses, and tutoring of the adolescent. Costs were calculated by multiplying the resources used by the unit price of each resource in the Netherlands. Shadow prices were used if an official price unit was not available and the friction cost method was used to calculate productivity losses of parents. Costs of CBT-I were calculated based on the hours spent by therapists to apply the CBT-I protocol. For both therapy

	modalities, therapists registered the hours spent to prepare and deliver the consults, for administrative purposes, and for intervision and supervision sessions. The unit price of group therapy was €468 and the unit price of Internet therapy was €397 (a difference of €71).
What are the strengths and limitations of this evidence?	The study is the first cost-effectiveness study on treatments for adolescents with insomnia. However, it is a relatively small trial that does not include evaluation against treatment as usual. In the costing of the Internet therapy, there are some uncertainties about which costs should be regarded as ongoing and which are sunk costs. The authors also identify that their study is limited in adopting an intention-to-treat analysis and not providing evidence on the non-inferiority of Internet therapy.
How was the study funded?	The Netherlands Organization for Health Research and Development ZonMw

Internet- Based Cognitive Behavioral Therapy for Insomnia: A Health Economic Evaluation, Thiart et al (2016)	
What are main differences in resource use and clinical outcomes between the technologies?	From the employers' perspective, over six months the intervention was estimated to save €78 due to absenteeism and €540 due to presenteeism per participant. With intervention costs at €200, the net benefit for €418 per participant at six months. However, these results were not significant at 95%; the probability of a positive financial return was 66%. 42.2% of participants were responders to the treatment in the intervention group, and 6.3% in the control group. There was an 87% probability that the intervention produced greater health effects at lower (direct and indirect) costs than the control condition.
How are the findings relevant to the decision problem?	The intervention being evaluated is guided dCBT-I, unlike Sleepio which is self-guided. Guided and self-guided dCBT-I interventions will have different resource use implications and may have different levels of efficacy. Although the study was conducted in Germany, the treatment as usual comparator is similar to what is typically available in England. However, the study does not investigate differences in resource use from a health care perspective.

Does this evidence support any of the claimed benefits for the technology? If so, which?	● Reduced downstream costs of untreated insomnia.
Will any information from this study be used in the economic model?	The results will be used in a secondary analysis incorporating societal costs. Although this study evaluates guided dCBT-I, we will use the reported findings to inform our estimates of the impact of Sleepio.
What cost analysis was done in the study? Please explain the results.	This study evaluated the cost-effectiveness and cost-benefit of providing a dCBT-I to symptomatic employees from the employer's perspective, using a randomised controlled trial. School teachers (N = 128) in Germany with clinically significant insomnia symptoms and work-related rumination were randomized to guided dCBT-I or a waitlist-control-group, both with access to treatment as usual (in the country setting, treatment as usual for elevated insomnia symptoms usually indicates visits to the general practitioner followed by more intensive interventions such as CBT and sleep medication if insomnia symptoms persevere or worsen). Economic data were collected at baseline and 6-month follow-up. Two analyses were conducted: a cost-effectiveness analysis with positive treatment response as the outcome and a cost-benefit analysis. Treatment response was defined as positive if the score on the Insomnia Severity Index (ISI) (1) decreased by 5.01 points and (2) fell below the cut-off score of 8, which classifies a participant as being symptom-free. Both analyses were performed from the employer's perspective, focusing specifically on absenteeism and presenteeism costs. Costs due to absenteeism were based on the human capital approach. In order to measure absenteeism, participants were asked how many days they had been absent from work during the past 3 months (work loss days). To measure costs, work loss days were then multiplied to the participant's average gross daily wage based on their self-reported monthly salary. Production losses due to presenteeism were measured by asking participants to report how many days during the past 3 months they went to work even though they were bothered by their health problems. The number of days was then multiplied by a self-reported inefficiency score, which ranged between 0 and 1 (where 0 means as efficient as when in good health and 1 means totally inefficient) to obtain workday equivalents lost to presenteeism. Subsequently, based on self-reported monthly salary, their gross wages per hour were calculated

	and were used to calculate the costs that occurred due to presenteeism.
What are the strengths and limitations of this evidence?	A key strength of this study is that it uses a randomised design. There are several sources of costs and resource use that the study does not capture, including workplace accidents. The sample is comprised solely of currently employed teachers, and so results may not be generalisable to a wider population. The sample size may have been too small to detect statistical significance with appropriate power in the cost-benefit analyses. The follow up period of six months may have been too short to detect all cost impacts.
How was the study funded?	The European Union funded this study.

The Effect of Reducing Insomnia Severity on Work- and Activity-Related Impairment, Kjørstad et al (2020)	
What are main differences in resource use and clinical outcomes between the technologies?	At 6-month follow-up, participants reported lower mean scores of presenteeism and WI but not absenteeism, compared with baseline mean levels. At 6-month follow-up, 37 participants (48.1%) met the response criteria, whereas 31 (40.3%) did not. 30 participants (39.0%) were in remission, whereas 38 (49.4%) were not. Responders reported lower levels of WI but there were no significant differences in absenteeism and presenteeism. Participants who were in remission from insomnia reported significantly lower mean levels in presenteeism and work impairment, but not in absenteeism compared with participants who were not in remission at follow-up. In a preliminary comparison of patients randomized to receive either digital or face-to-face CBI, there were no differences in absenteeism, presenteeism or total work impairment. Activity impairment may also be considered a facet of resource use from a societal perspective, for example in in terms of ability to provide informal care. Participants reported lower mean scores of AI impairment at 6 month follow up (M = 46.8, SD = 29.4) compared to baseline (M = 27.2, SD = 30.0; p < .0.001). Responders and participants in remission experienced greater decreases in AI impairment, but there was no difference between

	participants who received face-to-face CBT and those who received digital. No clinical outcomes reported.
How are the findings relevant to the decision problem?	The study does not inform us about the resource use effects of dCBT-I from an NHS and PSS perspective, but does provide context about these effects from a societal perspective.
Does this evidence support any of the claimed benefits for the technology? If so, which?	● Reduced downstream costs of untreated insomnia.
Will any information from this study be used in the economic model?	The results will be incorporated into our reporting of societal costs and economic outcomes, which are a secondary focus of our model.
What cost analysis was done in the study? Please explain the results.	The aims of this study were (1) to test if individuals with insomnia disorder who receive CBT for insomnia demonstrate any improvements in levels of work productivity or day-time activity following therapy, and (2) to examine if potential improvements in work-related outcomes differ according to the observed change in insomnia severity. The study represents a secondary analysis of data on a subset of a sample recruited to a Norwegian RCT comparing the clinical effectiveness of fully automated digital and face-to-face CBT for insomnia (Kallestad et al., 2020). The key eligibility criterion for inclusion in the secondary analysis was that the individual reported being in paid employment at the time of entry into the RCT. Individuals from both arms of the RCT were included (N=77). Pre- and post-intervention levels of absenteeism, presenteeism, work impairment and activity impairment were assessed using the work productivity and activity impairment questionnaire: general health (WPAI). Paired sample t-tests were conducted to test the hypothesis that levels of self-reported absenteeism, presenteeism, total Work Impairment (WI), and level of Activity Impairment (AI) 6 months post-CBT-I would be significantly lower compared with baseline levels. Independent sample t-tests were conducted to test the hypothesis that at 6-month follow-up, individuals with baseline insomnia disorder who then met criteria for insomnia response or remission would report lower work impairment scores compared with non-responders and non-remitters, respectively. Supplemental independent t-tests were conducted to test differences in

	variables between participants who received CBT-I either face-to-face or digitally.
What are the strengths and limitations of this evidence?	The WPAI has good psychometric properties and has been more frequently used than any other metric of productivity across various occupations and disease areas (Bolge et al., 2009). The main limitation of this study is that there is no control group, meaning it is not possible to ascertain whether the results are attributable to the CBT interventions. The results represent effects only on patients employed at the time of the intervention; inclusion of insomnia patients who are unemployed prior to treatment would be necessary to examine whether treatment of insomnia may help people regain employment. It is also unclear how generalisable the (relatively small) sample is to the employed population of the country of the study, and furthermore England.
How was the study funded?	The study was supported by St. Olavs University Hospital, The Norwegian National Advisory Unit on Sleep Disorders, and the Norwegian Dam Foundation for Health and Rehabilitation.

Effects of an Internet-Based Cognitive Behavioral Therapy for Insomnia Program on Work Productivity: A Secondary Analysis, Shaffer et al (2020)	
What are main differences in resource use and clinical outcomes between the technologies?	Participants randomized to SHUTi were about 50% less likely than those in the PE condition to report any absenteeism (logistic regression odds ratio [OR] = 0.48 [95% confidence intervals {CI} = 0.24,0.96]), total impairment (OR = 0.52 [95% CI = 0.29,0.93]), or activity impairment (OR = 0.50 [95% CI = 0.30,0.85]) at post-assessment; however, differences were not detected at 6- or 12-month follow-ups. SHUTi participants also reported lower overall levels of presenteeism (constrained longitudinal data analysis MDiff = −6.84 [95% CI = −11.53, −2.15]), total impairment (MDiff = −7.62 [95% CI = −12.50, −2.73]), and activity

	impairment (MDiff = −7.47 [95% CI = −12.68, −2.26]) at post assessment relative to PE participants. Differences were sustained at 6-month follow-up for presenteeism (MDiff = −5.02 [95% CI = −9.94, −0.10]) and total impairment (MDiff = −5.78 [95% CI = −10.91, −0.65]). No differences were detected by 12-month follow-up.
How are the findings relevant to the decision problem?	The study does not inform us about the resource use effects of dCBT-I from an NHS and PSS perspective, but does provide context about these effects from a societal perspective.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Reduced downstream costs of untreated insomnia.
Will any information from this study be used in the economic model?	The results will be incorporated into our reporting of societal costs and economic outcomes, which are a secondary focus of our model.
What cost analysis was done in the study? Please explain the results.	This RCT study aims to examine effects of (non-Sleepio) dCBT-I on work-related and daily activity productivity, which are examined through 1 year post-treatment. Adults in the US with chronic insomnia (N = 303) were randomized to dCBT-I (Sleep Healthy Using the Internet [SHUTi]) or to patient education (PE). Participants reported interference with absenteeism and presenteeism at paid employment and in daily activities outside work on the Work Productivity Activity Impairment scale at baseline, 9 weeks later for post-intervention assessment, and 6- and 12-month follow-ups.
What are the strengths and limitations of this evidence?	The one-year follow up period provides insight into the effects of dCBT-I on productivity over a longer time horizon than most other evidence available. Participants were recruited from across the US and could be employed or unemployed. This is a more diverse sample than in many comparable studies. The WPAI has good psychometric properties and has been more frequently used than any other metric of productivity across various occupations and disease areas (Bolge et al., 2009). The sample mainly comprised individuals who were non-Hispanic white and highly educated, so future studies with more racially, ethnically, and socioeconomically diverse

	participants are needed to better understand effects of dCBT-I across a broad range of work experiences.
How was the study funded?	The study was supported by grant R01-MH86758 to L.M.R. from the National Institute of Mental Health. Writing of the manuscript was supported in part by the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Numbers UL1TR003015 and KL2TR003016 to K.M.S.

Efficacy of a Self-Help Web-Based Recovery Training in Improving Sleep in Workers: Randomized Controlled Trial in the General Working Population, Behrendt et al (2020)	
What are main differences in resource use and clinical outcomes between the technologies?	Significant differences in favour of the dCBT-I group were evident at both assessment points for the mental health outcomes of depression and recuperation in sleep. Work-related health outcome was found to significantly differ between the 2 groups, with regard to recreational activities, presenteeism, and work ability at 8 weeks and 6 months post intervention. However, the between-group difference of absenteeism was nonsignificant at 6 months (P=.33). Relating to cognitive activity, significant differences between the 2 groups were identified for both measures of cognitive activity—work-related rumination and worry— at both assessment points. Relative to controls, participants who received dCBT-I reported significantly lower insomnia severity scores at post intervention (between-group mean difference −4.36; 95% CI −5.59 to − 3.03; Cohen d=0.97) and at 6-month follow-up (between-group difference: −3.64; 95% CI −4.89 to −2.39; Cohen d=0.86). The overall test of group-by-time interaction was significant (P<.001). Mediation analysis demonstrated that work-related rumination (indirect effect: a1b1=−0.80; SE=0.34; 95% boot CI −1.59 to −0.25) and worry (indirect effect: a2b2=−0.37; SE=0.19; 95% boot CI −0.85 to −0.09) mediate the intervention's effect on sleep.

	There were also significant effects on the mental health outcomes of depression and recuperation in sleep.
How are the findings relevant to the decision problem?	The study does not inform us about the resource use effects of dCBT-I from an NHS and PSS perspective, but does provide context about these effects from a societal perspective.
Does this evidence support any of the claimed benefits for the technology? If so, which?	● Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. ● Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. ● Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all. ● Provision of CBT service where face to face CBT is not available or has ● long waiting times. ● Reduced downstream costs of untreated insomnia.
Will any information from this study be used in the economic model?	The results will be incorporated into our reporting of societal costs and economic outcomes, which are a secondary focus of our model.
What cost analysis was done in the study? Please explain the results.	This study aimed to examine the efficacy of a (non-Sleepio) dCBT-I intervention amongst the general working population in Germany using an RCT. General and work-related cognitive activities were investigated as potential mediators of the intervention's effect. All interested workers could participate regardless of insomnia severity or any other sleep or workplace-specific characteristics. A sample of 177 workers were randomized to receive either the dCBT-I (n=88) or a control of a waitlist with access to normal care (n=89). Web-based self-report assessments were scheduled at baseline, at 8 weeks, and at 6 months following randomization. The primary outcome was insomnia severity, measured using the German version of the Insomnia Severity Index (ISI). Secondary work-related health outcomes included the frequency of recreational activities after work over the past week (Recreation Experience and Activity Questionnaire, consisting of 21 items with ratings ranging from 0 to 4; total range 0-84; alpha=.77) and work ability (single-item score from the Work Ability Index; range 0-10). To assess subjects' self-rated number of full days on sick

	leave (absenteeism) and self-rated number of full days with reduced efficiency at work while feeling ill (presenteeism) over the past 3 months, the German Version of the Trimbos/Institute of Medical Technology Assessment questionnaire for costs associated with psychiatric illness was used, both at baseline and at 6-month follow-up. Cognitive activity was measured in 2 different ways: as work-related rumination (Cognitive Irritation subscale; 3 items ranging from 1 to 7; total range 3-28; alpha=.86]) and as the subject's general tendency to worry (Penn State Worry Questionnaire, Ultra Brief Version, past week; 3 items ranging from 0 to 6; total range 0-18; alpha=.85). In an exploratory analysis, general and work-related cognitive activities, measured as worry and work-related rumination, were investigated as mediators.
What are the strengths and limitations of this evidence?	The sampling strategy provides an insight into the efficacy of dCBT-I for individuals with any sleep problems, rather than those meeting a clinical threshold for insomnia. This is helpful for understanding potential effects in real world setting where it is available as part of routine care to all interested individuals without referral. A range of robust measures are used to understand both outcomes and how they are mediated. The sample size for the study was relatively small and was reduced due to a curtailment in funding, although given the intervention's sizeable effect on the primary outcome, the authors believe that their conclusions are not substantially affected by the smaller sample size. There was a high dropout rate which may have biased the results, although this is partially controlled for by including the number of modules completed in the imputation model.
How was the study funded?	The European Union funded this study, project number: EFRE: CCI 2007DE161PR001.

Three-Year Follow-Up of Insomnia and Hypnotics after Controlled Internet Treatment for Insomnia, Blom et al (2016)	
What are main differences in resource use and clinical outcomes between the technologies?	During the entire period from the posttreatment to the 36 month assessment, sleep medication use decreased significantly more in the treatment group (M = −0.97,

	SD = 1.9) than in the control group (M = −0.28, SD = 1.6; t = −2.4, df = 146, P = 0.017) according to analysis of the sleep medication change index. In the treatment group 11 participants (15%) had tried some other insomnia treatment (e.g., mindfulness or yoga) from the posttreatment to 36 month assessment, compared with 32 (43%) in the control group. This difference was significant (χ2 = 13.6, P < 0.001). Large pre-treatment to posttreatment improvements in insomnia severity of the treatment group were maintained during follow-up. The control group exhibited significantly less improvement posttreatment (between-Cohen d = 0.85), but after 12 and 36 months, there was no longer a significant difference. The within-group effect sizes from pretreatment to the 36-months follow-up were 1.6 (treatment group) and 1.7 (control group), and 74% of the interviewed participants no longer had insomnia diagnosis after 36 mo.
How are the findings relevant to the decision problem?	These results provide an indication of the time horizon over which changes in resource use and clinical outcomes as a result of dCBT-I may be maintained. The use of an active control treatment as comparator that was also delivered online is particularly relevant to the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	● Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. ● Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life. ● Provides access to CBT for people who otherwise would have been provided with sleep hygiene, non-indicated pharmacotherapy or who would not have received any treatment at all. ● Reduces hypnotic usage and associated risks i.e. dependency, withdrawal, risk of falls and unresolved insomnia. ● Reduces hypnotic drug prescriptions and associated costs. ● Provision of CBT service where face to face CBT is not available or has long waiting times.
Will any information from this study be used in the economic model?	The results will be used to inform our choice of time horizon and assumptions around long term effects on primary care resource usage.

What cost analysis was done in the study? Please explain the results.	The aim of this paper was to investigate the long-term effects of therapist-guided Internet-based insomnia treatment on insomnia severity and sleep medication use, compared with active control. This study was an 8-week randomized controlled trial conducted in Sweden with follow-up post-treatment and at 6, 12, and 36 months. Participants were 148 media-recruited nondepressed adults with insomnia. Interventions were Guided Internet-based cognitive behavioural therapy for insomnia or active control treatment. The active control treatment was designed to be a low-intensity but credible insomnia treatment, delivered online, and comprised a sleep diary, psychoeducation about sleep, sleep hygiene and limited versions of relaxation training, stress management, and mindfulness. Primary outcome was insomnia severity, measured with the Insomnia Severity Index. Secondary outcomes were sleep medication use and use of other treatments.
What are the strengths and limitations of this evidence?	This study is the longest controlled follow-up on dCBT-I for insomnia thus far published. The use of an active control provides more confidence in the superiority of dCBT-I compared to alternative existing treatments. The data on sleep medication were measured with self-reports at each assessment point, as opposed to sleep diaries or registry data. Therefore, information about medication use between assessments can thus only be inferred. However, the authors believe there is no reason why the precision of the measure should differ between the two groups in any systematic way. Excluding patients with major depression limits the generalizability of the findings for this sizable subgroup.
How was the study funded?	This project was funded by the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, SöderströmKönigska Foundation, AFA Sickness Insurance Research Fund and the Bror Gadelius memory foundation.

Long-term benefits of digital cognitive behavioural therapy for insomnia: Follow-up report from a randomized clinical trial, Luik et al (2020)	
What are main differences in resource use and clinical outcomes between the technologies?	Of the total sample, 906 (52.9%) participants contributed data at week 24, and 365 (21.3%) participants contributed data at week 48. Beneficial effects of dCBT (Sleepio) were observed at week 48, effect sizes (Cohen's d) of change from baseline were moderate for functional health (difference: 2.45, 95% confidence interval [CI]: 2.03; 2.88, Cohen's d: 0.50, $p < .001$) and well-being (difference: 4.34, 95% CI: 3.70; 4.98, Cohen's d: 0.55, $p < .001$), and large for sleep related QoL (difference: −44.61, 95%CI: −47.17; −42.05, Cohen's d: −1.44, $p < .001$) and for insomnia (difference: 9.80, 95% CI: 9.29; 10.31, Cohen's d: 1.54, $p < .001$). At the conclusion of the controlled phase of the study (week 25), intention-to-treat analyses demonstrated that dCBT also reduced use of prescription (adjusted rate ratio [RR]: 0.64, 95% CI: 0.42; 0.97, $p = .037$) and non-prescription sleep medication (adjusted RR: 0.52, 95% CI: 0.37; 0.74, $p < .0001$; see also Table 2). Uncontrolled follow-up suggests that these effects were sustained for non-prescribed sleep medication (week 48: rate ratio 0.52, 95% CI: 0.40; 0.67, $p < .001$), but not for prescribed medication (week 48: rate ratio 0.78, 95% CI: 0.58; 1.05, $p = .10$). No effect of dCBT on the number of visits to GPs or specialist doctors was observed.
How are the findings relevant to the decision problem?	The study evaluates Sleepio as the dCBT compared with sleep hygiene education (SHE). The findings indicate lower resource use - prescribed medication, GP visits, non-prescribed medication, specialistic visits - associated with Sleepio, as well as positive long term effects on physical health, mental well-being and sleep quality of life.
Does this evidence support any of the claimed benefits for the technology? If so, which?	● Provides effective therapy that directly addresses the behavioural and cognitive underpinnings of insomnia. ● Improves other salient outcomes, particularly to mental health, wellbeing and to quality of life.

	● Reduces hypnotic usage and associated risks i.e. dependency, withdrawal, risk of falls and unresolved insomnia. ● Reduces hypnotic drug prescriptions and associated costs.
Will any information from this study be used in the economic model?	Inform estimate of reduction of resource use, prescription and non-prescription medication, associated with Sleepio.
What cost analysis was done in the study? Please explain the results.	The aim of this paper was to assess whether the benefits of dCBT, an effective treatment for chronic insomnia which also improves well-being and quality of life, is sustained and if the effects extend to the use of sleep medication and healthcare. In total 1,711 adults (48.0 ± 13.8 years, 77.6% female) with complaints of chronic insomnia participated in a previously published randomized controlled trial (ISRCTN 60530898) comparing dCBT (n = 853) with sleep hygiene education (SHE, n = 858). Assessments were completed at weeks 0, 4, 8, 24, 36 and 48. At week 25, SHE participants were offered dCBT, resulting in an uncontrolled follow-up from week 25 onwards. Primary outcomes were functional health, psychological wellbeing and sleep-related quality of Life. Secondary outcomes included daytime symptom measures of depression, anxiety, fatigue, sleepiness, cognitive failures , work productivity, job satisfaction, relationship satisfaction and life satisfaction. Important to this manuscript, use of prescribed and non prescribed sleep medication (self-reported number of nights of use in the last 2 weeks), and healthcare utilization (number of visits to a general practitioner and/or specialist doctor) were also measured as exploratory outcomes. Insomnia was assessed with the Sleep Condition Indicator.
What are the strengths and limitations of this evidence?	This study suggests that fully automated dCBT results in sustained benefits to insomnia and its daytime outcomes. It offers a scalable means to deliver CBT as first-line insomnia treatment and may help to reduce sleep medication use. However, there was no correction for multiple testing due to the exploratory nature of the work and the tendency of such approaches to be conservative when the statistical tests are related, as was the case in this study. Nevertheless, it should be noted that this approach increases the risk of

	type I errors. Additionally, the study suffers from a large dropout rate, common in fully online trials. This may have biased the results, as those who experience an improvement in their insomnia may have been more likely to complete the 48-week data.
How was the study funded?	Big Health Inc.

Internet-based cognitive behavioral therapy for insomnia in Appalachian women: A Pilot Study, Moloney et al (2020)	
What are main differences in resource use and clinical outcomes between the technologies?	Forty-six women enrolled; 38 completed the Internet based program (SHUTi) (retention rate = 82.6%). Mean participant age was 55.1. Positive and statistically significant ($p<0.01$) improvements were observed on mean score measures for the Insomnia Severity Index (15.1 to 6.5), the Perceived Stress Scale (20 to 14.6), and the Center for Epidemiologic Studies Depression Scale Revised (10: 9.8 to 5.2). The odds of reporting sleep aid use post-intervention were lower than pre-intervention (OR 0.28 [95% CI 0.11-0.74; p=0.01]). Qualitative interviews revealed that insomnia onset was often preceded by an acute social stressor (e.g., death of a child) and perpetuated by a chronic social stressor (e.g., raising a grandchild). Twenty-seven participants (73%) reported using any sleep medication at baseline, which decreased to 16 (43%) after SHUTi (OR 0.28 [95% CI, 0.11–0.74]). Among those using any sleep medication, prescription medication use decreased from 11 participants (30%) pre-intervention to 5 (13.5%) post-SHUTi.
How are the findings relevant to the decision problem?	Gives indication of decrease in reported sleep aid use post dCBT intervention
Does this evidence support any of the claimed benefits for the technology? If so, which?	● Reduces hypnotic usage and associated risks i.e. dependency, withdrawal, risk of falls and unresolved insomnia. ● Reduces hypnotic drug prescriptions and associated costs.
Will any information from this study be used in the economic model?	Inform estimate of reduction of resource use

What cost analysis was done in the study? Please explain the results.	The aim of this paper was to pilot test Sleep Healthy Using the Internet (SHUTi), a well validated Internet-based version of CBT-I among Appalachian women ages 45+ and to gather preliminary efficacy data on changes in insomnia severity, perceive stress, depression symptoms and sleep aid use.
What are the strengths and limitations of this evidence?	This study suggests that Internet-based CBT-I may be a useful, non-pharmacologic treatment that reduces insomnia severity, perceived stress, depression symptoms, and sleep aid use in the health disparities population of Appalachian women. However, this study lacked random assignment, post-intervention follow-up, and a control group. Although qualitative findings suggest participants experienced real improvement in insomnia symptoms, these effects may be the result of natural recovery, regression to the mean, or unknown factors. Thus, the study is unable to draw causal conclusions about SHUTi, sleep, and/or medication changes. While the sample was largely representative of the target population (Appalachian women aged 45+ with insomnia), its small size and the inherent selection bias from voluntary participation may weaken conclusions. The sample was also more likely to have private insurance and higher educational attainment, compared to regional demographics.Additionally, while the PSQI and ISI are used routinely in insomnia research, they are subjective and may have stronger correlation with daily sleep diaries and depression symptoms than with objective measures (e.g., actigraphy) (Grandner, Kripke, Yoon, & Youngstedt, 2006; Morin et al., 2011). Adjunctive objective sleep indicators are warranted but may be difficult to employ in in this region.
How was the study funded?	Supported by the Building Interdisciplinary Research Careers in Women's Health Program (NIDA grant: K12DA035150), pilot funding from the Igniting Research Collaborations Grant (University of Kentucky College of Pharmacy) and the University of Kentucky Center for Clinical and Translational Sciences (grant: UL1TROO1998).

2 Economic model

This section refers to the de novo economic model that you have submitted.

1.4 Description

Patients

Describe which patient groups are included in the model

The population for the model includes adults with insomnia symptoms. This may include people without a formal diagnosis, as represented in the sources for our parameters. Due to the paucity of economic evidence, we do not formally include any subgroup analyses in the model.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

The model compares Sleepio to two comparators: - treatment as usual, which includes sleep hygiene and sleep medication; and - face-to-face CBT for insomnia. The first (and primary) comparator is treatment as usual in England. Treatment as usual for insomnia in England is poorly defined, but often involves non-evidence-based treatments. It is most commonly managed by a general practitioner (GP) through verbal advice (100%), minimally effective sleep hygiene education (89%), and by sleep promoting medication (Everitt et al. 2014). Patients rarely receive access to first-line cognitive behavioural therapy (CBT) for insomnia (Rieman et al, 2017; Wilson et al., 2019). It is not possible to evaluate sleep promoting medication alone as a distinct comparator. This is because, since sleep medication is unsafe and generally not recommended for the long-term treatment of insomnia, there is a lack of evidence comparing Sleepio (or other forms of CBT) to sleep medication. While there are clinical trials demonstrating the superiority of Sleepio over sleep hygiene (Pillai et al, 2015; Cheng et al., 2019, Espie et al, 2019; Henry et al, 2020, Luik et al., 2020, Kalmbach et al., 2020), there are no studies presenting a costed comparison of resource use.

The second comparator is individual face-to-face CBT for insomnia. This comparator is recommended for the treatment of insomnia, but is scarcely available in the UK. Relevant cost estimates are available (Curtis, 2013). Group face-to-face CBT may also be used for treatment of insomnia, but is even less widely available, and there is a scarcity of evidence about its relative costs and effectiveness in treating insomnia.

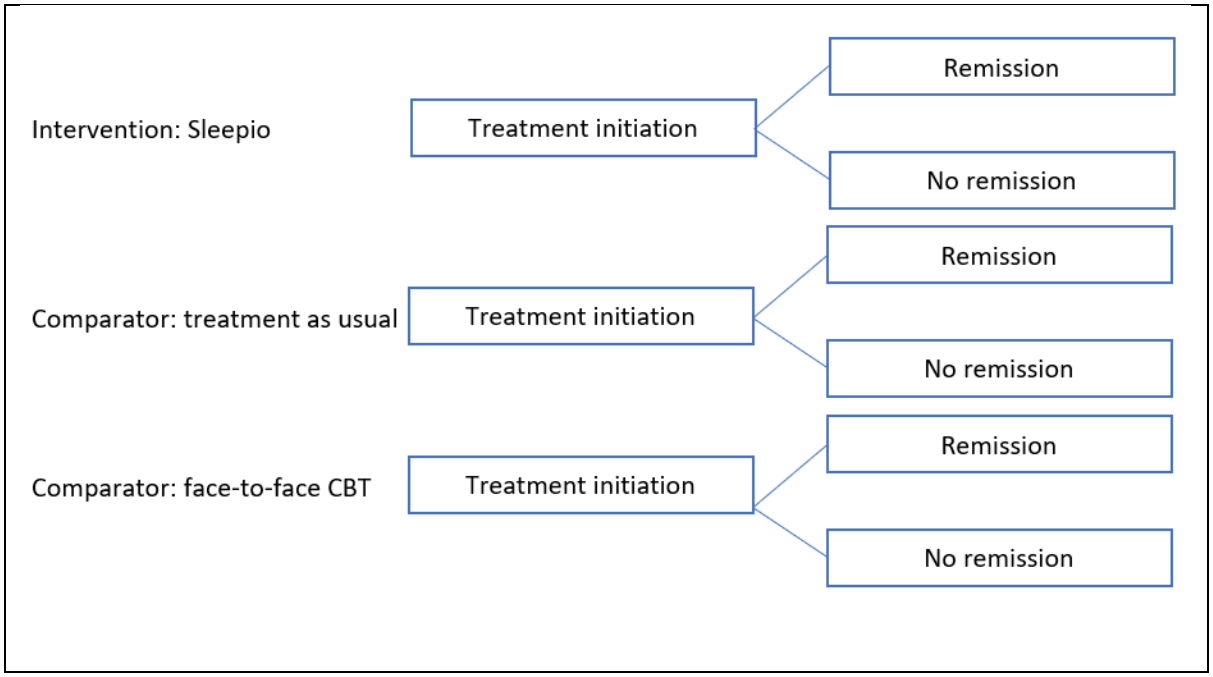
1.5 Model structure, assumptions and parameter values

Provide a diagram of the model structure you have chosen in Appendix B. Justify the chosen structure of the model by referring to the clinical care pathway(s) outlined in part 1, section 3 (Clinical context) of your submission.

As outlined above, there is a lack of economic evidence that differentiates resource use and cost implications according to rates of uptake, adherence, and completion, or in relation to remission status.

We recognise that an ideal modelling approach would be to accurately represent clinical pathways and to then attribute costs to these alternative pathways. However, the available evidence cannot support such an approach. Instead, we have developed a simple model structure that compares costs incurred for each comparator, based on overall cost impacts across the population.

The model structure differentiates between remission and no remission. However, our base case model does not differentiate costs between people who do and do not experience remission, because evidence is not available to support this distinction. In the base case model, all resource use is associated with treatment allocation, not treatment outcomes.



In table 2, list the main assumptions in the model, justify why each has been used and the source of the assumption.

Table 2 Model assumptions

Assumption	Justification	Source
All resource use and cost estimates can be estimated as relative to usual care. Thus, 'usual care' is associated with zero cost.	Treatment as usual for people with insomnia can be variable, but often involves no treatment or minimally effective treatment.	Methodological choice (i.e. incremental comparison). Everitt et al (2014) identify lack of effective strategies under usual care in England.
Resource use savings (both short-term and long-term) are independent of remission status.	Using the best available evidence for resource use savings, we are not able to distinguish between those who do and don't achieve remission.	The findings of Sampson et al (2021) demonstrate that – on average, across people who do and do not achieve remission – Sleepio is a substitute for alternative modes of primary care.
Total resource use savings associated with Sleepio are entirely attributable to Sleepio users (i.e. there are no spillover effects).	There is no reason to expect that Sleepio would have a significant impact on people who do not use it.	Sampson et al (2021)
Annual long-term resource use impacts of Sleepio (as projected by Sampson et al, 2021) are equivalent to those projected at the population level minus cost savings from new users.	This is a conservative assumption based on the notion that the savings reported in year 2 (and projected beyond) are derived in part from new users.	Sampson et al (2021)
Sleepio is equivalent to other forms of face-to-face CBT in terms of both remission and its impact on resource use.	Sleepio has been shown to have similar levels of clinical efficacy as face-to-face CBT	Soh et al. (2020, Derose et al., (in review) Manber et al., (in progress)
There is no difference in primary care resource use for patients treated with Sleepio compared to patients treated with face-to-face CBT	Based on clinical non-inferiority of Sleepio	Inferred from Derose et al and Manber et al.

In table 3, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Table 3 Clinical parameter, patient and carer outcomes and system outcomes

(See next page)

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Patient cohort	Big Health estimates of sales and uptake, based on Thames Valley roll-out	# of people starting CBT with Sleepio: 24,000. This is based on an assumption of 1% uptake amongst adults with access to Sleepio in year 1. In the Thames Valley roll-out, 1,220 patients using Sleepio reported that they were referred by GPs (this is likely to be a conserative figure, as not all patients will record their referral). Data collected by EMIS during the Thames Valley roll-out estimates that 56% of all patients referred to Sleepio register with the programme. Big Health operational data suggests that 46.07% of these initiate Session 1 of CBT (i.e. initiate treatment). 24.52% of initiations are by users who were referred by their GPs. Therefore, estimated uptake is 1,220*56%*46.07*/24.51% = 1284 users, or 0.99% of the total population of GP practices included in the study (129,865).	N/A - but lower bound of uptake of 0.7% is modelled in scenario analysis.	Estimated patient cohort of 24,000 in year 1

Percentage of patients experiencing post-treatment remission from insomnia - intervention (Sleepio)	Cheng et al. (2019)	Remission from insomnia in treatment group receiving Sleepio at 1 week post-treatment is 53.9%	95% CI [48.7 - 59.1] [Note that Cheng et al. 2019 is the only study which reports remission rates for Sleepio across a sample potentially generalisable to the whole treated population]	Remission rates for intervention: Base case - 53.9% Best case - 59.1% Worst case - 48.7%
Percentage of patients experiencing post-treatment remission from insomnia - comparator (treatment as usual)	Cheng et al. (2019)	Remission from insomnia in control group receiving sleep education at 1 week post-treatment is 14.0%	95% CI [10.4 - 17.6]	Remission rates for first comparator: Base case - 14.0% Best case - 10.4% Worst case - 17.6%

Percentage of patients experiencing post-treatment remission from insomnia - comparator (face-to-face CBT)	Cheng et al. (2019) Derose et al. (in progress) and Manber et al. (in progress)	As per Sleepio treatment group, remission of 53.9%. Sleepio is non-inferior to face-to-face CBT	95% CI [48.7 - 59.1]	Remission rates for second comparator: Base case - 53.9% Best case - 59.1% Worst case - 48.7%

Changes in primary care resource use	Sampson et al. (2021)	As described in section 1.5, we are restricted to modelling changes in patients' resource usage in terms of overall costs of medication and GP appointments combined, and independently of remission status. The change in primary care costs per patient in -£49.52 in the first year and annual saving of £45.04 in years 2 and 3 (total 3 year savings of -£139.59 - year 1 saving of -£49.52 = £90.07, divided by 2). (We use the savings per individual referred to Sleepio, as this provides the most precise estimate of the effect per *treated* patient. We also provide a different approach to estimating these savings in a supplementary model as part of our sensitivity analysis. This is outlined in section 1.17).	95% CI (£33.97 - £65.07) (note these are derived from the year 1 confidence intervals for the trend in primary care costs)	As per our assumptions in Table 2, there are assumed to be no changes in resource use due to the first comparator (treatment as usual), and the unit costs associated with changes in resource use due to the second comparator are equivalent to those modelled for the intervention.

1.6 Assumptions used to extrapolate clinical outcomes

If any outcomes listed in table 3 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

Clinical outcomes are not extrapolated. Cost savings associated with reductions in primary care resource use are extrapolated according to the method adopted by Sampson et al (2021). The study projects trends in costs over time at the population level, including any savings associated with new users beyond year 1. To address this, Sampson et al estimate annual cost savings at the individual level by subtracting the savings observed in the previous year and dividing by the number of people in the sample. Based on the study by Blom et al (2016), we assume that resource use impacts can be extrapolated to three years.

1.7 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table 4. You can adapt the parameters as needed.

Table 4 Other parameters

Parameter	Description	Justification	Source
Time horizon	3 years	There is evidence post-treatment improvements in insomnia and decreases in sleep medication usage are sustained over a 36 month follow-up period	Blom et al. (2016)
Discount rate	3.5%	Time horizon is greater than one year	As per model template
Perspective (NHS/PSS)	NHS plus PSS	Although we do not have evidence for any effects on PSS, there is no theoretical reason to limit the scope of the model to NHS only	
Model cycle length	N/A	N/A	N/A

Sources of unit costs	Big Health	Costs of intervention are determined solely by the Sleepio pricing model (the intervention requires no other NHS resource usage) and are provided by Big Health	Big Health
	Curtis (2013)	[As per our assumption above, costs associated with standard care are 0 in the model]. The most recent PSSRU estimates for generic CBT costs are from Curtis (2013). More recent estimates are specific to other non-sleep conditions. According to the PSSRU, one session of individual in-person CBT-I has an estimated cost to the NHS of £31 - £133 (Curtis, 2013). Taking the midpoint of the PSSRU estimate, the cost of six sessions comparable to the Sleepio programme is £82 x 6 = £492. Griffiths and Steen (2013) estimate the costs of CBT provided by IAPT to be £102-173, which we include in our sensitivity analysis.	Curtis (2013) Griffiths and Steen (2013)

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3 Resource identification, measurement and valuation

1.8 Price of technology

Provide the unit list price(s) for the technology, including all related charges such as licence fees and subscription charges (excluding VAT). Please explain if these charges vary by factors such as number of users. If these prices were not used in the economic model, provide a justification for the difference.

Sleepio is provided to NHS systems in a block funding model, whereby the system pays a fixed price per adult in their population to cover unlimited access to Sleepio. This cost also covers full implementation of Sleepio into existing services and ongoing outcomes reporting.

This pricing has been designed to deliver cost savings to NHS systems based on the health economic evidence behind Sleepio.

The pricing table below shows the price per adult charged at different population sizes. For example, an NHS system with a population of 200,000 adults would pay £200,000 p.a. for unlimited access to Sleepio.

Number of adults in the NHS system population	Price per adult p.a.
0 - 250,000	£1.00
250,001 - 500,000	£0.98
500,001 - 750,000	£0.96
750,001 - 1,000,000	£0.93
1,000,001 +	£0.90

1.9 NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

There is a lack of economic evidence about the cost of managing insomnia in the NHS at present. As outlined in section 1.4, treatment as usual may comprise a mix of verbal advice, minimally effective sleep hygiene, and sleep-promoting medications. However, because our model estimates the cost of the intervention (and second comparator) relative to normal care, these unit costs do not appear in the model.
Relevant unit costs for the care of people with insomnia are not readily available from standard sources (such as the Unit Costs of Health and Social Care publications).

1.10 Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix C.

Our data on resource use draws, as explained above, on the best available economic evidence for Sleepio's effects on resource use in an NHS setting, Sampson et al. (2021).

Our literature review, detailed in appendix C, also identified one other study which reported on Sleepio's effects on medication use, and on primary care and specialist appointments.

The study by Luik et al. (2020), with participants from the UK, as well as Australia and the USA, investigated the effects of Sleepio on prescription and non-prescription sleep medication and visits to GPs and specialist doctors. At the conclusion of the controlled phase of the study (week 25), intention-to-treat analyses demonstrated that dCBT reduced use of prescription (adjusted rate ratio [RR]: 0.64, 95% CI: 0.42; 0.97, p = .037) and non-prescription sleep medication (adjusted RR: 0.52, 95% CI: 0.37; 0.74, p < .0001; see also Table 2). The effects on prescription medication were not sustained at 48-week follow up, although this was uncontrolled, and assumes no increase in prescription medication would have occured in the absence of treatment with Sleepio (contrary to the findings of Sampson et al. (2021). There are no cost estimates associated with the changes in medication use, nor is it possible to meaningfully estimate these without the medications being specified.

Describe the resources needed to implement the technology in the NHS. Provide sources and rationale.

As noted in Section 2.3 of the clinical evidence review, launches of Sleepio in a healthcare setting will require clinicians and HCPs to attend a 30 minute - 1 hour training session to recap on 1) how to manage poor sleep and insomnia, and 2) how to prescribe Sleepio through their electronic patient record system, and 3) how Sleepio works and how to describe it for their patients.

In previous launches with the NHS, training sessions have been delivered remotely in existing meeting forums (e.g. Primary Care Network meetings) or over lunch. This avoids any cost associated with reduced time to see patients.

As noted in Section 3 of the clinical evidence review, Sleepio can integrate with the existing clinical pathway in a way that does not increase workload for NHS staff. Staff can refer patients to Sleepio by providing a URL and the programme is fully automated, without the need for ongoing interaction. This avoids cost to the system.

As noted in Section 3.3 of the clinical evidence review, other system changes associated with Sleepio are negligible. The Big Health team will support changes to systems (e.g. installing EMIS toaster alerts), while other changes such as adding Sleepio to primary care practice websites form part of regular activity for NHS services. Therefore there is no additional cost estimated.

Describe the change in resources associated with the change in patient outcomes after implementing the technology. Provide sources and rationale.

Having access to Sleepio creates an opportunity for patients to substitute digital CBT-I for more resource-intensive health service use, including primary care contacts and medications. These are estimated in Sampson et al. (2021).

The study by Sampson et al (2021) estimates the change in the trend of costs associated with primary care resource use that arises from population-level rollout of Sleepio. The authors estimate that the introduction of Sleepio resulted in primary care costs that were, on average, £49.52 less per Sleepio user after one year. The primary outcome of the study combined costs associated with GP practice attendances (including nurse contacts) and prescriptions. A secondary analysis suggested that a significant proportion of the savings arose from reductions in prescriptions, and that this was in part explained by sleep-promoting medications.

Describe the change in resources associated with the change in system outcomes after implementing the technology. Please provide sources and rationale.

Sleepio integrates with the current care pathway. We do not assume any changes in system outcomes, beyond the reductions in other forms of healthcare use described above.

There is evidence to suggest that Sleepio may support a more efficient management of anxiety and depression, in primary care and in IAPT services (Stott et al, forthcoming). We do not formally model these possible changes in resource use.

In table 5, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

Table 5 Resource use costs

See next page

	Technology costs	Comparator 1 costs	Comparator 2 costs	Difference in resource use costs (technology vs comparator 1)	Difference in resource use costs (technology vs comparator 2)
Cost of resource use to implement technology	£2,160,000 -Total population given access to Sleepio = 2,400,000 (see Table 11) -Therefore price per individual in population = £0.90 (see section 1.8) -Therefore total costs = 2,400,000*£0.90 = £2,160,000	£0 -Assume no change to costs for usual treatment comparator	£11,808,000 -Patient cohort = 24,000 -Midpoint estimate off 1 individual session of face-to-face CBT = (£31 + £133) /2 = £82 (Curtis, 2013). Cost of 6 individual face-to-face CBT sesions = £82*6 = £492. -Therefore total costs = 24,000*£492 = £118,080,000	£2,160,000 (Technology costs minus comparator 1 costs)	-£9,648,000 (Technology costs minus comparator 2 costs)

Cost of resource use associated with patient outcomes - year 1	-£1,188,480 -Patient cohort = 24,000 -Effect on primary care resource use per Sleepio user in year 1 = -£49.52 (Sampson et al. 2021) -Therefore total cost of resource use associated with patient outcomes in year 1 = 24,000*-£49.52 = -£1,188,480	£0 -Assume no change in resource use associated with patient outcomes for usual treatment comparator	-£1,188,480 -Assume change in resource use associated with patient outcomes for face-to-face CBT is equal to that for intervention	-£1,188,480 (Technology costs minus comparator 1 costs)	£0 (Technology costs minus comparator 2 costs)

Cost of resource use associated with patient outcomes - long term	-£2,053,494 -Patient cohort = 24,000 -Total 3 year cost savings for individual treated by Sleepio = £139.59 (Sampson et al. 2021) =Cost savings in years 2 and 3 = total 3 year cost savings - year 1 cost savings, or £139.59 - £49.52, = £90.07 Annual cost savings in years 2 and 3 = £90.07/2 =£45.04 Costs discounted at 3.5% for each year and multiplied by 24,000	£0 -Assume no change in resource use associated with patient outcomes for usual treatment comparator	-£2,053,494 -Assume change in resource use associated with patient outcomes for face-to-face CBT is equal to that for intervention	-£2,053,494 (Technology costs minus comparator 1 costs)	£0 (Technology costs minus comparator 2 costs)

Total costs per patient	**-£45.08** Sum of above costs/patient cohort of 24,000	£0 Sum of above costs/patient cohort of 24,000	£356.92 Sum of above costs/patient cohort of 24,000	-£45.08 (Technology costs minus comparator 1 costs)	-£402.00 (Technology costs minus comparator 1 costs)

1.11 Adverse events

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

Costs of adverse events were not formally modelled. However, we note that sleep promoting medication has been associated with workplace and road traffic accidents (Tannenbaum et al., 2015, Morin et al., 2020), as well as dependence, habituation, withdrawal effects, increased risk of falls, sleepwalking and complex sleep behaviors, and cognitive and psychomotor impairments (Glass et al., 2005). These harms have been associated with increased indirect healthcare expenditure (Tannenbaum et al., 2015). Therefore, the use of Sleepio as a substitute for medication may reduce NHS resource use associated with these adverse events.

In table 6, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Table 6 Adverse event costs

Adverse event	Items	Cost	Source
Adverse event 1	Technology	N/A	N/A
	Staff	N/A	N/A
	Hospital costs	N/A	N/A
	[Other items]	N/A	N/A
	Total	N/A	N/A
Adverse event 2	Technology	N/A	N/A
	Staff	N/A	N/A
	Hospital costs	N/A	N/A
	[Other items]	N/A	N/A
	Total	N/A	N/A
[Add more rows as needed]			

1.12 Miscellaneous costs, savings, resources and capacity changes

Describe any additional costs, resource or capacity considerations that have not been included elsewhere (for example, PSS savings, patient and carer costs, and changes to capacity of the service). If none, please state.

Cost of downstream health effects

Although these are not possible to formally model, there is strong evidence that insomnia has a significant negative impact on mental and physical health, including increased risk of anxiety, depression, and cardiometabolic disease (Taylor, et al., 2003; Javaheri, et al., 2017; Lin, et al., 2018; Hertenstein, et al., 2019; Li, et al., 2020).

It is reasonable to assume that providing patients with access to safe and effective treatment for insomnia (such as Sleepio) would reduce NHS costs associated with these conditions in those instances where they are caused or exacerbated by untreated insomnia. However, few studies have quantified the health economic impact of insomnia on the NHS.

Darden et al recently reported a model-based cost-effectiveness analysis from a US perspective. The study evaluated the use of Sleepio compared with pharmacotherapy and face-to-fact CBT, with outcomes driven by the achievement of remission from insomnia.

This study adopted a broader perspective than health and social care services, incorporating productivity losses. Nevertheless, the researchers reported that Sleepio was cost-saving in part due to reductions in health care use associated with lower direct costs of treatment and remission from insomnia. Digital CBT was estimated to dominate all other interventions with the net monetary benefit of $681.06 per patient over six months compared with no treatment.

Resource and capacity constraints to delivering face-to-face CBT-I

There is currently a severe lack of therapists trained in CBT-I in England (Thomas, et al., 2016), with only a handful of NHS sleep services offering this treatment. Building and maintaining a sufficiently large-scale CBT-I service to meet the level of need across the country is unfeasible in terms of cost and available workforce. As a substitute to face-to-face CBT, Sleepio can also reduce pressure on CBT practitioners already working within the NHS.

Impact on IAPT resource

Stott et al (in progress) assessed the clinical time required for people using Sleepio in an IAPT service. The study reports that Sleepio led to a small but significant increase in low intensity clinical time required (+53 minutes) and a decrease in high intensity clinical time (-20 minutes).

Societal effects

There is a strong body of evidence detailed in section 1.3 that Sleepio can generate productivity benefits for patients, when compared to treatment as normal (Kjørstad et al., 2020. Darden et al, 2020). This is because insomnia is associated with workplace absenteeism (Ozminkowski et al., 2007, Léger et al., 2006, and Stoller,1994) and presenteeism (Sarsour et al., 2011 and Kessler et al 2011,), as well as increased frequency and costs of workplace accidents (Shahly et al., 2012). However, given the perspective of the analysis, these have been excluded.

Are there any other opportunities for resource savings, including impact on capacity and demand, or redirection of resources that have not been possible to quantify?

No

1.13 Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost per treatment/patient/year over lifetime of technology including license fees	£2,160,000 per year - £0.90 per individual in population (i.e. £90 per patient at 1% uptake)	Big Health
Consumables per year (if applicable) and over lifetime of technology	(£2,160,000 per year in licence fees as above)	Big Health
Maintenance cost per year and over lifetime of technology	£0	N/A
Training cost over lifetime of technology	£0	N/A
Other costs per year and over lifetime of technology	-£1,188,480 resource use costs in year 1 -£2,053,494 resource use costs in years 2 and 3 combined	Sampson et al. (2021)
Total cost per treatment/patient over lifetime of technology	-£45.08 per patient per year in year 1 cohort over three years (conservatively assumed to be lifetime of treatment; costs for treating patients in this cohort equal to a single year of technology costs)	Big Health; Sampson et al. (2021)

Table 8 Total costs for the comparator in the model

	Comparator 1	Treatment as usual	Comparator 2	Face-to-face CBT
Description	**Cost**	**Source**	**Cost**	**Source**
Cost per treatment/patient /year over lifetime of technology or treatment	£0	Model assumption (see Table 2) - all resource use and cost estimates can be estimated as relative to usual care. Thus, 'usual care' is	£118,080,000 per year	Curtis (2013)

		associated with zero cost.		
Consumables per year (if applicable) and over lifetime of technology or treatment	£0	As above	(£118,080,000 per year in licence fees as above)	Curtis (2013)
Maintenance cost per year and over lifetime of technology or treatment	£0	As above	£0	N/A
Training cost over lifetime of technology or treatment	£0	As above	£0	N/A
Other costs per year and over lifetime of technology or treatment	£0	As above	-£1,188,480 resource use costs in year 1 -£2,053,494 resource use costs in years 2 and 3 combined	Sampson et al. (2021)
Total cost per treatment/patient over lifetime of technology or treatment	£0	As above	£402.00	Curtis (2013), Sampson et al. (2021)

4 Results

1.14 Base-case results

In table 9, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

Table 9 Base-case results

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator (£)**	**Mean discounted cost per patient using the comparator (£)**	**Difference in mean discounted cost per patient (£): technology vs comparator 1***	**Difference in mean discounted cost per patient (£): technology vs comparator 2***
Technology cost	£90 (£2,160,000,00/24,000)	£0	£492	£90	-£402
Training cost	£0	£0	£0	£0	£0
Staff cost	£0	£0	£0	£0	£0
Administration cost	£0	£0	£0	£0	£0
Monitoring costs	£0	£0	£0	£0	£0
Consumables	£90	£0	£492	£90	
Adverse events	£0	£0	£0	£0	£0
Effects on resource use associated with patient outcomes	-£135.08 (Year 1 effects of -£45.92)	£0	-£135.08 (Year 1 effects of -£45.92)	-£135.08	£0
Total	-£45.08	£0	£356.92	-£45.08	-£402.00

* Negative values indicate a reduction in cost, i.e. a saving, with the technology .
Adapt this table as necessary.

1.15 Scenario analysis methods

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

The major source of uncertainty in our results, external to the assumptions and data used in our model (which are investigated in the sensitivity analysis) is the real-world uptake of Sleepio. As noted in the decision problem, the relevant population for Sleepio is all adults with difficulty sleeping. As per section 1.8, Sleepio is provided under a block funding model. Therefore, the number of patients who use Sleepio in practice - and therefore experience associated effects on their resource use - will affect the total estimated costs associated with providing Sleepio.

Our base case analysis assumes uptake of 1%, based on findings of the Thames Valley roll-out where uptake was conservatively estimated to be 0.99%. However, we present a scenario analysis which shows that Sleepio continues to be cost saving under a scenario were uptake is estimated to be 0.7%

Describe the differences between the base case and each scenario analysis.

In the base case, the patient cohort is 24,000 (1% of 2,400,000).
In the scenario analysis, the patient cohort is 16,800.
Since the price paid remains constant, being derived from the size of the population, the cost savings associated with Sleepio decrease from -£45.08 to -£6.51.

1.16 Scenario analyses results

In table 10 describe the results of any scenario analyses that were done. Adapt the table as necessary.

Table 10 Scenario analyses results

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using comparator 1 (£)	Difference in cost per patient, technology and comparator 1(£)*	Mean discounted cost per patient using comparator 2 (£)	Difference in cost per patient, technology and comparator 2(£)*

Scenario 1 (total costs)	-£45.08	£0	-£45.08	£365.92	-£402.00
Scenario 2 (total costs)	-£6.51	£0	-£6.51	£356.92	-£363.43
* Negative values indicate a cost saving. Adapt this table as necessary.					

1.17 Sensitivity analysis methods

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Sensitivity analyses are conducted on the basis of best and worst case scenarios based on confidence intervals for key parameters. We estimate how patient outcomes change by the probability of remission. We also estimate how the costs associated with Sleepio change by the estimates of resource use savings associated with Sleepio .

We have identified no other parameters with meaningful variation to subject to sensitivity analysis.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Probabilities of remission following treatment with Sleepio and its comparators were varied using the 95% confidence intervals for these parameters, in order to demonstrate the potential variation in clinical efficacy of Sleepio and its comparators.

Resource use savings associated with Sleepio were varied using the 95% confidence
intervals for these parameters, in order to demonstrate the potential variation in cost
savings associated with Sleepio. We also submit an additional model that estimates these costs not for the sub-sample referred to Sleepio by their GP, but by the total number of individuals we estimate to have used Sleepio in the Thames Valley roll-out. This alternative estimate is felt to be valuable because of concerns about selection bias in the sub-sample. (We also use confidence intervals in the same way in this additional model.

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

There is no capacity in the model to vary the patient cohort expected in year 1. We therefore present a scenario analysis which shows the effects on costs of Sleepio if the patient uptake was lower than expected (0.7% of the population, compared to 1% in the base case).

1.18 Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

In the worst case scenario, remission rates reduce from 53.9% to 48.7% for Sleepio. This compares to a base case of remission of 14.0% for comparator 1 (usual treatment), or a worst case of 10.4%. The best case scenarios are 59.1% and 17.6% respectively. (We assume that the remission rates for comparator 2 (face-to-face CBT) are equivalent to those of Sleepio).

At the lower value of Sleepio's resource use impact, Sleepio reduces costs by £60.63 per patient compared to usual treatment. At the higher value, Sleepio maintains a cost saving of £29.53 per patient compared to usual treatment.

However, it should be noted that the total cost savings are reliant on long-term savings realised in years 2 and 3, which the model does not provide the option of varying.

We also submit a separate model where we estimate effects on resource use for Sleepio by dividing the total cost savings accrued across the full sample of nine GP practices in Sampson et al. (2021) [£49,930 in year 1, and £229,967 over three years] by the estimated number of users (including those not referred by their GP); 1,284 (see Table 3). In this model, we estimate the effect of Sleepio on resource use in year 1 to be £38.89 (£49,930/1,284), and £35.57 each in years 2 and 3 (see Sampson et al. (2021) for methodology for estimating long term cost savings). In this model, Sleepio reduces costs by £16.46 compared to treatment as usual.

What were the main findings of each of the sensitivity analyses?

Sleepio offers much higher remission rates than treatment as usual, even in the extreme scenario where Sleepio's worst case and comparator 1's best case were realised. Sleepio also continues to be cost saving using the upper bound of the estimates for Sleepio's impacts on resource use in year 1 (although the year 2 and 3 estimates cannot be varied in this model), and when effects on primary care resource use are modelled for an estimated total number of users. Although these latter estimates are likely to be less precise than the results for the sub-sample presented in our main analysis, this builds confidence that any bias in this sample is not the driver of Sleepio's overall cost saving compared to treatment as usual.

Uptake of Sleepio at the population level is the major source of uncertainty. Varying remission probabilities and year 1 resource impacts does not affect the overall conclusion that Sleepio is cost-saving.

What are the main sources of uncertainty about the model's conclusions?

1.19 Miscellaneous results

Include any other relevant results here.

N/A

1.20 Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model and resource use for the technology and comparator(s) pathways. Provide sources and cross-reference to evidence when appropriate.

Given the paucity of economic evidence for Sleepio and necessary simplicity of this model, there is also limited scope to validate the model. To compensate for this, we have used conservative estimates where uncertainty is high - for example, in the projection of the resource use savings associated with Sleepio beyond the study period of Sampson et al. (2021), and the base case estimates of the cost of face-to-face CBT.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

The model was developed by researchers at the Office of Health Economics, with advice and collaboration from clinical experts and researchers within Big Health. External opinion or validation was not sought.

5 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain the potential cost savings and the reasons for them.

Sleepio, digital cognitive behavioural therapy for insomnia, is cost saving when compared to face-to-face therapy and treatment as usual.

In the clinical evidence submission we demonstrated that Sleepio could deliver CBT digitally without compromising on clinical effectiveness. When compared with treatment as usual - which includes sleep hygiene, and sleep medication provided in primary care - Sleepio is cost saving, with an estimated saving of £45.08 per user accrued over three years. Across different uptake scenarios it has been shown that even at 0.7% enrollment, Sleepio continues to save costs, to a magnitude of £6.51 per patient. This was due to reduced primary care resource and medication use, a direct result of improved clinical care and patients being prescribed NICE recommended treatment rather than being given sleep hygiene or sleep medications - which are not evidenced to treat insomnia. Sleepio is also cost saving compared to the recommended face-to-face CBT for insomnia, costing £402.00 less per patient. However, this scenario is far less common in practice, but where CBT-I is available, the model shows Sleepio delivers clinically effective care at significantly lower costs.

Beyond direct cost benefits Sleepio also impacts on downstream primary care resource use, and potentially psychological therapy resource use. Sleepio has a range of societal benefits including improved productivity, reduced vehicle accidents, and fewer accidents at work.

As Sleepio is intended as a treatment for insomnia and difficulty sleeping, rather than a replacement for existing technologies or services, it is important to consider trade-offs in NHS expenditure more generally. To this end, we have included the available evidence on outcomes in terms of quality-adjusted life years (QALYs). Stokes et al. (in prep) estimate that at 24 weeks post study, Sleepio leads to a QALY gain of 0.018 compared to sleep hygiene. At a cost-per-QALY of £20,000, this equates to additional value to the NHS (over and above the cost savings described above) of £360 per patient. These findings suggest that Sleepio dominates the usual treatment comparator. It would also dominate face-to-face CBT, given clinical equivalence and lower costs.

In conclusion, Sleepio is cost saving compared to treatment as usual and face-to-face CBT in terms of reducing direct and downstream costs. In particular, there is a growing evidence base that Sleepio reduces prescription costs. It also improves quality of life compared to treatment as usual. Sleepio adds value to the broader healthcare system and society, and this has been shown to be likely across a range of scenarios.

Briefly discuss the relevance of the evidence base to the scope.

All of the studies identified in our review support the notion that digital CBT for insomnia can reduce costs. Some of these potential savings are within scope, including reductions in medication use (Blom et al, 2016; Bostock et al, 2016; Luik et al, 2020; Sampson et al, 2021), primary care costs (Sampson et al, 2021; de Bruin et al, 2016) and other health service use costs (Darden et al, 2020).

Other savings are beyond the scope but are an important aspect of the potential value of Sleepio, including productivity improvements (Thiart et al, 2016; Espie et al, 2018; Darden et al, 2020; Kjørstad et al, 2020; Shaffer et al, 2020; Behrendt et al, 2020), and workplace accidents (Darden et al, 2020).

The majority of the evidence does not perfectly align with the scope. There are limited comparisons between Sleepio (or other forms of digital CBT for insomnia) and sleep hygiene, sleep medications, or face-to-face CBT. This is in part due to the unsafe and variable nature of real world management of insomnia in England (Everitt et al, 2014), which leads to a paucity of evidence comparing Sleepio to non-recommended sleep medications.

Of the studies identified, Sampson et al. (2021) provided the most relevant assumptions for the model given the real world assessment of resource use at scale in a primary care population in England.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

There is relatively strong evidence that digital CBT for insomnia reduces medication use, with several studies from different settings identifying significant effects in terms of either the number of prescriptions or costs. The results of our model are consistent with this explanation.

The results of the modelling are consistent with a separate model-based economic analysis of Sleepio in the US setting. Darden, et al (2020) estimated the cost per QALY associated with Sleepio compared with pharmacotherapy and alternative modes of delivery for CBT. The researchers identified an incremental cost saving of $40.06 compared with no treatment and of $103.32 compared with pharmacotherapy, indicating savings of a similar magnitude to those identified by our model.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

Our analysis relies primarily on a study of Sleepio's impact on primary care resources in a broadly inclusive population. The majority of studies for Sleepio are based on populations that would have received treatment as usual or sleep hygiene (though these studies focus on societal costs). In the NHS, sleep hygiene or sleep medications are most often prescribed in primary care in lieu of long-term management strategies (Everitt et al, 2014). As such, our cost analysis is most relevant to a general primary care population.

Other studies have focussed on specific groups, such as pregnant women or adolescents, supporting the use of digital CBT for insomnia in these cohorts. By including a broad population in our analysis, our findings do not rely on a narrowly-defined scope. Evidence suggests that the use of Sleepio by some groups (such as people with a diagnosis of anxiety or depression) may be associated with greater savings than those for the average patient. Our estimates are derived from a population that includes people who are likely to use Sleepio, based on diagnoses and prescriptions, but may also include people who have not used Sleepio. Thus, we believe that our analysis provides a conservative estimate of the likely effects of Sleepio on health care resource use at the individual level, including all people who are likely to access digital CBT for insomnia.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

The key strength of the analysis is, arguably, in its simplicity. By looking at the overall costs in a broadly defined population, we reduce the risk of missing cost impacts or spillover effects in health care provision. Thus, our cost analysis is likely to provide an accurate estimate of the overall impacts of Sleepio rollout on health service costs.
The model relies primarily on a large study from a real-world setting that is highly specific to the scope.

There are some limitations to our modelling study that should be noted. The available evidence is lacking in randomised studies that identify the impact of digital CBT for insomnia on health care resource use and costs. This is due to the nature of current care in the UK (described above). For our estimates of resource use savings, we rely on one study. However, the findings of this study are consistent with previous work.

Detail any further analyses that could be done to improve the reliability of the results.

It is difficult to conceive of further secondary analysis without further primary data collection. Although it would be useful to model further uptake and remission rate scenarios, there is a lack of evidence to support this work.
It is unlikely that further randomised controlled trials would be an appropriate basis for the identification of differences in health care resource use. Due to the variability of care and off-label medication use that is routine in the UK, further studies conducted in a controlled setting may lack external validity.

Further data collection could assist in the identification of the drivers of cost savings and the subgroups in which cost savings are observed. The study by Sampson et al (2021) demonstrated that such analyses can be conducted using routinely available data in England. Further research should seek to validate the findings of Sampson et al (2021). However, based on the evidence reviewed above, it is unlikely that such research would alter the primary conclusion that Sleepio reduces health care resource use overall.

6 Resource impact analysis

The Resource Impact Team at NICE estimate the costs or savings (budget impact) associated with technologies so the NHS can plan for and implement guidance. In order to produce a resource impact report and template the Team requests the following information.

1.21 Population and uptake estimates

In table 11 provide estimates of the number of people who would be eligible to use your technology in years 1 to 5 and the expected uptake in each 5 years.

Table 11 Population and uptake estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of people eligible to use technology	2,400,000	6,500,000	12,600,000	20,700,000	30,800,000
Uptake of technology	24,000	65,000	126,000	207,000	308,000

1.22 Sales

In table 12 provide estimates of the number of this technology you expect to sell in years 1 to 5 in the UK.

Table 12 Sales estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
Sales of technology	2,400,000	6,500,000	12,600,000	20,700,000	30,800,000

1.23 Acquisition costs with and without VAT

In table 13 provide an estimate of the aggregate purchase costs of the technology and associated set-up and implementation costs across the NHS in each of the five years with and without VAT.

Table 13 Aggregate total costs

	Year 1	Year 2	Year 3	Year 4	Year 5
Purchase cost of technology excluding VAT	£2,160,000	£5,850,000	£11,340,000	£18,630,000	£27,720,000
Purchase cost of technology including VAT	£2,592,000	£7,020,000	£13,608,000	£22,356,000	£33,264,000
Other set-up and implementation costs	£0	£0	£0	£0	£0
Total costs excluding VAT	£2,160,000	£5,850,000	£11,340,000	£18,630,000	£27,720,000
Total costs including VAT	£2,592,000	£7,020,000	£13,608,000	£22,356,000	£33,264,000

If the purchase cost used in table 13 does not use the list price and other charges advised in section 4.1, advise what unit prices are used and explain the differences.

N/a

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Please include all references below using NICE's standard referencing style.

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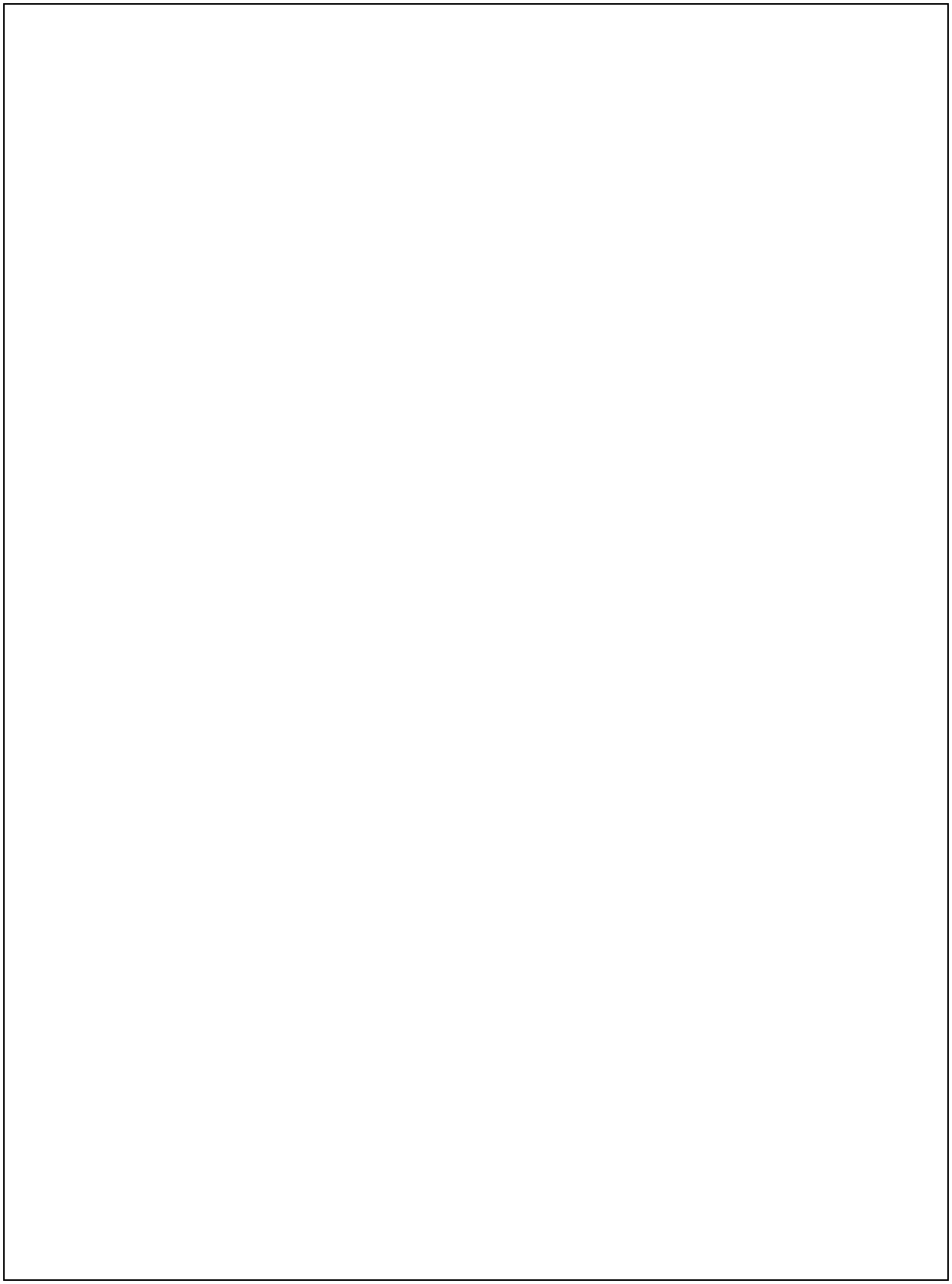


8 Appendices

Appendix A: Structured abstracts

Structured abstracts for unpublished studies

Study title and authors Digital cognitive behavioural therapy for insomnia and primary care costs in England: an interrupted time series analysis. Sampson, C. et al., 2021
Introduction This unpublished study evaluated population rollout of Sleepio in the Thames Valley region of England, supported by primary care engagement, compared with current practice. A cost-effectiveness analysis was not conducted and the study does not consider any direct costs associated with the rollout of Sleepio. A before and after quasi-experimental design was adopted, using interrupted time series (ITS) analysis to estimate the change in the trend in total primary care costs (including GP practice contacts and prescriptions) following the rollout of Sleepio. Nine GP practices in Buckinghamshire were recruited and individual-level data for 10,704 patients were obtained from electronic patient records for the 12 months prior to Sleepio rollout and up to 15 months after (October 2017 to January 2020). The analysis was also complemented by individual user data from Sleepio.
Objectives The primary outcome for the analysis was the average primary care costs per patient per week, where primary care costs included GP practice contacts and prescription costs.
Methods A segmented regression analysis of the ITS data was used to estimate the trend in the primary outcome. Four secondary analyses were also conducted: 1. Change in total prescription costs for people referred to Sleepio 2. Change in count of z-drugs prescribed for people referred to Sleepio 3. Subgroup analysis for people with a diagnosis of anxiety or depression 4. Longitudinal analysis modelling referral to Sleepio by a GP as the intervention
Results The main finding of the analysis was that the rollout of Sleepio in the Thames Valley region reduced primary care costs on average, including general practice contacts and relevant prescriptions (hypnotics and anxiolytics). Over the observed follow-up period, in the sample of 10,704 patients, the absolute difference in mean weekly costs per person, associated with Sleepio rollout, was a saving of £0.16 at week 65. This corresponds to £6.64 per person over the 65-week follow-up period (£4.66 in year one), including the initial rollout period. Sleepio rollout reduced primary care costs by £71,027 across the nine practices (95% confidence interval £49,291 to £92,762). A secondary analysis, based only on prescription costs, identified a greater saving (£8.61 per person at 65-week follow-up), suggesting that the overall cost saving is significantly explained by reductions in prescription costs.

Conclusion Sleepio is associated with cost savings in primary care including reduced general practice contacts and sleep medication prescriptions. The evidence suggests that the total saving of £6.64 per person over 65 weeks can be explained by reductions in the cost of prescribed medicines.
Article status and expected publication: Submitted for publication as a preprint at medRxiv (MEDRXIV/2021/249646) https://doi.org/10.1101/2021.01.10.21249646 (available shortly)

Study title and authors Treatment of insomnia with digital cognitive behavioural therapy improves quality-adjusted life years (QALYs) when compared with sleep hygiene education. Stokes, E. et al., in prep.
Introduction The aim of this study is to describe the potential gains in quality-adjusted life years (QALYs) with Sleepio compared with an active sleep hygiene education control intervention for those with insomnia. Outcome data were analysed from a previously published large effectiveness study (Espie et al., 2019).
Objectives The objective of this secondary analysis is to estimate QALYs for participants in the DIALS trial, by mapping PROMIS-10 Global Health items to the EQ-5D and calculating QALYs from EQ-5D utilities.
Methods PROMIS Global Health scores have been mapped to the EQ-5D-3L using the methods reported in Thompson et al. (2017). Specifically, the model applies equipercentile equating to the predicted values of a linear regression model, where PROMIS items are treated as categorical predictors. A limitation of this work for a UK audience is that the mapping by Thompson et al. uses the US value set for the EQ-5D-3L, not the UK value set. The QALY profile for each participant from baseline to 24 weeks was estimated, and the area under the curve of utility measurements was used to calculate the number of QALYs accrued by each participant. QALYs were calculated assuming that each participant's utility changes linearly between each of the time points (baseline, 4, 8 and 24 weeks). Beyond the controlled comparison to 24 weeks, assumptions were made about the control arm to extend analyses to 48 weeks.
Results EQ-5D scores were significantly ($p<0.05$) greater in Sleepio participants at week 4 (mean difference [95%CI] = 0.020 [0.005, 0.036]), week 8 = 0.043 [0.026, 0.060]), and week 24 = 0.035 [0.018, 0.052]. The mean difference for QALYs gained was 0.018 [0.010, 0.025] higher ($p<0.05$) in Sleepio participants than controls. QALYs from 24 to 48 weeks were also estimated. However, the control group had access to Sleepio from week 24, and assumed individual EQ-5D scores at week 24 were carried forward to weeks 36 and 48 for each participant. Scores for participants in the Sleepio arm were used directly from captured data. At week 48, the mean difference [95%CI] was 0.030 [0.016, 0.043] ($p<0.05$) greater with Sleepio and QALYs gained was 0.013 [0.007, 0.018] ($p<0.05$)

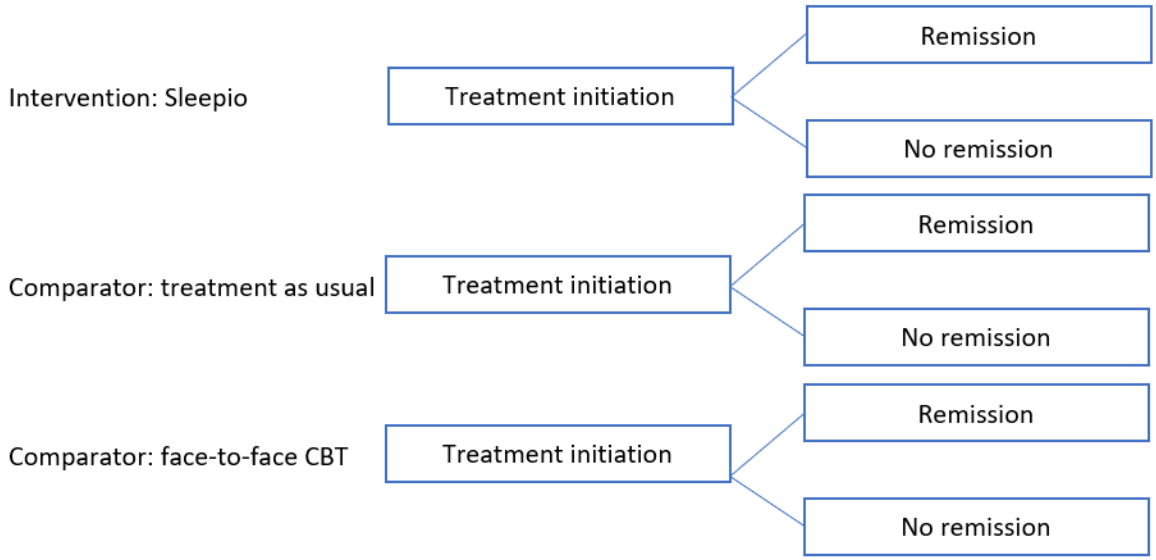
compared with the sleep hygiene education control. In a sensitivity analysis, multiple imputation was used to handle missing values and found similar results.
Conclusion EQ-5D scores were significantly higher in the Sleepio arm than the control arm at 8 and 24 weeks, and this resulted in significantly higher QALYs gained to 24 weeks within the trial. Beyond the controlled comparison within the trial, EQ-5D scores and QALYs from 24 to 48 weeks were also estimated to be significantly higher in the Sleepio group.
Article status and expected publication: In preparation for submission to a clinical sleep journal in 2021.

Study title and authors Effectiveness of Adjunctive Digital Insomnia Application in Routine IAPT Care. Stott, R et al., 2021
Introduction This is a large, observational, service-led study evaluating the routine incorporation of Sleepio into a clinical mental health setting. Participants were recruited over a 12 month period from one IAPT service in Buckinghamshire, UK, and those who scored 2 or above on the sleep item of the PHQ-9 (trouble sleeping more than half the days a week), or who otherwise specifically volunteered that sleep was a primary difficulty, were offered Sleepio as an optional adjunctive treatment to run alongside treatment as usual for their depression or anxiety disorder. 510 patients had final outcome data available at the time of data analysis. Outcome metrics were the Patient Health Questionnaire-Depression scale (PHQ-9; Kroenke, Spitzer and Williams, 2001) for general mood, the GAD-7 (Spitzer, Kroenke, Williams and Löwe, 2006) for anxiety, and the Work and Social Adjustment Scale (WSAS; Mundt, Marks, Shear & Greist, 2002) providing a simple, reliable and valid measure of impaired functioning. All measures were collected at a minimum of two timepoints, thus data was available at baseline assessment and at last contact before discharge.
Objectives To evaluate the effect of the routine incorporation of Sleepio as an adjunctive treatment on mental health outcomes in a clinical health setting.
Methods A control group (510 matched pairs) was established from contemporaneous patients of the service who did not adopt Sleepio, using propensity score matching methodology (Rosenbaum and Rubin, 1983) with 2:1 nearest neighbour matching. Sampling was undertaken with replacement. This obtained a control group matched on initial clinical variables (baseline PHQ-9, GAD-7, WSAS, initial sleep item score) as well as demographic variables (age, gender, ethnicity). All patient data was anonymised and

statistical analysis was independently conducted using STATA by one of the co-authors (RE).
Results Patients undertaking Sleepio showed a significantly larger reduction in mean scores at the final assessment score on PHQ - 9, GAD -7, and WSAS, compared to the matched controls. The strongest effect was on the GAD-7 where the final score was approximately one full point below that of the matched controls (6.6 vs 7.6 respectively). The sleep item dropped pre-to-post in all three cohorts but in this case the treatment effect between Sleepio and matched controls was non-significant.
Conclusion This evaluation revealed significant value in introducing a digital sleep intervention at scale within a clinical mental health service. Significantly improved outcomes in mood, anxiety and social functioning were found in those undertaking fully automated digital CBT, Sleepio, compared to statistically matched control patients. This study adds real-world weight to the notion that sleep can and should be better targeted in mental health settings.
Article status and expected publication:

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



Appendix C: Search strategy for resource use

The search strategy was designed to ensure that all economic evidence relating to Sleepio, and other comparable dCBT-I interventions, was captured.

The following search was performed in PubMed:
(Sleep OR Insomnia) AND (digital CBT OR digital CBTI OR dCBT* OR internet CBT OR internet CBTI OR iCBT* OR web CBT OR web CBTI OR Sleepio) AND (econ* OR cost* OR resource* OR productiv* OR workplace* OR "sleep medication use")

In addition, we include several unpublished studies. Sampson et al. (2021) has not been formally published, but it is available as a preprint on medRxiv.

The inclusion and exclusion criteria correspond to satisfaction of those specified in Table 1. Additionally, we excluded studies not written in the English language.

Population	Adults over the age of 16 with difficulty sleeping
Intervention	● dCBT-I delivered using Sleepio ● dCBT-I delivered using another digital technology
Comparators	● Sleep hygiene ● Hypnotic drugs ● Face-to-face CBT for insomnia ● Usual care ● Digitally facilitated CBT for insomnia
Outcomes	● Health care resource use, e.g.: ○ Medication / prescriptions ○ Primary care attendances ● Work productivity
Study design	● Any study design

Table 1: PICOS criteria for literature search

Identified citations were first screened for inclusion on the basis of their title, abstract, and keywords. Citations not excluded at this stage, including those for which enough information could not be obtained, progressed to full text screening.

For a randomly selected sample of 10% of citations, a second independent reviewer screened citations to ensure consistency in the selection process. According to our protocol, any disagreements were discussed until a consensus was reached; if there was significant variation in the selection of articles, the second reviewer would have screened all citations.

Appendix D: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No	X	If no, please proceed to declaration (below)
Yes	☐	If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	12 January 2021
Print:	Professor Colin Espie	**Role / organisation:**	Chief Medical Officer and co-founder, Big Health
Contact email:	Colin@bighealth.com		

MT443 Sleepio addendum to company submission

Summary of additional information

The following documents were submitted by the company on 16th Mach 2021 as additional confidential information to support the Sleepio evaluation. The documents were supplied to address queries that were raised by the lead team. The submitted documents are listed below with a short summary of the documents' contents.

1. Sleepio MTEP submission: New Data

The submitted document includes the following:

- New data supporting the uptake in year 1. These data include the North Hampshire roll out of Sleepio and the NHS England staff roll out.
- New data to support the assumption that year 2 and 3 will have a consistent % uptake.

The company claim these data support their assumptions in their economic model.

EAC's response to the new data

[redacted]

[redacted]

2. Big Health's quality management system procedures and risk management

This document has been written specifically to address queries raised during the evaluation of Sleepio. The document addresses two queries:

- How are we [Big Health] screening patients to ensure they're not suffering from poor sleep due to other co-morbid conditions?
- How do we [Big Health] ensure the sleep restriction session doesn't turn into an adverse event.

The following documents have been uploaded as supporting information that are referenced to within this document.

[redacted]

Sleepio MTEP submission: new data

To support the MTEP process for Sleepio, Big Health would like to share additional data on our live implementations with the NHS. This data will help meet two requests from NICE made via email on Friday 12th March 2021:

1. New data supporting the uptake % in Year 1
2. New data supporting maintained uptake % in Year 2 onwards

Definitions used in this document:

- Uptake: the number of people starting Session 1 of CBT in Sleepio.
    - The patient journey in Sleepio starts at the Onboarding Sleep Test which culminates in registration – where they set up their account.
    - Then, their journey is not linear, they are free to access the first session of Sleepio and once they've done so, each subsequent session is unlocked each week. Each of the 6 sessions are standalone apart from the first and last. Therefore, it is up to the individual to go through each session, for example, some may repeat session 1 or 2 multiple times, before proceeding to session 3.
    - Therefore, given the non-linear nature of the programme, we do not calculate 'completion' of the programme.
- Adults: people aged 18 years or above
- Year To Date (YTD) data: describes the period from the start of a 12-month period up until the current date. For the purposes of this document, the current date is 11-Mar-2021 (to coincide with latest data pull from Sleepio)
- Annualised data: describes YTD data that has been extrapolated to give a forecast across a full 12-month period

1. New data supporting the uptake % in Year 1

The data below covers two Sleepio implementations with the NHS: North Hampshire CCG (where Sleepio is offered to the general public) and NHS England & Improvement (where Sleepio is provided to all NHS staff in England). [redacted]

[redacted]

[redacted]

Project	Implementation model used	Adult population (18+)	Start date	Uptake [redacted]	Uptake (annualised)	Uptake (annualised, %)
North Hampshire CCG	Standard implementation model for patients	176,280	[redacted]	[redacted]	[redacted]	[redacted]
NHSE&I	Bespoke implementation model aimed at staff	1,320,014	[redacted]	[redacted]	[redacted]	[redacted]

Sources:

- North Hampshire CCG adult population
  - Total population = 226,000 (NHCCG (2019). Year in Review, 2018-19. Retrieved from: https://northhampshireccg.nhs.uk/Downloads/Key%20documents/Publications%20and%20corporate%20documents/Year%20in%20Review%202018-19.pdf)
  - % adults 18+ in UK population = 78% (Office for National Statistics (2019). Overview of the UK population. Retrieved from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/august2019)
  - Therefore total adult population = 226,000 x 78% = 176,280
- NHSE&I total population
  - Total staff headcount in England = 1,320,014 (NHS Digital (2020). NHS workforce statistics. Retrieved from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-workforce-statistics/november-2020)
- Patient-reported data in Sleepio

2. New data supporting maintained uptake % in Year 2 onwards

As part of the Thames Valley project, we delivered our standard implementation model to 9 of the total [redacted] in Buckinghamshire CCG in the period October 2018 to March 2019. [redacted]

Channel (patient-reported)	Year 1 uptake	Year 2 uptake	Year 3 uptake YTD	Year 3 uptake (annualised)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

We note there is a significant increase in uptake in Year 3. We believe this is due in part to increased demand for instant access to insomnia treatment during the Covid-19 pandemic.

Sources:

- Buckinghamshire CCG adult population and number of GP practices
    - Total population = 530,000. Number of GP practices = 48 (BCCG (2021). Our Member Practices. Retrieved from: https://www.buckinghamshireccg.nhs.uk/public/about-us/who-we-are/our-member-practices/)
    - % adults 18+ in UK population = 78% (Office for National Statistics (2019). Overview of the UK population. Retrieved from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/august2019)
    - Therefore total adult population = 530,000 x 78% = 413,400
- Patient-reported data in Sleepio

National Institute for Health and Care Excellence

Collated comments table

MTG Medtech Guidance:

Expert contact details and declarations of interest:

Expert #1	ARI MANUEL, Sleep and Ventilation consultant, Liverpool FT NHS Trust,
	Nominated by: BSS
	DOI: NONE
Expert #2	Dr Chris Davies, GP Partner, Head of Research, Medicas Health, Click here to enter text.
	Nominated by: Expert from adoption via company
	DOI: Financial – Our research group was paid to participate in the Sleepio trial and this was divided amongst the participating practices. No personal financial benefit.
Expert #3	Georgina Ruddle, Assistant Director [all age] MH, LDA, Click here to enter text.
	Nominated by : Expert from adoption via company
	DOI: NONE
Expert #4	Jason Ellis, Professor of Sleep Science, Northumbria University, Click here to enter text.
	Nominated by: BSS
	DOI: NONE
Expert #5	Kirstie Anderson, Consultant Neurologist and Sleep Specialist, Newcastle upon Tyne NHS Hospitals Foundation Trust, Click here to enter text.
	Nominated by:
	DOI- I have no financial conflict of interest, I helped design clinical components of sleepstation 2012, at no stage had any financial reward, left company 2017 and I recommend either sleepio or sleepstation clinically if best for patient
Expert #6	Prof Mike Wang, Emeritus Professor of Clinical Psychology, University of Leicester
	Nominated by: ACP-UK
	DOI: NONE
Expert #7	Tim Cooper, GP, Chineham Medical Practice and North Hampshire CCG, Click here to enter text.
	Nominated by: Expert from adoption via company

	DOI: Clinical lead for North Hampshire CCG

			Response
1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	Expert #1: I work in the one of the largest sleep services in the UK. As part of my NHS practice we have a large number of patients with insomnia who require treatment. I am familiar with Sleepio (from a clinical and academic stand point) 1/3 of all UK population summary with insomnia at some point. Currently there are a number of free (sleepstation) and paid (Sleepio) online platforms that are used in the UK for the treatment for insomnia. Currently there is very limited NHS services for insomnia in the UK (F2F appointments are limited due to COVID-19) We currently do not use it as it not free for patients to use. I am unclear on how extensively it is used, but my thoughts are limitedly (due to cost and the availability of similar free insomnia advice available to patients)	

		It is “prescribed” by sleep specialists only although there will be primary care doctors who will prescribe it There is no patient selection per se, but as per MERGE trial; 30% of patients with OSA report insomnia symptoms so it’s treatment would be done with OSA treatment	
		Expert #2 The practices within our research group, Medicas, covering 68,000 patients, agreed to trial the Sleepio programme within General Practice. We continue to have access to, and use the programme for our patients. Our IT systems prompt us to consider Sleepio when we enter an Insomnia code, or presribe a hypnotic drug. Access to the programme can also be given to patients without these prompts using clinical judgement, or direct access by patients seeing posters in the surgery.	
		Expert #3 Familiar with the technology. Qualified cognitive behavioural therapist and health psychologist. Area of interest and research experience – insomnia.	

		Only in BSW N/A MH Commissioner	
	–	Expert #4 I have extensive experience both in terms of research and clinical practice with CBT-I (the framework on which Sleepio is based). I also have experience of co-creating online and app delivered CBT-I for vulnerable populations. I do not use Sleepio myself as I deliver CBT-I face-to-face although I do advocate digital CBT-I (Sleepio or Sleepful) when there are no face-to-face services available in a region or if there are special circumstances that prevent face-to-face delivery. I believe that Sleepio was available, for free, within some Trusts as a pilot and others have commissioned it for a fee although I do not know the exact levels of uptake across the UK. I also understand that in the current COVID crisis, Sleepio is available, for free, to the NHS workforce until December.	

		Sleepio can be provided by GPs and is also used in other specialities.	
	–	Expert #5 Very familiar with both CBTi and digital CBTi having both developed, used and auditied both within both clinical and research work in our Regional Sleep Service for over 12 years. Our regional sleep service delivers individual and group CBT for insomnia (CBTi), trains others to deliver this in annual sleep training days, our trust administers another digital CBTi – Sleepstation but I have also had patients who have used sleepio Sleepio is recommended by others in sleep medicine, our own local Talking Therapies uses Space for Sleep within Silvercloud and I am aware of the frequent use of digital CBT across IAPT – however there remains less demand for insomnia CBT than anxiety and depression CBT based on their local reports. I am involved in selection of patients for insomnia CBT and have been for many years	

	–	Expert #6 Yes. Yes. It is currently available to all NHS staff and part of the Resilience Hubs offer to staff. Yes. I have some experience of “sleep hygiene” intervention as offered on one-to-one basis.	
	–	Expert #7 We have been offering sleepio to patients for the past 6 weeks. We have started a pilot to utilise it as a first line treatment of sleep disorder. This is happening across the whole of North Hampshire CCG. This is being offered by all of primary care and our social prescribing / wellbeing teams.	

	–	Expert #8	
2	– Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: **I have done bibliographic research on this procedure.** I have done research on this procedure in laboratory settings (e.g. device-related research). **I have done clinical research on this procedure involving patients or healthy volunteers.** **Currently looking at migraine and insomnia** I have published this research. I have had no involvement in research on this procedure.	
		Expert #2 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. X I have published this research. I have had no involvement in research on this procedure.	

		Other (please comment)	
		Expert #3 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. I have had no involvement in research on this procedure. Other (please comment) – *systematic review of CBT treatments for insomnia with comorbid MH/physical health conditions.* *Psycho-educational group intervention – CBT for adults with insomnia with comorbid MH/PH*	
	–	Expert #4 I have done bibliographic research on both CBT-I in general and when delivered digitally. I have done research on CBT-I in laboratory settings.	

		I have done clinical research on CBT-I involving patients or healthy volunteers and I have published this research. I have not done any specific research on this product. As such, unless specifically noted, my responses are contained to either CBT-I in general or digital CBT-I specifically	
	–	Expert #5 I have done bibliographic research on this procedure. X I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. X I have published this research. X – published in similar areas but NOT specifically with Sleepio I have had no involvement in research on this procedure. Other (please comment)	
	–	Expert #6 I have done bibliographic research on this procedure.	

	–	Expert #7 I have done bibliographic research on this procedure. I have done research on this procedure in laboratory settings (e.g. device-related research). I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. I have had no involvement in research on this procedure. x	
	–	Expert #8	

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: There is no NHS service per se in most of the UK for insomnia. There are small bespoke services in the UK; but as a large service we do not routinely see patients with insomnia. Therefore, in some regards it is novel. However there are similar free App platforms and the bespoke services in the UK provide face to face CBT for insomnia (which I feel is likely superior but unlikely to return post-COVID-19) Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Definitely novel and of uncertain safety and efficacy. **The first in a new class of procedure. – not the first – there are number of free variations such as sleepstation**	
		Expert #2 The means of access – digitally rather than in person is new.	

		Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Definitely novel and of uncertain safety and efficacy. X The first in a new class of procedure.	
		Expert #3 Interesting digital solution to delivering an insomnia focused intervention Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.	

		Unable to answer – not commissioned in local area	
		Expert #4 The current standard of care is limited to hypnotic use, antidepressant use or sleep hygiene guidelines. As such, CBT-I is innovative and considered the first-line treatment for insomnia by several international organisations. That said, this has largely been based on face-to-face CBT-I and digital CBT-I has not yet been endorsed as the method of delivery to my knowledge. Definitely novel and of uncertain safety and efficacy.	
		Expert #5 At this stage in 2020 – this is no longer innovative and I would say that digital CBT has become a mainstream standard for example in Immediate Access to Psychogical Therapies (IAPT), multiple digital CBT are regularly prescribed across services	

		Established practice and no longer new.	
		Expert #6 It is innovative in that the current standard is written instructions, booklets and handouts. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.	
		Expert #7 As its direct referral (often through a hyperlink) it avoids having to go through another service (such as our local IAPT provider). Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. x Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure.	

		Expert #8	
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: As above many centres do not offer an insomnia service. This would fill this void. However, success is modest for these patients. Equally 30% patients with Obstructive sleep apnoea (MERGE) report insomnia; so it would be important that this group of patients are not denied an overnight sleep study by being referred directly to this service in primary care	
		Expert #2 This has the potential to replace standard care	
		Expert #3 At this stage unable to answer – would require further applied evidence/evaluation	
		Expert #4 It certainly has the potential to replace standard care.	
		Expert #5 It is addition to standard care – uptake rates and completion across IAPT show that digital	

		outcomes are similar to face to face if patients complete but many do not log on initially and in our service a high percentage of initial referrals had other sleep disorders and were not suitable	
		Expert #6 Yes, has the potential to replace the current standard.	
		Expert #7 It could be used as an addition to our current offering for sleep disturbance	
		Expert #8	

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: As above – minimal insomnia services in large OSA services. Small bespoke services in the UK	
		Expert #2 Hypnotic drugs, short term, or access to psychological treatments, but access is slow and limited in availability	
		Expert #3 Treatment in the context of other conditions i.e. depression with insomnia.	
		Expert #4	

		There is no real standard of care for the management of insomnia at present. There are a few centres that provide face-to-face CBT-I but it is sporadic at best. This is also dependent upon the referral pathway. The use of digital CBT-I is also being used in a few areas but again sporadic and it is not necessarily Sleepio that is being prescribed.	
		Expert #5 Standard of care is to screen for other sleep problems, discuss sleep hygiene in primary care and then to offer either short course of hypnotic or off licence tricyclic or a behavioural therapy	
		Expert #6 One-to-one sleep hygiene or behavioural intervention or CBT (not internet-based)	
		Expert #7 We utilise NICE CKS for this (last reviewed in Jan 2020). This suggests use of sleep hygiene, short course hypnotics and CBTi	
		Expert #8	
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this?	Expert #1: Sleepstation There are a number of similar technologies and all the time new technologies are being developed (especially in the post-COVID-19 era) in this area	

	If so, how do these differ from the procedure/technology described in the briefing?	I have not seen any head to head data of efficacy of these technologies	
		Expert #2 No	
		Expert #3 no	
		Expert #4 There are two other digital CBT-I products available in the UK – Sleepful by Professor Kevin Morgan (Loughborough University) and Sleep Station by Dr. Kirstie Anderson (Newcastle University). Both are also available to the NHS. There are also several international variants. However, we must be mindful that although each uses the principles of CBT-I; as there is no standard for CBT-I there is likely to be variable quality, which may be reflected in outcomes. There exists no independent data comparing these three products. I don't have a briefing to refer to.	
		Expert #5 Yes – Sleepstation has been established for some years with current contract for NHS england, Space for Sleep is now available within the Silvercloud package and outside UK multiple	

		other digitial CBTi are also used and have been validated in trials There is no difference between the key components of CBTi with education around sleep, anchor points and for example they all use sleep diaries as a key to recording and managing insomnia The CBT itself is well established with protocols manualised for over 20 years and they are all very similar, issues are around how interactive and supported therapies are, therefore evidence supports therapist either supervising, some form of telephone or email support during therapy as more effective in encouraging completion. Sleepio is designed to be entirely automated but many IAPT services have still used it alongside telephone support. Sleepstation does provide email support where needed but so do the enhanced packages of other programmes	
		Expert #6 No	
		Expert #7 I understand there is a resource called sleepstation which needs a referral and also there are some modules online through our local IAPT resource silvercloud (these are online CBTc). These are accessed by self referral.	

		Expert #8	
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1: Remote treatment of Insomnia in a proportion of patients (useful in COVID-19)	
		Expert #2 A new treatment with easy, fast access. Reduced prescribing of potentially harmful drugs.	
		Expert #3 Flexile access for those not able to engage with scheduled appointments, or those who would prefer to engage with a digital option.	
		Expert #4 This has the potential for widespread dissemination and implementation of CBT-I. Insomnia Disorder is a highly prevalent disorder but the majority of individuals with Insomnia Disorder to not seek treatment or know about CBT-I. Similarly, many healthcare professionals are unaware of CBT-I or that it can be delivered digitally.	
		Expert #5 Those with insomnia or comorbid insomnia lasting over 3 months and causing functional impairment	
		Expert #6	

		Effective treatment of insomnia with consequent daytime waking quality of life benefits, occupational efficiency and decreased sickness leave.	
		Expert #7 It is a direct link to sleep support with a tailored assessment and programme	
		Expert #8	

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: Likely educated, technology users	
		Expert #2 Most patients struggling with sleep	
		Expert #3 Potentially greater cohort at present due to lock down restricting ability to engage as otherwise might have Shift workers Those with mobility issues	
		Expert #4 We have utilised this for our patients with anxiety, depression and primary insomnia. It supports digitally literate patients (this is a	

		population group that is highly represented in our anxiety and depression population. Hard to reach groups, patients with conditions which are characterised by fatigue and are unpredictable (MS, Fibromyalgia etc.) whereby standard CBT-I – face to face over six consecutive weeks is likely to result in high levels of attrition.	
		Expert #5 Those with access to email and internet, not suitable for those without this or with literacy issues	
		Expert #6 Chronic insomnia	
		Expert #7	
		Expert #8	
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1: This is very difficult to quantify – insomnia plays a large role in many conditions (not just sleep) with benefits in QALYS and visits to primary care However, the evidence on outcomes and hospital visits or less invasive treatments is not certain (to date)	
		Expert #2	

		Yes – reduced prescribing, reduced waiting times.	
		Expert #3 N/A not commissioned in local area	
		Expert #4 Yes. Considering the lack of efficacy for sleep hygiene guidelines in this population and the issues and burden on the healthcare system surrounding long-term use of hypnotics. Managing insomnia, using CBT-I in this way, has the potential to prevent several long-term conditions. That said, we must be mindful of uptake and attrition levels in this context, which may have an increased negative long-term impact on cost.	
		Expert #5 There is little to no hospital visits recorded in UK directly due to insomnia so any definite health economic data is hard to evaluate, this is not say insomnia does not have significant burden and is an important risk factor for future depression, simply that this data in UK is lacking It may decrease primary care consultations, to date there is no evidence for decreased hypnotic prescribing as a direct result of CBTi, digital or otherwise	
		Expert #6 Yes, all of these	

		Expert #7 Yes I think it would bring this sort of resource to the front door of primary and community care.Rather than having to be referred to another service you could directly access it. There would also be no reason why our care navigation and social prescribing team could offer this directly. It would reduce the reliance on a doctor to prescribe support by providing direct access.	
		Expert #8	
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1: This is likely to cost more as Sleepio will be available on licence and we currently do not have a treatment for insomnia in most sleep services Also if the licence is made available only via sleep clinics it will cause increase strain on busy sleep services (need referrals to be screened for OSA and then appropriate referrals to Sleepio to be made)	
		Expert #2 As the new technology requires fewer staff and prescribing, it has the potential for reducing overall costs.	

		Expert #3 N/A not commissioned in local area – evaluation to inform answer not undertaken	
		Expert #4 It is likely to cost more than the standard use of medication in the short term. The costs would, in my view, be frontloaded and associated with training staff in when this treatment should and should not be given and additional safeguarding.	
		Expert #5 It is likely to cost more than a hypnotic but to be safer with more evidence based outcome but would only be one part of the therapies offered by for example IAPT as our own work shows that not all want or will use digital CBT therapies	
		Expert #6 It should cost less since it avoids one-to-one clinician input.	
		Expert #7 I suspect about the same though if done at scale there is likely to be a cost saving	
		Expert #8	
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more	Expert #1: More than standard care and more time for staff and equipment, if these patients need to be	

	or less than standard care, or about same-in terms of staff, equipment, and care setting)?	screened for OSA prior to be referred for Sleepio	
		Expert #2 I am unaware of the proposed costings, but suspects that with fewer staff and drugs involved, savings are possible.	
		Expert #3 N/A not commissioned in local area – evaluation to inform answer not undertaken	
		Expert #4 In the longer term I see the resource impact being reduced compared to standard care. Whilst face-to-face CBT-I is effective in approximately 70% of cases, research suggests digital CBT-I may not be as effective as face-to-face treatment but it would still relieve a considerable burden on the healthcare system.	
		Expert #5 As above, and other similar technologies are already available and being used in the same healthcare market	
		Expert #6 It should cost less since it avoids one-to-one clinician input.	
		Expert #7 Likely to cost less than face to face CBTi and may also have an impact on hypnotic	

		prescribing (we are looking at this in our current pilot in North Hampshire)	
		Expert #8	
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: No change needed – this would be an App based solution	
		Expert #2 Minor updates to GP computer systems and staff awareness campaigns	
		Expert #3 N/A not commissioned in local area – evaluation to inform answer not undertaken	
		Expert #4 There would need to be training for delivery and implementation for anyone who may prescribe it.	
		Expert #5 None beyond more sleep medicine education for primary care providers – however this has improved over time and GP training does reflect this, already in use along with multiple digital CBT	
		Expert #6 None.	
		Expert #7 None – it's done in the patient's own setting	

		Expert #8	

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1: Not that I am aware of	
		Expert #2 A brief understanding of what the programme involves – an brief online session should suffice	
		Expert #3 N/A not commissioned in local area – evaluation to inform answer not undertaken	
		Expert #4 Yes, as there are several sleep disorders that can 'mask' as insomnia and one type of insomnia that is not suitable for CBT-I, whoever is prescribing this should have the knowledge about these conditions and how they can be screened for. Moreover, there are some occupations and groups for which either additional gatekeeping is needed or CBT-I is contraindicated.	
		Expert #5	

		Yes – screening to avoid incorrect referrals	
		Expert #6 No.	
		Expert #7 No	
		Expert #8	

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1: As noted above – risk of patients referred directly to Sleepio rather than having a formal sleep (apnoea) assessment – from MERGE we know 30% of patients report insomnia symptoms Treatment failure will likely be around a third Many patients will not want to use it as a solution for their insomnia (prejudice, resistance) Not sure how affect it will be in groups that do not like technological solutions (elderly, not technologically aware) – this has been seen with issues around video consultations in the post-COVID-19 era – there is a significant proportion of patients who do not want these solutions	

		Need more evidence of its success in the BAME and lower socioeconomic population (seen in major cities in the UK)	
		Expert #2 I am unaware of any adverse effects.	
		Expert #3 N/A not commissioned in local area – evaluation to inform answer not undertaken	
		Expert #4 This is difficult to answer as I do not know what specific parameters Sleepio has set in terms of prescribing sleep restriction and stimulus control, both of which increase daytime sleepiness, albeit briefly. As I mentioned earlier, additional gatekeeping above a prescription of Sleepio will, in my view, be needed if dealing with safety-critical occupations (e.g. pilots, surgeons, bus drivers, train drivers etc.) and some illnesses contraindicated to CBT-I. There is also the potential for the cognitive components of CBT-I (again I am not sure what these are in Sleepio compared to the other digital or face-to-face variants of CBT-I) to increase negative thought spiralling in some populations (those with intellectual disabilities, certain mental health conditions).	
		Expert #5	

		Sleep restriction phase of programme can impact on driving safety and potential for harm if using unsupervised – this is mitigated in the programme with clear explanation In our service, we have patients who have used sleepio despite evidence of other sleep disorders eg restless legs and sleep apnoea but infrequent and occurs with the other digital CBT therapies, therefore need for health professional to screen ideally before recommendation	
		Expert #6 No obvious harms or likely adverse risks.	
		Expert #7 None known, my only concern would be those who aren't digitally literate or who have access to a computer – they would miss out on this type of resource.	
		Expert #8	
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1: Improvement in insomnia markers – Length of sleep, quality of sleep, PROM	
		Expert #2 Patient-reported improvement in sleep	
		Expert #3 N/A not commissioned in local area – evaluation to inform answer not undertaken	

		Expert #4 The key outcomes would be improvements on both night time and daytime symptoms of insomnia. This could be measured using a psychometric (e.g. Sleep Condition Indicator or PROMIS-Insomnia or Insomnia Severity Index). Measures also derived from a sleep diary could also be used in terms of reductions in time awake at night and levels of sleep efficiency. I would also be mindful about uptake levels, as these have been highlighted in the past when people are offered digital CBT-I. Also, attrition levels as these have also been suggested to be quite high when CBT-I is delivered digitally.	
		Expert #5 Sleep efficiency before and after therapy as recorded by diaries, PHQ9 and GAD7 outcomes as defined by IAPT minimum dataset and some marker of insomnia severity before and after treatment eg ISI or PSQI	
		Expert #6 Improved sleep and daytime cognitive and occupational function including improved quality of life.	
		Expert #7 Multiple RCTs but key ones are: 76% of poor sleepers achieve healthy sleep - Placebo-controlled trial of digital CBT for insomnia Espie, C.A. et al. (2012) Sleep 68% of those with anxiety or depression move to recovery Treatment of anxiety and depression	

		with digital CBT for insomnia Luik, A. et al. (2017), Behavioral & Cognitive Psychotherapy Significant reductions in insomnia, paranoia and hallucinations among university students The effects of improving sleep on mental health (OASIS) Freeman, D. et al. (2017), The Lancet: Psychiatry	
		Expert #8	
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1: Difficult to translate PROM to actual significant benefits e.g. visits to primary care	
		Expert #2 No safety concerns, efficacy at least as good as standard care	
		Expert #3 N/A not commissioned in local area – evaluation to inform answer not undertaken	
		Expert #4 My main concern is for people and populations that are just offered digital CBT-I but would probably benefit from face-to-face CBT-I. The likelihood here is that that individual who does not benefit or who drops out is not going to ask for face-to-face CBT-I as they will believe the therapy is unsuccessful as opposed to the mode of delivery.	

		Expert #5 Lack of published data (as of course often the case with commercial) about those referred who a. Logged on b. Completed c. Had meaningful improvement Outside of trial setting	
		Expert #6 None	
		Expert #7	
		Expert #8	
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1: Controversy - Several rival to Sleepio. I do not know if there have been head to head studies looking at which is superior. There are free online portals for self-help in insomnia. These resources need to be also considered Uncertainty – in the post COVID-19 era – insomnia and anxiety are likely to have increased within the population. As a respiratory consultant, I would be keen for all patients with "long COVID" to have a robust clinical assessment prior to being labelled as having reactive insomnia alone and treated with Sleepio exclusively	
		Expert #2	

		Not all patients will have easy digital access	
		Expert #3 N/A not commissioned in local area – evaluation to inform answer not undertaken	
		Expert #4 I believe an independent study comparing the three competing products in the UK should be completed. Moreover, If we think about a new medication, it would be unusual to rely on data from the pharmaceutical company where the specific make up of the drug; its dosage and timing of delivery are not outlined in the existing literature. It is one thing to say we incorporate the stimulus control or sleep hygiene components of the treatment but another to say what specific recommendations are given under these two headings as these are known to differ between therapists and delivery modalities.	
		Expert #5 No real reason for a single provider to be used at this point in the technology – while sleepio has good data and clear high quality RCT validation, many other companies use the same technology so there should be choice and competition	
		Expert #6 Not that I am aware of.	
		Expert #7 my only concern would be those who aren't digitally literate or who have access to a	

		computer – they would miss out on this type of resource.	
		Expert #8	
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. **Cannot predict at present**	
		Expert #2 Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. This could be rolled out to all general practice settings. Cannot predict at present.	
		Expert #3 Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.	
		Expert #4	

		Most or all district general hospitals.	
		Expert #5 Most or all district general hospitals. – **no reason use in secondary care, a primary care resource – best suits IAPT service or GP access and use** A minority of hospitals, but at least 10 in the UK. – not applicable Fewer than 10 specialist centres in the UK. Cannot predict at present.	
		Expert #6 Most or all district general hospitals. And also NHS staff in community and primary care.	
		Expert #7 Most or all district general hospitals. X (all of primary care) A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.	
		Expert #8	

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1:	
		Expert #2 I have seen no reports	
		Expert #3 none	
		Expert #4 Unknown	
		Expert #5 Wilson S, Anderson K, Baldwin D, Dijk DJ, Espie A, Espie C, Gringras P, Krystal A, Nutt D, Selsick H and Sharpley A. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. Journal of Psychopharmacology 2019, Vol. 33(8) 923 –947. Xu Z and Anderson KN. Real-world evaluation of digital CBT for insomnia in the primary care setting – many should not log on to doze off. DOI: https://doi.org/10.1017/S1754470X19000242	

		Espie, C.A., Kyle, S.D, Williams, C., Ong, J.C., Douglas, N.J., Hames, P., Brown, J.S.L. (2012). A randomized, placebo-controlled, trial of online Cognitive Behavioral Therapy for chronic Insomnia Disorder delivered via an automated media-rich web application. SLEEP 35, 769-781.	
		Expert #6 Not aware.	
		Expert #7 N/A	
		Expert #8	
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1: Recent grant award from BRAIN Charity looking at insomnia in Migraine	
		Expert #2 We have been part of a trial, but the I do not have the data, the Sleepio team will have.	
		Expert #3 Not to my awareness	
		Expert #4 Unknown in relation to Sleepio but there are numerous international trials of online CBT-I on-going at present	
		Expert #5	

		Not aware.	
		Expert #6	
		Expert #7 N/A	
		Expert #8	
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1: Difficult to say – how many people have clinically relevant insomnia that needs treatment in an NHS setting. We have 5000 referrals a year – likely between 500-1000 have a combination of sleep apnoea and insomnia	
		Expert #2 At least 70% of those with Insomnia	
		Expert #3 Unable to answer	
		Expert #4 This is difficult to ascertain. The prevalence of Insomnia Disorder is somewhere between 9-15% of the population – older, female, and some illness groups are more vulnerable and would represent higher rates than the population prevalence.	
		Expert #5	

		Covid affected online therapies but I am aware that our local hospital contract from the sleepstation contract available to England patients has suggested that approximately 1000 patients a month are referred by GPs but this was an significant rise during the lockdown months	
		Expert #6 It is estimated that around a third of the UK population suffer from insomnia. Given shift working and current pressures on NHS staff, it is likely the figure is even higher for them.	
		Expert #7 We have looked at costings in North Hampshire for 2192 per year (from a population of 225000)	
		Expert #8	

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1 No	
		Expert#2 It did not work well on a mobile phone in its trial format	
		Expert#3 Unable to answer – have not had access to the technology directly	
		Expert #4 Anything delivered digitally can pose challenges for some populations where the technology is unfamiliar, inaccessible or undesirable	
		Expert #5 Only good internet access and need for email	
		Expert #6 Availability of the technology and access to the internet.	
		Expert #7 Just that it is digital only.	
		Expert #8	
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1 Not that I am aware of	
		Expert#2 The take up was good in our practices	
		Expert#3 Thorough evaluation of research (including economic eval.) required – I am sure	

		that CCGs/ICS's would request more explicit detail depending on the configuration of their current service/pathways etc.	
		Expert #4 Knowledge of the availability of digital CBT-I is the main issue.	
		Expert #5 no	
		Expert #6 No	
		Expert #7 No	
		Expert #8	
24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert#1 Need more real-world data – BAME and lower socioeconomic groups with insomnia as well as the elderly	
		Expert#2 I am not familiar with the evidence base so far.	
		Expert#3 Applied evaluation on UK population, with economic eval, and PREMs/PROMs	
		Expert #4 Yes, see 17	
		Expert #5	

		No further research of the technology itself only the healh economics which is still lacking and would be of real interest to all of us who treat this group of patients	
		Expert #6 Acceptability in specific populations e.g. age groups, ethnic minorities, religious groups etc.	
		Expert #7 No	
		Expert #8	
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert#1 Beneficial outcome measures: sleep diary improvements Adverse outcome measures: Treatment failure. Refusal to complete course of treatment. Re-referral into sleep service. Missed diagnosis of OSA. Requirement of sleep medications (sedations, anxiolytics)	

		Expert#2 Beneficial outcome measures: Self-reported improvement in sleep satisfaction at the end of the programme and 6 months later Adverse outcome measures: Any worsening of sleep or other well-being over the same period	
		Expert#3 Beneficial outcome measures: would depend on cohort for audit, happy to consider if more information was provided. Adverse outcome measures:	
		Expert #4 Beneficial outcome measures (pre-post and follow up at 6 months): Changes in disorder status (psychometrics)	

		Reductions in insomnia symptoms (psychometrics and sleep diary data) Increased quality of life (psychometrics) Reduced anxiety (psychometrics) Reduced depression (psychometrics) Adverse outcome measures: Uptake (collected by prescriber at the point of prescription) Adherence (collected by initial prescriber post intervention) Attrition (two months and six months post prescription) Sleepiness (psychometrics pre-post intervention)	
		Expert #5 Beneficial outcome measures: those who complete and impact on other outcome measures of mood and anxiety Adverse outcome measures: those who have unacceptable sleepiness and cannot do the therapy, accurate drop out rates	

		Expert #6 Beneficial outcome measures: See: PeerJ. 2018; 6: e4849. Published online 2018 May 25. doi: 10.7717/peerj.4849 A survey on sleep assessment methods Vanessa Ibáñez, Josep Silva, and Omar Cauli This shows that the best measure is polysomnography, but this article also reviews the many sleep questionnaires available. Adverse outcome measures: Not applicable	
		Expert #7 Beneficial outcome measures: Reduction in hypnotic prescribing when used in primary care Improvement in sleep quality for those utilising Qualitative feedback studies on patient experience Adverse outcome measures: Number of patients not completing the full 6 week programme Qualitative feedback studies on patient experience	

		Expert #8	
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert#1	
		Expert# 2 From the practitioner perspective, this is a new and very useful tool to have in our armoury for treating a common symptom with, currently, poorly effective or difficult to access treatments	
		Expert#3	
		Expert #4 I have serious concerns about the title – Sleepio for adults with poor sleep. This product has been designed for Insomnia Disorder and not poor sleep per se. There are no studies which examine its efficacy, effectiveness, barriers or	

		side effects with individuals with other sleep-related conditions which could be characterised as ‘poor sleep’.	
		Expert #5 Digital CBT is widely used, there are multiple packages out there and they work if people do them, it is all about engagement and support Space for sleep, sleepio and sleepstation all look very similar and small difference will not be in the components of therapy but the speed of changing web design and usability	
		Expert #6 None.	
		Expert #7	
		Expert #8	

Additional questions directed towards commissioners.

Role in commissioning 1. Please briefly describe your role and responsibilities in commissioning services for the NHS	Expert #3: Assistant director for all age mental health, learning disabilities and autism services (BSW CCG)
	NICE expert panel member #1 : Scrutinising the use of high cost drugs and devices and ensuring the best patient outcomes are being obtained for the best value.
	NICE expert panel member #2 - Commissioning planned care services – East Surrey within Surrey Heartlands CCG
Commissioning technologies for insomnia treatment 2 Is CBT for insomnia available to patients in your area? Are you aware if there is a waiting list or capacity issues for this treatment?	Expert #3: In the context of other comorbidities some CBT-I strategies may be covered in therapy Are you aware if there is a waiting list or capacity issues for this treatment? n/a as in the context of other treatment.
	NICE expert panel member #1: CBT is available but only when the insomnia is linked to mental health disorders
	NICE expert panel member #2 - no
3. Do you have any experience of commissioning Sleepio or any similar technology for insomnia patients? If so please describe your experience?	Expert #3: no
	NICE expert panel member #1 : No experience
	NICE expert panel member #2 - no
Proposed Sleepio business model	Expert #3: A definition of region would be helpful – health commissioning is managed at STP/ICS and ICA level. Region tends to

4. The Sleepio company are proposing a regional pricing model based on the adult population in a region. This would enable people to access the technology using their postcode. People may have been referred by their GPs or they may self-refer. Is this regional pricing model preferable to a user-based pricing model?	refer to South-west/south-east etc which would be too broad. Assuming that the contractual model would be open access to the entirety of our population.
	NICE expert panel member #1 : Quite possibly prefer the regional pricing, but it would be hard to say without knowing the prices and then doing our own modelling.
	NICE expert panel member #2 - I'm unclear where the funding would come from for a service such as this however, if the funding is via the CCG, the pricing model would either need to be CCG (ie. agree to pay for a certain level of licences for a CCG area) or user based model - I'm not aware of a regional funding pot, unless it's NHS England funded or funded through a clinical network.
5. With the regional pricing model what data would you expect from the Sleepio company to demonstrate value for money, for example no. of registrations, access to modules, completion of the course etc.?	Expert #3: I think what is being asked here is what key performance indicators would we expect? I feel this would need to be co-produced with system partners and people (those accessing services), but my initial thoughts would be: • Number of registrations • Number of activation • Baseline insomnia severity score • Number of modules completed/full model completion rate • Insomnia severity score on completion

	• Experience outcome measure
	NICE expert panel member #1 : Would need to know how many people are accessing it, how many have completed the course or how much they have used it, how often people are using it.
	NICE expert panel member #2 - If a contract is agreed, KPIs, data would be agreed as part of this and would usually cover the key numbers, response rates, outcomes etc
6 What outcome data would you expect the Sleepio company to provide to GPs to demonstrate how the technology is meeting patient's needs and is effective	Expert #3: As above – dashboard would be shared with GPs at patient level re outcome/summary report.
	NICE expert panel member #1 : They should be able to see what effect it is having on the patient's sleep, i.e. is the patient reporting improvements and feel that it is helping
	NICE expert panel member #2- Similar to Patient Reported Ouptcome Measures – before and after comparison of the impact.

Results of NICE PIP patient survey
MT443 Sleepio for adults with poor sleep

Between December 2020 and February 2021 NICE's public involvement programme posted an online survey, 71 responses were received.

All responders confirmed that they read the information sheet provided which explains the purpose of the survey and how the information will be used. All responders consented to NICE using the information as described.

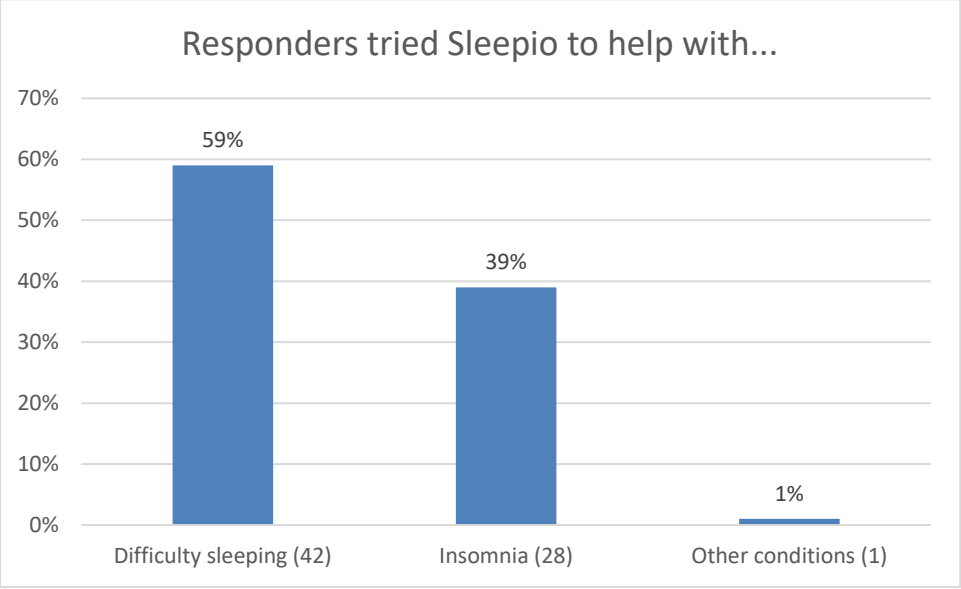
1. Responder demographics

All responders describe themselves as being "a person that uses Sleepio".

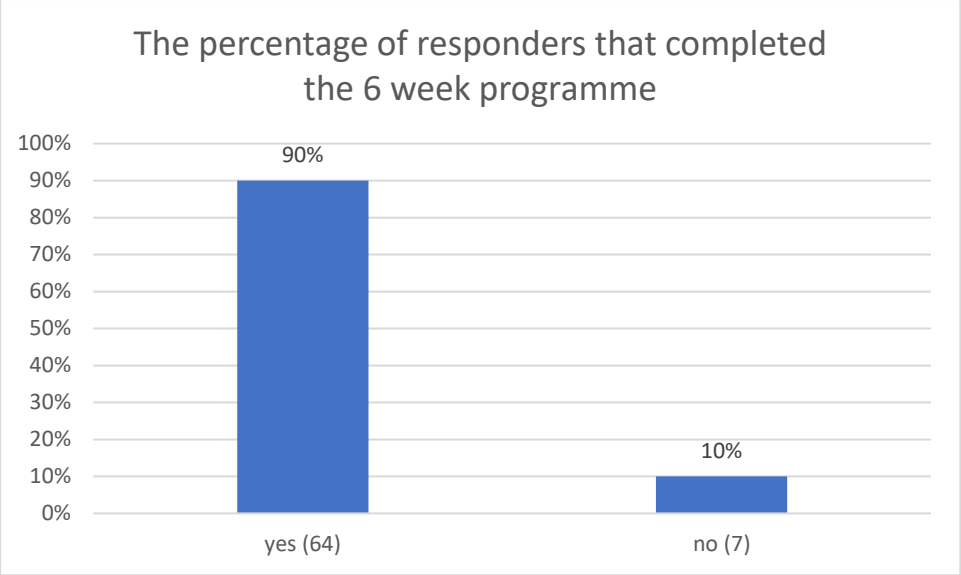
Mean age of responders was 58 years, ages ranged from 30 years to 76 years. 72% of responders were female and 28% were male.

2. Device usage

Responders used Sleepio to help with difficulty sleeping, insomnia and 1 other condition described as unrefreshing sleep and early waking.



The length of time responders used the technology for ranged from 10 days to 3 years. 90% of responders stated that they competed the 6-week programme.

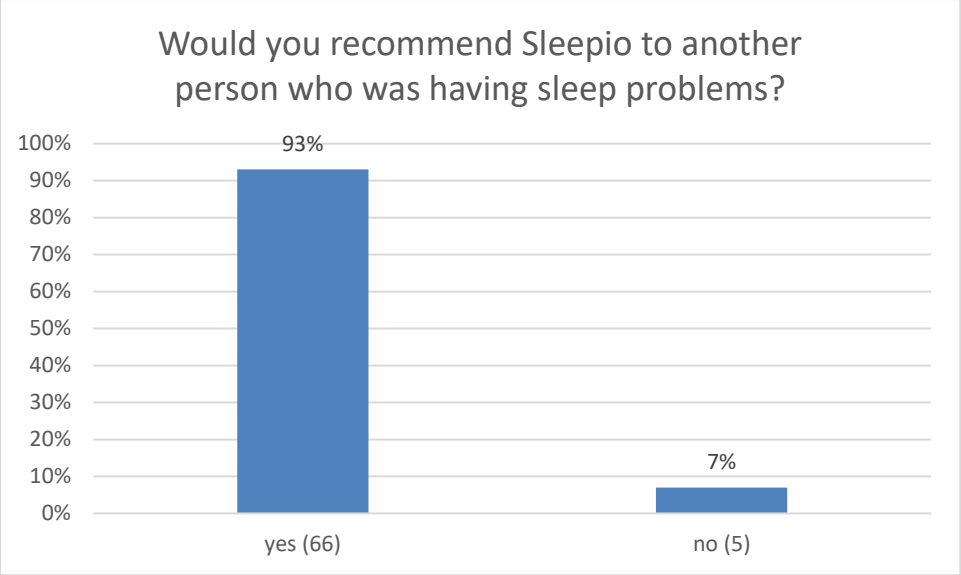


People that answered “no” to having completed the 6 week programme were asked why, and asked to suggest what would have helped them to complete the programme. Responses were as follows:

- *I am halfway through the programme and on advice from the community will spend more time (longer than a week) at session / week 3 to work on sleep restriction and the quarter hour rule before moving on to session 4. I will be completing the programme.*
- *Keeping a sleep diary was very difficult and stressful. It caused more sleep disruption and anxiety*.
- *Sleep got better after short time*
- *The ability for the programme to be a bit more realistic*
- *I am still on the programme and will continue till the end. I wish it was a longer course for a more gradual changes and advise from the proff*

3. Effectiveness of device

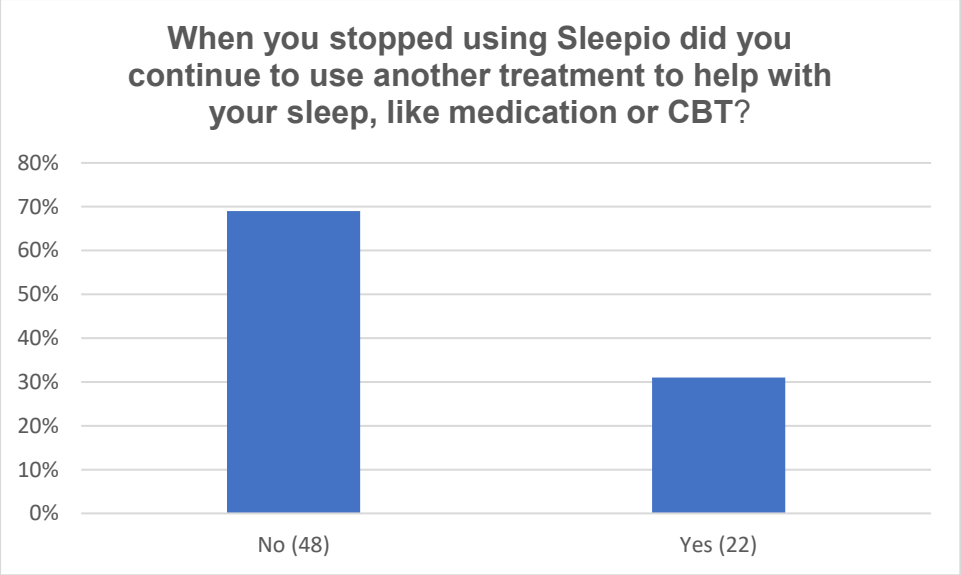
Responders were asked if they would recommend Sleepio to another person who was having Sleep difficulties, 93% said they would and 7% said they wouldn’t.



Responders were also asked why they either would or wouldn't recommend the technology. their free text responses are listed in section 5 (Q5 table below)

4. Other medications/treatments

Responders were asked if, after using Sleepio, they needed to use another treatment to help them sleep, 69% of user said they didn't and 31% of users did.



Responders that answered yes were asked to state the other treatments they have been using. The responses were as follows:

- Continued use of technique learned through Sleepio (6)
- Some form of medication (11; answer included sleeping pills or tablets, amitriptyline, mirtazapine, melatonin, 5-HTP tablets, codyrdramol)

- Face to face CBT for other mental health conditions and also addressing sleep (1)
- Improving environment or surroundings (2: including use of mouth guard, tempura pillow, “help to stop snoring gargle”, sleep headband with quiet noise speakers)
- Herbal remedies (1)

5. Patient statements

Responders were asked some open-ended questions. The 5 questions and responses received are listed below in a series of 5 tables. The number of the responses do not refer to individual responders.

Q1	**Please describe experiences which stand out for you when using Sleepio over the course of the programme? Were any weeks harder than others? When did you notice any improvements?**
1	I did the cbti course at uch and then followed up with Sleepio. It helped but the program is very difficult to stick to. I managed to keep going for about 6 months and then it just got too hard as I could not progress past 5 hrs sleep a night and still felt exhausted but I used the sleep diary
2	I followed all the dietary advise and the rules around only going to bed to sleep. The hardest was getting up if awake for more than 15 minutes if I couldn't sleep, simply because I'd be leaving a warm cosy bed for a colder room. But I only had to do that twice. Repeating the word "the" to stop the thinking process has been amazingly successful
3	easy to understand, simple tips and explanations, putting new perspective on what is normal and expected causing less anxiety about sleeping
4	I have only completed to session 3 so far and am sticking with the course. I noticed improvements in my mental attitude to sleep almost immediately, as I felt I had more control over my sleep with taking steps to make positive changes and having access to advice and support. The website and community aspect stands out to me, as it feels like a resource to use at any time to get some encouragement and advice. I previously would take a long time to go to sleep, and had to listen to a podcast or sleep meditation to fall asleep. I now do not take my phone into the bedroom, and following Sleepio's advice (trying to go to sleep when you get into bed, not reading or using a phone in bed, progressive body relaxation) I usually fall asleep within 15 minutes Session 3 is sleep restriction which is challenging, but now at 10 days in I slept through the night last night without waking up once - I cannot even remember the last time I did that, it must have been many months or even over a year ago.
5	I stumbled in to Sleepio - I would have ignored it if I'd understood it was a sleep restriction programme as I didn't think I'd be able to do that. The sessions with the Prof

	were extremely useful and, even though they are not personalised in any way, they did feel personal. I do not use social media at all and yet I was drawn into the online community. I sought help when the going got hard and I then was able to pass on support in turn to other users. The first two weeks were not helpful - as a long time insomniac I knew the theory and had already implemented the suggestions so that left me frustrated. The sleep restriction weeks were incredibly hard - staying awake til 1.30 and getting up at 6.30 was unbelievably challenging. What I hadn't bargained for was how hard it also was for several weeks after that. I had naively assumed that I'd gain 1/4 hour per week and be up to a reasonable amount of sleep really quickly - I hadn't really understood how hard I'd have to work at it. The improvements came in stages - weeks 4 or 5 to fall asleep more quickly, 3 to 4 months to stop waking an hour too early and still now waking in the night several times. However the main improvement which I've noticed more recently is not being obsessed by sleep, or lack of it, and having a completely different mindset when I don't sleep well.
6	Starting sleep restriction was difficult. I used to go to bed at 10.00 - 10.30 pm to read, then nod off. My Sleep Restriction hours were 1.00 - 6.00 - just five hours sleep! But then I didn't normally sleep for five hours, so I was very willing to try this! The Quarter of an Hour Rule: f we think we have been awake lying in bed for approximately a quarter of an hour, then we must get up and go to a different place to sit and try meditation or mindfulness, do a boring, quiet activity to get sleepy again. This was brutal at first because I started this part of the programme in December 2019 - it was cold getting up and coming downstairs to a chilly sitting room. I noticed improvements in my sleep from session 3 (the first week of Sleep Restriction) and on my fifth night of SR I went from the worst sleep efficiency (SE) of 9% which had happened in the previous three weeks, up to 90%, followed by 95% and that week ranged between 81% and an amazing 98% Christmas week. If we are hitting around the 90% SE target over a week, Sleepios are awarded an extra 15 minutes sleep time. I started hitting these targets part way through that first week of SR and received 15 minutes most weeks - however I wasn't always able to sleep in the extra time. The choice is given to Sleepios to add the extra time to our bed or rise time. I had difficult settling in with it at bed time - I had become used to going to bed at 1.00 am. so I added my 15 minutes to the rise time and set my alarm later. Other things affected me - the dark mornings meant I slept in longer in January and February but as the mornings became lighter, I would wake up earlier, so I started bringing my bed time forward. The clock change in the spring was a nuisance and altered the sleep of many Sleepios. The Sleepio Community is very helpful and I stay to help new Sleepios and graduates of the programme.
7	Sticking to my first sleep window of 5 hours was difficult as was not napping in the evening but sticking to these things did slowly improve my sleep. But it is very very hard to do. I have got used to the sleep window and recognise how this improves my sleep even though it is for a shorter time but trying to stay awake in the evening remains incredibly difficult. I did find using the Community Pages a mixed experience. At the start, when I was feeling low, I wrote about my experience and had a lovely support response from other members. However. when reading about other users experiences, especially those who were desperate and struggling to fall asleep, I found that this impacted my sleep on some nights.

8	The first few weeks were difficult, but you need to stick with it because (in my opinion and experience) it works when you put in the work yourself. It is not a quick fix.
9	I noticed improvements as soon as I started sleep restriction. The first few weeks of the course were nothing new for me but SR really was, I have managed above 80% sleep efficiency (and ofter 90%+) quite consistently since restricting my sleep but have had the odd dip aswell. The first week of SR was very hard but also quite exciting to think it might address a long term problem, it's still hard now (I graduated from the course about 2 weeks ago) especially in the mornings when my alarm goes off and staying awake until my sleep time, but overall I am feeling better than before I started Sleepio.
10	My difficulty is early waking. After 3 months I still haven't fully mastered the art of falling back to sleep after waking in the early hours. The QHR (quarter hour rule) doesn't help me resume sleep, but at least it stops me fretting in bed. Once I am out of bed though, that's it, there is no resuming sleep for me. Even so, there have been some noticeable improvements. These have come about some 3-4 weeks after graduating. My state of mind is a lot calmer these days. I no longer get stressed about 'only' having 5 hours' sleep - now, I think that's a good result! For me, the best thing has been learning to stick with regular routines, not just bedtimes and waking times but also diet, exercise, attention to mental health matters e.g. dedicated worry time, and wind-down time in the evenings. Even if these things don't seem to have a direct impact, collectively they do help to stabilise my daily rhythms and give me a certain peace of mind which helps my sleep.
11	The program is productive in direct proportion to each participants efforts. The beginning is the most difficult as the process of breaking one's unwillingness to change is starting and no one relinquishes their beliefs easily.
12	I had suffered with poor quality sleep on & off for years, but it came to a head in 2019 after I had been travelling a lot & coping with different time zones. I was only managing 2-4 hours sleep per night. My concentration & confidence was getting affected. I had been using sleeping pills to help my insomnia for some time but decided I didn't want to become dependent on them, so my GP recommended I try Sleepio. I found the 6-week course hard & challenging to do at first, especially SR & QHR. The Prof. recommended changes to my lifestyle which I followed religiously but found that it was too strict & getting me frustrated so I had a bit of a break, read through some notes I had made, tried to understand the science behind the course & decided which tools would help me best. One of the most important things I came to realize & accepted was that each one of us requires different amounts of sleep, some 5-6 others 6-9 hours. I had always believed everyone needed at least 8 hours sleep to survive happily. I came to understand that if I wanted to improve my sleep, I would have to get rid of some bad habits e.g. reading at night using electronic devices in bed, cutting down on alcohol etc. Following the program & sticking each day to filling in the Sleep Diary, doing SR, QHR (hardest part of the program first few weeks) was important. Doing PTDR, Wind Down to relax 1.5 hours before going to bed definitely started to help me. Using these tools when I am going through a blip stage continues to help me. Most importantly I began to recognise that I was not alone, lots of people had sleep problems. Having the support of the Community, sharing our problems & advice was

	the best thing about Sleepio. Everyone encouraging each other to stick with the program when the going got tough. The support was enormous. Also the Sleepio team helping whenever help was needed was fantastic too.
13	I started Sleepio after a period of poor sleep over several months. The sessions are calming and informative, after floundering around getting more desperate about sleep it is a relief to feel you have clear instructions to follow. Initially I really struggled with the sleep restriction and quarter hour rule - it was so difficult each night to keep awake till my later-than-normal bedtime. But after a few weeks my sleep window was adjusted a little earlier, and things became easier. I began sleeping very well and did so for many months. I recently returned to sleepio and self imposed sleep restriction and quarter hour rule because my sleep had gone off again. I had begun to relax in bed rather than get up, I had begun to read in bed...I'd become too relaxed about the rules and my bed sleep connection was lost. After a week or so (easier this time round I know what I'm doing) I am back on track.
14	Sleep Restriction is very hard, week 3 and QHR and the first time I tried it I gave up very quickly. But I'm trying again having read up on it. A couple of weeks in and there are some improvements.
15	The first two weeks were mostly about monitoring existing sleeping patterns so they didn't make a huge impact, though it was helpful for me to be able to measure my sleep and the extent of my problems. It became very difficult when the sleep restriction was introduced as that was an extremely sudden disruption to my routine and affected my partner as well. However I began to notice improvements after about two weeks of sleep restriction.
16	The benefit of Sleepio was the sleep restriction programme and how it helped me monitor my sleep, set a restricted programme and stick to it. I noticed improvements 2 weeks or so into the programme. It got me back into a routine and out of a severe period of insomnia
17	Good basis of information at the start of the programme to explore some of the principles behind what it is going to do and get you to think about some of the reasons for your sleeping problem/s. Then followed (I think in week 2) the abject horror of putting the sleep hygiene in place! It was thoroughly painful to begin with, to stick to my wake-up time regardless of what time I had fallen asleep, I remember feeling rather ill during that period as it was just so hard to stay awake during the day when I had had 0-2 hours sleep the previous night/s, but the programme was good at emphasising the importance of sticking to it. I felt the principles well-explained and knew it was evidence-based and this was reassuring. That week (week 2 I think, when the time-controlled sleep hygiene on the clock came in) was probably the hardest, physically. I think I also had a bit of a mental dip around week 4-5 as well but got back into it by going back to the strict timing. I noticed improvements in week 2-3. I was also struggling with depression and was on anti-depressants which of course contributed to my already unhealthy sleep habits. Sleepio definitely helped me overcome my acute insomnia within a matter of weeks. This was late 2016 when I used Sleepio. After I did the Sleepio programme, I had two further periods of insomnia and problems with sleep,

	during the rest of my depression and I returned to the notes I made from the Sleepio lessons and they were invaluable. Each time the Sleepio principles worked to help me overcome my sleeping problems. The voice of 'The Prof' was very likeable and soothing!
18	Mid term was the hardest - around weeks 3-4. I like the quality of the online courses and the specific advice. The techniques for calming my mind were helpful but it is wrong to pick out one thing, it is the whole package that works. I am certainly noticing improvements.
19	Hard starting sleep restriction. Hard to get out of bed when not sleeping after quarter of hour. Slight improvement during ititial 6 weeks then plateau with some ups and downs
20	There has been an improvement. But I have had insomnia all My life.
21	How unbelievablely reassuring it was to be shown figures in week 1 as to just how many people struggle with sleep.
23	Useful times and recaps throughout the app were helpful. Keeping the logs was sometimes challenging if I didn't have my phone to hand or forgot and had to go back and do them retrospectively
24	I have always hated routine. I still struggle with this, but am able to manipulate this with the techniques I've learnt using Sleepio
25	I understand the CBT theory but the sleep restriction method just couldn't work for me as some nights I may get as little as one hours sleep or no sleep at all. On the following night I just could NOT stay up until my allotted bedtime. I JUST COULDNT - I just had to sleep when I was at exhaustion point. However there were a few useful tips.
26	Improvement cane quickly, so it struck me that the individual steps were well judged and in the right order.
27	I noticed improvements straight away, and then when sleep restriction started I felt rested for probably the first time in my life
28	The first few weeks are tough having to go to bed late and still get up at the same time at the weeeknd when you want a lie in. But it worked really well for me
29	I liked the fact that it gets you to focus on your particular issues and that you can track progress.
30	You and your partner, in my case, have to commit to this. They have to be tolerant of you going to bed and or getting up at times dictated by the programme. I found it difficult at times, some of the advice went against how I felt but it worked so I committed to it. It resolved issues I had had for years. I noticed improvements almost straight away.

31	I looked forward to each week's email and took the class each Sunday. I have continued to use these techniques which I learned from Sleepio each evening.
32	The sheer quantity of different techniques was very helpful but the main standout techniques were limiting sleep hours by going to bed much later to optimise the sleep window and to avoid lying awake in bed (make bed for sleeping only, so if awake get out if bed and only go to bed when sleepy). These techniques were difficult and tiring but did yield results
33	I like the simple techniques the relax and unwind, ways to switch off your brain. I have never had the same issues at night since using sleepio and recommend it to friends.
34	Each session gave me advice which I followed.
35	The professor interaction and explanations were helpful.
36	It slowly changed my attitude to not sleeping well during the course
37	Signed up for free trial (in Oxfordshire) and rigidly followed the course until the trial ended. First week was very difficult and frustrating as I tried to record my sleep and resulted in a number of exceptionally poor nights' sleep which gave a very low base from which to start. I subsequently used a fitbit to help me assess my sleep effectiveness as I went through the course. The stages of tuition were very well laid out. I liked the explanation of the scientific basis for all the recommendations and had high confidence the programme would help me. I followed the steps closely, starting with a very short sleep window, which was based on the artificially low first week records. Initially progress was good - I found the relaxation techniques very effective at getting me to sleep quickly - but the improvement stopped with a level of sleep similar to that I had before starting the trial. It seems a key component of the programme is peer support and I was personally not comfortable with this. I didn't need encouragement to keep going, rather informed opinion as to why there didn't seem to be improvement and what to try to correct this. I found one correspondent who seemed to be having a similar response to mine and the feedback he got was typically 'i worked for me' or 'you're doing something wrong' neither of which I felt were helpful. One particular challenge was the rule that if you're awake for more than 15 mins then get up and do something until you're ready to get to sleep again. Although this did help me to get to sleep again I found the level of tiredness the next day had a significant impact. In particular I occasionally felt very unsafe driving and minimised my journeys. I felt the level of support after completion of the initial training was very low. After having a review I might be told I'd get an email but I hardly ever did. There was also no opportunity fr feedback at the end of the course.
38	Used it about 2 months, followed advice and am ok now
39	I used Sleepio quite a while ago, so cannot remember for how long. The hardest part was consolidating the time frame of actually being in bed for sleep only. For me it was not very successful - but I could see the logic and did try to do it.

40	Learning to accept not sleeping and not to stress about it by using the strategies to deal with it e.g. if still awake after 15 minutes get up out of bed and go to a different room. Having a regular getting up time and just doing it no matter how tired you feel. The last week because it was near the end. Also having to log sleep and wake times was abit of a chore. About half way through.
41	Up and down no longer practice
42	I realised that apart from the unrefreshing sleep due to the menopause (and Sleepio didn't help with that, I had to increase HRT to sort that issue) that I slept poorly when I was, even mildly, anxious about things. I think I realised this at about week 5. I found the sleep logging the most useful aspect and kept up with this until my free access to Sleepio was lost. As I nearly always slept for 6+ hours I didn't have to do much sleep deprivation
43	Although I found the narative quite calming, I felt that having an American based programme did not make sense, neither did some of the suggestions to achieve a better sleep pattern, works in todays life style
44	It was interesting to keep a record of all my wake times as I hadn't realised how little sleep I actually was achieving. Week 3 and 4 are very hard with the sleep restriction window set and also trying to keep to the rule of getting out of bed if you are not sleeping within 15 mins...the QHR. If you get very little sleep your body just wants to rest so its incredibly difficult to drag yourself out of bed a number of time. I have yet to manage that area I am able to stay up till my earliest bed time but getting up at 5 is proving difficult as sometimes I haven't achieved sleep or have ONLY JUST SLEPT so feel exhausted and Know my body needs to rest so I can look after my family for the day, home school and work. So far no sleep improvement for myself but I have faith in the process and I am hoping that if I can get to the point where I am able to do exactly what is asked my sleep pattern could change. The relaxation techniques certainly do help you to become calm and ready for sleep and I also find a lot of the articles in the library are very informative.
45	It helps with the general understanding of sleep patterns and the influence of stress
46	I did not find it helped i did all they suggested
47	A gradual improvement generally in maintaining the ability to get to and stay asleep.
48	Noticed reduced anxiety due to acceptance that I did not need as much sleep as my wife and accepted that I was getting as much as I needed.
49	I used Sleepio after finding mindfulness so it was an add on for me as Mindfulness had a huge benefit. I found the advice around changing your attitude to sleeplessness the most helpful
50	I noticed an improvement after thinking of focusing on sleep in the room rather than reading first.

51	A little difficult to accept putting ‘reduced sleeping times’ requirement into practice. Cheated a little to start but realised the need and followed within reason.
52	Subjective improvement when decided to get up after being awake for more than an hour rather than remaining in bed
53	Sorry, can’t remember exactly when it really started to help.
54	I used the Sleepio programme for six months two years ago. My sleep pattern is altered when I am upset or worried about something. The suggestion of giving my thoughts / worries a limited time to think or worry has really helped. Also the suggestion of getting up if you cannot sleep helps. I often read if I wake in the night , or get up and watch some television and then upon returning to bed can usually sleep.
55	yes, trying to not go to sleep too early then waking up early the next morning
56	I completed the course in 2019, so can't remember how long I used it for, it was the duration of the course, although I have used the autogenic training since.
57	The earliest weeks were the hardest, getting up when I couldn't get back to sleep. I did start to notice imrovements after a month or two although a couple of good nights often meant a couple of bad nights. I also struggled to stay awake until my allotted bedtime. To be honest I think it helped that we went into lockdown as I was working every other week. Although there was general improvement it was noticeably more during my weeks at home. After about 6 months my sleep had improved enough that I didn't need to use repo any more as I was aware of the principles to follow and I have been doing well. Even if I get the odd bad night it is nothing compared to what I was going through.
58	I found it extremely helpful very quickly and recognized some of the relaxation techniques. I might not have been entirely strict during the sleep deprivation weeks as the programme was already working for me.
59	Restriction of sleep was difficult. Improvements after a few months
60	At first the enforced lack of sleep to make you tired were very hard. After a few weeks, adapted and was tired enout to sleep.
61	I used it for about 3 months about 2 or 3 years ago. I enjoyed the programme and it worked really well for me. I really liked the professor character, his voice & accent and his little dog. I found it very profound when I suddenly hit a stable sleep pattern for 2 weeks. I really enjoyed waking early on non-working days. The first 2-3 weeks showed modest improvements - but after that it increased dramatically. I felt much more rested and capable on a steady bank of sleep repeated over 10-12 days plus. I found my sleep pattern is about 7.5 hours and I use this for my target each night.
62	I didn’t see much improvement
63	I realised that Sleepio was a great framework to explore my sleep but in the end I’m not really sure it helped me directly. But indirectly I realised I had to explore and investigate

	other reasons for my poor sleep. In the end I realised that my hypertension medication was probably to blame and eventually I got it changed. My sleep is better, but still needs work. Perhaps the final realisation is that I could probably usefully go through the programme again to see if I could make further improvements.
64	The weeks when I had to restrict my time in bed, going to bed extremely late and trying to keep awake until my allotted bed time, trying to stop my thoughts from running away with me, concentrating on one word to calm my mind. All the ways which should have helped me drift off. It took about 2 weeks to notice any improvement.
65	the changes came with a different attitude to quality of perceived sleep

Q2	**Please describe any positive effects that Sleepio has had for you, your condition and/or your quality of life? Please consider things such as: Your ability to perform daily activities Your quality of life, lifestyle and/or social life Your physical symptoms Your state of mind, emotional health and/or wellbeing The effect on family, friends and others**
1	Although I did have things like long periods of being awake in the night, before, I did not regard them as a major problem. I was partly trying out Sleepio from a patient representative perspective for when recommending it to other people. That said, I did take it seriously and found it a worthwhile program to use. I wouldn't say it has had a major effect on my quality of life, in the ways suggested in the question, because I was already dealing with the issues and was not letting them worry me. When I have slept better, I have appreciated it though.
2	It helped having a routine to stick to but my insomnia never really went away. I found the behavioural stuff more helpful than the cognitive stuff
3	I've stopped worrying about sleep and now my energy has increased
4	I am more relaxed about sleeping and know that even if I have days/weeks with little sleep, I am still able to function as my body takes what it needs. It made me more aware about activities and food/drink which can influence my sleeping and I notice after a chocolate evening that I can't sleep, whereas I didn't make the (quite obvious) connection before. Sleepio was a reassuring programme to show what is normal sleep and what is still tolerated and how the body copes even with interrupted sleep. Advise to get up was another good one rather than lying in bed worrying.

5	My wellbeing has definitely improved since feeling more in control of my sleep and having a resource to deal with sleep problems, even when more tangible changes were not yet apparent. I used to moan about my sleep and blame my mood or performance on poor sleep but now I take a more positive attitude which has improved my state of mind. I now feel more able to access other wellbeing tools such as meditation and overall this has contributed to improving my relationships with others.
6	I feel much more in control of my life - I am still not sleeping as well as I'd like but it doesn't make me miserable like it used to. I also don't have the awful sleepless nights I used to have where I'd worry e.g. I was unsafe to drive. I have much more energy during the day - this is also a by product of better habits. I have always looked after my health but since Sleepio my general well being has improved partly I think due to getting up earlier and therefore having time to go for a walk every day before work.
7	I have slept much better over all, since doing the programme. I remain a Sleepio member to help new people with terrible sleep problems and some mental health problems and I feel better able to help. I do more volunteer work with the NHS Responders. I have the energy to do my work at home and garden. I am now able to manage awakenings as I still have a couple each night but can get myself back to sleep. I have managed to decrease my antidepressant by half the dose and am maintaining that now through the worst months (winter) and feel able to cope even on days when I've had a worse night. I feel happier in. Myself and have learnt even more about what affects our sleep and enjoy passing that on to the new insomniacs who come on the programme. I don't let the worst nights/blips affect me any more. My health has improved and even during lockdown from March 2020, I continued with the 'couch to 5k' running, I had more energy and felt happier and followed a diet and lost 3 stone between February 20 and September 20. This has helped my fibromyalgia too. I don't wake with the same pains I used to have and the notes I made in my sleep diary on Sleepio show the differences in what was waking me up. Unfortunately now that my husband is back sharing the bed - he still has night terrors and snores - so I still get woken up!
8	When I first started Sleepio I had completely lost the ability to sleep thanks to being ill with Covid. The big improvement for me has been regaining that ability though my problem now is sleep maintenance. I am able to function during the day and reducing my anxiety around sleep has the effect of improving my mood and energy levels.
9	It had a huge impact - I was able to function properly, and ceased to worry about the occasional, inevitable, bad night.

10	Generally feeling more energised and positive in my work, and a bit more positive about things in general. I do feel like I am still sleep deprived though and looking forward to extending the sleep window a bit more I feel it will be challenging to continue the good habits once lockdown is eased and socialising becomes more of a thing, at the moment SR is relatively easy to implement.
11	I think I am in a much calmer state of mind since starting Sleepio. I was able to function reasonably well before starting the programme, but was feeling overwhelmed sometimes with anxious thoughts. I could sometimes feel myself slipping into a state of depression with spiralling negative thoughts. I think Sleepio has helped me overcome this negativity and anxiety. I'm not fully 'recovered' as such, but in a much better place and I hope will continue to make improvements.
12	All aspects are improved....ALL
13	Although I have the occasional blips, I am now able to perform my daily activities without any problems. My quality of life has improved & my emotional health is in a much better place. I have learnt to deal with any blips using the tools Sleepio has provided. My friends have noticed a big change for the better in me. I don't look so tired or anxious any more.
14	Sleepio taught me how to sleep again, and has given me invaluable insights into the unconscious art of falling and staying asleep. It’s transformative. I’m still a light sleeper but I have the tools now to help myself.
15	I feel more in control of my sleep so worry less about it. This then gives me head space to cope with day to day life, which previously was difficult due to worry and tiredness.
16	My ability to perform daily activities improved when my sleep began to improve as I had more energy during the day. Quality of life/lifestyle improved because I had more energy to exercise and was more motivated to eat healthily. Once I started sleeping better I didn't constantly have headaches, fatigue and stomach upset from sleep deprivation. I became less anxious about sleep and saw a slight reduction in my general anxiety. When I slept better I found it easier to manager relationships as I was in a better mood and able to think more clearly.
17	It impacted upon all of the above, because not sleeping impacted the above in a negative way
18	I had depression at the same time as my insomnia (obviously a common pairing) and the positive effects that Sleepio had are: - Ability to better tackle my depression. Hard to describe how big an impact this was. Insomnia and sleep problems were the cruellest part of depression for me as they removed

	the energy I needed to think about even just getting through the day, nevermind anything bigger than that like going to work, making GP appointments, thinking about medication changes, trying to keep your life going. They're two very closely entwined health problems having a tool to directly address the sleep issues gave me confidence to feel I had some control over at least one part of what was a difficult period of health issues. - Employment. My sleep issues were causing problems with my employer due to the amount of time off I was taking. Sleepio helped me reduce the number of sickdays I had to take due to insomnia; helped me engage with my employer (NICE) about the impact of sleep problems on work; and ultimately helped me get back on my feet at work. - State of mind / emotional health. See above re depression. I had depression for a further 3 years after I used Sleepio but have no doubt I would have struggled with sleep problems for much longer and may have been at risk of losing my job if I hadn't been recommended Sleepio and gone through with the programme.
19	It's mainly my state of mind but only following a good night's sleep. When I get a bad night, my state of mind reverts to how it was.
20	Sleep quality improved on average. Better able to cope when sleep more stable.
21	My eyes are tired very often. I am lucky if I can get 4 hours sleep. My Husband supports Me.
23	My anxiety around sleep has significantly decreased, meaning anxiety stopping me sleeping has become a thing of the past. My mental health has significantly benefitted by using sleepio.
24	As I started sleeping better, I had more energy during the day to carry out my daily activities, work and social activities. I was also less irritable and less anxious
25	I now believe I can fall off to sleep without medication
26	A good night’s sleep aids the next day in every way, including but not limited to energy, mood and relationships.
27	Happier, easier to concentrate and focus, less irritable. I stopped affecting my partners sleep as well, as me sleeping badly affected him
28	I would say the benefits improved all areas listed above and also enables me to have better control over my appetite
29	All positive affects that it has, wear off over time. Refresher courses are needed, but must be wanted. Same issue as losing weight, giving up smoking etc.

30	I sleep much better so feel much calmer in my daily life.
31	I was able to prepare for sleep and sleep better. I was better rested each morning. I have instituted new habits which have served me well. My wife also benefits from the improvements we made in our bedroom.
32	It have me confidence to get good sleep again, huge difference to alertness during the day, mood, energy, general quality of life for me and those around me
33	I slept much better using techniques described in the course. I became less tired in the day and was able to function more.
34	Felt mentally and physically more alert
35	Mood and productivity
36	Although I don't feel I achieved any benefit in my sleep performance and have achieved no benefits in the example areas given, I am more resigned to my situation so that I don't lose as much sleep as a result of worrying about not losing sleep! I am fortunate in now being retired so the impact of my poor sleep is less consequential.
37	Don’t worry if I cannot sleep - which means my sleep is better and less tired
38	A very structured routine, which was focused, planned for me, so I didn't have to think about what to do. From memory, I do feel it helped at the time, and sleeping improved for a while. The little man became part of my weekly interaction, as I felt he was talking just to me. I thought he was made up - but did see him on TV once - and really is like his character !
39	I was more alert Less crabby Lost a small amount of weight Less concern from my husband as I wasn't wandering the house at night
40	Better quality of life
41	It has helped my relationship with sleep. I have learned from the sleep logging that when I get really tired I will sleep for longer for a couple of nights.
42	It has made me feel less isolated and that I am not alone in this awful nightmare that continues day in day out. It has given me hope that things can be changed. It has given me access to talk with people going through the same scenarios who have empathy and advice, so my family don't have to listen to me constantly droning on about how awful I feel and who don't have the ability to

	help. I guess the pressure has been taken off a little. I am hoping once the programme is complete I will have other positive feedback.
43	As before, wider my understanding of sleep process.
44	I am worse now than before I started average about 5hr a night I have not seeped more than 5hr 30min for Years
45	I need to use it again! My sleep is better but depending on medication and mental health, have relapses
46	QOL improved considerably as I no longer feel permanently tired and have lost the stress associated with the worries of lying awake while feeling dog tired.
47	Reduced concern that I was getting less than 8 hours
48	State of mind improves with the change in perspective. The knowledge that it is not happening only to you and you can change the way you view it so it is less of an issue/negative
49	It helped me to be more disciplined about my routine and approach to sleep. It helped me feel more confident and this improved my ability to manage better day to day (before lock down).
50	I felt better
51	Far happier and settled with life when sleeping pattern is not being pulled apart. Able to accept that missing sleep may happen and ability to remove fear from this stops the situation from spiralling.
52	Improved state of mind following a poor nights sleep
53	My ability to perform daily activities, my quality of life and my state of mind and emotional health
54	My interaction with those close to me has improved when I am worried or stressed. My concentration has improved.
55	At the time sleeping improved. Since lockdown everything has become more difficult and the programme has been allowed to slide.
56	Just getting a good sleep was of benefit. My sleeping difficulties caused tiredness and frustration and Sleepio assisted with resoving it.

57	I feel so much better and more cheerful. When I started Sleepio it was because I was getting about 2 hours sleepa night and Iwzs really struggling with concentration and energy. I am much happier now and more focussed
58	Sleepio has made a huge difference to my life in that I no longer use Aminotrptalin routinely, sleep well and don't feel lethargic and hang over in the morning. I am much more positive. I should say that major life changes eg retirement occurred at the same time. Since lock-down my exercise has increased along with better sleep and weight loss. Far fewer headaches following poor sleep. Much less grumpy so good for husband too! I have told friends how good Sleepio is and they are also finding it beneficial.
59	Not worried as much
60	Quality of life improved because able to rest. Properly rested so able to carry out daily activities better. Overall learned not to worry about not sleeping and then occasional bouts of insomnia. I became easier to live with and passed on tips to friends who were having problems - like if you can't sleep, go and do something else away from bed then try again.
61	More rested & capable. More resilient to stress/anxiety/depression/change. Really enjoyed the quiet, early mornings. My mind is very relaxed and receptive in the mornings.
62	No noticeable effects
63	I failed to complete course
64	I have realised that I cannot go to bed early. I have to stay awake until at least midnight then make sure I wake up at the same time each day even if I have to use an alarm. If I have slept well I can concentrate better and feel less depressed. I feel I am able to carry out tasks without dreading them. I feel like a zombie if I don't get enough sleep. It's a myth that everyone should get 7-8 hours' sleep a night. I think that may have a negative effect on people and out them under pressure to get that amount of sleep. One size does not fit all. The media and medical professionals make it sound do easy when they keep going on about getting 7-8 hours' sleep a night. Ha, if only it was that easy!!
65	Much better attitude to what I perceived as poor sleep, the worst part of the programme was noting my wakefulness which I felt emphasised and woke me up more than if I just glanced at the clock and tried to get back to sleep.

Q3	**Please describe any negative effects that Sleepio has had negative effects for you, your condition and/or your quality of life? Please consider things such as: Your ability to perform daily activities Your quality of life, lifestyle and/or social life Your physical symptoms Your state of mind, emotional health and/or wellbeing The effect on family, friends and others**
1	Initially it was just so hard to stick to the course on so little sleep it affected my social life.
2	Not much, just looking forward to extending my sleep window and being able to go to bed earlier when I hit my 90% sleep efficiency
3	Initially at the start of sleep restriction I felt very tired at times and felt that my new schedule was challenging. It affected my ability to do things in the day, like read for example, as I felt tired. However this only lasted a short amount of time and Sleepio had warned me that this part of the course is the most challenging. I was willing to go through some temporary difficulties for the gains and I am now seeing this start to come to fruition.
4	I don't feel Sleepio has generally had a negative effect. During the sleep restriction weeks however I was very tired and often despondent, and this probably impacted on my family. Ditto the ability to perform daily activities was severely impacted - lessened by being in the midst of a pandemic and not travelling to work.
5	I was exhausted starting the sleep restriction - it was hard trying to stay up til 1.00 am I would nod off on the settee in the evenings and Miss programmes and then spoil my sleep at bed time but this was part of how SR and the QHR work. The clock watching nearly drove me spare in the first two weeks then I found out we could guesstimate! So that made it easier.
6	Graduating from the course after 6 weeks without having resolved my sleep problems did impact my mood a little. I didn't realise that completing the course was only the start of resolving my sleep problems. I am still using Sleepio after 10 months and now regard it as a tool kit to employ when my sleep gets even worse as it has still not resolved. My other negative experence has been of the Community Pages. I suffer from anxiety around sleep and reading the experiences of desperate people panics me and I absorb the negativity usually experiencing an exceptionally bad night or two. I don't often look at the Commnity Pages now though I recognise their importance to some people and I have taken advantage myself.
7	It's hard to say the effects on my social life as we are living through a very unsocial time, but I do worry that I will struggle to maintain the programme and have an active social like in the future. I like going to pubs and seeing friends, I

	wonder if this will impact my good sleep habits I do feel extremely tired in the mornings at the moment but seem to gradually perk up as the day goes on, which is normal i suppose, but my body is crying out for a bit more sleep. Not much negative effect on any activities really.
8	There haven't really been any negatives. Observing the QHR has been hard, but now that I am used to it I just accept that I should get up if I cannot resume sleep. Over time I've learned that I can still continue to function, even if I have only had a couple of hours' sleep. It's hard sometimes battling the mid-afternoon fatigue, hence why I often have tea or coffee mid-afternoon.
9	CBT, SLEEPIO or just plain REFLECTION have ZERO NEGATIVE EFFECTS. Other than one's beliefs come under attack. Fear is the underlying issue(s) that is universal to everyone, only the magnitude and duration between individuals is different. An unwillingness to examining the fear(s) allows it to manifest into problems in one's thinking. A peaceful mind finds sleep, a mind not at peace will not, hence, underlying fears. What the mind focuses on the mind feeds and what the mind feeds grows.
10	Yes there are occasions when I feel negative mostly when I have a 3-4 day blip & can't see Sleepio helping. Especially when using SR & QHR I get grumpy & short tempered. Of course Covid has not helped the situation as one can't share one's problems with friends or family which is very frustrating so one has to use tools provided
11	I really miss being able to have morning coffee in bed, or to read - but those are the rules, and you mess with them at your peril.
12	Initially during sleep restriction you feel worse, which isn’t really explained. I was very tired, irritable and frustrated and took it out on my family.
13	During the first phase of sleep restriction, I was getting even less sleep than before, as my sleep window prevented me from catching up when I'd fallen asleep late. As a result I was more or less constantly sleep deprived for about two weeks. This made it harder to perform daily tasks, exercise, and relate effectively to others. I also had headaches and felt exhausted at times. Introducing sleep restriction was a huge disruption to my and my partner's daily routine and was difficult for us both to adjust to.
14	I was very tired in weeks 3-4 but usually in the evenings so did'nt affect my health.
15	Sleep restriction etc difficult with partner.
16	Sleepio had no negative effects for me.

17	As described I just couldn’t do the sleep restriction. That would have had a worse affect on my family and my life
18	I felt slightly more irritable during the first couple of weeks when I was tired. But not adversely as I was aware of this
19	It has difficult/challenging techniques that took time to work. Needed determination
20	I was more agitated, tired, and frustrated. My sleep pattern was worse during the program but there was some improvement once I stopped.
21	I think it has left me slightly more depressed at not having been able to achieve a better result after a year's worth of effort and , in particular, with no clear way forward.
23	I could not sustain the limited timeframe of being in bed to sleep. This did have a negative impact on my mindset, as I felt I had failed, and still felt tired. Since doing the programme, I do try and keep a routine of going to bed and getting up at the same time, however on occasions I simply can't stay awake and have an afternoon nap - maybe that is just an age thing though!
24	I cannot recall any negative effects
25	As yet the sleepio programme has not had a negative impact apart from having to stick to such a structure and routine for sleep routines. My sleep has been so poor it has already had a negative impact on most areas of my life.
26	all of the above
27	Initial stages left me more tired of a day but was able to feel a little more comfortable with this after a short while.
28	I negative effects at all
29	Towards the end of the course, I was really focussing on time I hadn't slept well. Although I understand that this was a course used by many, when I hadn't reached a milestone or had done, the course automatically moved on.
30	Sleepio was a really good tool for me and was a positive experience
31	There is an important, unpleasant side effect: My wife goes to sleep very late (about 02:00), sleeps late and works late into the night. So our body clocks and socialising are put under stress through my own ideal pattern of about 11.00-06.30. Sleepio would benefit from a module on handling this kind of problem.

32	Lifestyle made it too difficult to do this online
33	I am totally unable to do most of the calming exercises they suggest (maybe I am hyperactive). It made me feel useless that I was unable to do these things and a feeling of failure yet again. I have, however, adapted some of the suggestions with a modicum of success and I don't worry so much if I don't sleep well.
34	as stated in the previous question about logging periods of wakefulness, but on balance a positive experience

Q4	**If Sleepio has had an impact on any other areas of your life that are not covered by the questions above please tell us about them here.**
1	If Sleepio has had an impact on any other areas of your l...
2	I think it is valuable but it’s difficult to stick to the program whilst also trying to manage other mental health problems mainly chronic long term depression and anxiety
3	Its given me a longer evening and given me permission to chill out before I go to bed. Loved this programme it has been life changing
4	no
5	It has made me more sympathetic! I have also used the techniques in other situations not just for sleep.
6	One of the most important effects has been that it has stopped me worrying about insomnia. Only someone who has really suffered can get how critical that is.
7	For many participants a greater awareness is created that they utilize in there lives not just their sleep. Life could be defined as a journey to greater awareness whether that is by formal education, experience or reflection. It could also be stated a greater awareness is the greatest gift anyone can give themselves. Nothing stated is religious a nature.
8	I have recently had someone who is dealing with Cancer for both herself & husband with terminal cancer. They are not sleeping well & I am not sure how to help them. I'm not sure the tools given are appropriate for their problem. Perhaps they need to see the Cancer doctor

9	Good sleep allows me to fully engage with life and lifts my mood. It’s everything!
10	I believe it’s impacted my social life positively as I am less exhausted so more willing to attend social events
11	Improved my confidence
12	The non-judgemental, positive CBT approach is generally applicable.
13	Highly recommend Sleepio
14	I just think it helped me to see things different. I sleep better so I am not so tired during the day, I am calmer and have more patience.
15	I am healthier for getting a better night's sleep.
16	I cannot think of anything.
17	Yes using the techniques for managing negative thoughts. i have been able to use this in other areas of my life aside from sleep
18	None. I would have liked to carry on with my sleep logging so was disappointed when my access ran out. I had hoped it would address menopausal unrefreshing sleep but it didn’t really. By unrefreshing sleep I mean the feeling that one sleeps soundly but wakes up feeling exhausted and that exhaustion persists throughout the day making it difficult to function.
19	It changes your attitude so you step out of victim mode and become more accepting and positive
20	It's helped me to take steps to tackle anxiety.
21	Perhaps extra exercise and consequent weight loss?
23	None
24	Gives me more quality hours in the day.
25	I recommended it to my daughter.
26	I've learnt that making up for list sleep doesn't take as long as you might think. I don't feel guilty about having a snooze during the day. Unfortunately, just as I was getting into a good routine of sleep, I became ill with a virus which three everything out of the window and I just couldn't face going through the horrendous time of restricted bed time again. This will never go away so I just make the most of the days when I have had a reasonable night's sleep.

Q5	Please explain why [you said you would or wouldn’t recommend Sleepio to another person who was having difficulty sleeping]
1	Particularly if they haven't tried anything already, the suggestions in it are sensible and evidence based, they are well presented thro the app, and it leads you a process of improvement over a reasonable period of time.
2	For those with chronic insomnia there is often nothing else to try. It hasn’t solved my insomnia nad I have ‘relapsed’ but I will try it again when I have the stamina to do the initial hard part of the sleep restrictions
3	Because I thought my sleep problems were just due to the menopause and I just had to put up with them. But this programme has hot me sleeping again
4	easy and simple way to understand and change sleeping habits
5	Absolutely - I avoiding dealing with my sleep properly for years and let it affect my life for far too long. Occasionally I would attempt to make a change to help my sleep but it wouldn't stick and I would feel helpless. I started to think that I was just someone who didn't sleep well and that was my lot. Sleepio has changed all that for me and I feel back in control of my sleep. I know that my sleep won't always be perfect but that doesn't mean that I can't have some great nights of sleep if I stick with what I learn from the course. I know that many others could benefit from this too, if they are in the right frame of mind to commit to the course.
6	It is hard to get medical help for sleep problems and this is a way of doing something about it for yourself. It is a self help programme and it gives you a whole range of strategies to use to overcome sleeplessness. The online community is also very beneficial. You have to be very committed to want to change though and it is hard to stick to the programme so it won't suit everyone.
7	It sorts your poor sleep habits and you develop better habits. Even keeping an eye on your sleep using the ‘sleep diary’ starts to bring regularity and the brain likes this. It’s not an easy programme but is worth the effort we put in. The Community of Sleepios help each other and share what tricks and techniques work for them and help each other. For the whole time you are on the programme you have your own library with all the information included so you

	can visit it any time to go over sections or replay the animated sessions with the professor. It works ;)
8	Sleepio provides a structure to manage poor sleep. Before Sleepio I was lying in bed for hours not able to fall asleep, not able to maintain sleep, not able to have good quality sleep. Now, with changes to my bedroom and routine and so long as I follow the Sleepio rules, I can fall asleep more easily, sleep with fewer awakenings and it is of a better quality. I still need to work on lengthening my sleep. It is a long old road but Sleepio does help you on that journey.
9	BECAUSE IT WORKS!
10	Because it's improved my sleep more than any other thing i've tried in years
11	I think the most important thing I've learned is to be aware of myself - my daily rhythms, my thoughts, my strong desire to control things, learning to let go of the uncontrollable things. The way the programme is structured has allowed me to gain this awareness over time in a measured way, to try out new techniques and to find out what works for me (or doesn't). It's an ongoing learning process and I can see myself staying on the programme for a good while yet. As a result, my sleep is better than it was, though there is still a lot to improve upon.
12	Certainly, but many participants don't examine their underlying beliefs and only seek to change bad habits and therefore negatively distort the effectiveness of the program and never achieve permanent resolution. That is not a deficiency of the program as it is only a deficiency in the willingness and awareness of the participant to apply the program to it's maximum benefit. Similar to going to a gym but only socializing. Many participants only socialize and believe the program failed them when the opposite is true.
13	I would definitely recommend Sleepio, but give them plenty of warning that to see a positive result they will have to stick with completing the course if it is to be of any benefit to them. The tools & advice given will be good for them to use in the future should they have sleep problems again
14	It gives you a rule book to follow which works. It will allow you with practice (and having fallen off and got back on, I can see it is a lifelong discipline) to sleep well without medication or supplements.
15	It’s evidence based, relatively easy to use. Something you have control over as well as access to an online community who are very supportive.
16	Before using Sleepio I wasn't aware of all the habits that were contributing to my sleep problems. Sleepio helped me to address those. The methods in the course were effective in improving my sleep. It made a noticeable difference.

17	There are not many options apart from medication, it will hold your hand and support you into a restriction programme of sleep which I found very beneficial
18	It worked for me each of the three times I did it (once using the online programme itself, then twice using the notes I had made the first time). It's over 4 years since I did it but the visual used in the programme (back then in 2016) of the clockface showing an unhealthy broken sleep routine being forced from both sides into unbroken hygienic sleep by simply sticking to a bedtime and wake time has really stayed with me. I've talked to lots of my friends and family about the programme since then - and drawn out the clock visual a few times too!
19	It's simple, free, and makes sense. Plus some of the solutions I've never heard of before
20	Some things I found out were counterintuitive. AI delievered CBT was better than I expected. Some people would like Support function from community of users.
21	It works
23	Its better than a GP who only gives out sleeping pills. Many GPs are not aware of the Sleepio programme.
24	It worked. Plain and simple. It wasnt a difficult course to commit to and it was extremely effective.
25	It is a great guide for adapting sleep behaviour without needing medical intervention
26	Transformed my life enabling me to quit taking strong sleeping tablets
27	Because I think there are people that would benefit from Sleepio but just didn’t work for me.
28	It is not judgemental, introduces new steps gradually and is fairly easy to adopt. There are no downsides so why not give it a go?
29	It solved the problem
30	Because it made total sense and it felt like it reset my body clock. Also making small changes of my choice gave me some control rather than it being totally prescriptive
31	Because as stated, I felt that it worked well while being used.

32	If I can do it and improve my sleep, after all these years. I would hope it could help anyone. Give it a go what have you got to lose?
33	I have recommended it to others who are not experiencing satisfactory sleep.
34	The breadth of techniques offers hope to many people with different sleep issues. Even though I still suffer poor sleep sometimes, I know I can revert to sleepio techniques to break out of it
35	Because it works. Simple as that.
36	It helped me understand more about myself and sleep
37	It didn’t work out for me but that doesn’t mean it wouldn’t help someone else.
38	It helped me
39	I believe that for many the programme might work and I would cautiously recommend giving it a try but with caveats.
40	Excellent and evidence-based programme. Easy to use, clear and reassuring
41	At the time - I did see the benefit, and the sessions were put together very well.
42	I would recommend to try and help there problems
43	I think Sleepio covers basic sleep hygiene well and it seems to be supportive during the sleep deprivation. The community is helpful in hearing about other people’s issues. Also I did find it helpful!
44	when you can t sleep you have nothing to lose' so its worth a try. To be able to have access to good information and support from the sleepio community can only be a positive
45	It might help in managing the stress associated with the ability to have a restful night.
46	it did not help
47	I recommend it a lot. a shame it can't be accessed nationally.
48	Because it has solved my previous problems.
49	It tauught me to accept my situatuin.
50	And I did recommend to my sister which she found incredibly useful

51	It helps you think about sleep in a more positive way and helps you take action.
52	It is up to the individual, I don't want to be blamed if it is not right for someone.
53	It worked for me and allowed me to see a way to break the self taught cycle I kept getting myself into.
54	Medication free and programme does no harm
55	It works
56	I found a structured programme very helpful in fact I have recommended it to a friend. It also helps to know one is not alone with this problem.
57	It was helpful for most of the course.
58	Sleepio really helped me and provided me with the tools I need if I find I have sleep issues in the future. It was difficult to do but improved my sleep massively
59	It made such a positive difference to me.
60	Good supportive community to help with difficulties. Lots of information on different topics. You can question a psychologist each week. I've carried on with the program for another year I find it so useful. Tech support excellent and friendly.
61	Teaches you to relearn the habit of sleeping using a sensible and simple plan.
62	No question. It is a superb App. Easy to understand and engage with. Easy to start getting regular blocks of sleep. Easy to see small benefits at first (this bit is critical).
63	It is a good start, I only did it after seeing a documentary on TV
64	See earlier comments. A great framework to explore one’s relationship with sleep and to take on better sleep related habits.
65	Impersonal so motivation dropped off
66	Because you may be able to adapt the suggestions for getting a good night's sleep or you may discover you don't need the 'standard' amount of sleep. Also, you might discover that you have been going to bed and getting up at all the wrong times. Some of the 'tools' may work for you, some may not but there are plenty of things to try or adapt.

67	I think it helped me to appreciate that I was probably sleeping more than I thought and also accept the sleep I was having.

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT443 Sleepio

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise)* *Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*
1.	16/12/2020	**Company** Initial questions	Sleepio's intended use is for any adult with poor sleep, but presumably it will primarily be used in people diagnosed with insomnia – is this correct?	See appendix 1 for responses.

			a. Is this as a primary or secondary diagnosis?	
2.			After the 6 sessions, are there any further reminders (or other activities), and can the user repeat the sessions for as long as they want/need?	
2.			Is the same version of Sleepio used in all studies presented? e.g. from Espie 2012 up to more recent studies. a. If not, what are the differences? Would you expect any difference in outcomes? b. When the improvements that are currently underway are implemented, do you expect that this will have an effect on clinical outcomes? c. How often do you think that content will be updated iteratively?	

			d. Is the AI component of the programme fixed?	
3.			We understand that the app is only available for iOS mobile devices as a desktop application – is this still the case? a. Are there plans to include other platforms?	
4.			Where do you expect Sleepio to fit within the clinical pathway? Should the app be used in conjunction with a primary care, sleep medicine, or psychiatry health care provider? a. If yes, what happens in cases of self-referral?	
5.			What are the sources for the clinical pathways outlines in pages 26-27?	

6.			Would you anticipate Sleepio being used in place of, or in addition to, current interventions? Which current interventions might it replace? a. How many CBT appointments do you think the average user would be likely to have attend if they weren't using Sleepio?	
7.			There are a number of ongoing or unpublished trials in table 3. Is there any data available from these studies (these would be treated as academic in confidence)?	
8.	19/01/2021	**Company** Additional questions	Please would you provide more information about the current status of the ongoing IPD meta-analysis and any possible completion date?	The results of the meta-analysis are complete. The main benefit of having individual patient data is that it enables us to conduct moderator analyses. We are currently awaiting further data from four studies that were published last year. Once we have received these data we will finalize the moderator analysis and then write up and submit for publication. We expect this to be later this year.
9.			What are the planned sub-group analyses (the scope include pregnant women, people who have not had an insomnia diagnosis, people with short-	We are investigating subgroup effects using analyses of treatment effect moderation. Specifically we are investigating whether there is evidence of interactions between the offer of digital CBT and a number of possible moderators in terms of their effects on sleep outcomes at post-treatment and follow-

			term insomnia (symptoms present for less than 3 months), or with long term insomnia (symptoms present for 3 months or longer), and people with insomnia and a comorbid condition?	up. The possible moderators are severity of baseline sleep problems, severity of baseline depression, severity of baseline anxiety, duration of insomnia, age, sex, ethnicity, education, relationship status, income, employment, comorbidities, use of medications.
10.			How was study heterogeneity accounted for? We see that the I^2 value indicates very high heterogeneity for the insomnia measure (95.5% and 86.2%).	Heterogeneity was accounted for by including a random effect for study in the meta-analysis. The use of a random effect is suggested by the statistical literature when the I squared is large. We believe the high level of heterogeneity is a consequence of the fact that there are differences in the studies' target populations and the outcomes they have used (we have combined two insomnia measures: the SCI and ISI).
11.			How have you/will you account for loss to follow-up in the analyses?	We are using linear regression with maximum likelihood to calculate parameter estimates. These models assume that data are missing at random, i.e. we are assuming that the probability of missingness is independent of the outcome given the observed data. We considered using multiple imputation (MI) to potentially relax the missing at random assumption but decided against this. Differences between studies in the variables that were recorded meant that it would have been impossible to find a set of variables that could predict missing outcomes in the imputation step of MI.
12.			In the electronic model, inputs section>resource use int/comp sheets, the costs of operating theatre, day case, etc has been included. Why is this being included in the electronic model?	Deleting the rows associated with these costs caused a type mismatch error (Run-time error 13), so we left the template unchanged. There are no units associated with these costs so they do not feature in the analysis.

13.			Can you please explain again how you estimated the cohort size of 24,000 ?	24,000 is 1% of the population which is estimated to be eligible to use Sleepio in year 1. The intervention cost of Sleepio assumes a population of 2,400,000; in the model the *percentage* of this population which is estimated to make use of Sleepio (not the absolute size of the eligible population, or the population which uses Sleepio) is important for determining the estimated effect of Sleepio on resource use, and therefore the net cost of Sleepio. In the Thames Valley rollout, the estimated percentage of the total population (in the nine GP practices included in the main analysis) who made use of Sleepio was 0.99%. This estimate was calculated as follows: of the total population in the nine GP practices (129,865), 1,220 individuals were recorded as being referred to Sleepio by their GP (Sampson et al. 2021). Data from the EMIS App Library provided to Big Health estimated that 56% of individuals referred to their GP registered with Sleepio. Big Health operational data from the Thames Valley roll-out shows that 46.07% of individuals who registered with Sleepio initiated CBT. Therefore, the total number of users referred by their GP, who make use of Sleepio, is estimated to be 1,220 * 0.56 * 0.4607 = 314.76. Big Health operational data shows that 24.52% of the individuals using Sleepio stated they were referred by their GP. Therefore, the total number of users across the population making use of Sleepio is estimated to be 314.76 / 0.2452 = 1284. 1284 as a proportion of the total population of 129,865 is 0.99%. We round this to 1% to avoid spurious precision. More generally, we wish to stress that the uptake estimates involve many assumptions (for example, in practice not all GPs are likely to have recorded Sleepio referrals accurately). For this reason, we submitted a sensitivity analysis which provides reassurance that, even, at 70% of the estimated uptake (0.7%), Sleepio continues to be cost saving.

14.			The cost of CBT from Curtis 2013 uses the 2012 prices. Have they been inflated to current prices and has a sensitivity analysis performed on these estimates?	We did not inflate the prices – thank you for identifying this oversight. Using the HCHS/NHSCII pay and prices inflation index included in the Unit Costs of Health & Social Care 2020 (Lesley and Burns 2020), the average price of 6 sessions of face to face CBT is £541.36 (as opposed to £492 in the original model). A revised model with inflated prices can be provided. This change increases the cost savings associated with Sleepio as compared to face to face CBT. We did not provide any sensitivity analysis in the first instance as there is no scope in the template to vary the intervention cost of the comparator. However, we can submit two sensitivity analyses using the upper and lower bounds included in Lesley 2013 (£31 and £133 per session, for 6 sessions), inflated to 2020 prices (£204.66 and £878.05 in total). Sleepio continues to be cost saving compared to face to face CBT in all instances.
15.			Is there a further justification on why change in primary care resource use has been included for those with no remission, whom we expect to use services as usual. We see that these have been pooled in the Sampson et al paper too.	There is no comparative evidence on the resource use implications of Sleepio according to remission status. The only comparative evidence relates to use or non-use of Sleepio. Therefore, it is only possible to attribute cost impacts to Sleepio use and not the (health) consequences of Sleepio use. Arguably, the extent to which differences in costs associated with Sleepio are attributable to remission status is incidental to the decision problem. Our evidence does not rely on a two-stage causal pathway whereby Sleepio achieves remission and remission is in turn associated with changes in resource use. The proposed mechanism for cost savings – as evidenced – is that Sleepio use reduces prescriptions (and other health care costs).

16.			It is not clear from the Sampson paper how a cost of £45.04 change in primary care use has been arrived at and applied to year 2 and 3. The £139.59 (£228.07 minus £88.48) figure already has reduced the 2 years savings, why then is the year 1 saving further subtracted. Could you please explain it more clearly.	Evidence suggests that the effects of digital CBT for insomnia (for an individual patient) are maintained up to three years. However, the Sampson et al (2021) analysis only collected data for a 65-week follow-up. Furthermore, the analysis projects trends at the population level, rather than the individual level. Savings may grow indefinitely at the population level, as new users access Sleepio. However, it is not reasonable – on the basis of current evidence – to assume that year-on-year savings would grow indefinitely at the individual level. The estimate of £139.59 is an individual-level cumulative saving derived from a population-level trend. Thus, the £228.07 minus £88.48 removes the second-year savings attributable to people commencing use in year two. The result (£139.59), as an individual-level estimate, remains cumulative. Therefore, the savings attributable to the individual, in years two and three, are £139.59 minus £49.52, which equals £90.07. This figure is then halved to find an average saving for year two and year three.
			Is Pubmed the only database used to search for economic evidence, and what is the date span of the search.	PubMed is the only database we searched. The focus of our research was on comparative analyses of health technologies, for which we believe PubMed to provide adequate coverage. Both the Big Health team and the Office of Health Economics team have a good knowledge of the evidence base relevant to Sleepio and we believe that it is extremely unlikely that there are any relevant studies that are included in other databases but not included in PubMed. There was no date restriction on the search.

				References: Curtis, Lesley A. and Burns, Amanda (2020) Unit Costs of Health & Social Care 2020. Unit Costs of Health and Social Care . PSSRU, University of Kent, 185 pp. ISBN 978-1-911353-12-6.
17.				I'm also including a few other materials and updates relevant to our discussion: • This geographic assessment of qualified CBT for insomnia providers, highlighting the lack of provision in the UK (link to publication) • Papers for Jamie E and the EAC team (Darden et al., Soh et al., Thomas et al.) • Re: the Derose study - revisions to the paper are due to be sent shortly and the authors feel it would be best to wait until the article is accepted to share. This may only take a couple more weeks. We will share as soon as we can • Re: Studd et al. (our real-world study from Sleepio's NHS rollout in the Thames Valley) - we aim to have a draft to share in the next two weeks
18.	22/01/2021	**Expert – Dr Kirstie Anderson (Clinical Neurologist)** Additional question	The company has cited the Soh et al 2020 meta-analysis into 94 articles that indicates that digital CBT is non-inferior to face to face CBT for insomnia according to the ISI (face-to-face CBT produced greater improvement in ISI, however, this was within the non-inferiority interval). Is it plausible to assume similar results for Sleepio compared with face to face CBT?	The reference cited is evidence of benefit for CBTi, digital or face to face with slight increase in benefit face to face. It is not evidence for economic benefit, this is a real gap in the research. Sleepio do have the ability to provide some of this data (accepting some commercial sensitivity) to NICE given greater London had access to the programme for some time, they do have real world clinical data. Higher dropout, a lack of any head to head comparisons at all between the different online CBTi programmes and difficulty with engagement remains the issue.

				This is a nice summary https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6329555/ Health economics data is lacking for many of the existing commercial digital CBTi despite robust RCT data that they treat insomnia in a trial setting with prior screening. None of the RCTs have really studied implementation or dissemination, few have incorporated stake holder perspectives. Therefore very little data for Sleepio or other systems on enhanced personalisation, implementation into health care systems and health economics Additionally the market size for dCBTi is not possible to assess but does not seem anything like as big as that for anxiety or low mood. There is a clear difficulty in the UK making some of these assessments because of the need to improve measures within the IAPT minimum dataset. However one reference below https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541623/ Use of online in Manchester IAPT sleepio offered to 1078 who completed baseline assessment - 80 chose sleepio among 3 digital therapies on offer It is not plausible to expect similar results for face to face CBTi compared to Sleepio if both are on offer, initial take up and drop out rates when in any health care market there is choice must be factored in to real world clinical data. If digital CBTi was the only choice, take up would of course be higher and this is exactly what we saw during last year with alternative digital CBT.

19.		**Expert – Dr Ari Manuel (Consultant in Sleep and Ventilation)** Additional question	The company has cited the Soh et al 2020 meta-analysis into 94 articles that indicates that digital CBT is non-inferior to face to face CBT for insomnia according to the ISI (face-to-face CBT produced greater improvement in ISI, however, this was within the non-inferiority interval). Is it plausible to assume similar results for Sleepio compared with face to face CBT?	No sure it can be equivalent I guess the equivalent would be a class effect that would be seen if we were looking at medication (but no guarantee it would work).
20.		**Expert – Professor Michael Wang (Honorary Consultant Clinical Neuropsychologist)** Additional question	The company has cited the Soh et al 2020 meta-analysis into 94 articles that indicates that digital CBT is non-inferior to face to face CBT for insomnia according to the ISI (face-to-face CBT produced greater improvement in ISI, however, this was within the non-inferiority interval). Is it plausible to assume similar results for Sleepio compared with face to face CBT?	In my opinon it is *plausible* to assume *similar* results from Sleepio compared to face-to-face CBT-I on the basis of the meta-analysis. However this is not the same as saying the two interventions are *identical* in their effects.
21.	26/01/2021	**Expert – Dr Kirstie Anderson (Clinical Neurologist)** Additional question	In your opinion can the results from people who complete the Sleepio programme be assumed to be non-inferior to those who complete face to face CBT?	No, we can't say this, it extrapolates from multiple different interventions some of which have supported elements but there are no direct head to head good quality RCTs that I am aware using sleepio, which is automated without therapist support, albeit good online user support forums The important detail of the Soh paper is that 33 RCTs reported dCBTi, therefore over 4000 people studied. However 29 were dCBT versus waiting list or control group. Only 4 of these studies compared dCBTi to face to face, none used sleepio for this - one studied actively serving soldiers in the US army, there is a trend across the 2 meta-analyses (2016 and this one 2020) to suggest

				that dCBTi is getting better with lower dropout but still worth highlighting that most of these studies recruited actively in the digital media Of the 4 studies, 3 relevant to NICE decision and the ungiuded and automated f2f versus dCBTi showed f2f better, the guided showed non-inferiority. Therefore dCBTi is effective in those who complete compared to no treatment with moderate to large effect sizes compared to sleep hygiene or treatment as usual with sustained benefit and FU out to one year (although this is for SHUTi - evidence based and effective intervention with now FDA approved Somryst launched by Pear therapeutics, more established and more available data) One additional point from the somryst and FDA approval is that they picked > age 22 - going back to what both Jason and I said about cut off of age 18 may well be too young based on the common mimic of delayed sleep phase. I think this would be a much safer age for example for sleep restriction protocols.
22.	02/02/21	**Company** Additional questions	We are currently reviewing the unpublished Sampson paper and would appreciate a little more information about the data modelling. Can we be sent the graphical representations of the 5 models from table 5?	All of the models have the same specification as that shown in the one equation that is in the paper, except that they vary in the components included in X (as specified in the table), models 4 and 5 exclude X altogether, and model 5 models Y_{it} thus excluding u_j

23.			What we're struggling with is reconciling the models with the data in Figure 1. In the figure the cost trajectory appears to rise after the introduction of Sleepio but the models suggest it falls. That seems to apply regardless of seasonal adjustment. Can you explain why the coefficient on post is negative? What is it that drives up the trajectory in the raw data that the models are adjusting for?	The trend line in Figure 1 represents a simple linear prediction of the average cost in each week with *t* as the only predictor. And it does this separately for the pre-rollout period, rollout period, and post-rollout period. So, it is slightly different to Model 5, which simultaneously models the impact of the rollout period and the new post-rollout trend. That's why they differ. I should remove the trend lines from Figure 1. They aren't very helpful. The rollout period occurred in October, which I believe is when more GP appointments occur in the NHS than in any other month, and I think November is the second or third busiest month, before a big drop-off in December. This means that the results will be very sensitive to how we handle these things in the model and that a naïve look at the trend in the data won't tell us much at all about the impact of Sleepio. Seasonal adjustment has a big effect in models 1-3, which explains the disappearance of any (significant) difference in trend when it's excluded from the model (models 4 and 5). It would take me some time and effort to prepare predicted values from the different models and show them graphically. But you can easily plot the predicted trends yourselves if you wish, by using the coefficients in Table 5. I've attached a simple example of how this can be done in Excel, for the preferred model. To answer your two questions directly: - The coefficient on post is negative because the week-on-week change in total costs *after* Sleepio rollout is <u>less than</u> the week-on-week change in total costs *before* Sleepio rollout (once we control for those things specified in Table 5). - What is it that drives up the trajectory in the raw data that the models are adjusting for? Mostly, that there are two Octobers and Novembers in the post-rollout period, and

				only one in the pre-rollout period. Therefore, there were more appointments per week on average in the post-rollout period for reasons that have nothing to do with Sleepio. (Consider Figure 1 having data only as far as week 104 and it paints a very different picture, though it is good that we have these extra months because it means we can do a better job of controlling for these seasonal variations.)
24.			Would you be able to share the graphs that you visually inspected to assess the goodness of fit for the 5 models? We were also wondering which software, or softwares, were used for the analysis?	The analysis was conducted in R. I didn't plot the distributional fit for all 5 models, as models 2-5 are really just for the sake of testing the robustness to exclusion of the other variables. The inspection of plotted values was to aid the identification of the distribution and link functions – I can't recall whether I made that clear in the paper. I don't have the plots of predicted values for different specifications saved, and it would take me some time to recreate them. But I'm not sure how informative they would be anyway, as they don't really characterise goodness of fit of different models per se, but rather the suitability of alternative distributions. I could provide you with the null and residual deviance and AIC estimates from the 5 models, which you could use to infer goodness of fit, but I also don't have those to hand and would need some time to re-run the models (which are not quick!).
25.	05/02/2021	**Expert – Professor Michael Wang (Honorary Consultant Clinical Neuropsychologist)**	What is a sufficient length of follow up time to indicate that the benefits of CBT-I have been maintained?	This is a bit like asking "how long is a piece of string?". The first follow-up measurement point to be reasonably considered would be the same duration of the intervention from the point of the end of the intervention.

		Additional questions		Many studies look at a 6-month follow-up and, rarely 1 year or longer. I would say at least a 6-month follow-up would be preferrable.
26.			Our current understanding is that Sleepio should be offered to people over the age of 25, with mild to moderate insomnia that has lasted for over 3 months. What other patient selection factors should be considered?	Intellectual ability, English language level, ethnicity and culture, whether engaged in shift work should be taken into account. Specific sleep disorders such as narcolepsy and parasomnias may be contra-indicated.
27.			Are there other patient factors that may predict better engagement with the tool?	People who are used to modern technology and the internet. Health locus of control is also likely to be important in that some patients expect others such as doctors and healthcare professionals to take responsibility and don't react well to being expected to do something for themselves.
28.		**Expert – Dr Kirstie Anderson (Clinical Neurologist)** Additional questions	What is a sufficient length of follow up time to indicate that the benefits of CBT-I have been maintained?	Follow up if based on trial data ranges from 4-8 weeks although many RCTs have used 9 or 12 weeks as better as reality is that flexibility to complete sessions over time improves outcome and many build on the techniques. In clinical face to face setting – review would be at 3 months. So if you are asking for maintained then 12 weeks. You would expect at least a 50% attrition rate and for at least half to two thirds not to be eligible of those complaining of poor sleep at GP (and that is trial based and therefore prior perfect selection, it will be higher in real world, this is a good recent trial and the flowchart looks similar to many others https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30135-7/fulltext

29.			Our current understanding is that Sleepio should be offered to people over the age of 25, with mild to moderate insomnia that has lasted for over 3 months. What other patient selection factors should be considered?	I agree with those selection criteria – exclusion of those actively involved in another CBT or psychological therapy as it is hard to do 2 things at once. Different goals. Exclusion of high Epworth sleepiness score, high risk for sleep apnoea (that is untreated) or moderate or severe restless legs. Rotating shift work is an exclusion criteria in RCTs. But home access to both email and computer and ability to use them and fluent in english.
30.			Are there other patient factors that may predict better engagement with the tool?	Better engagement – duration of symptoms does not seem to affect outcome – ie insomnia many years still responds well. Higher educational levels predict slightly better engagement and absence of severe depression, however other comorbidities do not tend to worsen outcome as long as the key problem is insomnia.
31.		**Expert – Dr Ari Manuel (Consultant in Sleep and Ventilation)** Additional questions	What is a sufficient length of follow up time to indicate that the benefits of CBT-I have been maintained?	I would be steered by the research but somewhere in the range in 6-12 months at least (otherwise what's the point - the GP with refer back to secondary care)
32.			Our current understanding is that Sleepio should be offered to people over the age of 25, with mild to moderate insomnia that has lasted for over 3 months. What other patient selection factors should be considered?	Educational status, access to IT, ethnicity and age and poor vision and use of hands
33.			Are there other patient factors that may predict better engagement with the tool?	See above.

34.		**Expert – Dr Chris Davies** Additional questions	What is a sufficient length of follow up time to indicate that the benefits of CBT-I have been maintained?	I would suggest that a minimum of 3 months, and preferably 6 months after the end of treatment to suggest taht benefit has been maintained.
35.			Our current understanding is that Sleepio should be offered to people over the age of 25, with mild to moderate insomnia that has lasted for over 3 months. What other patient selection factors should be considered?	An alternative underlying cause for the insomnia that would need different treatment, eg other mental health diagnoses such as depression.
36.			Are there other patient factors that may predict better engagement with the tool?	Willingness to self-refer having been given contact details

Insert more rows as necessary

Appendix 1.

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

File attachments/additional information from question X:

MT443 Sleepio Company meeting – Minutes – 17.12.20

Introductions and roles:

KiTEC:

- Kate Goddard – Health Technology Assessor - joint project lead
- Jamie Erskine – Health Technology Assessor – joint project lead
- Mark Pennington – Health Economist
- Anastasia Chalkidou – Associate Director –project oversight
- Jo Boudour – Project Manager

NICE:

- Bernice Dillon – Technical Adviser
- Neil Hewitt – Technical Analyst

Company:

- Charlotte Lee – UK Director - Big Health
- Chris Miller – Research Lead – Big Health

Discussion on questions:

1. **Sleepio's intended use is for any adult with poor sleep, but presumably it will primarily be used in people diagnosed with insomnia – is this correct?**
    a. **Is this as a primary or secondary diagnosis?**

CM – Intended use is in the UK and US for people diagnosed with insomnia. We don't recognise terms primary and secondary any longer. It also treats people with sleep difficulty.
BD mentioned that 'insomnia symptoms' are mentioned in the submission.

CM confirmed this is a different description for the same population.
CM added it is often self-referral instead of via GP. BD added this is a is a bit different and will impact the economics.
CL advised there may also be a GP recommendation to use Sleepio but you don't necessarily need to see the GP.
MP asked that if patients self-refer, is there any process of diagnosis or are they assumed to have insomnia?
CL confirmed there is an onboarding sleep test and you are given a score and personalised advice at the end. You then choose whether you start CBT or not. There is a cost for accessing this first step.
CM added even if your sleep score is good, you have access to some useful information regarding sleep. You can then sign a contract at the end.

2. **After the 6 sessions, are there any further reminders (or other activities), and can the user repeat the sessions for as long as they want/need?**

CL confirmed the user can repeat sessions for as long as they need, they have free access for a year.

3. **Is the same version of Sleepio used in all studies presented? e.g. from Espie 2012 up to more recent studies.**
    a. **If not, what are the differences? Would you expect any difference in outcomes?**
    b. **When the improvements that are currently underway are implemented, do you expect that this will have an effect on clinical outcomes?**
    c. **How often do you think that content will be updated iteratively?**
    d. **Is the AI component of the programme fixed?**

CM confirmed the same versions are used in all the studies.
CM advised that Sleepio is a web based programme. Once they have registered, they can download the app. It is only iOS enabled at the moment.
CM confirmed that there have been no modifications content-wise. Any modifications are technical, relating to access or linking to a fitbit etc.
CL added it is not available to android for technical reasons. There are plans to expand this to android in the middle of next year.
CL confirmed the AI component is fixed. It is a decision tree with fixed points which makes it modular and manageable.

4. **We understand that the app is only available for iOS mobile devices as a desktop application – is this still the case?**
    a. **Are there plans to include other platforms?**

See response to question 3.

5. **Where do you expect Sleepio to fit within the clinical pathway? Should the app be used in conjunction with a primary care, sleep medicine, or psychiatry health care provider?**
    a. **If yes, what happens in cases of self-referral?**

    CL advised the clinical pathway is primary care only, prescribed by a GP or nurse. It can be used in secondary care but it's not recommended.
    CM advised potentially excluding self-referral, which is more public health/prevention.

6. **What are the sources for the clinical pathways outlines in pages 26-27?**

    CL advised the source for the first one was NICE guidance and the second one was a group discussion with sleep medics and clinical psychologists. It includes guidance taken from European guidelines. The sources can be shared with you.

7. **Would you anticipate Sleepio being used in place of, or in addition to, current interventions? Which current interventions might it replace?**
    a. **How many CBT appointments do you think the average user would be likely to have attend if they weren't using Sleepio?**

    CL confirmed that Sleepio would replace first line hypnotics and sleep hygiene. In rarer instances where someone may be offered CBT for insomnia (ULCH mentioned) treatment it may replace that too as there are long waiting times for in-person treatment.
    CL added that if you are based in a region where CBT appointments are available, there would be provision for 6-8 sessions.
8. **There are a number of ongoing or unpublished trials in table 3. Is there any data available from these studies (these would be treated as academic in confidence)?**

    CM asked if we could let them know which studies are of interest and they can contact the studies authors and let us know if data can be made available (Derose study mentioned).

AOB:

1. CL asked if it would be helpful if they set out the symptoms more? NH confirmed this would be helpful for the committee and would help distinguish those who are genuinely sleep deprived from those who maybe just aren't getting enough sleep.

2. AC asked if the studies are sponsored by Big Health. CM confirmed Big Health don't wholly sponsor studies by themselves, they are usually run with an academic partner.

MT443 Sleepio Expert Engagement meeting – Minutes – 11.01.21

Introductions and roles:

KiTEC:

- Kate Goddard – Health Technology Assessor - joint project lead
- Jamie Erskine – Health Technology Assessor – joint project lead
- Farhad Shokraneh – Systematic Reviewer and Information Specialist
- Murali Kartha – Health Economist
- Anna Bulyova-Gola – Health Economist (Observer)
- Khanh Ha Bui - Health Economist (Observer)

NICE:

- Bernice Dillon – Technical Adviser
- Neil Hewitt – Technical Analyst
- Rebecca Owens – Technical Analyst
- Chris Chesters – Senior Technical Analyst MTEP
- Victoria Fitton – Project Manager
- Heather Stephens – Senior Health Technology Adoption Manager

Experts:

- Ari Manuel – Sleep Consultant, Liverpool
- Jason Ellis – Professor of Sleep Science, Northumbria

- Mike Wang – Clinical Psychologist at the University of Leicester with a special interest in Insomnia
- Kirstie Anderson – Neurologist based in Newcastle
- Chris Davies – GP in Buckinghamshire, part of Sleepio Pilot

Discussion on questions:

1. **Terminology and Diagnostic Criteria**
    a. **How is insomnia defined and how is it diagnosed?**

KA: Insomnia is difficulty falling asleep and staying asleep that affects health the following day. Often people are incorrectly referred to the regional sleep clinic with Sleep Apnoea or restless legs. There must be screening in these tools for referrers to be aware of insomnia mimics.
JEL: Young people with circadian drift are also commonly incorrectly referred.
KA: Agreed, we should exercise caution in using the technology in people at 18 years old. Very few people coming through at age 18 really have insomnia. Urge caution at the age that people are referred for this and all online technology.
JEL: Circadian drift ends around 25 years old.
AM: There is an issue around education around sleep disorders and this can lead to many incorrect referrals from primary care.

    b. **Is 'People with difficulty sleeping' a reasonable population to include?**

MW: Firstly, is Sleepio going to be aimed at primary or secondary care?
BD: Primary care, often through self-referrals. Should we be looking at 'people with insomnia symptoms' rather than 'difficulty sleeping'?
KA: In a recent audit, we found that 40% of people were wrongly referred and screening failures (e.g. referring people who are sleeping badly or have restless legs) have a cost – this is important for the health economic modelling of this technology. Insomnia and also importantly what it's not, is important, otherwise prescribing these interventions will be very costly.
JEL: I would be cautious with looking at difficulty sleeping. Insomnia symptoms for at least 3 months would be better. 48% of the population have at least 1 insomnia symptom. Looking at DSM criteria is down to about 15%, so we need to focus on chronic insomnia (i.e. more than 3 months) or we will capture far too many people. Acute insomnia (between 2 weeks and 3 months) may well resolve itself – 50-70% remit naturally without intervention.
MW: A lot of patients at GP are complaining about sleep trouble and are prescribed medication – we need to be thinking with a primary care focus. There may be an issue with lack of training for GPs to properly diagnose and prescribe to people with trouble sleeping that isn't chronic insomnia. Majority should be given sleep hygiene advice, but this probably isn't happening.
KA: RCGP guidelines suggest sleep hygiene advice as a first line treatment – this probably is being done in GP practices. RCT data shows that there is actually a reluctance to prescribe drugs.

CD: This is a very common presentation in primary care, sleep hygiene will be offered first, drugs e.g. zopiclone only very short term, referrals to CBT-I or Sleepio are usually only made if problems have persisted for a while and there doesn't seem to be an obvious course of action. Lack of options for referral is the main issue in the Thames Valley, so Sleepio would be a useful tool after 2-3 months of problems.

2. **Understanding the Clinical Pathways**
    a. **Where does Sleepio fit within the current pathway?**

KA: CBT-I is used at the IAPT level. We support Sleepio's use at primary care.
AM: We have 150-200 referrals in Liverpool per week. After a virtual clinic, they could be offered Sleepio – i.e. at the interface between primary and secondary care.
KA: We need to make sure that GPs don't reach for the easiest option; GPs need to be trained in medicine prescription when the service is rolled out in those areas.
JEL: Many GPs don't include questions about sleep in their general questioning and so insomnia can be missed in many places; some services see hundreds of cases a week and some see none.
CD: Agree that GP training in insomnia and sleep disorders is patchy and varied.
BD: Can you tell us a bit more about the training offered by Sleepio in particular?
CD: A meeting of local GPs, online training and face to face training were offered, so Sleepio are making an effort but maybe there should also be training by someone who isn't financially attached to an app/service.
KA: There also has to be some transparency from any contract given on the amount of patients who pass the screening test and how many finish each session. A lot of screen failures can be costly. Makes doing the Health Economics difficult.

    b. **How widespread is CBT-I? It appears to be rare. Would Sleepio be an alternative to this or to medication?**

JEL: We trained 3 IAPT trusts in CBT-I. There are alternatives, CBT-I services are less patchy and unavailable than they were. A lot of training is available for GPs and across all healthcare services. People are talking about 'sleep hygiene' but there is no agreed definition of this. Some parts of sleep hygiene may also be a part of CBT-I so we should define Sleep Hygiene better. However this is rolled out, we want to avoid duplication.
KA: It is also important to recognise that lots of people don't want to do this online. Engagement can be very poor. 20% will probably log on. Some people require face-to-face sessions. Sleepio and similar online interventions will be very valuable to **some** patients, **some** of the time. It's all about initial selection and patient choice.
MW: It is important to recognise that IAPT has major problems with waiting times. I greatly support CBT in general but it may not be the only solution. Sleepio could help where access to CBT-I is not enough. I strongly agree, however, that it will be a minority that engage.

JEL: Do we know whether Sleepio can diagnose paradoxical insomnia (5% of population)? Because CBT-I could harm these patients.
KA: We see where the technology fails so it may be that the technology cannot distinguish these cases. We need the outcome data from the app going back to the GP to identify these types of cases. Need feedback on numbers in and numbers recovered.
CD: Agree that feedback is really important as a prescriber and we haven't had any on the pilots.
KA: Plus pilot results are always better than standard.

3. **Integrating the technology into the clinical pathway**
    a. **Do any of the experts have any personal experience of integrating Sleepio into their services?**

CD: Patients get the information from their GP to do a self-referral either online or on the phone to the GP. In the pilot they had to give their postcode and GP surgery, as it was only available within certain areas.
BD: Did you get feedback on the number of those who actually logged on?
CD: No, we didn't get any feedback at all. The self-referral option can help to 'weed-out' those who would never engage with Sleepio.
AM: Our referrals are email derived. Can get into a cycle where a patient is referred to us, we refer someone to Sleepio then people are sometimes sent back 18 months later without any information on what happened to them in this time. It would be useful to get some feedback.
KA: We have same problem. Some patients will say Sleepio didn't work but they didn't actually log on. But this information isn't fed back from the app. We need more info on the outcome data. In IAPT you would have the outcomes from CBT-I, for example. That level of outcome reporting should be there.
AM: In order to convince NHS clinics to use Sleepio instead of face-to-face, they will need audit/outcome data that shows it'll work in their local population.
HS: We spoke to the IAPT team at NHS England, they said someone could not be referred to IAPT services from primary care with a diagnosis of insomnia alone, there had to be underlying anxiety and depression, is this the case?
KA: We do have examples where IAPT services can make it work financially, such that the services can be offered for people without the underlying conditions.
HS: The full platform is only available on a PC. A mobile app is available but it has limited features. We have seen in the past that people prefer to use their phone where possible for similar services – does this ring true in the expert's experience?
KA: Absolutely, in general. It may be slightly different here as insomnia patients are a slightly older group and the sleep diaries are harder to fill out on a mobile phone.

    b. **Are there any particular patient selection criteria that should be considered?**

JEL: I would recommend looking at the patient characteristics of those dropping out in the literature. This should let us know who is more likely to engage.

KA: People with depression are far less likely to engage but they may not be referred for this anyway.
CD: I agree that we would try other interventions for depression.
BD: Would insomnia and depression be treated together?
JEL: I would suggest that the insomnia is treated first.
KA: You can only do one CBT at a time; dual referrals are not recommended (although they sometimes occur).
JEL: Treating the insomnia would have a knock-on effect on other conditions so it makes sense to treat that first.
CD: I agree, we'd view insomnia is part of depressive illness. We can treat the depression and often the sleep pattern improves without specifically going down the CBT line for insomnia.
KA: People with other sleep problems may benefit from CBT-I e.g. severe restless legs or sleep apnoea but is risky. For example, I would worry about sending people with daytime sleepiness down an online route. Consistently, the important factor is patient selection. If there is a significant medical problem, probably secondary assessment first.

c. **What factors may impact engagement with Sleepio? Are there particular patient groups where it is more likely to be beneficial?**

JEL: Mild to moderate insomnia without complicating factors.
KA: Anecdotally, a younger group may benefit.
BD: What about pregnant women?
KA: I have pregnancy as an exclusion criteria.
BD: This hasn't come up from discussions with the company and there are papers describing Sleepio use in this population.
KA: There is a high rate of restless legs in pregnant women and a 'boggy airway' which is similar but not the same as sleep apnoea. Problems often resolve post-partum, but there are then issues due to having a baby, which is different. With high rates of obesity in the population as well, there is a chance that there would be a lot of incorrect referrals in these groups.
MW: Agree with the exclusion of pregnant women.

4. **Understanding the Evidence**
   a. There are lots of different indices of sleep quality reported in the evidence for Sleepio (e.g. ISI). What are the standard/ most widely recognised measures used in sleep research? What are considered to be clinically meaningful changes in those indices?

JEL: ISI is the most well used. A reduction of 8.4 is moderate, 9.9 is marked improvement. ISI has been copyrighted so may incur a cost. Mainly used due to the well-researched benchmarks.
KG: At what time point should we look at these outcomes? We gather that they can be cyclical.

KA: Sleepio is a 6-8 week programme so outcomes will be measured at the end of the programme. However, patients may continue to improve long after that. If patients start feeling better, they will stop responding to company/app, so difficult to gather long term outcomes. 8 weeks might be realistic where you can see recovery, fully accepting it's a compromise.
MW: I see no disadvantage to collecting longer term follow up but there will be a high attrition rate. It is important need to know if interventions are continuing to be used over longer periods of time.
JEL: 3 months post-treatment would be ideal, especially as 3 months is the time-period that defines chronic insomnia in the first place. Sleep efficiency shouldn't be used, this only means that a patient has been adherent, not that they have improved. Edinger's criteria suggests that we would want a 50% reduction in symptoms of Sleep Latency and Wake after Sleep Onset.
KA: PSQI is often used by companies as it is free, but this is not recommended. ISI is preferred. To add to the point about follow up – Sleepio won't be able to hold onto patient data for long after collecting it, so it will be hard to get long term outcomes.
CD: We don't use these measures. More subjective information in terms of impact on people's lives. Don't tend to hear back if people do well.
BD: BD so these measures are really only used in research and secondary care settings.
JEL: SCI is being used more and more but this doesn't have the same data-backed benchmark as ISI. PSQI shouldn't be used in insomnia because it doesn't really measure insomnia.
BD: Any other questions?
MK: What would be the next best choice if Sleepio is not available? E.g. face to face CBT-I?
KA: There are now 25-30 regional sleep services that are available, so there are options for CBT-I.
JEL: I've trained over 200 people in this country, so there is provision, but it may not be as available as we would like. I would still prefer face-to-face sessions where possible, but we need to be mindful about dissemination and implementation.
KA: In one of the RCTs for this technology, recruitment almost failed because people didn't want to be randomised to the online treatment. So CBT-I is still the preference.
MW: We mustn't overestimate access however, even disregarding inappropriate diagnosis, if as much as 30% of individuals are experiencing sleep problems then this would suggest that Sleepio has a role in terms of increasing access to CBT-I. On balance, this would be a useful addition to what is available.
JEL: Agree that although we have trained a lot of people, access is still patchy. Would also reiterate that Sleepio's place is in mild to moderate insomnia.
KA: Self-referral is key; those would self-refer are more likely to succeed with any programme such as those offered through IAPT or Sleepio.
AM: To add to that, with Covid, there are large waiting lists of people with Long-Covid symptoms, including difficulty sleeping.
JEL: I question if this is insomnia or if this is something else altogether.
KA: Agreed, it is too soon to say.
AM: My point isn't that it should be used for Covid, but I'm worried that services may look to use Sleepio for this as they will be looking for a solution due to the unusually high numbers and this probably shouldn't be used in this population.

FS: I have 2 further questions – Firstly, regarding low engagement; how many sessions of Sleepio or CBT-I would a patient have to complete for us to consider that they have had the intervention?
MW: It is feasible to improve after 2 sessions. So you don't necessarily need all 6.
KA: Agree, but we need outcome data from Sleepio to understand how many sessions are being completed.
JEL: We should use information on the time spent with the app open as this may be misleading. 4 sessions may be optimal based on some recent research (of face-to-face CBT-I). But sometimes even 1 session is enough.
KA: Most of us would feel that 4-5 hours of face-to-face CBT-I would be optimal. Better engagement from patients (in terms of filling in a sleep diary) will improve outcomes.
FS: Secondly; What other comorbidities should be excluded?
KA: Comorbidities such as schizophrenia should be excluded if the patient is under the care of a psychiatrist. But a GO could also override this.

MT443 Sleepio Company Engagement Meeting – minutes – 21.01.21

1. **Welcome & introductions:**

   NICE:
   Chris Chester – Senior Health Technology Assessment Adviser (Chair)
   Bernice Dillon – Technical Adviser
   Lee Berry - Programme Manager
   Victoria Fitton - Project Manager
   Neil Hewitt – Technical Analyst
   Rebecca Owens – Technical Analyst

   Company:
   Chris Miller – Research Lead
   Will Goddard – Partnerships Manager

Chris Sampson – Health Economist
Eleanor Bell – Health Economist

KITEC:
Jamie Erskine - Health Technology Assessor – joint project lead
Murali Kartha – Health Economist
Farhad Shokraneh – Systematic Reviewer
Anastasia Chalkidou – Associate Director – project oversight
Jo Boudour – Project Manager

2. EAC clinical evidence review:

JE - We have the same group of RCTs as in the company submission - 12 RCTs (5 secondary analysis papers). We have excluded 2 non-randomised studies (leaving 11 non-randomised studies). The RCTs in general are well designed and reported. Most are reported as adequately powered (we are checking with our statistician).
JE - Focussing on the RCTs there are various populations – from student populations (mean age < 25 years) to people with self-reported depression. All measures (in RCTs at least) are self-reported.
JE - There are various outcomes reported at various time points (e.g. insomnia, psychological wellbeing, productivity) and methods of measuring outcomes vary – main indices of insomnia (ISI and the SCI), but also SE SOL, WASO etc. Comorbidities also measured (anxiety and depression scales). One study also measures blood pressure so physiological outcomes.
JE - The heterogeneity in populations, comparators and outcomes should be considered when we are thinking about the generalisability of results – we'll come on to this again when we talk about the meta-analysis.
JE - The reported outcomes on sleep improvement, psychological wellbeing, improved labour market participation and productivity, and reduced prescribing of hypnotics are all relevant to the NHS care pathway.
JE - The non-RCTs are also very heterogeneous in population, comparator, and design. Often only 1-2 secondary outcomes are within scope (although the majority of these do support Sleepio's ability to improve insomnia symptoms). These studies are unlikely to play a pivotal role in the decision problem but some sub-group analysis is welcome in showing that age, gender and race do not appear to affect the efficacy of Sleepio and that where follow-up is available at 24-48 weeks, a reduction in insomnia severity can still be seen.

JE - There is good quality clinical evidence that Sleepio improves sleep. The evidence is consistent in that results favour Sleepio over waiting list, sleep hygiene education or placebo (e.g. Espie 2012 imaginary relief therapy) in people who have self-reported insomnia symptoms. Though there is considerable significant heterogeneity between studies.
JE - The baseline characteristics of the participants varies as does the effect size reported by the studies, but those are consistently in favour of Sleepio.
JE - Evidence does seem to demonstrate that the effectiveness for those who complete the course is maintained over the longer term e.g. Luik et al (2020) found that benefits were maintained 48-weeks after receiving Sleepio (using Espie 2019 data). Sleepio also led to significant reductions in prescription and non-prescription medication use at 24-weeks, with this effect maintained for non-prescription medication at 48-weeks.
JE - Therefore the EAC believes Sleepio has potential to have a positive impact for adults with insomnia compared with standard care (as above).
JE – some uncertainties or gaps in the evidence are as follows:

1) High levels of study heterogeneity – different type of population and the effect size varies between studies, therefore difficult to draw conclusions from pooling results.
2) None of the studies compared Sleepio with face-to-face cognitive behavioural therapy for insomnia (CBT-I) or hypnotic drug therapy.

   Is there evidence for the former comparison in particular that the company is aware of? For example, we've found the Lancet meta-analysis (Luo et al.) from May 2020 that indicates that eCBT and face to face effectiveness is similar for depression (again, there were issues of heterogeneity in their analysis).

3) Population was self-referred and self-reported and therefore participants were not formally diagnosed with insomnia. May not be typical population.

4) Obviously almost all of the studies involve someone who is involved with the company, which may not be an issue but it is important to understand that there is a lack of completely independent research and this may be a source of bias.

3. Discussion about the issues raised in the clinical evidence review:

CM - The main results of the ongoing IPD meta-analysis are complete. The main benefit of having the meta-analysis was to conduct a moderator analysis. Nobody has done it on this scale for insomnia treatment so it has taken us more time than we would have hoped. We are hoping to submit it this year.

CM – We conducted moderator analysis instead of sub-group analysis. Two independent trials.
CM - Concerning heterogeneity we accounted for this with random effects modelling.
CM – We use linear regression to account for loss to follow-up in the analyses. We assumed that missing outcome data was missing randomly.

JE – What was the rationale behind this?

CM – We analysed the baseline variables and didn't find any correlation between these and where outcome data was missing.

CC – Does KiTEC have any questions regarding US studies and generalisability?
JE – We have not discussed this in detail. The main thing we need to know is availability of face-to-face CBT in the US compared with the UK. Generalise clinical outcomes to the UK? Assuming CBT same in the US as UK.
CC – Thoughts on what should be the comparator?
CM – In the US sleep hygiene advice is still considered to be first line treatment and hypnotics are not recommended apart from for short prescriptions in a small number of cases.
WG – We had some difficulty in establishing what the right comparator was. Face-to-face CBT is the natural comparator. Medication not recommended for anything but short-term use.
CM - Face- to-face CBT is often not available. Treatment not used at this stage clinically. Difficult comparator for us.
JE – Agree – when we spoke to the experts, disagreed between themselves about availability of face-to-face CBT. Is availability getting better over time?
WG – There is a growing availability of CBT in general. Not growing at the rate that the need is growing. Growing mental health burden.
CC – Has the availability of CBT improved because of more use of telecoms/digital methods?
WG – Digital providers now doing direct instead of referral. Sleepio is fully automated. Opportunities for digitally enabled.

4. **Questions on the economic evidence:**

MK – There are 12 papers. We only look at those with evidence related to the technology so will only be including two.
MK – Model – comparators are face-to-face CBT and sleep hygiene.
MK – The company didn't segregate between remission and non-remission and suggested a scenario analysis would have been useful.
CS – Scenario analysis you described is relevant – we attributed cost savings to people who experience remission and those with no remission.
CS - Modelling study – Darden paper – limited insofar as it doesn't report primary analysis of data and US based. Sampson study doesn't differentiate between remission. Had a very inclusive population, not able to distinguish between people who do and don't experience remission. Accurate way is then to apply it to everybody, acknowledge there is likely to be some difference between group that experience remission and group that don't.
MK – How has the change in primary care use of £45.04 been calculated and applied to Years 2 and 3.
CS – Population estimate in trend, multiple year projections – isn't following a fixed cohort and also it's cumulative, need to adjust this to come up with year 2 and year 3. Trying to be conservative. We will send our written responses.

MK – Sleepio users after one year – same as pre roll out?
CS – Our analysis projects a linear trend after rollout. Pre rollout trend, assume would have continued without introduction of Sleepio, our model estimates a new post roll out trend – over time two trends diverge, increasing savings cumulatively week on week, year on year.
CC – Model assumes it's non-inferior to face-to-face CBT-I.
MK – There is a paper (Soh et al) that shows it's non inferior.
JE – There's no direct comparative study between the two (face- to- face CBT and Sleepio). We don't know for certain it's non-inferior.
CC – Some experts would argue in person CBT would be better.
CC – Model relies on the assumption that Sleepio is non-inferior to face-to-face CBT-I though, that's how it generates the cost savings. If committee are not convinced it's at least as good clinically, wondering what the committee might think of this issue.
AC – Has the company done a smaller scale study to look more at behavioural changes etc., Sleepio v. face-face CBT - and could that evidence be presented to the committee.
CM – Might be good to have the Darden paper MA - would be very helpful. Happy to provide the markov model for this specific MA.
BD – The way you price Sleepio is a bit different. For the Thames Valley rollout is there some real world usage data you can make available? People that accessed the website and numbers that completed. This might help the committee.
CM – We are currently writing up an implementation report on the Thames Valley implementation. Should be included as part of the Studd paper. It's not a finalised manuscript yet but we can share more of the results.
WG – We attempted to provide the model that landed best with commissioners, commissioners are trying to work out where it fits. There would always be questions about the funding model. The effects of Sleepio in terms of savings were determined at population level – we have most confidence in this. This is the reason behind presenting this pricing model.
CC – If committee wanted to restrict recommendations to a sub group – how could you implement restricted recommendation with your funding model?
WG – Thames Valley – people accessing Sleepio there via primary care and self-referral – assessing if someone might or not be suitable for Sleepio. Could make it clear to GPs there should be certain restrictions. Making sure that training follows through into practice. Sleepio isn't necessarily just for those with a clinical diagnosis of insomnia.
CC – Are there different definitions of sleep hygiene in the studies and could this affect results?
JE – This is less of an issue than the variation between different comparators, rather the variation between this particular comparator.
JE – You mentioned a study where the comparator was group face-to-face CBT.
CM – De Rose study - will need to seek permission to share this.
CM – Manber study - this is currently recruiting and we don't have any data analysis at this stage.
FS –Because the existing MA is not published and we don't have access to the data we can't rely too much on this. Will there be a sub-group MA?
CM – We have published previous sub group analyses so look at the methodologies in these papers.

FS – The IPD MA you have provided has three outcomes – includes population that are healthy, pregnant women and people with insomnia. We're not clear about inclusion and exclusion criteria of patients in each of the studies in the IPD MA.
CM – Look at the individual studies. 12 trials.
CC – Website platform has more features than the iOS version.
JE – We talked about this in the last meeting. Web platform used in the studies. Not a concern.
CM – Sleepio is unique in the sense it's fully automated. No coach or facilitator. Can interact with a psychologist if need to.
FS – Drop outs, after and before randomisation. Do you have information on the characteristics of these people.
CM – We can supply a written response. Is there any specific population we are not engaging? Haven't looked at moderators for engaging. There is some information in the Lancet Psychiatry paper.
WG - Sleep Station – evidences shows how digital CBT for insomnia works. We are saying Sleepio works – here is the evidence for Sleepio.
CM – Web based platform not an app. In our trials we would give access to the platform. App is just a supporting feature. All studies based on website version.
WG – We recognise Sleepio is a digital programme – we point people to areas where they can access internet – working with public libraries etc. There is a future plan for there to be an android app as well so we can improve the user experience.

5. **Next steps:**

WG – Company will share the Darden markov model and MA, the Studd et al academic in confidence study and will check about the De Rose study. We will also send our written responses.
VF – the fact check is due to the company on 9th February.
VF – Draft guidance MTAC is on 19th March.

File attachments/additional information from question X:

Insert

File attachments/additional information from question X:

Insert

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

MT443 Sleepio for adults with poor sleep

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from [insert EAC] to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **19th February 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

16th February 2021

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Circadian drift in under 25's used as a rationale for not recommending Sleepio under 25's. "Some populations may be less appropriate for treatment with Sleepio… people under the age of 25 years may be still experiencing circadian drift, rather than insomnia."	In line with the clinical evidence, amend the age limit of 25 for Sleepio use	1. Circadian drift is an ambiguous term 2. Evidence that Sleepio is effective in under 25's **Circadian drift** We believe 'circadian drift' is both ambiguous and used in error. Circadian drift is not a clinically defined term and appears to have been used out of context. Those aged 18-25 may display a tendency for a normative delay in sleep-wake phase rhythm, resulting in them going to bed later and rising commensurately later the next morning (if school or work requirements allow). In Sleep Medicine, 'circadian drift' is more suggestive of the successive delays in sleep-wake phase seen in patients with an inability to entrain to a 24-hour circadian cycle. This is a separate disorder termed Non-24-Hour Sleep-Wake Rhythm Disorder (non-24 SWRD; ICD-10-CM: G47.24). This is a rare condition that can occur in both adults and adolescents and is often seen in patients with no photoreception.	KG – thank you. We asked experts to further clarify the term and they suggested there was no standardised term for this effect, so we will remove it from the report ("delayed sleep phase" was suggested as a more precise description). During our discussion with experts, it was stated that caution should be exercised in younger adults. For example, one expert noted that from their experience very few people at age 18 really have insomnia. Younger adults may have sleep patterns that mimic insomnia. We can reword this and will highlight that there are also studies into these populations so the committee can discuss more fully. We have amended wording to reflect that Sleepio may be appropriate in these populations if other disorders or non-insomnia factors have been ruled out.

		Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4582061/#B5 https://academic.oup.com/sleep/advance-article/doi/10.1093/sleep/zsaa281/6134797 We believe the EAC should remove this term throughout. **Sleepio is effective in under 25's** Sleepio has more than sufficient evidence to show that it is effective in those aged 18-25 with insomnia (Freeman et al., 2017), subthreshold insomnia symptoms (Denis et al., 2020) and insomnia and comorbidities including symptoms of depression (Henry et al., 2020). RCTs including Freeman et al., 2017 (mean age = 25) and Denis et al., 2020 (mean age = 19) specifically sampled younger populations. Cliffe et al., (2020), report excluded, shows uncontrolled improvements with Sleepio in those aged 14 – 17 years. In total from the IPD meta-analysis of all 12 RCTs included, 3,141 individuals	

		were aged 25 years or younger (40% of the total sample of 7,845).	

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pregnant women are not indicated. *"For example, clinical experts felt that pregnant women may not be appropriate for Sleepio (for example, insomnia symptoms may be due to restless legs) and problems may resolve post-partum."*	To include a statement that Sleepio is safe and effective for use in pregnant women.	Two randomised controlled trials have demonstrated that Sleepio is safe and effective for pregnant women. Kalmbach et al., (2020) randomised 91 pregnant women to either Sleepio or Sleep Hygiene Education control and found greater reductions on the insomnia severity index at post treatment compared with control. Felder et al., (2020) randomised 208 patients with insomnia symptoms at baseline and found Sleepio significantly improved insomnia measured by the insomnia severity index and effects were maintained at 4 months from randomisation. It was also found that those randomised to standard care were more likely to use prescription medication for sleep than those who received Sleepio at 10-weeks follow-up. This is important because the standard of care by NICE is currently Sleep Hygiene for sleep difficulty (not specified):	KG – Also see issue 1 above. We have amended to indicate that there is evidence in pregnant women, but that insomnia mimics should be ruled out before referral.

		https://www.nice.org.uk/guidance/cg192/ifp/chapter/sleep-problems-in-pregnancy For acute insomnia management, NICE recommends: *"Do not prescribe hypnotics to older people or women who are pregnant or breastfeeding"*: https://cks.nice.org.uk/topics/insomnia/management/managing-short-term-insomnia-less-3-months/. NICE does not recommend any management for pregnant women who suffer from chronic insomnia: https://cks.nice.org.uk/topics/insomnia/management/managing-long-term-insomnia-greater-3-months/ We believe that it is important for pregnant women who suffer from insomnia to be able to access non pharmacological treatments for insomnia as a first-line treatment, in line with the BAP treatment guidelines.	

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Completion of Sleepio session 3 is incorrectly defined as Sleepio completion. Sleepio session 3 completion is defined as engagement in the real world study.	Amend references to the real world study 'completion' rate as engagement rate. For example "In a real-world study into the feasibility of implementing Sleepio over a large scale in the UK, Studd et	1. Clarifying how Sleepio works 2. Definitions of uptake and engagement **Clarifying how Sleepio works** Sleepio is not intended as a linear programme where patients are	KG – thank you for clarifying. We have amended completion to engagement in the report where appropriate and explained the definition as set out by the paper.

"In a real-world study into the feasibility of implementing Sleepio over a large scale in the UK, Studd (unpublished), found that 11.3% (1,769/15,615) of people with insomnia who registered to use Sleepio completed the programme."	al (unpublished), found that uptake (starting session 1 from registration) was 46% (7,278/21,208), acceptability (completing session 2 from starting session 1) was 38% (2,746/7,278) and engagement (completing session 3 from completing session 2) was 65% (1783/2746). 58% of those completing session 2 experienced insomnia remission."	expected to complete all 6 sessions to experience benefit. Sessions can be repeated according to individual preference. Similar to other Psychology services including IAPT, patients may gain clinical improvements from individual therapy sessions and may not require full programme completion for maximal benefit. Indeed many CBT for insomnia components, introduced in Sleepio from Session 2 onwards, are clinically beneficial as stand-alone interventions for insomnia management (Edinger et al., 2021: https://jcsm.aasm.org/doi/10.5664/jcsm.8986) Partial compliance to Sleepio has been assessed in supplemental statistical analyses of trial data, finding ed insomnia symptoms from higher mean SCI-8 scores with Sleepio than control from those who complete session 2 onwards (Freeman et al., 2017: https://www.thelancet.com/cms/10.1016/S2215-0366(17)30328-0/attachment/41e7c0bc-ea93-4834-a274-91bdee1e973e/mmc1.pdf). Therefore, drop-out can be due to patients gaining benefit, or due to issues with the product experience.	"Engagement was defined in the paper as completing session 3 where patients go through sleep scheduling, stimulus control and sleep restriction. The company note that session 3 is the most challenging session, which makes completion an appropriate marker for engagement."

		Definitions of uptake and engagement Uptake, acceptability and engagement have specific definitions in the paper. Uptake is the proportion of those starting the first session - an introduction to CBT where patients sign a compact with the virtual prof. Acceptability is defined as completing session 2 where patients learn how to optimise their lifestyle and bedroom, learn progressive relaxation and thought checking. Engagement is defined as completing session 3 where patients go through sleep scheduling, stimulus control and sleep restriction. Session 3 is the most challenging session, which makes completion an appropriate marker for engagement. <u>Summary:</u> Therefore, the stated 11% completion rate is incorrect - it defines engagement and due to the nonlinear nature of the programme, it cannot be used as a completion rate.	

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Inconsistent use of language throughout the report. Confusing poor sleep and insomnia. Confusing uptake and engagement.	Amend mentions of poor sleep to insomnia Amend language on uptake and engagement Examples: "Sleepio for adults with insomnia symptoms" "Sensitivity analyses indicate that Sleepio becomes cost neutral when uptake is between 0.6 and 0.7%, therefore adequate *implementation* is key to recommending the adoption of Sleepio." "Adequate patient uptake and engagement are crucial to seeing benefits of Sleepio in the health system, therefore, investigating how to *optimise uptake at scale* would be valuable."	As above, uptake is defined as the proportion of patients starting the first session of CBT from registering. It describes access to treatment and should not be conflated with engagement. Engagement is the completion of session 3 and describes progression within Sleepio. The critical factor in the economic model is how we ensure good uptake - the implementation model. Therefore, we would recommend clarifying statements where the EAC are referring to the effectiveness of the implementation model at scale by using the terms 'implementation model' or 'distribution model' instead of engagement, adherence, uptake or selection.	KG – thank you. We have amended the report where appropriate. We have also clarified the definition of uptake and engagement (as above) "Uptake is defined as starting the first session of the programme. Engagement was defined in the paper as completing session 3 where patients go through sleep scheduling, stimulus control and sleep restriction. The company note that session 3 is the most challenging session, which makes completion an appropriate marker for engagement." Where we have noted both uptake and engagement, we are indicating that both initiating the programme is important, as is continued use of the programme.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Cohort size in Year 1 Use of Buckinghamshire referral figure (0.58%) from Sampson et al. (2021) rather than estimated uptake figure for the study cohort (0.99%)	1. Amend the base case assumption for year 1. 2. Remove following passage as clarity has now been provided on why the proportion of users required estimation: *"The EAC is unclear why the proportion of users required estimation rather than using the figures reported in Sampson et al. (2021). The EAC further believes that the figure used for estimation of GP referrals from the 9 GP practices may be incorrect. The company has used a figure reported in Samson et al. 2021 for the 'estimated patients based on Sleepio data' of 1220. The EAC considers this to be the estimate of the overall users of Sleepio in the nine GP practices (0.94% of the practice population). The EAC believes the number of GP referrals on which the company should have based their calculation is given by the data reported as 'estimated patients based on EMIS data', which was 1,008. If the latter figure had been used the estimated proportion of Sleepio users is 0.81%."*	There are four areas where we would like to provide clarity and/or additional evidence: 1. Definitional clarity 2. Sleepio distribution model 3. Sleepio implementation support 4. Additional real-world evidence to validate Year 1 cohort assumptions 1. Definitional clarity: as above **Referrals** are defined as when a GP sees a patient with a sleep problem, refers them to Sleepio, and remembers to code that they referred a patient to Sleepio. Referrals are therefore distinct from uptake: not every Sleepio referral leads to a patient actually registering and then using Sleepio. Referrals data in the Sampson et al. study were collected from EMIS data. Sleepio also captures user-reported data on how they found Sleepio. Comparing the two figures, a higher number of Sleepio users self-reported	2.The EAC thanks the company for providing clarity on the calculation used to arrive at a figure of 0.99% for uptake. The EAC notes that the figure for the number of GP referrals in the company's calculation is taken from the self report data. The EMIS data, also published by Sampson provides a lower figure for GP referrals. The EAC figure of 0.58% is based on data reported in Sampson as the 'estimated patients based on Sleepio data' for Buckinghamshire. The EAC understands this to refer to data on uptake for patients in Buckinghamshire. The EAC believes this data is likely to be accurate, as respondents were required to provide their postcode to access Sleepio, allowing verification of those residing in Buckinghamshire. The EAC considers the data for Buckinghamshire to be the most relevant estimate of uptake for a population based model. 3.The EAC has based its estimate of uptake on the data provided in Sampson. The EAC considers this the most appropriate estimate in the absence of further evidence of uptake

		that they were referred by their GP than the EMIS data captures. This suggests that GP referrals from EMIS provide a significant underestimate. **Uptake** is defined as the number of people starting session 1 of Sleepio. This is the cohort of people entering treatment and is used in the economic model. <u>2. Sleepio distribution model:</u> The Thames Valley implementation model focused on three different routes through which patients could access Sleepio: 1) GP 2) IAPT and 3) self-referral. This model was in operation during the health economic analysis conducted by Sampson et al. Therefore, we must consider the impact on primary care costs of patients accessing Sleepio from all three routes, not just those accessing via their GP. For example, patients who self-referred to Sleepio might previously have visited their GP to seek treatment for insomnia, but after Sleepio's introduction may have accessed Sleepio directly without requiring a GP appointment. This would have an effect on primary care	of Sleepio following scale up of the implementation model. 4. The EAC notes that this is new evidence that was not available when its assessment was undertaken. The EAC also notes that these data refer to specific practices, rather than the whole of Northamptonshire. The cost of Sleepio is based on a population model in which commissioners will be paying for access for the entire adult population for their area. In the light of this, the EAC is of the view that uptake estimates should be based on data for a relevant population rather than specific GP practices. These data exist for Buckinghamshire and for the Thames Valley and were reported in Sampson. The EAC remains of the view that, in the absence of further population level data, the data in Sampson provide the best evidence of uptake, and that the estimate of uptake should be based on a commissioning population inline with the pricing structure. The EAC's assessment report has considered the evidence in the company's economic submission. The new evidence presented in this response will have be considered following publication of the draft guidance. No further changes have been made in the report.

		costs but would not have been coded in EMIS as a referral. The calculation of the 0.99% uptake figure - which accounts for patients using Sleepio across 1) GP 2) IAPT and 3) self-referral distribution routes - is as follows: ● N = 129,865 = Total patient population for nine practices in economic analysis ● a = 1,220 = Total GP referrals from nine practices ● b = 0.56 = Proportion of patient referrals that lead to Sleepio registration (i.e. signing up for Sleepio) ● c = 0.4607 = Proportion of Sleepio users that initiate treatment (i.e. starting Session 1 of CBT = uptake) ● d = 0.2452 = Proportion of all initiations that are from GP referral ● ((a*b*c)/d)/N = 0.0098845 = 0.99% uptake Therefore we feel there is no basis in evidence for the adoption of 0.58% uptake as a base case scenario. <u>3. Sleepio implementation support</u> The EAC is correct to point out that the GP practices in the study received a higher level of implementation	

		support than other areas of the Thames Valley. However, the EAC is mistaken to view this level of support as different from Big Health's standard package delivered to commissioners. ● The Thames Valley project was a real-world study funded by Innovate UK and the Oxford AHSN on the basis that Big Health must develop and test an implementation model that could subsequently be scaled across larger areas ● The collective implementation team between Big Health and the Oxford AHSN was small. Therefore it was necessary to deliver implementation in targeted 'waves' of GP practices. It was not possible (or desired) to deliver the same level of support to all regions at once ● The model used in the study cohort was successful and has therefore become Big Health's standard package. This model is now more scalable and able to deliver support to all practices in a region. <u>4. Additional real-world evidence to validate Year 1 cohort assumptions:</u>	

		Additional real-world evidence validates the scalability and effectiveness of this implementation model: ● We used this model to roll out Sleepio across 16 GP practices in North Hampshire CCG (October 2020) ● Each practice received an education & training session, support to integrate Sleepio into local EPR systems, and digital materials to share with patients ● Uptake is currently 0.8% (YTD, correct as of 22 Feb 2021). This is in line with our forecasts as uptake tends to be lower in the first 3 months of a project. We expect to reach c. 1% uptake by end September 2021 (12 months post launch) ● We also note that the rollout in North Hampshire does not include Sleepio access via the local IAPT service. This is likely to reduce uptake vs. the Thames Valley rollout (where IAPT was referring patients to Sleepio) All available evidence (included from the North Hampshire implementation not previously shared with the EAC) suggests that uptake exceeds 0.7%	

		and that 0.99% is achievable uptake in a realistic scenario.	

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Cohort size in subsequent years Assumption that Sleepio uptake will reduce with each subsequent year *"The EAC considers it highly unlikely that the cohort observed in Sampson et al. (2021) will be replaced by a similar sized cohort of new users in each subsequent year." (pp. 103-4)*	1. Remove assumption that there won't be a similar size cohort each year 2. Revise assumed 0.2% uptake in subsequent years	The economic model (not Sampson et al) assumes that year 1 uptake is representative of any post-implementation year in practice. There are two pieces of evidence that support the assumption that uptake will not decrease in subsequent years. We appreciate these were not included in the original submission so the EAC did not have the opportunity to use this data to inform its assumptions: 1. (a) Evidence around prevalence of insomnia (b) Evidence around incidence of insomnia 2. Follow-up data from the Thames Valley <u>1. (a) Evidence around prevalence of insomnia:</u> The prevalence of insomnia is increasing over time because of a lack of adequate treatment access	The EAC did not have access to data on the uptake of Sleepio beyond the first year at the time of the report. The EAC considered two scenarios, one in which uptake remained at the same level as the first year and one in which uptake fell. The EAC considered it likely that uptake would fall in subsequent years on the basis that some patients accessing Sleepio in the first year of roll-out are likely to have had insomnia for a number of years. Indeed, the data in Sampson appears to reflect a prevalence sample of patients, although the timeframe for sampling is not reported. 2.The EAC understands the uptake in the Thames Valley region to be 12,374 over a period of 65 weeks following rollout of Sleepio, as reported in Sampson. The EAC is unable to reconcile the data provided in this document with that reported in Sampson.

		in England (almost doubling from 1993 to 2007). Prevalence today far exceeds the incidence of 1% used in the economic model. ● Insomnia diagnosis: 1993 = 3.1%, 2000 = 5.0%, 2007 = 5.8% ● Insomnia of at least moderate severity: 1993 = 9.3%, 2000 = 11.5%, 2007 = 13.2% ● Insomnia symptoms: 1993 = 35%, 2000 = 38%, 2007 = 38.6% Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3274339/ 1. (b) Evidence around incidence of insomnia Further recent data from Canada suggest a far higher rate of new insomnia caseness than determined by the EAC. Insomnia incidence rates from those who were initially good sleepers at baseline was found to be 3.8%, 9.3% and 13.9% after 1-,3-, and 5-years. This suggests the rate of new insomnia cases will be replaced through time.	The 0.2% uptake in subsequent years is used by the EAC in its pessimistic analysis, given the lack of data at assessment. Further evidence on uptake following the first year will be considered following publication of the draft guidance.

		Source: https://jamanetwork.com/journals/jamanetworkopen/article-abstract/2772563 1. (c) The annual incidence of acute insomnia in the UK sample was between 31.2% and 36.6%. Source: https://pubmed.ncbi.nlm.nih.gov/22379244/ 2. Follow-up data from the Thames Valley Real-world uptake figures from the Thames Valley do not support the assumption that uptake reduces after Year 1. Uptake figures are as follows: ● October 2018 - September 2019 (inclusive): 4,677 ● October 2019 - September 2020 (inclusive): 4,931 Big Health delivered less implementation support in the second year than in the first (when GP practices were onboarded in 'waves' - see Issue 5). Activity in both years included digital ads to raise awareness in	

		the population, reporting on outcomes to GP practices, provision of printed and digital resources for patients, and promotional campaigns with public- and third-sector partners. This data from the Thames Valley real-world study (not previously shared with the EAC) suggests that uptake is unlikely to drop in Year 2, and the high and rising prevalence of insomnia suggests that Year 2 uptake levels could be maintained indefinitely.	

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Length of follow up being relatively short e.g. Pillai et al. 2015 (1 week), Barnes et al. 2017 (10 weeks from randomisation), McGrath et al. 2017 (8 weeks), Kalmbach et al. 2020 (6 weeks)." And, relatedly: "More evidence into the longer-term impact (at least 3 to 6 months) of Sleepio on insomnia symptoms to assess whether results are maintained."	Remove length of longer-term (at least 3 to 6 months) impact as a limitation and uncertainty.	Many RCTs of Sleepio contain follow-ups beyond 3 months from randomisation. For example, Espie et al., 2019 assessed outcomes at 24 weeks from randomisation, and again at 48 weeks from randomisation (Luik et al., 2020); Felder et al. (2020) assessed outcomes at 18 weeks (4 months) from randomisation; Freeman et al. (2017) at 22 weeks (5 months) from randomisation and Kyle et al. (2020) at 24 weeks (5.5 months) from randomisation. In these	KG – thank you. We have clarified in the bullet point highlighted that this refers to particular and not all studies: "• Length of follow up *in some studies* being relatively short". We note that the experts mentioned 3 – 6 months as a minimum to assess if results are maintained, but agree that there are studies into Sleepio that are longer term. We have amended the study implication bullet point to: "• There are currently RCTs that indicate that Sleepio is beneficial in the

		studies we see that the effects of Sleepio on insomnia symptoms are maintained at these time points. We believe, therefore, that this provides evidence for the longer-term impact of Sleepio (3 - 6 months).	longer term (at least 3 to 6 months) for insomnia symptoms. Future studies, for example into different population subgroups, would also benefit from including longer term follow up as part of their study design."

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"The company claims that providing digital CBT-I would improve access to CBT services, for example, providing a CBT service where face-to-face CBT is not available or has long waiting times. Clinical experts noted that long waiting times for face-to-face CBT are a significant challenge."	Make this specific to insomnia management	It is unclear if this relates to access to CBT in general or for CBT for insomnia more specifically. In Sleepio's use case the benefit would be to increase access to CBT for insomnia, as recommended in NICE guidelines.	KG – Thanks, have amended to "The company claims that providing digital CBT-I would improve access to CBT services, for example, providing a CBT service *for insomnia* where face-to-face CBT is not available or has long waiting times. Clinical experts noted that long waiting times for face-to-face CBT *for insomnia* are a significant challenge."

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Completed but not reported or unknown status	Removal of these trials in this section.	Results published in Crawford et al., (2020) and Kyle et al., (2020), respectively.	KG – thank you. We have removed these.

Crawford MR, Espie CA, Luik AI, Taylor HL, Burgess HJ, Ong JC. Women with insomnia and debilitating migraines: Sequential administration of online treatment-the Windsor study Kyle SD, Hurry MED, Emsley R, Luik AI, Omlin X, Spiegelhalder K, et al. Effects of digital Cognitive Behavioural Therapy for Insomnia on cognitive function: study protocol for a randomised controlled trial. Trials. 2017;18(1):281. [ISRCTN89237370: DISCO]			

KiTEC

MT433 – Sleepio: Extra Analysis

1 Project Details

Work package reference	MT433 – additional module
Work package name	Sleepio for adults with poor sleep
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Table of Contents

1 Project Details 2

2 Introduction 4

3 Review of the analysis presented in the assessment report 4

4 Review of statistical analysis described in Sampson et al (2021) 6

4.1. Time series regression model 6

4.1.1 Review of Sampson et al. 2021 paper 6

4.1.2 Revised time series regression model 9

4.2 Revision of Cost Modelling requested by NICE. 11

4.2.1 Big Health Data 14

4.2.2. Results of Longitudinal Latent Class Analysis (LCA) 18

4.2.3. Sleepio sessions and Drop-outs in the Literature 20

4.3. Exploration of Patient Pathways 23

4.4. Economic analysis (Scotland pricing model) 24

5. Conclusions 26

6 References 27

7. Supplementary materials 28

4.2.1 Revised time series regression model 31

2 Introduction

The Medical Technologies Advisory committee (MTAC) discussed the evidence for Sleepio on 19th March 2021. It requested some additional work be undertaken by the EAC regarding key issues raised by the committee related to model structure, referral pathways, comorbidities, socio-economic status and outcomes. Also included is a further economic analysis using an alternative pricing model proposed by the company(Scotland pricing model) . This report presents a review of an analysis of EMIS and Sleepio data and the results of the requested additional work, including a brief overview of the EAC's economic analysis.

3 Review of the analysis presented in the assessment report

The company's analysis modelled a single cohort over 3 years based on an extrapolation of the Sampson et al. (2021) paper that used costs observed over 65 weeks. The company analysis was not designed to segregate the analysis according to referral channel, and was a mix of self-referrals and GP referrals. In practice, NHS providers would be expected to pay a fee per capita per annum for ongoing access to Sleepio for their populations. Therefore, alongside the projected savings, each subsequent year of use will accrue additional costs for the provision of Sleepio. Any savings will therefore be a combination of both a reduction in use of primary care resources for patients accessing Sleepio in that first year as well as the extrapolated ongoing savings for previous years' cohorts who had accessed Sleepio.

For the assessment report the EAC undertook analysis to quantify the rolling total costs since inception for 1, 3, 5, 10 and 20 years after commencing provision of Sleepio for a population of 2,400,000. The EAC model assumed cost savings over 3 years as described in the company's base case submission (table 1) and an uptake of 0.58% of the population in the first year. The analysis compared 2 scenarios for uptake in the Thames valley region, for years following the initial provision of Sleepio. In the "optimistic" analysis, it is assumed that uptake was maintained at 0.58% of the population across the different durations. In the "pessimistic" analysis the uptake falls to 0.2% of the population for each year beyond the first year. Tables 2 and 3 present the rolling total costs for both these scenarios respectively.

The key results of the economic model for this EAC analysis were as follows:

- The EAC regards the reported uptake of Sleepio in Sampson et al. (2021) of 0.58% for Buckinghamshire to be a more realistic estimate of uptake in the first year of access to Sleepio than that proposed by the company of 1%, or the figure reported in Sampson et al. (2021) across 9 GP practices of 0.94%
- Sleepio was not cost saving (-£20.09) compared to current the standard of care which is sleep hygiene. Sleepio becomes cost saving at an uptake rate of 0.666%. Sleepio becomes cost saving when the cost of Sleepio per head falls to £0.78
- Sleepio was cost saving (£386.83) compared to face-to-face CBT. This comparator is recommended for the treatment of insomnia but may have limited availability in parts of the UK.
- In both optimistic and pessimistic scenarios, the overall cost of provision rises over time.

Table 1: EAC's estimated cost savings – population model

EAC	Technology costs	Primary care cost savings (Year 1)	Primary care cost savings (Year 2 &3)	Sleepio cost savings (1year)	Sleepio cost savings (3years)
Sleepio	£155.17	£49.52	£85.56		
TAU	£0	£0	£0	-£105.65	-£20.09
CBT	£542	£49.52	£85.56	£386.83	

Table 2: Optimistic scenario: it is assumed that uptake was maintained at 0.58% of the population across the different durations

Years	Sleepio cost	Primary care costs averted	Overall cost saving*
1	£2,160,000	£689,318	£1,420,948
3	£6,263,340	£3,775,110	£2,404,087
5	£10,093,851	£7,221,208	£2,775,500
10	£18,592,603	£14,867,063	£3,599,556
20	£31,773,249	£26,724,958	£4,877,576

*A positive value denotes that the technology is cost incurring

Table 3: Pessimistic scenario: it is assumed that the uptake falls to 0.2% of the population for each year beyond the first year

Years	Sleepio cost	Primary care costs averted	Overall cost saving*
1	£2,160,000	£689,318	£1,420,948
3	£6,263,340	£2,533,712	£3,603,505
5	£10,093,851	£3,722,022	£6,156,357
10	£18,592,603	£6,692,681	£11,497,509
20	£31,773,249	£11,547,712	£19,541,582

*A positive value denotes that the technology is cost incurring

4 Review of statistical analysis described in Sampson et al (2021)

The economic model hinges on the cost savings as reported by the Sampson et al. (2021) paper. The committee had some queries about the methodology of the analysis described in the paper and how the choice of the inclusion of confounding factors was made. KiTEC were asked to review the Sampson et al.[1] analysis and to present independent results from an analysis of the data and to investigate the appropriateness of the choice variables of interest and no interest.

Since this is essentially an analysis of time series data the EAC considered two commonly employed approaches; ARIMA Box-Jenkins analysis and time series regression-based modelling. The former will not be discussed further in this report as it is outside the remit of this evaluation project. The reader, if interested, is directed to the appendix section for an initial exploratory analysis of this method. The EAC present the review of the Sampson et al. model and the results of the additional analyses performed using an extended version of the time series regression modelling to account for individual patient variability and modification of the underlying population distribution model.

4.1. Time series regression model

4.1.1 Review of Sampson et al. 2021 paper

Sampson et al. 2021 report the results of an in-depth analysis of primary care cost data coming from 8 general practices located in Buckinghamshire. This paper

analysed the costs of Sleepio using time-series regression modelling. Specifically, their final model is a multilevel generalised linear model (GLM) using quasi-gamma distribution with a logarithmic link function. The assumed structure of the model adopted by Sampson et al. 2021 also accounts for correlations among observations nested within practices. Their model also specified adjustment for seasonal effects, represented by a 4-level factor variable to reflect each quarter of the year. Their final model also includes a list of confounders for which the results are also adjusted: age, sex, diagnosis of depression/anxiety, insomnia, diabetics, hypertension, asthma, IHD, heart failure, arthritis, and chronic pain. Their model also included 3 further variables representing baseline and post-intervention effects of time, to capture modulation over time on the outcome variable. The presence of autocorrelation was tested using the Durbin-Watson (DW) test.

The model presented by Sampson et al. 2021 correctly recognizes that the structure of the data is hierarchical with individual observations across weeks that could possibly correlate with each other. Sampson et al. correctly assume that this type of data should be modelled within the multilevel framework and specification of the proposed model assumes nesting. However, the way it is implemented in this paper ignores the effect of individual patients since the individual observations from weeks are assumed to be nested only within surgeries (Figure 1). This may have a profound effect on the results since ignoring the level of individual patients increases the risk that standard errors obtained by Sampson et al. 2021 might be biased and consequently, the conclusions from the paper could be misleading or unreliable.

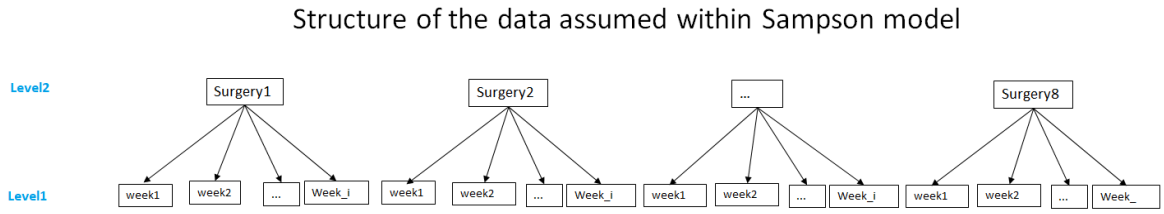

Figure 1. Data structure assumed in Sampson et al. 2021 Note that level 1 is the weekly costs and level 2 each of the GP surgeries

NICE review raised the issue as to the appropriateness of the link function[1] and error distribution in the GLM model that Sampson et al have used. The authors describe clearly in their paper, that the choice of these assumptions were as a result of the application of the modified Park's and link tests that helped to decide on specific form of the model, a commonly accepted and applied strategy.
The outcome variable in the Sampson et al. model is cost per individual patient recorded weekly, however, this maybe an over simplification and excludes a number of alternative models available under the GLM framework. The first excluded characterisation of the data is related to the range of possible values of the cost variable, namely, it is left side restricted and the possible values are only non-negative. Another characteristic is that the variable is continuous. Third is the fact that empirical distribution of costs tends to be skewed towards the right (a lot of observations cumulated at lower levels and "long-tail" consisting of a low number of observations with large and very large values). Related to this is the fact that the largest fraction of observations has zero values (ie. A zero-inflated distribution) which poses additional statistical complication and further restricts the number of potential use. These characteristics have consequences for statistical modelling under the GLM framework as they exclude modelling under the assumptions of classic linear model. In addition, all models for discrete data are immediately excluded. However, even after taking all of this into account their remains only a few theoretical options and they are all reasonably covered by Park's test which was used in the Sampson et al paper to justify their assumptions.

NICE also queried the authors' choice of confounding variables. There is no explicit description of why age, sex, diagnosis of depression/anxiety, insomnia, diabetics, hypertension, asthma, IHD, heart failure, arthritis, and chronic pain might affect the efficacy of the treatment. The inclusion or not of certain confounders could cause the direction of some of the model factors to reverse (change an increasing cost into a decreasing cost) depending on the list of other confounders present in the model, a common conseqeunce of co-linearity across multiple variables.). This is especially the case for variables representing effects of intervention (Sleepio rollout) that change the conclusions from the study.

[1] The relationship between the linear predictor and mean of the distribution function.

In order to address these points, the EAC repeated this analysis adding the effect of individual patients to the model and to investigate further the choice of confounding variables.

4.1.2 Revised time series regression model

This following section presents the results of the independent analyses prepared on all the (EMIS) data included in the original assessment report and addresses all the issues raised above. Initially EAC conducted exploratory analyses to examine the issue of lack of nesting at all relevant levels, i.e including the individual patient as contributing factor to the model. Due to very large size of the data set the estimations for that part were conducted on a sub-set of the data taken from the original EMIS data. Cases (patients) were sampled as clusters (with all their available weekly records for costs) i.e. cluster sampling. The obtained results for a GLM with a Gaussian distribution and 3 levels to account for possible correlations at the GP level suggested, that the major part of the cost dispersion lies at the lowest level of the weekly measurements and only a small share of total variance can be attributed to the individual patient level and a very small part to surgeries. The full results of this exploratory analysis are available in the Supplementary material.

GLM Multi-level Modelling - Assuming a Poisson distribution quasi-maximum likelihood regression model

In light of the results obtained, a possible better option is the Poisson quasi-maximum likelihood regression model which can be used for time-series and consistent for any non-negative data. The approach proposed by Wooldridge (1999) is currently accepted and estimates the fixed effects with robust standard errors for clustering variables which in this case, would be individual patients and seems to be a better option than adjustment for the correlations at the GP surgery level.
The starting point was to include variables to construct an interrupted time series model (model 1), next the seasonal adjustments were added (model 2), then age and gender and finally comorbidities (model 3).

The first Model uses 3 levels plus the 2 time-related variables and the intervention. The results showed that there is a very small (but statistically significant) upward trend in costs across time for people suffereing with insomnia. This effect is mitigated by the intervention and the trend following the intervention, however both effects are statistically non-significant (post-intervention trend from the beginning and the intervention after the adjustment for seasonality) and therefore there is little difference in costs between the intervention (sleepio) and no intervention.
The second model builds on the first by adding the counfounding variables for seasonal adjustments, followed by age and gender.
The third model builds on the previous two by adding comorbidities.

The results of these computations are included in Table 5. This time there is no reverse in effect for the intervention even after adding the counfouding variables. Model 2 (see table 4) would seem to suggest that seasonal adjustments are important as their effects are strong and remain so even after introducing adjustments for diagnosis of comorbidities to the model (i.e Model 3). The final model shows that apart from heart failure (HF) and arthritis, all other comorbidities (depression/anxiety, insomnia, diabetics, hypertension, asthma, IHD, and chronic pain) have a significant and positive effect on costs (i.e., increased costs). Therefore, Model 3 is the proposed final model on which the EAC made economic projections of cost savings per person at week 65 and for the period of 1-year onwards from this time point.

Table 4. Results of Conditional fixed-effects Poisson regression with grouping variable set at patient level.

Pccosts	Model1				Model2				Model3			
	coeff.	P	lower	upper	coeff.	P	lower	Upper	coeff.	p	lower	upper
Time	0.003	0.000	0.002	0.005	0.003	0.003	0.001	0.005	0.003	0.002	0.001	0.005
Intervention	-0.077	0.023	-0.143	-0.011	-0.069	0.094	-0.150	0.012	-0.075	0.069	-0.156	0.006
Post	-0.001	0.203	-0.003	0.001	-0.001	0.287	-0.003	0.001	-0.001	0.285	-0.003	0.001
q1					0.125	0.000	0.073	0.177	0.121	0.000	0.069	0.173
q2					0.089	0.000	0.040	0.138	0.083	0.001	0.033	0.133
q3					0.142	0.000	0.097	0.188	0.136	0.000	0.090	0.182
d_insomnia									1.738	0.000	1.567	1.909
d_anx_dep									1.718	0.000	1.637	1.799
d_diabet									0.593	0.000	0.379	0.807

d_hyper									0.602	0.000	0.470	0.734
d_copd									0.600	0.000	0.408	0.792
d_asthma									0.556	0.000	0.362	0.750
d_ihd									0.701	0.000	0.346	1.056
d_hf									0.124	0.611	-0.354	0.602
d_arthritis									0.222	0.125	-0.062	0.505
d_chronicpain									1.047	0.000	0.951	1.142

The difference in mean weekly costs per person, associated with Sleepio rollout is saving £0.097 at week 65 which corresponds to yearly saving of £5.53 (weeks from 65 to 117). The results of our preferred model show that the absolute difference in mean weekly costs per person, associated with Sleepio rollout, is a saving of £0.16 at week 65. This corresponds to £6.64 per person over the 65-week follow-up period, including the initial rollout period. The 95% confidence interval for this estimate is a saving of between £4.60 and £8.67. In conclusion the addition of the individual patient level, seasonal adjustment and relevant comorbidities did not change significantly the result of the Sampson et al 2021 paper.

Since the modifications to the Sampson et al paper that the EAC carried out, do not change the conclusion of the Sampson et al paper significantly, we propose to continue to use the 2 level GLM to perform the Health Economics analysis. There are additional models that may be explored that can forecast data ranges based on inputs from a specified time series that would avoid the need to include 3 levels and a much reduced computational time but further exploration is outwith the remit of this evaluation project.

4.2 Revision of Cost Modelling requested by NICE.

The company submitted a simple one-stage decision tree model for the evaluation. The parameters of the model were based on the Sampson et al. 2021 paper. The EAC revised some of the parameters but did not change the structure of the model. The model includes a simple one-stage decision tree using remission status after treatment initiation. However, costs are not a function of remission status and hence, the decision tree model plays no role in the analysis of costs. The model compares Sleepio to 2 comparators: treatment as usual, which includes sleep hygiene and sleep medication; and face-to-face CBT for insomnia. Remission from insomnia in the treatment group receiving Sleepio is assumed to be 53.9% in the base case. The

source of this estimate is Cheng et al. 2019, which is the only study that reports remission rates for Sleepio across a sample potentially generalisable to the whole treated population. Using the 95% confidence interval, a best case (59.1%) and worst case (48.7%) is also used. The EAC notes that Cheng et al. (2019) includes patients with insomnia and depression. Given that there is no other evidence related to remission, this estimate is considered reasonable by the EAC. However, the EAC notes that cost savings are not estimated as a function of remission status in the company model. The percentage of patients experiencing post-treatment remission from insomnia for the first comparator (treatment as usual sleep hygiene) is estimated to be 14.0% and used in the base case (Cheng et al. 2019). Using the 95% interval, a best case (17.6%) and worst case (10.4%) is also used. As above, the EAC notes that Cheng et al. 2019 study includes patients with insomnia and depression. Given that there is no other evidence related to remission, this estimate is considered reasonable by the EAC. Again, the EAC notes that remission status is not used to estimate costs. The company's economic analysis estimates the overall cost of providing access to Sleepio to a large population of patients. Technology costs are a function of the total population size. Access to Sleepio is assumed to reduce primary care costs in patients accessing it. The size of the reduction in annual costs and the proportion of patients accessing Sleepio are based on data from Sampson et al. 2021. Sampson et al. 2021 reports the overall impact on primary care costs of providing access to Sleepio for a cohort of patients identified from records as potentially suffering from insomnia. The study does not differentiate resource use and cost implications according to rates of uptake and engagement, or in relation to remission status. The analysis includes the cost of the technology and comparators and the changes in primary care resource use costs (based on Sampson et al 2021) extrapolated over a 3-year time horizon. Given these issues, the EAC felt that the model structure appropriate for this assessment should be based on uptake rates for Sleepio users and include the cost savings as applied by Sampson et al analysis. It is not possible to segregate the cost savings for Sleepio users according to remission status.

The EAC has access to the EMIS/Sleepio data to check if cost savings could be segregated according to remission status. With the review of the EMIS data and communication with the company, the EAC concludes that it is not possible to

calculate a meaningful estimate of cost savings by remission status from the EMIS data for the following reasons:

- The study design is not suited to this question.
    - Accurate identification of resource use differences by remission status would require an entirely different study design. EMIS data relies on population rollout as the treatment (not individual use of Sleepio) and a quasi-experimental design (without randomisation). The likelihood of remission in our sample would very likely be related to an individual's propensity to use Sleepio and the observed effect would be biased as a result
- Remission status, resource use, and Sleepio use cannot be reliably linked at the individual level.
    - In order to observe a (biased) estimate of resource use according to remission status, it would be necessary to link remission status to Sleepio use in the company's data. It is not possible to do this reliably. Resource use is observed in the primary care (EMIS) data, while remission status would be most reliably observed in data from Sleepio. These cannot be linked. Furthermore, Sleepio use is not reliably observed in the primary care data set.
    - The only option for identifying remission status in the primary care data would be to observe the presence (or absence) of insomnia diagnosis. However, we believe this to be a highly unreliable indicator for remission. Furthermore, it would rely on an unreliable indicator for Sleepio use (GP referral).

In the absence of matched EMIS and Sleepio data, it would be inappropriate to apply an assumption for the proportion of patients in Sampson et al. 2021 who remitted (using real-world Sleepio data outside the study cohort). There is high variability in the cost associated with patients living with insomnia, due to variation comorbidities and the management of insomnia in primary care:

    - Some patients living with insomnia may have one or multiple comorbidities that impact the cost associated with their care. Therefore,

the cost impact of Sleepio will differ based on the impact remission (or non-remission) has on these comorbidities.

- Some patients living with insomnia will receive repeat prescription medication, while others will receive sleep hygiene only. Some may visit their GP regularly, some may not. This varies significantly by GP practice, given the recommended treatment of CBT for insomnia is not routinely available. Therefore, the cost impact of Sleepio will differ based on the way that individual's insomnia is managed by their GP practice.

Therefore, it is not possible to assume a 'standard' cost impact of Sleepio based on remission status, since the current cost associated with them varies highly from patient to patient based on comorbidities and how their insomnia is currently managed.

4.2.1 Big Health Data

The available dataset on Sleepio users contained information on 29,904 patients. From the data available to KiTEC, we were not able to derive any descriptive statistics describing group of Sleepio users in terms of their socio-demographic characteristics. The available data shows only times at which given user took part in subsequent Sleepio sessions and what was their score on Sleepio Condition Indicator 2 (SCI-2) which are summarized below. The SCI-2 is a 2-item version of the commonly used SCI-8 score. This is a clinically validated measure (Luik et al. 2019) of insomnia and provides a score of 0-10 for each user. A score of 2.50 or lower is considered to be indicative of insomnia, so those who begin with an SCI-2 score of less than 2.5 and then later have a score of greater than 2.5 are considered to be in remission.

Missing data

The data available shows that out of 29,904 registered users, only 14,363 (48%) patients took part in session 1, 6,220 (21%) in session 2, 3,734 (12%) in session 3 and 2,649 (9%), 2,140 (7%), 1,783 (6%) in sessions 4, 5 and 6, respectively. This increasing drop-out rate may occur due to an improvement in symptoms, or due to

the user finding it ineffective. The available data does not enable us to disentangle this issue.

Descriptive statistics for Sleepio scores (SCI)

Having this in mind and being aware there are a lot of missing data, we could, however, summarize the Sleepio scores across sessions. The EAC extracted some basic descriptive statistics of the Sleepio score distributions across sessions.
The descriptive statistics presented in Table 8 below show that among users taking part in baseline session 43% had a score equal or larger to 2.50 threshold (57% with insomnia). Among the constant users of Sleepio (those who used it at least twice) there is a clear upward trend on Sleepio scores indicating there is a remission of insomnia in time. And this percentage systematically grew up over the subsequent sessions to the levels 63%, 77%, 83%, 89% and 92% for session 2 through 6, respectively. This might suggest high effectiveness of Sleepio application. On the other hand, it also deserves some consideration whether the value of 2.50 is indeed the best threshold for discriminating between people experiencing insomnia and those in remission.

In available data, the means on Sleepio scores are systematically growing from 2.07 (95% CI: 2.05-2.09) at baseline session to 6.24 (95% CI: 6.11-6.38) in the sixth session. Even if we try to summarise the trend in different way for example by comparing baseline measures with the last available measurement (4.53 95%CI: 4.45-4.60) or the 12th week follow-up post-test (4.93 95%CI: 4.76-5.10) the conclusion about the upward trend remains the same. However, these values are now clearly lower.

It is also worth noticing the dispersion of the result is also growing with each subsequent session. That might indicate that not every patient using Sleepio application is following the same path. There might be some different groups of users who follow different trajectories. For this reason, we decided to apply a longitudinal latent class analysis (LLCA) to explore this question more thoroughly.

Table 5A: Sleepio scores across sessions.

	Baseline (OstSCI2)		Session 2 (S2SCI2)		Session3 (S3SCI2)		Session4 (S4SCI2)		Session5 (S5SCI2)		Session6 (S6SCI2)		Latest available session (latestSCI2)		Week12 Posttest (Wk12PostTestSCI2)	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%
insomnia(SCI<2.50)	17,049	57.28	2,202	37	834	23.22	441	17.17	224	10.7	147	8.45	1,595	24.14	331	23.51
remission (SCI 2.50+)	12,716	42.72	3,725	62.85	2,757	76.78	2,128	82.83	1,869	89.3	1,593	91.55	5,013	75.86	1,077	76.49

Table 5B: Sleepio scores across sessions among those patients who had insomnia (SCI<2.50) at baseline.

	Session 2 (S2SCI2)		Session3 (S3SCI2)		Session4 (S4SCI2)		Session5 (S5SCI2)		Session6 (S6SCI2)		Latest available session (latestSCI2)		Week12 Posttest (Wk12PostTestSCI2)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
insomnia(SCI<2.50)	1,871	48.92	725	31.52	378	23.41	204	15.41	126	11.6	7	21.21	278	34.24
remission (SCI 2.50+)	1,954	51.08	1,575	68.48	1,237	76.59	1,120	84.59	960	88.4	26	78.79	534	65.76

Table 6: Means for Sleepio scores across session

		95% CI		
	mean (SD) on SCI scale (0-10)	lower bound	upper bound	N
Baseline	2.07 (2.17)	2.05	2.09	29,765
session2	3.14 (2.47)	3.07	3.20	5,927
session3	4.18 (2.71)	4.10	4.27	3,591
session4	5.11 (2.96)	4.99	5.22	2,569
session5	5.79 (2.89)	5.67	5.92	2,093
session6	6.24 (2.87)	6.11	6.38	1,740
latest available session	4.53 (3.04)	4.45	4.60	6,608
wk12 posttest	4.93 (3.24)	4.76	5.10	1,408

4.2.2. Results of Longitudinal Latent Class Analysis (LCA)

In order to identify trajectories describing the process of recovery from insomnia among Sleepio users, the EAC used a Longitudinal Latent Class Analysis (LLCA2) model, which is a member of wider family of statistical models called mixture models.

Despite being highly diverse, all mixture models are based on a common assumption. A set of observed cases consists of the composition of multiple subsets (classes or subpopulations) and membership of each observation in any subgroup can be modelled probabilistically. From the methodological point of view, mixture models are latent variable models with categorical underlying variables (unobserved) and indicator variables (observed / manifest variables) being either continuous or categorical. Latent Class Analysis (LCA) is a part of that latter group of models (with categorical indicators). The LCA model has been conceived and widely used for cross-sectional settings (data at one time point on several indicators). In recent decades, it has been applied successfully to longitudinal data as an instrument for identification of distinct subgroups of cases with similar patterns of change across discrete time points. In that version, the series of time points is used as a vector of indicators of latent variables. LCA applied this way is referred to in the literature as LLCA, or sometimes also Repeated Measures Latent Class Analysis (RMLCA) (Collins & Lanza, 2010). The results of these analyses are latent classes of which each is exhibiting specific trajectory over time.

This analysis was conducted on the dataset consisting of Sleepio users who participated in at least 3 sessions. There were 3,617 (12%) such patients. For this analysis the original Sleepio scores were dichotomized according to the threshold of 2.50, used as a clinical indicator of insomnia. Sleepio scores below this threshold were recoded as 0 and scores of 2.50 or above recoded to 1.

[2] Also known as a repeated-measures latent class analysis (RMLCA) (Colins & Lanza, 2010)

Overall, in LLCA, the EAC estimated models distinguishing from 1 (null model) up to 5 classes following different trajectories on Sleepio scores. To assess the quality of each model and to decide on final solution with given number of classes we used Bayesian-Schwarz Information Criteria (BIC), likelihood ratios, and entropy. We also considered the criteria of interpretability of the results.

The results of LLCA show that a model containing 4 classes of Sleepio users had reasonable fit to the data and an interpretable pattern of changes across time. The main part of results for each distinguished group of patients show probabilities of being in remission (SCI-2 score > 2.50) at each session. Every class shows a different pattern. Below are the main characteristics of each class described and presented schematically in Figure 2.

Class 1: Quick remission group (56%). This is the largest group of Sleepio users. The pattern for their Sleepio scores indicates that their baseline probabilities for remission status are relatively high (above 0.5) and this probability is growing very quickly to 0.9 and above.
Class 2: Slow remission group (30%). The trajectory of this group shows that their baseline status is most likely in insomnia and from this point we can observe systematic improvement towards remission.
Class 3: Relapsing group (6%). Among this group of Sleepio users the pattern is quite specific. Namely, at the first session the probability of remission status grows very quickly and next, from session 3 it starts falling down towards lower levels.
Class 4: Ineffective therapy (9%). This group of Sleepio users have relatively low level of probability of being in remission over all timepoints.
With the current dataset we are not able to provide any information on the profile (sociodemographic characteristics) of the distinguished groups/classes.

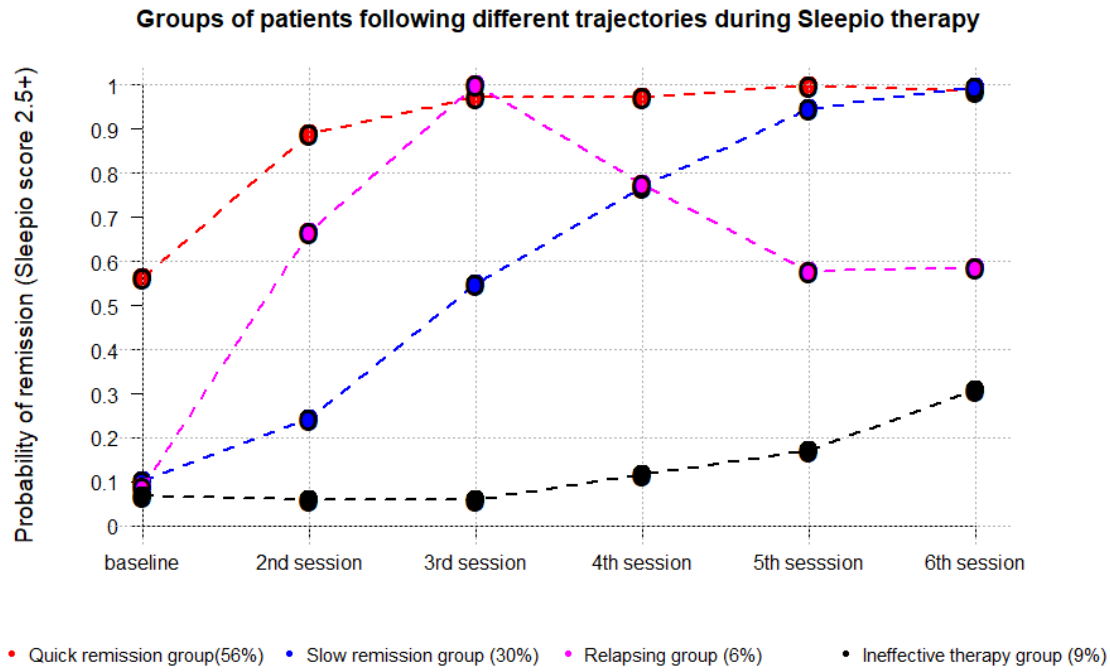

Figure 2: LLCA results showing distinct groups of Sleepio users following different trajectories across time.

The exact results of this analysis are provided in Supplementary material at the end of this document.

4.2.3. Sleepio sessions and Drop-outs in the Literature

Several questions were posed to the EAC regarding the drop-out rate that was seen in the data provided by Big Health.

1. *Does Sleepio reflect standard CBT-I approach (2 introductory sessions and then move to sleep restriction) or is it a combination of sleep hygiene and CBT-I?*

There are 6 Sleepio sessions, similar to some CBT-I programmes. The initial sessions are structured as follows:

- Session 1: Formulation, goal setting, diary keeping, motivational contract. Aim - Identify the cause of poor sleep and set goals for the programme.
- Session 2: Sleep hygiene (lifestyle & bedroom), progressive relaxation, thought checker. Aim - Learn to optimise the daytime for sleep

- Session 3: Sleep hygiene (schedule), stimulus control, sleep restriction. Aim - Boost the connection between bed and sleep.

The remaining sessions differ based on priorities.
This suggests that the early sessions do not only include sleep hygiene advice and also have CBT-I elements like goal setting and diary keeping. There is also access to the Sleepio community and compatibility with fitness trackers that suggest the early sessions are more than just sleep hygiene advice, that would otherwise be given in primary care.

2. *Are the Sleepio dropout rates similar to face-to-face CBT-I for people with insomnia?*

This cannot be ascertained from the Sleepio literature, as it has not been compared directly with face-to-face CBT-I. One comparison with Treatment as Usual (TAU) in university students (which is not adequately described in the paper), was reported in Freeman et al. 2017. They report that "the dropout from the study assessments was high (50%) during the course of the study and was greater in the treatment group than in the control group".
Van Ballegooijen et al. 2014, performed a meta-analysis of adherence to online iCBT and Face-to-face CBT for depression, and "did not find studies that compared guided iCBT and face-to-face CBT in a single trial. Adherence to guided iCBT appears to be adequate and could be equal to adherence to face-to-face CBT". Again, it is unclear how comparable these results are to Sleepio and insomnia but suggests that this information is not available in the current literature for depression (and therefore may not be available in insomnia literature, which is considerably scarcer in general).

Lancee et al. 2016 compared online and face-to-face CBT for Insomnia (not Sleepio, however). They reported that "In the online condition… 22 (73.3%) participants completed at least four sessions (which has previously been described as an adequate dose of this intervention, and 15 participants (50.0%) completed all six sessions. In the face-to-face condition… 28 participants (93.3%) attended at least four sessions, with 21 (70.0%) attending all six sessions. The completion rates did not significantly differ between the online and face-to-face conditions, four session: $\chi 2$ (1) = 4.32; P

= 0.08; all sessions: χ2 (1) = 2.50; P = 0.19". This is probably the most reliable example, as while it is not Sleepio, it is an online CBT programme for insomnia. The results suggest that, here, dropout rates were lower for face-to-face CBT but not significantly so. However, the dropout rates in the online CBT arm were also much lower than has been observed in Sleepio.

3. *Are there estimates for the remission rates for patients with (1) insomnia and (2) insomnia symptoms?*

No, Cheng et al. 2019 report remission rates but all included participants were self-reported insomnia based on DSM-5.

4. *Are there estimates for the dropout rates for patients with (1) insomnia and (2) insomnia symptoms?*

No, similarly, all papers that report drop-outs in the literature recruited patients with diagnoses of insomnia. Freeman et al. 2017 included participants with insomnia based on SCI-8. In the intervention group, 1302 participants (69%) logged on for at least one treatment session, 953 (50%) accessed at least two sessions, 672 (36%) accessed at least three sessions, 497 (26%) accessed at least four sessions, 390 (21%) accessed at least five sessions, and 331 (18%) accessed six sessions." – therefore, 61% completed ≥4 Sleepio sessions. Espie et al. 2019 included patients with self-reported insomnia based on DSM-5 or SCI-8. 58% of participants completed ≥4 Sleepio sessions. These estimates are significantly higher than what can be seen in the Big Health data presented above, likely due to the fact that these participants were part of an active research study. Unfortunately, we cannot segregate between those with insomnia symptoms and those with clinical diagnoses. However, we can see from Freeman 2017 and Espie 2019, that a similar number completed session 4.

4.3. Exploration of Patient Pathways

NICE would like the EAC to explore if the model could be revised to better reflect the likely patient pathways and outcomes if the technology is made available across regions. For example, it may be possible to consider the different patient cohorts: GP referrals and self-referrals separately. In addition, using the more detailed patient-level data, costs associated with particular groups of patients could be included e.g. patients with co-morbidities, those who have prescription drugs for insomnia. The EAC can also explore if it would be helpful to include outcomes from either the literature or the data held by the company. The committee also had a discussion about potential barriers to uptake in areas of lower socio-economic status. The EAC could explore if there is any information available about this in the Thames valley data or in other data available from the company.

Neither the EMIS dataset nor Sleepio data set contains data that supports this analysis based on pathways, comorbidities or socio-economic status. On communication with the company whether such an analysis is possible, they responded with the following:

- The Sampson et al. study looked at EMIS data on GP referrals only (i.e. the number of patients coded as having been referred to the programme by their GP). It was not designed to segregate the analysis according to referral channel (e.g. GP referral vs. self-referral etc.)
- [# patients coded as a GP referral] is not equal to [# patients that started Sleepio after a GP referral]. For example, a patient coded as a GP referral in EMIS might go home and forget / choose not to start the programme
- Sampson et al. used patient-entered data captured in the Sleepio programme to estimate how many patients started CBT with Sleepio through different referral channels within the study cohort. This data cannot be linked definitively to the EMIS dataset so is not suitable for inclusion here
- Therefore, it is not possible to segregate the analysis of EMIS data by referral channel

- The Sleepio data do not specifically report the referral channels. The only variable available is the registered user reporting how they 'heard about sleepio', which is not same as referrals.

4.4. Economic analysis (Scotland pricing model)

Sleepio is provided to NHS systems in a block funding model, whereby the system pays a fixed price per adult **per year** in their population to cover unlimited access to Sleepio. The pricing table below shows the price per adult charged at different population sizes.

Table 7: Sleepio pricing model in company submission

Number of adults in the NHS system population	**Price per adult p.a.**
0 - 250,000	£1.00
250,001 - 500,000	£0.98
500,001 - 750,000	£0.96
750,001 - 1,000,000	£0.93
1,000,001 +	£0.90

In the revised economic model, for a population of 2,400,000, the price used was £0.90 (total cost £2,160,000) and the cost savings in Table 1 and 2 were reported. Sensitivity analysis also showed that Sleepio becomes cost saving when the cost of Sleepio per head falls to £0.78. The company now has a slightly different pricing model followed in Scotland, where contracts are designed around anticipated annual treatment volumes. Overall price is calculated based on the tiered pricing model (table 11) below, where treatment reduces in price as volume increases and these treatment tiers are accretive, e.g. 1100 patients will be calculated as (1000*£80) + (100*£70) = £87,000.

Number of treated patients	Price per patient treated.
1 - 1,000	£80
1,001 -5,000	£70
5,001 -10,000	£65
10,001 -15,000	£60
15,001 -	To be negotiated

Table 8: Treatment tiers and pricing model used in Scotland

The EAC used this pricing model on the revised economic analysis (table 9) and the results are reported below.

Table 9: EAC's estimated cost savings – Scotland model

EAC	Technology costs	Primary care cost savings (Year 1)	Primary care cost savings (Year 2 &3)	Sleepio cost savings (1year)	Sleepio cost savings (3years)
Sleepio	£66.11	£49.52	£85.56		
TAU	£0	£0	£0	-£16.59	£68.97
CBT	£542	£49.52	£85.56	£475.89	

For a population of 2,400,000, with an uptake rate of 0.58% (13,920), the total annual cost is £920,200. With the Scotland pricing model, Sleepio is cost saving when compared to usual care (£68.97) and face to face CBT (£475.89). The cost savings conclusion has changed because the consumables cost has reduced from £155.17 to £66.11 per patient. The difference is because the Scottish model is based on treated patients and in the submission, the company has used a block funding model.

5. Conclusions

The EAC performed an independent analysis of the data reported in Sampson et al 2021 and were able to reproduce their results concluding that the results as reported are robust. The EAC also carried out several extended statistical analyses to explore the appropriateness of the model used and inclusion of various clinical and demographic data as confounders in the model, as requested by the panel. The extended analysis was able to show that the choice of a 2-level GLM assuming a Gaussian distribution that doesn't include the individual patient effects and with the inclusion of the confounding variables (i.e. Sampson et al 2021) is an appropriate model to use when performing health economic analysis for this technology.

In an analysis of 29,904 patients included in a Big Health dataset, the EAC investigated remission status after each session but noted that there was a lot of missing data and any conclusions should be made with caution. The EAC used an LLCA and classified Sleepio users into 4 classes: quick remission (56%), slow remission (30%), relapsing (6%) and ineffective therapy (9%). With current data, the EAC are unable to provide any information on the patient characteristics of these groups.

Finally, the company provided an alternative pricing model based on patients treated, such as in Scotland, Sleepio becomes cost saving compared to usual care (£68.97) and face to face CBT (£475.90).

In summary, Sleepio is cost saving when pricing is based on treated patients rather than population-based block funding.

6 References

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JM Wooldridge, 1999, Distribution-free estimation of some nonlinear panel data models, Journal of Econometrics 90 (1), 77-97

7. Supplementary materials

As the graphical representation of the time series from suggested the upward trend, the EAC began from testing whether the time series should include this trend. Specifically, we tested whether the process can be modelled as random-walk, with or without drift. In other words, we started by the testing the general model, not assuming anything is constant, and the trend parameters were both non-restricted. The resulting p-value for the test <0.001, suggesting that the time-series is stationary for these settings. However, the regression results associated with this test showed that the trend parameter in the model appears not to have significant impact on the series. Therefore, in the next step we have used the same test but without the trend (testing for random walk with drift; the model included restriction on the trend parameter to equal zero). The results of the regression for this test are shown in Table S2. The p-value for the test <0.001 suggesting the model is not unit root. Finally, we also wanted to investigate whether it would be reasonable to assume the process can be regarded as random walk without the drift (both trend and constant parameters restricted to zero). The results of a Dickey-Fuller test with such specifications are presented in Table S3 and suggest the model without constant and trend would not be an appropriate solution.

Table S1: Assessment of normality

Mean	23.04
Standard Deviation	4.09
Skewness	-1.41
Kurtosis	6.87

NB: As the distribution was slightly left skewed, this was deemed negligible. The kurtosis parameter indicated a leptokurtic distribution.

Table S2: Random walk, with or without drift.

D.pccosts	Coef.	Std. Err.	t	P	[95% Conf.	Interval]

Pccosts L1.	-0.867	0.099	-8.750	0.000	-1.064	-0.671
_trend	0.022	0.011	1.890	0.062	-0.001	0.044
_cons	18.686	2.237	8.350	0.000	14.253	23.120
Dickey-Fuller test for unit root	Test statistic Z(t)			P		
	-8.751			<0.001		

Table S3: Random walk, with drift

D.pccosts	Coef.	Std. Err.	t	P	[95% Conf.	Interval]
Pccosts L1.	-.814	.096	-8.47	0.000	-1.004	-.623
_cons	18.722	2.262	8.27	0.000	14.237	23.208
Dickey-Fuller test for unit root	Test statistic Z(t)			P		
	-8.466			<0.001		

Table S4: Random walk, without drift

D.pccosts	Coef.	Std. Err.	T	P	[95% Conf.	Interval]
Pccosts L1.	-.029	.019	-1.46	0.146	-.068	.010
Dickey-Fuller test for unit root	Test statistic Z(t)					
	-1.465					

GLM exploratory analyses conducted on a sub-set of the original data

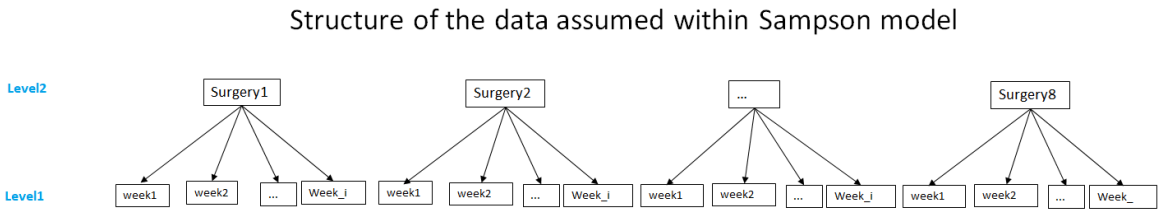


Figure 1. Data structure assumed in Sampson et al. 2021 Note that level 1 is the weekly costs and level 2 each of the GP surgeries

The panel review raised the issue as to the appropriateness of the link function[3] and error distribution in the GLM model that Sampson et al have used. The authors describe clearly in their paper, that the choice of these assumptions were as a result of the application of the modified Park's and link tests that helped to decide on specific form of the model, a commonly accepted and applied strategy.

The outcome variable in the Sampson et al. model is cost per individual patient recorded weekly, however, this maybe an over simplification and excludes a number of alternative models available under the GLM framework. The first excluded characterisation of the data is related to the range of possible values of the cost variable, namely, it is left side restricted and the possible values are only non-negative. Another characteristic is that the variable is continuous. Third is the fact that empirical distribution of costs tends to be skewed towards the right (a lot of observations cumulated at lower levels and "long-tail" consisting of a low number of observations with large and very large values). Related to this is the fact that the largest fraction of observations has zero values (ie. A zero-inflated distribution) which poses additional statistical complication and further restricts the number of potential options. These characteristics have consequences for statistical modelling under the GLM framework as they exclude modelling under the assumptions of classic linear model. In addition, all models for discrete data are immediately excluded. However, even after taking all of this into account their

[3] The relationship between the linear predictor and mean of the distribution function.

remains only a few theoretical options and they are all reasonably covered by Park's test which was used in the Sampson et al paper to justify their assumptions.

The panel also queried the authors' choice of confounding variables. There is no explicit description of why age, sex, diagnosis of depression/anxiety, insomnia, diabetics, hypertension, asthma, IHD, heart failure, arthritis, and chronic pain might affect the efficacy of the treatment. The inclusion or not of certain confounders could cause the direction of some of the model factors to reverse (change an increasing cost into a decreasing cost) depending on the list of other confounders present in the model, a common conseqeunce of co-linearity across multiple variables.
In order to address these points, the EAC repeated this analysis adding the effect of individual patients to the model and to investigate further the choice of confounding variables.

4.2.1 Revised time series regression model

This following section presents the results of the independent analyses prepared on the same (EMIS) data that addresses all the issues raised above.

Effect of including individual patients as an additional level

To investigate the possible bias introduced by not including the individual patients in the model a sub-sample of data was slected from the original EMIS data. Cases (patients) were sampled as clusters (with all their available weekly records for costs). This ensured that the final sample contained enough people from every surgery presented in the original data. The sample constructed that way contained 8 surgeries (level 3), 392 patients (level 2) and 46,800 weekly costs as presented in Figure S1. Although this model is now 3 levels as opposed to 2 as described in the original Sampson paper, the first level of the model remains a single weekly cost but the 2nd level now models individual patients instead of GP surgeries which are now modelled at

the 3rd level. This form of the model was checked using a Modified Park's and link test as described in the Sampson paper. The results suggested that a model assuming log-link and either a Guassian distribution or Poisson distribution are both viable options.

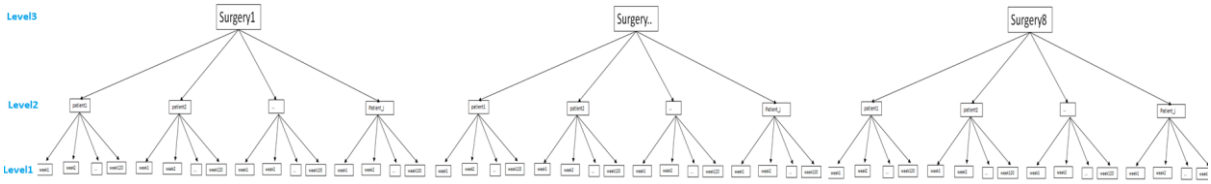


Figure S1. Corrected data structure assumed in the model below. Level 1 is still the weekly costs as used by Sampson et al 2012 but level 2 is now each patient and level 3 each GP surgery.

GLM Multi-level mModelling – Assuming a Gaussian Distribution

The first model used 3 levels with but no confounding variables. It was estimated as a baseline model in which only the decomposition of the variance between all levels was conducted. This was the initial step in understanding the effect of not including individual patients as a separate level within the model described in Sampson et al. 2021 (results are shown in Table S5). The results of the EAC analysis actually demonstrate that most variance is indeed present at the individual weekly cost level and only a small part of the variance lies at patient level with the remainder modelled at the level of GP surgeries. In conclusion then the 2 level model described by Sampson et al is robust.

The second model used 3 levels plus the 2 time-related variables and the intervention. The effect of the intervention clearly shows a decrease in weekly costs.

The third model builds on the second model by adding the confounding variables one at a time: seasonal adjustments, followed by gender and age. Contrary to Sampson's model, these confounders had little effect.
The fourth model also builds on the second model by including a series of comorbidities: depression/anxiety, insomnia, diabetics, hypertension, asthma,

IHD, heart failure, arthritis, and chronic pain. Only insomnia as a comorbidity had an effect.

Testing the validity of the models

At every stage, as new variables were added to the existing model, the LR test was conducted in order to assess whether the explanatory power of the model was increasing. For every case, the p-value associated with the LR test was significant (<0.001) confirming that adding new variables to the model was increasing the explanatory power of the model. The conclusion emerging from this very initial exploratory analysis was that all variables included in the model and their adjustment for the list of confounders were appropriate.

Limitations

While these results were conducted on a rather small sample of the original data for the purpsoes of expediency, it does mean that the data were skewed and in fact not fully matching a Gaussian distribution (while examining the residuals there was a clear tendency for some points to drift away from the assumed distribution). The EAC are confident however, that even with an expansion in the data set it would not change the conclusion that a 2 level model of this kind is justified.

Table S5. Results of GLM multi-level modelling - Gaussian distribution on a sub-set of the EMIS data

	Null model				Model1				Model2				Model3			
	coeff.	p	lower	upper	coeff.	P	lower	upper	coeff.	p	lower	upper	coeff.	p	lower	upper
cons	2.774	<0.001	2.604	2.945	2.40	<0.001	2.197	2.612	0.628	<0.001	0.006	0.015	0.734	0.003	0.256	1.212
time					0.01	<0.001	0.007	0.016	0.01	<0.001	-0.600	-0.237	0.011	0.000	0.006	0.015
intervention					-0.30	<0.001	-0.448	-0.145	-0.42	0.002	-0.012	-0.003	-0.428	0.000	-0.610	-0.246
post					-0.01	<0.001	-0.015	-0.006	-0.01	0.001	-0.373	-0.098	-0.008	0.002	-0.012	-0.003
q1									-0.24	0.065	-0.007	0.238	-0.238	0.001	-0.376	-0.100

q2									0.12	0.011	0.030	0.239	0.111	0.077	-0.012	0.235
q3									0.13	0.045	-0.437	-0.005	0.132	0.013	0.027	0.236
gender									-0.22	<0.001	0.020	0.028	-0.260	0.017	-0.473	-0.046
age									0.02	<0.001	0.123	1.134	0.023	0.000	0.019	0.027
insomnia													0.424	0.360	-0.484	1.332
variance																
level1	60487.59				60442.58				60248.64				60248.91			
Level2	0.61				0.61				0.72				0.72			
level3	0.07				0.06				0.31				0.27			
					LR test null vs model1		<0.001		LR test model1 vs model 2		<0.001		LR test model2 vs model3		<0.001	

Full results of LLCA describing all models estimated and their goodness of fit statistics.

Table S6. Goodness of fit statistics for LCA models (N=3,617 for all models).

LLCA solution	LR	df	p	χ^2	df	p	BIC	Entropy
1class (independence model)	1098.5	54	<.001	1672.9	54	<.001	18220	-
2classes	396.5	50	<.001	452.5	50	<.001	16195	0.740
3classes	117.3	43	<.001	221.7	43	<.001	15973	0.666
4classes	49.7	36	0.064	83.9	36	<.001	15963	0.664
5classes	23.72	29	0.743	43.9	29	0.037	15994	0.679

Table S7. Distribution of classes within each model

	Number of classes in model				
	1class	**2cl**	**3cl**	**4cl**	**5cl**
1-Class	100%	26%	33%	56%	54%
2-Class		74%	59%	30%	4%
3-Class			9%	6%	29%

4-Class				9%	7%
5-Class					6%

Table S8. Conditional probabilities (profiles) for every model estimated

1class solution	**Conditional probabilities of particular categories**					
1-Class solution	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.643	0.387	0.232	0.172	0.107	0.084
remission	0.357	0.613	0.768	0.828	0.893	0.916
2class solution	**Conditional probabilities of particular categories**					
1-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.939	0.87	0.716	0.548	0.374	0.285
remission	0.061	0.13	0.284	0.452	0.626	0.715
2-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.537	0.213	0.059	0.043	0.018	0.023
remission	0.463	0.787	0.941	0.957	0.982	0.977
3class solution	**Conditional probabilities of particular categories**					
1-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.897	0.743	0.426	0.237	0.084	0.044
remission	0.103	0.257	0.574	0.763	0.916	0.956
2-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.459	0.11	0.027	0.033	0.018	0.028
remission	0.541	0.89	0.973	0.967	0.982	0.972
3-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**

insomnia	0.936	0.923	0.888	0.888	0.863	0.715
remission	0.064	0.077	0.112	0.112	0.137	0.285
4class solution	**Conditional probabilities of particular categories**					
1-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.437	0.11	0.029	0.029	0.001	0.015
remission	0.563	0.89	0.971	0.971	0.999	0.985
2-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.896	0.757	0.451	0.23	0.053	0.006
remission	0.104	0.243	0.549	0.77	0.947	0.994
3-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.911	0.333	0	0.225	0.423	0.414
remission	0.089	0.667	1	0.775	0.577	0.586
4-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.933	0.941	0.939	0.882	0.83	0.692
remission	0.067	0.059	0.061	0.118	0.17	0.308
5class solution	**Conditional probabilities of particular categories**					
1-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.431	0.092	0.028	0.035	0.001	0.015
remission	0.569	0.908	0.972	0.965	0.999	0.985
2-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.932	0.23	0.002	0.251	0.447	0.481
remission	0.068	0.77	0.998	0.749	0.553	0.519
3-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.878	0.75	0.38	0.09	0.062	0.02
remission	0.122	0.25	0.62	0.91	0.938	0.98

4-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.912	0.807	0.776	1	0.318	0.085
remission	0.088	0.193	0.224	0	0.682	0.915
5-Class	**baseline**	**2session**	**3session**	**4session**	**5session**	**6session**
insomnia	0.947	0.987	0.957	0.864	0.924	0.931
remission	0.053	0.013	0.043	0.136	0.076	0.069

8. Addendum

Below are presented some additional tables and figures as requested by MTAC. The information is structured in four points each addressing specific query asked by MTAC.

Query 1: Why is the direction of co-efficients different in corresponding EAC and Sampson models?

We hypothesise that these differences possibly stem from the different nesting structures used in the analyses, as well as the different theoretical models, different specifications and estimating algorithms employed by programs used by Sampson (R, hglm2) and EAC/MG (Stata, xtpqml). So, when applying a slight change to EAC model, for example, replacing the patient ID at the 2nd level with the practice ID it results in the effect of the intervention becoming not statistically significant.

Query 2: Potentially validate model results when individual patient level is removed.

TableS9. The coefficients and corresponding p values for the EAC final model using nesting within the patient level and no nesting.

	Final model EAC without patient level				Final model EAC with patient level			
Pccosts	Model3		95%CI	95%CI	Model3		95%CI	95%CI
	coeff	p	lower	upper	coeff.	p	lower	upper
Time	0.003	0.000	0.003	0.003	0.003	0.002	0.001	0.005
[redacted]								
q1	0.121	0.000	0.120	0.122	0.121	0.000	0.069	0.173

q2	0.083	0.000	0.081	0.084	0.083	0.001	0.033	0.133
q3	0.136	0.000	0.135	0.137	0.136	0.000	0.090	0.182
d_insomnia	1.738	0.000	1.733	1.743	1.738	0.000	1.567	1.909
d_anx_dep	1.718	0.000	1.715	1.720	1.718	0.000	1.637	1.799
d_diabet	0.593	0.000	0.588	0.598	0.593	0.000	0.379	0.807
d_hyper	0.602	0.000	0.597	0.607	0.602	0.000	0.470	0.734
d_copd	0.600	0.000	0.592	0.608	0.600	0.000	0.408	0.792
d_asthma	0.556	0.000	0.550	0.562	0.556	0.000	0.362	0.750
d_ihd	0.701	0.000	0.690	0.711	0.701	0.000	0.346	1.056
[redacted]								
d_chronicpain	1.047	0.000	1.044	1.050	1.047	0.000	0.951	1.142
Cons		0.000	2.848	2.903				

Query 3: How did Sampson derive primary care cost savings for year 1, and subsequently for years 2 and 3? (Same as RIA question 3 above)

EAC took model parameters and projected costs for the whole period for two conditions: 1. Assuming there was intervention. 2. Assuming there was no intervention. Difference for every time point was assumed to be the measure of cost saving. Sums of these differences for weeks 65-117 gave costs saving for sought time periods as presented in Table2 below.

TableS10. Costs saving

Saving per patient (in £)	Sampson model	EAC model
1year (65-117w)	6.64	5.53
2year (65-169w)	13.00	11.83
3year (65-221w)	21.48	19.14

Query4: Provide visual representations of Sampson and EAC models, as well as cost saving extrapolations. (NICE has also contacted Sampson for any further visual data)

Figure S2. Costs per patient predicted from final EAC Model.

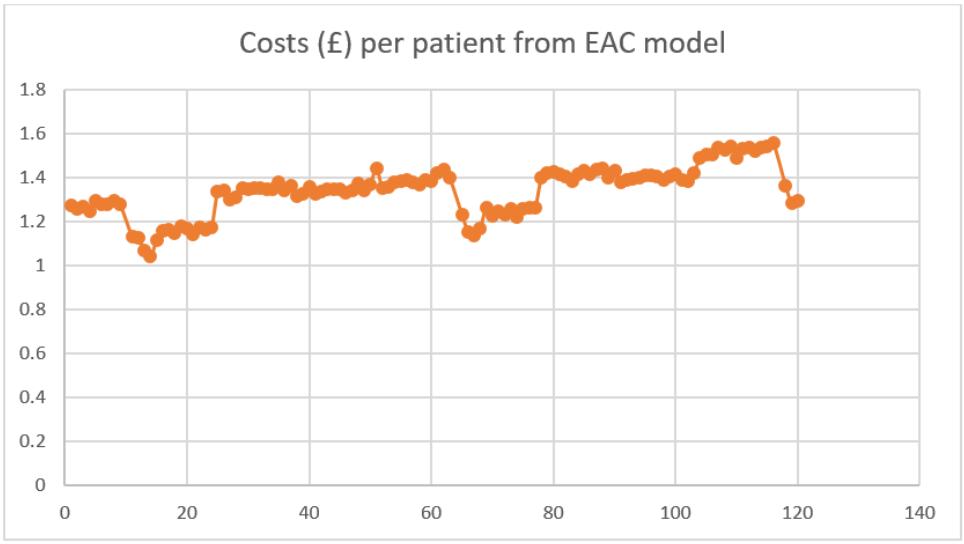


Figure S3. Projection of costs from final EAC Model. INTERVENTION.

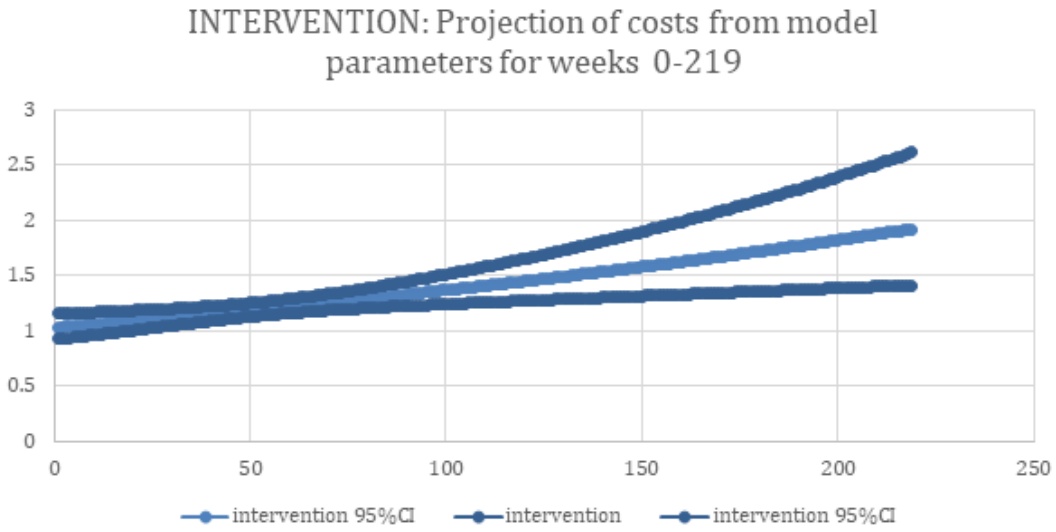
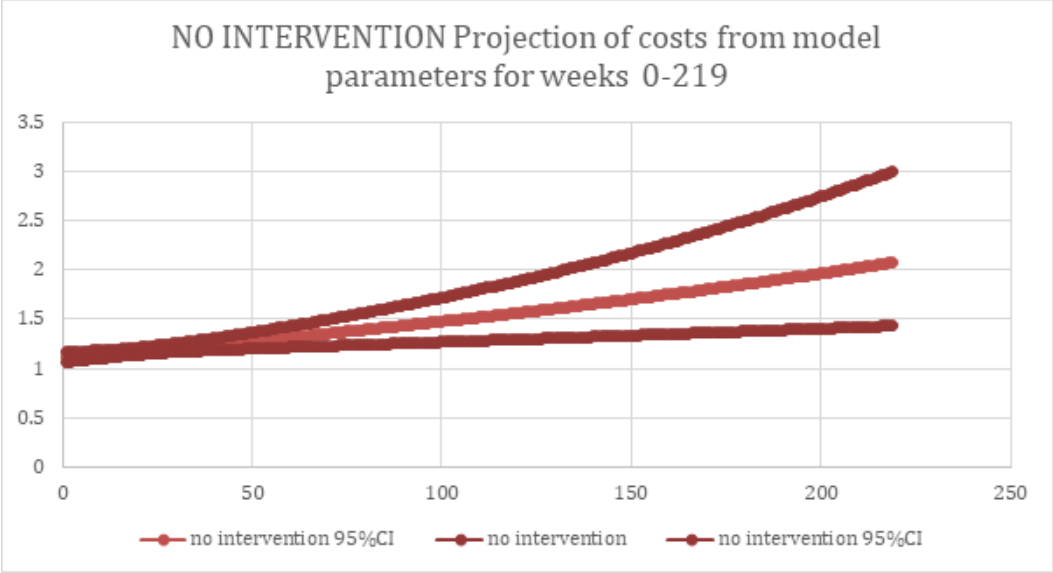
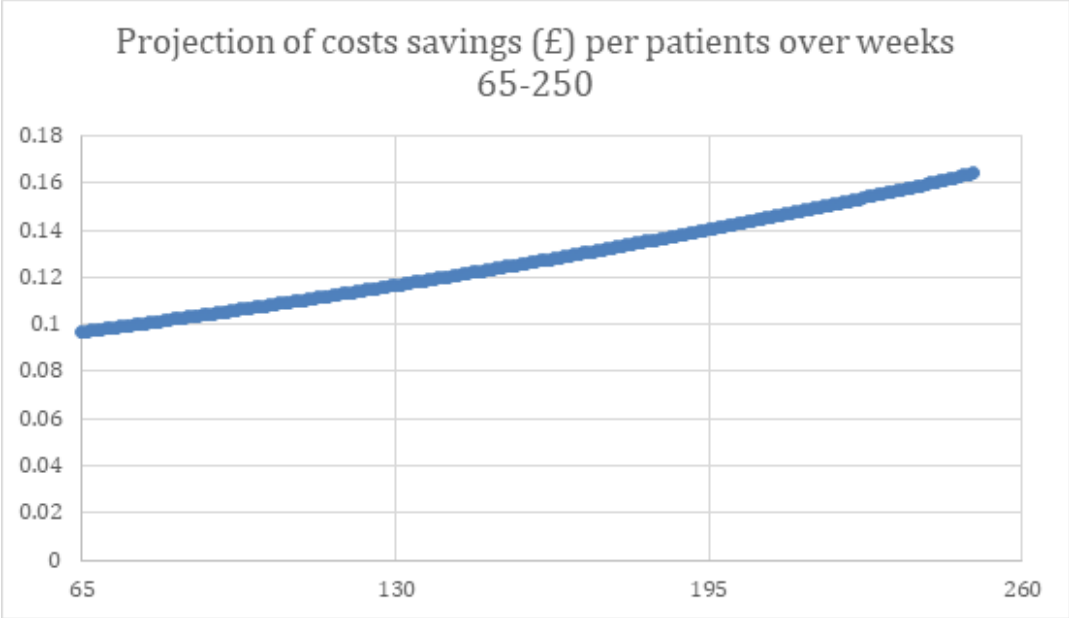


Figure S4. Projection of costs from final EAC Model. NO INTERVENTION.



FigureS5. Projections of costs saving as a difference between projections assuming intervention and lack of intervention.



Addendum to Sleepio: Extra analysis

KiTEC - King's Technology Evaluation Centre October 2021

Statistical analysis results

The statistical analysis results from the EAC were slightly different to Sampson's results (£5.53 vs £6.64). The economic model results using the EAC figure is produced for both the population and Scotland pricing model (table 1 and 2).

Table 1 : Cost savings with newer statistical estimates-population model

EAC	Technology costs	Primary care cost savings (Year 1)	Primary care cost savings (Year 2 &3)	Sleepio cost savings (1year)	Sleepio cost savings (3years)
Sleepio	£155.17	£48.00	£80.27		
TAU	£0	£0	£0	-£107.17	-£26.90
CBT	£542	£48.00	£80.27	£386.83	

Table 2 : Cost savings with newer statistical estimates-Scotland model

EAC	Technology costs	Primary care cost savings (Year 1)	Primary care cost savings (Year 2 &3)	Sleepio cost savings (1year)	Sleepio cost savings (3years)
Sleepio	£66.11	£48.00	£80.27		
TAU	£0	£0	£0	-£18.11	£62.16
CBT	£542	£48.00	£80.27	£475.89	

Threshold Analysis

Due to uncertainty with the extrapolation of 65 weeks data to 3 years, the MTAC requested a threshold analysis at year 1 for the population and Scotland model. The results of the EAC's threshold analysis at 1 year is as follows:

Population model

- Sleepio becomes cost-neutral at a price of £0.29 per population
- Sleepio becomes cost-neutral at an uptake rate of 1.82%

Scotland model

- Sleepio becomes cost-neutral at cost per Sleepio user of £49.67
- Sleepio becomes cost-neutral at an uptake rate of 0.77%

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

RX281 Sleepio economic modelling

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise) Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*
1.	29/03/2021	Company/Office of Health Economics		Please see attached: - An example data set. The data are made-up, but show all variables. The actual data set includes a little more than a million rows. - 'Term dictionary', which lists out the service use included in the service use count data.

				- 'Search Options', which lists the types of consultations included. The data are, of course, described in our preprint: https://www.medrxiv.org/content/10.1101/2021.02.15.21249646v1
2.	30/03/2021	Company/Office of Health Economics		Just chiming in to say that there is a 0% chance that the EMIS data could be linked to the Sleepio data. We don't have any individual identifiers in the EMIS data (except for IDs specific to the dataset). In fact, we don't have any individually identifiable data in EMIS at all – not even date of birth – so it would not be possible to match records on this basis.
3.	19/05/2021	Company/Office of Health Economics		Here is the analysis script relating to what we just discussed. Please bear in mind that, when I wrote this, I did not imagine that anyone would need to review it in future. My GLM script includes a lot of playing around (i.e. stuff that wasn't part of the final analysis), so I've instead attached an excerpt that just shows the main model. The costing script refers to a spreadsheet of drug costs that we prepared. I have attached that too. But note that your use of this would also mean adopting any errors that we made in preparing it!
4.	29/06/2021	Company Additional information		Ahead of our catch-up tomorrow I wanted to share a few details which may be helpful: • **Billing point:** Confirming that the billing point for Sleepio is at the start of Session 1 of the CBT programme. Individuals can take the onboarding sleep test, access the

				Sleepio community and receive light support before this point
				• **Product experience**: Linked to the above, you can use http://sleepio.com/bh2020 to get a sense of the user journey. I've also invited Dr. Dimitri Gavriloff, one of our sleep scientists, to the meeting later to answer any product or sleep related questions. Farhaan, let me know if that's come through on the Zoom invite, otherwise you can add him directly (dimitri.gavriloff@bighealth.com)
				• **Questionnaires**: patient health is measured based on the 2-item Sleep Condition Indicator (SCI-2), a short form of the SCI-8. Detail behind the usage and validation of SCI-2 can be found here and here and the flow of questionnaires asked throughout the programme is as follows:
				  ○ Onboarding: SCI-8, GAD-2, PHQ-2
				  ○ In Session (2-5) in-app: SCI-2
				  ○ In Session S6 : SCI-8, GAD-2, PHQ-2
				  ○ 8 weeks post-Onboarding to all Onboarding Sleep Test completers, via email: SCI-8, GAD-2, PHQ-2
				• **Remission rate calculation**: We evaluated the proportion of individuals with probable insomnia at registration (≤2.5 on the SCI-2) who completed session 2 and then scored >2.5 on the SCI-2, indicating remission on their last observation. We used last observation carried forward (LOCF) to account for missing data
				• **Wider impact**: please find attached a summary of Sleepio's impact in IAPT used as an adjunct to regular treatment

5.	01/07/2021	Company
		
		Additional information
				The Word doc attached contains updated data and additional context in the same format as previously supplied on 16th March 2021. I've flagged the updates in yellow in the doc. Let me know if any questions.
				
				The team also asked why we collect user responses in two post-tests (i.e. questionnaires) at two intervals after starting Sleepio. I spoke to our Clinical & Research team today and they provided the following clarification:
				
				• To clarify, two post-tests are used to capture responses from Sleepio users:
				  ○ **Post-test 1**: Session 6 of Sleepio includes Post-test 1. Users who progress to Session 6 will answer this post-test during their session. Users who do not progress to Session 6 will not answer Post-test 1
				  ○ **Post-test 2**: Therefore we also send Post-test 2 to users via email outside of the Sleepio programme (i.e. rather than within a Session). This allows us to capture clinical outcomes and feedback from users who do not complete Session 6. By sending this post-test 12 weeks after starting Sleepio, we can also capture follow-up data from users who did complete Post-test 1 (as they are likely to have finished Session 6 within c. 6 weeks)
				• Additional context
				  ○ CBT for insomnia is typically delivered in 6 to 8 sessions. Sleepio comprises 6 weekly sessions

6.	13/07/2021	Company/Office of Health Economics	I wonder if you could let us know about the following points: - why the final model in paper is not nested within patients and GPs but only within GPs. - Also wanted to confirm with you your model was fine in terms of convergence. I am trying to replicate your model in R/STATA and if I do this in both programs algorithms run into difficulties. To get the solution I had slightly change the parametrization.	Briefly, the model is not nested within patients simply because I did not have the time available to adjust my analysis such that my machine could run a model of that size. With respect to convergence, I do not recall having too many difficulties.
7.				

Insert more rows as necessary

Appendix 1.

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

RX281 Meeting KiTEC and Oxford AHSN – notes - 01.04.21

Oxford AHSN

Guy Rooney – Medical Director

James Rose - Head of Clinical Innovation Adoption

Matt Williams - Digital Health Engagement Manager

KiTEC

Jamie Erskine – Health Technology Assessor

Joanne Boudour – Project Manager

Mariusz Grzeda – Medical Statistician

Murali Radhakrishnan – Health Economics Lead

- Oxford AHSN do not own the data, this is owned by the GP surgeries, so we will need a DSA with each.
- We can amend the previous DSA's rather than starting from scratch.
- Some of the GP surgeries are part of federations so this should reduce the number of signatures required.
- After this, KCL can sign a DSA with Oxford AHSN to receive the data. We will hold the data for 6 months.

RX281 Meeting KiTEC and Office of Health Economics – notes - 08.04.21

Office of Health Economics

Chris Sampson – Principal Health Economist

KiTEC

Jamie Erskine – Health Technology Assessor

Mariusz Grzeda – Medical Statistician

Murali Radhakrishnan – Health Economics Lead

- KiTEC will require an nhs.net email address to receive the data.
- Patient ID cannot be removed but this does not relate to NHS number or other identifier, this is simply a number 1-10,000 to denote the patients in the Oxford dataset.
- The interrupted time-series analysis was used as it is impossible to tell who is referred from where from the EMIS data.
- EMIS does have diagnosis data, however.
- We may be able to explore if those using Sleepio are less likely to have a diagnosis of insomnia further down the line.

RX281 Meeting KiTEC and Big Health – notes - 15.04.21

Big Health

Will Goddard – Partnerships Manager

Charlotte Lee - UK Director

KiTEC

Jamie Erskine – Health Technology Assessor

Mariusz Grzeda – Medical Statistician

Murali Radhakrishnan Kartha – Health Economics Lead

- Several clinical insomnia scores are collected
  - SCI8
  - PHQ9
  - Various others
- They have population level remission data but not individual level.
- The referral field in the data is very loose as some users may enter that they were referred from a GP but in fact they simply saw an advert for the service on a poster in the GP surgery.

- They can send us a DSA to sign but we will need to look at the available fields and decide what analysis is possible.
- We should have a separate discussion on their pricing model after we have looked at the data.

RX281 Meeting KiTEC and Office of Health Economics – notes – 19.05.21

Office of Health Economics

Chris Sampson – Principal Health Economist

KiTEC

Mariusz Grzeda – Medical Statistician

Murali Radhakrishnan Kartha – Health Economics Lead

Joanne Boudour – Project Manager

MG - is there is a variable in which we can find the costs in the patient summary3 file.
CS – the patient summary file is just a collapsed version of the weekly summary. The weekly summary file is the data set we analysed.
MG – it is difficult to know how to model and reproduce work with the adjustments required by NICE.
CS – I can send the script that we used to do the costing, we didn't create a data set that consisted of cost data as such.
MG – could you give me an idea of which variable I should take as the intervention.
CS – we didn't analyse the data that way, the intervention is the time point. Whether or not we are in the time period that is pre rollout or post rollout. There is no variable that represents intervention.
MG – which variable can we use to distinguish the time period before and after Sleepio?
CS – in the primary analysis we didn't look at Sleepio referral as this wasn't reliable. Point of segmentation/discontinuity in the regression is week 52 and we assume a 6 week rollout period.

CS - the main input to the ITS model will be the overall time point in the data set, number of 1 to 117, depending on which week - 117 weeks, the indicator of the actual intervention period – 6 weeks, then a variable of how many weeks post intervention it is. Three time related variables that will go into the model: overall time in the model, whether it's the intervention time period and whether it's post intervention.
CS – we numbered all of the weeks 1 to 117, may all be numbered in the weekly summary file. Intervention time period will be 0, or a 1.
MG – with regard to the insomnia variable, these are not binary variables, there are more than two values. This is column M in the Excel file.
CS – the weekly summary might be binary, if there are two or three instances in that week, if somebody has had more than one contact with their GP.
CS – confirmed we will send pricing model script in R and the script used for the analysis.

RX281 Meeting KiTEC, NICE and Big Health – notes – 30.06.21

Big Health
Ushma Baros - Partnerships Manager
Will Goddard – Partnerships Manager
Dr Dimitri Gavriloff – Clinical Lead at Big Health

NICE
Rebecca Owens – Technical Analyst
Farhaan Jamadar – Technical Analyst

KiTEC
Murali Radhakrishnan Kartha – Health Economics Lead
Mariusz Grzeda – Medical Statistician
Jamie Erskine – Health Technology Assessor
Jo Boudour – Project Manager

FJ – how could the outcomes data be factored into KiTEC's analysis?
UB – in terms of outcomes, there is data for who has continued onto various sessions.
FJ – drop-off rates – how are these calculated by Big Health and how calculated by KiTEC?
WG – anecdotally our drop-off rates are similar to IAPS. The calculations are done in a similar way.

WG – for Sleepio the main clinical outcome is remission. We take the latest score as the marker. The most important outcome is remission using the SCI-2. There are more qualitative measures – increase in sleep time, improvement in how sleep affects your stress levels, relationships etc. but this doesn't really come into an analysis like this.
FS - clinical outcomes quite difficult to marry up with the data.
JE – how can we use that remission data usefully for our economic modelling?
MK – we can't use the remission data and I have highlighted this from the start. We can't do cost savings according to remission. Remission analysis has limited use in the economic model.
MK - How did you come up with threshold of 2.5?
WG – this is a remission rate calculation - 2.5 is the clinical threshold, equal to or below this figure. If there is a score of 2.5 or less, this would determine there has been remission.
UB – there are two papers that reference this threshold and these were in the email sent on 29 June 2021.
MG - confirmed we can categorise and split the data using the 2.5 threshold.
FS– session 3 and 4 are quite personalised – do outcomes differ per session?
WG – the more sessions a group completes, the higher the remission rates in the group.
FJ – follow-up 6 weeks and 12 weeks – is there a reason for choosing these follow-up time points?
WG – I think this aligns with how clinical trials were conducted but would need to check this.
MK –the Scotland pricing model is based on volume. I have applied this cost, it is much lower than an earlier pricing model. Uptake rate of 0.58% – cost saving.
FS – which model gives the best value for the NHS?
UB – The model we have used in Scotland has been received really well.
RO – is it possible to obtain an updated snapshot of the Northamptonshire and Buckinghamshire data?
RO – this does not need to be included in the draft report.
WG – we will send this by next week.