Study Title: An investigation into the efficacy of online cognitive behavioural therapy for insomnia ("Sleepio") to improve sleep after stroke.

Internal Reference Number / Short title: Improvi**n**g **s**lee**p i**n **re**habilitation after **s**troke (INSPIRES)

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Protocol summary: 30/10/2020

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Sponsor:	University of Oxford

1. SYNOPSIS

Long Study Title	An Investigation into the Efficacy of Online Cognitive Behaviour Therapy for Insomnia ("Sleepio") for Stroke Survivors	
Short Study Title (to be used on participant-facing documents, if applicable)	**I**improv**i**n**g** **s**lee**p** **i**n **re**habilitation after **s**troke (INSPIRES)	
Nature of Study Participants	Stroke survivors	
Intended number of participants	86	
Design	Randomised controlled	
Location	In the participant's home / online	
	Objectives	**Outcome Measures**
Primary	The primary objective of this study is to assess whether self-reported sleep quality in stroke survivors is improved following online Cognitive Behavioural Therapy for Insomnia ("Sleepio" programme).	The primary outcome measures for this study will be the change in Sleep Condition Indicator score following completion of the programme.
Secondary	The secondary objectives are to assess changes in measures of sleep quality and self-reported measures of quality of life and anxiety following the intervention and at 8 week follow up. To assess the cost-effectiveness of online CBT-I in stroke survivors when compared to a brochure of sleep hygiene information.	Changes in sleep fragmentation and wake after sleep onset, assessed with actigraphy, sleep onset latency assessed through the sleep diaries, anxiety and depression using the PHQ9 and GAD7, quality of life using the Stroke impact scale-8 and Euroqol-5 Dimensions- 5 Levels (EQ-5D-5L) Changes in healthcare costs during the 8-week follow up.

2. BACKGROUND AND RATIONALE

Stroke is one of the leading causes of adult disability. Current physical therapies for stroke are both limited in their success and are time demanding, with the latter factor increasing the cost of therapy. It has been reported that following stroke, many people experience issues with sleep, which has been shown to play an important role in consolidation of learning. Our current research confirms this, indicating that chronic community dwelling stroke survivors experience poorer sleep quality than age matched healthy controls.

"Sleepio" is an online Cognitive Behavioural Therapy for Insomnia (CBT-I) programme developed by researchers at the Sleep and Circadian Neuroscience Institute (SCNI), University of Oxford, to improve sleep quality. The programme takes the users through a six-week programme designed to educate the user on their sleep and to improve their sleep quality. The efficacy of this intervention has been demonstrated in people with chronic insomnia[3] but has not yet been tested in people with stroke. We have recently conducted a mixed methods feasibility study to explore stroke survivors perceptions of using the programme, and this has indicated that with some additional information provided to participants, the programme is useable in its current form. Therefore, the present study will investigate the efficacy of digital CBT-I for chronic stroke survivors.

3. STUDY DESIGN

The study will be a single-blinded randomised controlled trial involving the completion of a six-week digital CBT-I programme. Following written informed consent, participants will be posted baseline questionnaires to complete and an actigraphy monitor to record objective sleep measures for one week. After this, participants will be randomised to CBT-I or control using an online randomisation software (rando.la) with minimisation of between group differences based on age and baseline self-reported sleep quality (Sleep Condition Indicator (SCI) score). The control group will be given access to an online sleep diary to complete daily for one week. They will also be given a brochure containing sleep hygiene information. 8 weeks later they will be asked to complete the online sleep diary again for one week.

Participants allocated to Sleepio will complete daily online sleep diaries for the duration of the study and will receive weekly online CBT-I sessions as part of the programme. Both groups will complete their programmes at home.

Participants will be sent the questionnaires and actigraphy monitor again to be worn for another week immediately following completion of the programme (Sleepio) or following the 6-week sleep diary (control) and at 8 weeks follow up. At 8 weeks follow up, participants in the intervention group will also be sent a debriefing questionnaire to get feedback on the programme and the research study.

Participants allocated to the control group will be sent a web link and activation code for the Sleepio programme following completion of the 8 week follow up.

4. PARTICIPANT IDENTIFICATION AND RECRUITMENT

4.1. Study Participants

68 people who have had a stroke and want to improve their sleep.

4.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 18+ years
- > 3 months post stroke
- Interest in improving sleep
- Can understand verbal and written English well enough to engage with the programme and study procedures (with assistance from carer if needed).
- Current stable health
- Reliable access to internet
- Currently living in the U.K

4.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Serious physical health concerns necessitating surgery, scheduled in the next 5 months
- Undergoing a psychological treatment programme for insomnia (with a health professional or online)
- Pregnancy
- Uncontrolled seizures
- Untreated diagnosed obstructive sleep apnoea
- Habitual night shift, evening or rotating shift-workers
- Other serious clinical condition that may affect participation in the study

5. STUDY PROCEDURES

5.1. Recruitment

Participants will be identified through several channels, including advertising online via social media e.g. Twitter and Facebook, newspaper advertisements, relevant charity websites and by presentations at local stroke support groups and giving out leaflets (attached) at our public engagement events.

Additionally, we will re-contact participants from previous studies who have consented to being contacted about future research studies by email.

5.2. Screening and Eligibility Assessment

We will identify participant eligibility from discussion with any interested people via email or phone conversations. Through these channels we will ascertain whether participants have had a stroke and meet the inclusion criteria. If they meet these criteria and are interested in the study, we will send them a copy of the participant information sheet (PIS) and the consent form.

5.3. Informed Consent

Written versions of the Participant Information and Informed Consent will be sent to the participants. The participant will be allowed as much time as they wish to consider the information, and have the

opportunity to question the investigators, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature.

5.4. Randomisation

Participants will be randomised into the CBT-I or control group based using an online randomisation software (rando.la) with minimisation of between group differences based on baseline SCI score and age.

All participants randomised to the control group will be offered the opportunity to undergo the Sleepio programme after completion of the 8-week follow up.

5.5. Baseline Assessments

After the signed consent form has been received by the researchers, the participant will be sent the GAD-7, PHQ-9, SCI, Stroke Impact Scale-8, Stroke Efficacy questionnaire and EQ-5D-5L to complete. Participants will also receive a questionnaire asking them to recall over the last 8 weeks all the contacts they have had with the healthcare service. This will be a modified version of the Client Service Receipt Inventory (CSRI).

We will also ask them to wear an actigraphy monitor on their wrist for one week and to complete a sleep diary at the same time. We will provide them with a prepaid envelope to send the materials back.

We will also record demographic variables including; age, sex, partner status, whether they share a bed, medications, employment status and date of stroke.

5.6. Subsequent Assessments

Participants randomised to the intervention group will receive access, via web link and activation code to the digital CBT-I programme “Sleepio”. This programme will require the participant to keep a daily sleep diary and engage in weekly sessions comprising weekly CBT-I content. Participants randomised to the control group will be given access to an online sleep diary to complete for one week. They will also receive a brochure with sleep hygiene information and then will be asked to complete the online sleep diary again 8 weeks later.

During the trial, participants will be asked to keep a record, in a specially designed log book, of their contacts with the healthcare service.

Upon completion of the programme, participants will once again be sent questionnaires to complete (PHQ-9, GAD-7, SIS-8, Stroke Efficacy questionnaire and EQ-5D-5L), in addition to the wrist worn actigraphy monitor and the sleep diary to use for one week.

At 8 weeks follow up, all assessments conducted as baseline will be repeated and the intervention group will complete a debriefing feedback questionnaire.

6. Feasibility and Adverse events

6.1. Feasibility of recruitment and adherence

We will record the number of people who express an interest in participating, the number who consent and the number who complete the study as an estimate of feasibility of recruitment to the study and completion of the CBT-I programme for this population.

Where known, we will record any reason for declining to take part or withdrawal from the study.

We will also send a debriefing questionnaire to participants at the end of the study to ask for their opinions of the study and the sleep improvement programme, and whether they had any CBT-I from other sources during the course of the study.

6.2. Adverse events

We will record any adverse effects that we are notified of, regardless of group allocation.

7. Definition of End of Study

The end of study is the date of the last follow-up response of the last participant.

8. STATISTICS AND ANALYSIS

8.1. Description of Statistical Methods

The efficacy of Sleepio will be assessed by comparing the SCI scores of the intervention and control groups from baseline to immediately post-intervention, following an intention to treat analysis approach. Changes in the primary outcome measure from baseline to post-intervention will be assessed with analysis of variance (ANOVA) (or linear mixed model or non-parametric equivalents if necessary) with inclusion of baseline score as a covariate.

Secondary outcomes will be assessed with ANOVA (or linear mixed model or non-parametric equivalents if necessary). EQ-5D-5L responses will be converted into utility values using population preferences (van Hout et al., 2012) and combined with survival information to calculate Quality Adjusted Life-Years (QALYs). All resource use will be valued using 2018/19 unit costs obtained from healthcare compendiums, (Curtis and Burns 2018) NHS reference costs, (https://improvement.nhs.uk/resources/reference-costs/) and British National Formulary (https://www.bnf.org/). Costs of CBT-I will be obtained from the trial.

An incremental analysis will be performed, assessing the differences in costs between the two interventions and dividing by the difference in QALYs gained in order to generate an incremental cost-effectiveness ratio (ICER). ICERs will be estimated using an NHS perspective. The 10 000 bootstrapped pairs of incremental costs and incremental QALYs will be plotted on cost-effectiveness planes to display the uncertainty in the estimated ICER. Cost-effectiveness acceptability curves (CEACs) will be derived to display the probability of the CBT treatment being cost-effective, as the ceiling ratio for the maximum acceptable cost-effectiveness ratio varies from £0 to £85 000 per QALY gained.

8.2. The Number of Participants

68 full datasets (1:1 ratio intervention to control) are intended to be collected for this study. This is based on a power calculation using the between groups effect size estimate (d=1.2) from a previous study of digital CBT-I in people with insomnia (Espie et al., 2012). This would therefore require 24 participants in total to find an effect. However, we wish to also include people with sleep disturbance who do not meet the criteria for insomnia. Based on our open-label feasibility study for digital CBT-I in this population (Smejka et al., 2022) we anticipate that 50% of participants will not meet the criteria for insomnia, and based on that study we would anticipate a more modest effect size (d=0.7), which would require 68 participants (assuming α=0.05 and power of 80%). Allowing for approximately 25% drop out, we therefore aim to recruit 86 participants in total. This should allow us to do a subgroup analysis including only people who meet the criteria for insomnia, as well as a full group analysis.

8.3. Expenses and Benefits

Postage of study materials will be covered by the research group by sending prepaid envelopes to the participants. Participants will receive a £15 shopping voucher per assessment time-point (baseline, post-intervention and 8 weeks follow up – total £45) as reimbursement for their time to complete the questionnaires/assessments. Participants in the control group will be given free access to Sleepio after the 8 week follow up.

PARTICIPANT CONSENT FORM

Version 1 - 07/02/2020

Ethics Reference: R40803/RE001

Study Title: Improving sleep in rehabilitation after stroke (INSPIRES)

		Please initial each box
1	I confirm that I have read and understand the information sheet version _____dated _____ for the above study. I have had the opportunity to consider the information carefully, ask questions and have had these questions answered satisfactorily.	☐
2	I confirm that I am at least 18 years of age and have had a stroke. To the best of my knowledge, I do not meet any of the exclusion criteria outlined in the information sheet for this research. If this changes at a later date during study participation, I agree to notify the researchers immediately.	☐
3	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without any adverse consequences or academic penalty.	☐
4	I have been advised about the potential risks associated with taking part in this research and have taken these into consideration before consenting to participate.	☐
5	I understand that data collected during the study may be looked at by designated individuals from the University of Oxford. I give permission for these individuals to access my data.	☐
6	I understand who will have access to personal data provided, how the data will be stored and what will happen to the data at the end of the project.	☐

7	I agree for data collected in this study to be shared with other researchers, including those working outside of the UK and the EU, to be used in other research studies. I understand that any data shared will be fully anonymised so that I cannot be identified.	☐
8	I understand that any personal information I input into the Sleepio programme will be available to Big Health Ltd.	☐
9	I understand how this research will be written up and published.	☐
10	I understand that this project has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee.	☐
11	I understand how to raise a concern or make a complaint.	☐
12	I agree to take part in the study	☐

Optional: I agree for my contact details to be kept in a secure database for the purpose of contacting me about future studies. I understand that agreeing to be contacted does not oblige me to participate in future studies.

	Yes	No
	☐	☐

_____ dd / mm / yyyy