Clinical Study Protocol

Personalised Electronic Record Supported Two-Stage Observational Study of Sleep in Patients with Breast Cancer

Short title:
PERSONAL-SLEEP IN BREAST CANCER

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Protocol Version and date:
Protocol 28Sept2021 Version 1.0

RESEARCH REFERENCE NUMBERS:

Trial Registry Number and date: (EudraCT/Clinicaltrials.gov)	**NCT05093426**
IRAS Number:	**302786**
REC Number:	**21/SW/0156**
Sponsor Number:	**CLM-INS-004**
Funder Number:	**Closed Loop Medicine**

SIGNATURE PAGE:
The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:
..../...../.....

Name (please print): Dr Leanne Gardner
.....

Position:
.....

Principal Investigator:

Signature: Date:
..../...../.....

Name: (please print): Dr Anne Armstrong
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Statistician:

Signature: Date:
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II. LIST OF ABBREVIATIONS

AE	Adverse Event
BDZ	Benzodiazepine
DCR	Data Clarification Requests
CMO	Chief Medical Officer
eConsent	Electronic Consent
ePRO	Electronic Patient Reported Outcomes
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ER	Oestrogen Receptors
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HER2	Human Epidermal Growth Factor Receptor 2
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
ISI	Insomnia Severity Index
ISMS	Information Security Management System
ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
PIN	Participant Identification Number
PIS	Participant Information Sheet
PR	Progesterone Receptors
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
TMF	Trial Master File
UEQ	User Experience Questionnaire

III. STUDY SUMMARY

Study Title	Personalised Electronic Record Supported Two-Stage Observational Study of Sleep in Patients with Breast Cancer
Short Title	PERSONAL - SLEEP IN BREAST CANCER
Primary registry and trial identifying number	
Secondary identifying numbers	REC: IRAS: 302786 Sponsor Number: CLM-INS-004
Sponsor/Funder	Closed Loop Medicine
Sponsor Contact	Leanne Gardner
Co-ordinating Principal Investigator (PI)	Anne Armstrong
Countries of recruitment	United Kingdom
Conditions or focus of study	Sleep and insomnia in breast cancer
Interventions	N/A
Eligibility criteria	**Stage 1:** Inclusion criteria: To be eligible to participate in Stage 1, the following criteria must be met: 1) Age $\geq$ 18 years. 2) Informed consent to Stage 1 of the study 3) Diagnosis of Stage I, II or III breast cancer within the previous 12 months Exclusion criteria: Participants are not permitted to enrol in the study if one or more of the following criteria are met: 1. Participants who have limited or no understanding of spoken and/or written English. 2. Other diagnosis of cancer, not including basal cell carcinoma of the skin or cervical carcinoma in situ, within the previous 5 years. **Stage 2:** Inclusion criteria: To be eligible for the second stage of the study, the following criteria must be met: 1) Informed consent to Stage 2 of the study 2) Current Sleep Disturbance; a score of 8 or more on the Insomnia Severity Index. 3) History of sleep disturbance prior to the screening/baseline consultation; with beginning or worsening of sleep disturbance since breast cancer diagnosis e.g. sleep problems began or get worse with the diagnosis of breast cancer or with chemotherapy. 4) Possession of a suitable smartphone that participant can use independently. Exclusion criteria: Participants are not permitted to take part in Stage 2 if one or more of the following criteria are met: 1. Co-morbidities incompatible with study participation e.g. that result in a participant being unable to complete daily entries satisfactorily via his/her smartphone.

	2. Known and/or treated sleep apnoea 3. Regular shift work or night work (defined as >1 overnight shift per month) 4. Breast feeding
Clinical Phase	N/A
Study Design	Two-Stage Observational Study
Study Participants	Tertiary-care-based breast cancer cohort in the UK
Planned Sample Size	Plan to enrol a minimum of 285 breast cancer patients into Stage 1, with 125 of the participants expected to be eligible for Stage 2 of the study.
Observational duration	3 weeks
Study duration	<8 weeks
Planned Trial Period	5 months
Primary Objective	To assess the prevalence of insomnia in a cohort of breast cancer patients.
Secondary Objectives	1. In patients with breast cancer experiencing insomnia (defined as score of 8 or more on the Insomnia Severity Index; ISI scale), to assess the following parameters over a three-week period i) Insomnia Severity ii) Sleep efficiency iii) Quality of Life 2. To assess, at the end of the three-week assessment period, i) Compliance of data entry into the digital sleep diary ii) Feasibility and experience of patients with breast cancer to input data relating to their sleep into a mobile phone application daily iii) Safety related to using the digital sleep diary 3. To determine associations between insomnia prevalence and severity and quality of life with clinical or treatment characteristics of breast cancer patients.
Primary Outcome Measures	Prevalence of insomnia defined as the proportion of screened patients determined as having insomnia defined as a score of 8 or more on the ISI. Prevalence of insomnia will be determined by administration of the Insomnia Severity Index questionnaire to participants in Stage 1 of the study. Participants scoring 8 or above will be categorised as having insomnia.
Secondary Outcome Measures	1. In patients with breast cancer experiencing insomnia (defined as score of 8 or more on the Insomnia Severity Index; ISI scale), to assess the following parameters over a three-week period i) Proportion of patients in each Insomnia Severity category measured using the ISI ii) Sleep efficiency calculated from sleep diary entries iii) Quality of Life index values obtained from EQ-5D-5L and Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES). iv) Compliance of data entry into the digital sleep diary v) User experience and feasibility of the digital sleep diary assessed using the User Experience Questionnaire (UEQ) vi) Safety assessed by Adverse events (AEs), particularly AEs considered associated with the digital sleep diary. 2. Insomnia prevalence and severity and quality of life assessed by clinical or treatment characteristics of breast cancer patients.

IV. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organizations providing funding and/or support in kind for this trial)
Closed Loop Medicine Ltd. Babraham Research Campus Babraham Cambridge CB22 3AT Email: leanne.gardner@closedloopmedicine.com

V. ROLE OF TRIAL SPONSOR AND FUNDER

Closed Loop Medicine will be the Sponsor and funder of this study, and is responsible, in conjunction with the PI, for the design, writing the protocol, data analysis and interpretation of results.

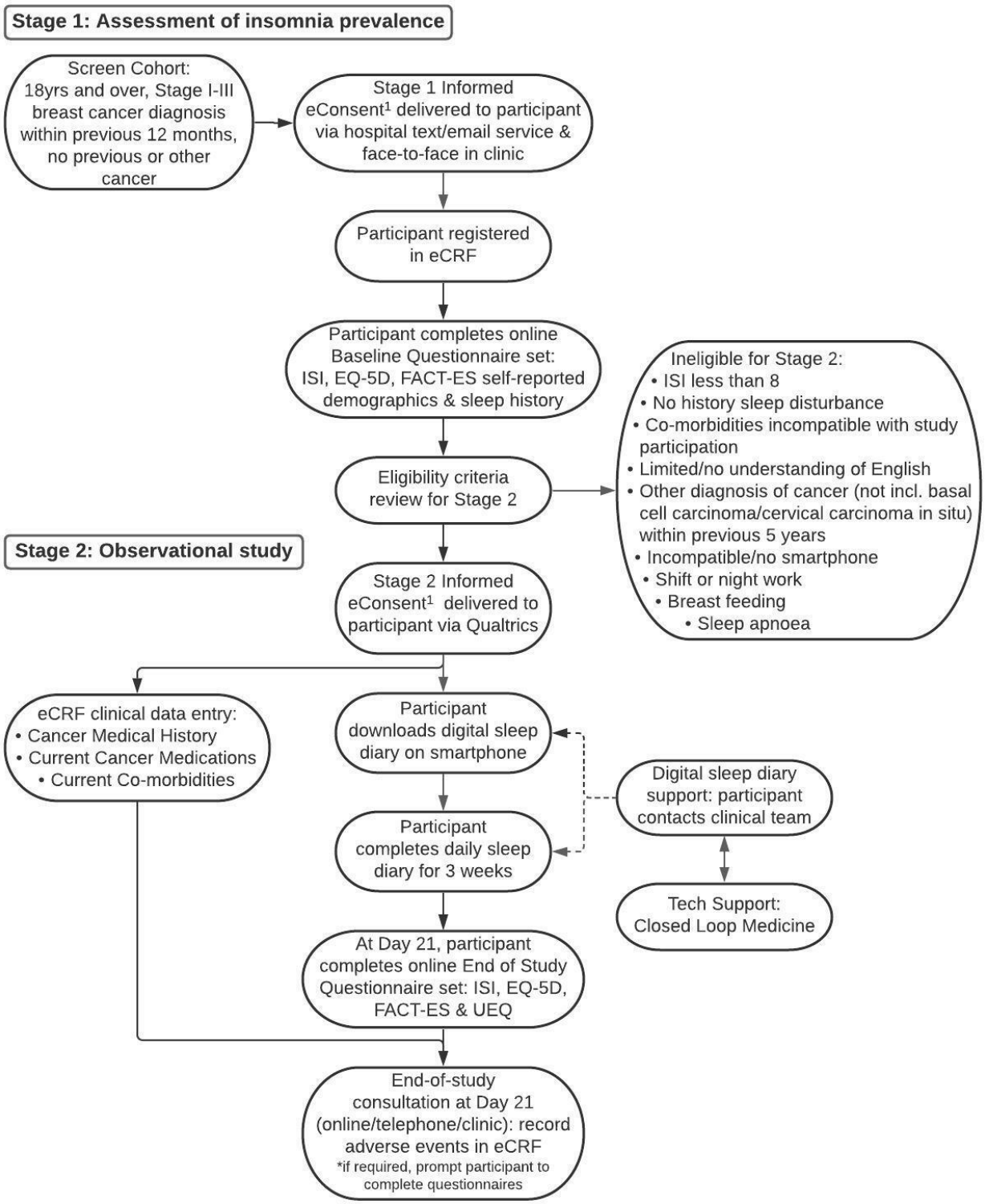
VI. ROLES AND RESPONSIBILITIES OF TRIAL MANGEMENT GROUPS AND INDIVIDUALS

Trial oversight group members will be confirmed prior to commencement of the study. Roles and responsibilities of the trial oversight group include co-ordination of the study, maintaining data quality and managing the budget. This group will meet regularly throughout the study period. The group will act where needed to ensure successful recruitment and follow up of study participants.

VII. KEYWORDS

Sleep, insomnia, breast cancer, sleep diary, prevalence.

VIII. STUDY FLOW CHART



[1]eConsent can be performed via phone, online and face-to-face under Christie onboarding. In the absence of a smartphone, tablet or computer informed consent can be performed using paper documentation.

1 INTRODUCTION AND BACKGROUND

Sleep is vital for human functioning, immunity, and well-being [1, 2]. Sleep disturbance and insomnia cause significant health problems and impact on the quality of life in a substantial proportion of the general population[1]. Insomnia, defined as difficulty initiating or maintaining sleep, is highly prevalent in primary care, more commonly affecting women, older adults, and individuals suffering from co-existing medical and psychiatric disorders [1]. Studies show incidence of insomnia to be disproportionately high in cancer patients; up to three times higher than the general population [3]. Breast cancer patients experience the highest rates, with prevalence ranging from 19% to 69% [4-10]. Further to this, up to 60% breast cancer survivors continue to suffer from sleep difficulties and associated health problems including cognitive impairment [11].

Within the UK, more than 55,000 women are diagnosed with breast cancer each year. Insomnia is one of the most commonly reported health complaints in the general population in the UK, with cancer patients being disproportionately affected by the condition[12]. The impact of insomnia on cancer patients' lives can be pronounced and is associated with many adverse psychological and physical side effects, being closely linked with depression, cancer-related fatigue, increased pain, reduced quality of life, decreased immunity, disease progression, and survival [2, 13-15]. Moreover, insomnia can dysregulate circadian rhythm, a 24-h system in part responsible for regulation of the sleep-wake cycle. Disruption in circadian rhythm is linked to worse overall health outcomes including shorter survival in cancer [16]. The treatment options for insomnia range from nonpharmacological including sleep hygiene, and cognitive behavioural interventions to pharmacological interventions such as the benzodiazepine (BDZ) group of drugs, BDZ-like drugs such as zolpidem. These drugs are associated with unwanted side effects; and there remains an unmet medical need [17, 18].

Early diagnosis and more effective breast cancer treatments have led to improved survival rates [5]. Thus, more individuals are now living with and surviving breast cancer. As the prevalence of sleeping difficulties and insomnia are significant within this population, improved insomnia treatments and increased access to these treatments is required to better the quality of the life for these individuals. However, prior to this, a better characterisation of sleeping difficulties and insomnia in patients with breast cancer is required. To date, studies in breast cancer cohorts show large variation in reported insomnia prevalence rates, as mentioned, and the type and severity of sleep complaints in these patients have been difficult to assess. This is due in part to differences in sleep disturbance definitions, types of assessment used, and length of and variation in sample characteristics. Thus, there is a need to investigate these issues further using standardised and validated measures.

The Insomnia Severity Index (ISI) is a validated self-report instrument for detection of insomnia [19]. The ISI comprises seven items which assess perceived severity of difficulties initiating sleep, staying asleep, early morning waking, satisfaction of sleep pattern, interference with daily functioning, any impairments attributable to the sleep problem, and the degree of personal distress or concern about the sleep problem [19]. The seven items are allocated a score between 1-4 and are added to give a total score. Total scores are categorised as: 0–7 no significant insomnia; 8-14 subthreshold insomnia; 15-21 clinical insomnia (moderate severity); and 22-28 clinical insomnia (severe). With relevance to this current study, the ISI has been validated for detection of insomnia in breast cancer patients and a clinical cut-off score of 8 is associated with optimal sensitivity and specificity for the detection of sleep difficulties in this population [20]. Further to this, ISI is also sensitive to therapeutic changes and as such will be invaluable for evaluating the effect of future treatments in clinical trials for insomnia in breast cancer [20].

Using validated measures, this two-stage observation study is designed to generate valuable data regarding insomnia in a tertiary-care-based breast cancer cohort in the UK. Specifically, we will assess:

- Insomnia prevalence, severity, and concurrent self-reported quality of life (Stage 1)
- Daily sleep diary including sleep efficiency and sleep quality in an eligible group of patients with insomnia (Stage 2)
- Feasibility and acceptability of self-inputting by patients of data relating to their sleep into a mobile phone application (Stage 2).

The first stage of the study will involve the assessment of insomnia prevalence in the breast cancer cohort. Eligible participants will be asked to consent to the study and complete an ISI and two Quality of Life Questionnaires (EQ-5D-5L and FACT-ES). Eligible participants experiencing insomnia will be asked to consent to the second stage of the study. In this stage, participants will be asked to keep a sleep diary and to input their sleep timings into a digital sleep diary provided as a mobile phone application (app) over a three-week period. This will replace the paper sleep diaries participants are usually asked to keep as part of a sleep study. At the end of the three-week observation period, participants will be asked to complete a User Experience Questionnaire (UEQ) to report feasibility and acceptability of the mobile phone application, repeat the ISI, EQ-5D-5L and Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES), and report any adverse events (AE) experienced.

2 RATIONALE

This two-stage observational study will generate results that provide a better understanding and characterisation of the insomnia disease burden in patients with breast cancer in the UK. It will inform future target clinical trial population definition (eligibility criteria) and inform selection of a future panel of clinical trial assessments. This study will also establish a well-defined cohort of breast cancer patients with insomnia in readiness for potential recruitment into a subsequent interventional trial.

In the long-term (outside the scope of the present study), there is interest in whether modifying melatonin could be used therapeutically to improve sleep in breast cancer patients. To date, exogenous melatonin has been reported to positively influence sleep quality in cancer patients [21]. Further to this, completion of a questionnaire to evaluate user experience of participants at conclusion of this study, will provide invaluable information regarding the ability of breast cancer patients to self-input data relating to sleep into a mobile phone application in the community setting. Using the data generated it should be possible to refine the application and optimize user acceptability and experience.

2.1 Assessment and management of risk

There are no perceived risks in for participants in this study. There are no direct benefits for patients taking part however this study is designed to generate valuable data regarding insomnia in a tertiary-care-based breast cancer cohort. Results will be used to design future clinical trials aimed at testing the efficacy of treatments for insomnia.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

To assess the prevalence of insomnia in a cohort of breast cancer patients.

3.2 Secondary objectives

1. In patients with breast cancer experiencing insomnia (defined as score of 8 or more ISI scale), to assess the following parameters over a three-week period:
    a. Insomnia Severity (ISI scale; Appendix 16.1)

   b. Sleep efficiency (sleep diary)
   c. Quality of Life (EQ-5D-5L and FACT-ES; Appendix 16.2 and 16.3)
2. To assess, at the end of the three-week assessment period, the feasibility and experience of patients with breast cancer to input data relating to their sleep into a mobile phone application daily (UEQ; Appendix 16.3).
3. To determine associations between severity of insomnia and clinical or treatment characteristics of breast cancer patients.
4. To assess safety of participants using the digital sleep diary.

3.3 Primary endpoint/outcome

Primary evaluation criteria:

i. Prevalence of insomnia in the screened cohort of patients with breast cancer; including subsidiary breakdown by breast cancer stage and type of breast cancer treatment. Prevalence of insomnia will be assessed as the proportion of screened patients determined as having insomnia according to the ISI total score (where a score of 8 or more indicates insomnia).

3.4 Secondary endpoints/outcomes

Secondary evaluation criteria:

i. Insomnia Severity (ISI): Severity of insomnia will be determined at screening/baseline (all screened patients in Stage 1 of the study) and following the 3-week observational period (all patients enrolled in Stage 2 of the study), based on the total ISI score obtained by summing the seven items to provide a score from 0-28 categorised as follows:
   - 0–7 = No clinically significant insomnia
   - 8–14 = Subthreshold insomnia
   - 15–21 = Clinical insomnia (moderate severity)
   - 22–28 = Clinical insomnia (severe)

ii. Sleep efficiency (Sleep diary): Participants' responses collected from the sleep diary will be used to calculate sleep efficiency during the observational period: Sleep efficiency =Total sleep time/Total time in bed.

iii. Quality of Life (EQ-5D-5L): Data from the EQ-5D-5L self-classifier, which includes five dimensions (mobility, self-care, daily activities, pain/discomfort, and anxiety/depression) will be used to calculate an index value as a measure of the participant's health, both at screening/baseline (all screened patients) and following the observational period (all enrolled patients).

iv. Quality of Life (FACT-ES): Data from the FACT-ES, which includes five subscale domains (physical well-being, social/family well-being, emotional well-being, functional well-being and endocrine symptom subscale), will be used to calculate an index value as a measure of the participant's health, both at screening/baseline (all screened patients) and following the observational period (all enrolled patients).

v. Compliance of data entry into the digital sleep diary: Compliance will be assessed as the proportion of participants completing the digital sleep diary on at least 17 out of 21 days.

vi. User Experience Questionnaire (UEQ): Patient experience, feedback, and satisfaction rating from use of digital diary. This will be assessed once (at the end of study), using the UEQ designed to evaluate the participant's experience of the digital sleep diary. Participants who withdraw from the study will be offered the questionnaire.

vii. Adverse events: The numbers of AEs and serious adverse events (SAEs) will be determined. Participants enrolled in Stage 2 will report AEs at the conclusion of the three-

week observational period in a telephone consultation with the clinical study team. Any relationship with the AE/SAE to the usage of the digital sleep diary will be recorded.

viii. Assessment of any associations between prevalence and severity of insomnia and quality of life with clinical or treatment characteristics of breast cancer patients. In addition to the full analysis set (all enrolled patients), analyses will be conducted on subgroups for the primary and secondary evaluation criteria i)-iii) including assessment according to breast cancer stage, treatment regime and baseline insomnia severity (ISI).

3.5 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective:		
Prevalence of insomnia in a cohort of breast cancer patients.	Proportion of screened patients with insomnia defined as a total ISI score of 8 or more.	Stage 1 assessment of insomnia severity performed at baseline via administration of the ISI.
Secondary Objectives:		
To assess insomnia severity in breast cancer patients experiencing insomnia (ISI≥8)	Proportion of participants in each ISI category of insomnia severity based on the ISI total score.	Assessment of insomnia severity will be performed at baseline/screening and day 21 via administration of the ISI.
To assess sleep efficiency in breast cancer patients experiencing insomnia (ISI≥8)	Sleep efficiency defined as total sleep time relative to total time in bed.	Sleep efficiency will be assessed via the digital sleep diary completed daily over the 3-week observation period for patients enrolled in Stage 2.
To assess quality of life in breast cancer patients experiencing insomnia (ISI≥8).	Data from the EQ-5D-5L questionnaire which includes five dimensions (mobility, self-care, daily activities, pain/discomfort, and anxiety/depression), will be used to calculate an index value as a measure of the participant's health.	Quality of life will be evaluated at baseline on all eligible participants in Stage 1 and at Day 21 on all participants enrolled in Stage 2.
To assess quality of life in breast cancer patients experiencing insomnia (ISI≥8).	Data from the FACT-ES questionnaire which includes five subscale domains (physical well-being, social/family well-being, emotional well-being, functional well-being, and endocrine symptom subscale), will be used to calculate an index value as a measure of the participant's health.	Quality of life will be evaluated at baseline on all eligible participants in Stage 1 and at Day 21 on all participants enrolled in Stage 2.
To assess compliance of data entry into the digital sleep diary.	Compliance will be assessed as the proportion of participants completing the digital sleep diary on at least 17 out of 21 days.	Compliance will be calculated for each participant completing the three-week observational period in Stage 2.
To assess the feasibility and experience of patients with breast cancer to input data relating to their sleep into a mobile phone application daily.	Feasibility and experience of patients using the digital sleep diary will be assessed using the UEQ.	Performed at Day 21 on all participants enrolled in Stage 2. Participants who withdrew from the study will be offered the questionnaire.
To assess safety of patients using the digital sleep diary.	Numbers of AEs and SAEs.	Participants will be asked to report any AEs experienced during the three-week observational period at Day 21 in a telephone consultation with the study team.
To determine associations between severity of insomnia and clinical or treatment characteristics of breast cancer patients.	Assessment of insomnia prevalence, severity, and quality of life in subgroups based on clinical/treatment characteristics including breast cancer stage, treatment regime and baseline insomnia severity.	Performed on data collected at Stage 1 and across Stage 2.

4 TRIAL DESIGN

This is a two-stage prospective observational study of insomnia in patients with breast cancer. This is designed as a remote observational study to be conducted in the community with no participant visits required to investigational site. However, there will be the option to recruit participants in-person, if required.

In the first stage of the study, eligible breast cancer patients consenting to participate will complete the ISI scale to determine prevalence of insomnia. Additional data will be collected from participants and is described in the Assessment Schedule (Table 1). Participants scoring ≥8 on the ISI, will then be assessed for eligibility to Stage 2.

Following stage 1, eligible participants will be invited to consent to taking part in Stage 2 of the study. Those consenting will be asked to download and complete a daily digital sleep diary on their smartphone over a three-week observation period. At the end of the three-week observation period, participants will be asked to complete a series of questionnaires and additional procedures as outlined in the Assessment Schedule (Table 1).

5 TRIAL SETTING

This is a single centre study to be carried out at the Christie NHS Foundation Trust. Breast cancer patients at the hospital will be screened for eligibility to the study.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

To be eligible to participate in Stage 1, the following criteria must be met:

1. Age ≥ 18 years.
2. Informed consent to Stage 1 of the study.
3. Diagnosis of Stage I, II or III Breast Cancer within the previous 12 months.

To be eligible for Stage 2 of the study, the following criteria must be met:

1. Informed consent to Stage 2 of the study.
2. Current Sleep Disturbance; a score of 8 or more on the Insomnia Severity Index.
    - Total ISI score categories: 0–7 = No clinically significant insomnia
      8–14 = Subthreshold insomnia
      15–21 = Clinical insomnia (moderate severity)
      22–28 = Clinical insomnia (severe)
3. History of sleep disturbance prior to the screening/baseline consultation; with beginning or worsening of sleep disturbance since breast cancer diagnosis e.g. sleep problems began or get worse with the diagnosis of breast cancer or with chemotherapy.
4. Possession of a suitable smartphone that participant can use independently.

6.2 Exclusion criteria

Participants are not permitted to enrol in the study if one or more of the following criteria are met:

1. Participants who have limited or no understanding of spoken and/or written English.
2. Other diagnosis of cancer, not including basal cell carcinoma of the skin or cervical carcinoma in situ, within the previous 5 years.

Participants are not permitted to take part in Stage 2 if one or more of the following criteria are met:

1. Co-morbidities incompatible with study participation e.g. that result in a participant being unable to complete daily entries satisfactorily via his/her smartphone.

2. Known and/or treated Sleep apnoea.
3. Regular shift work or night work (defined as >1 overnight shift per month)
4. Breast feeding.

6.3 Concomitant Medication

Concomitant Sleep Medication:
Participants are permitted to continue taking existing sleep medication (usage to be documented). Introduction of new sleep medication during the three-week study period is not permitted.

7 TRIAL PROCEDURES

Table 1. Assessment Schedule

	Stage 1		Stage 2			
Assessment/ Procedure	Screening (-14 days)	Day 0	Screening (-28 days)[5]	Day 0	Days 1-21	Day 21 (+8 days)
Stage 1:						
Informed Consent[1] for Stage 1 & Registration	x					
ISI[2]		x				
EQ-5D-5L[2]		x				
FACT-ES[2]		x				
Demographics[2]		x				
Sleep History[2]		x				
Stage 2:						
Informed Consent for Stage 2[1]			x			
Review Eligibility Criteria			x			
Cancer Medical History				x		
Current Cancer Treatment				x		
Current Co-Morbidities				x		
Digital Diary Download[3]				x		
Daily Sleep Diary Entry[3]					x	
ISI[2]						x
EQ-5D-5L[2]						x
FACT-ES[2]						x
UEQ[2]						x
Adverse Events[4]						x

[1] Where possible will be online remote eConsent but can be completed in clinic (online/paper).
[2] Participant completes online questionnaire (paper questionnaires will be available for clinic use).
[3] Participants completes on their own smartphone.
[4] AEs will be collected at follow-up telephone consultation at Day 21 (+8 days).
[5] Stage 2 Consent should occur no later than 28 days post Stage 1 Consent, however ideally this would occur as soon as possible after consent for Stage 1 has been provided.

7.1 Recruitment

Recruitment will take place at the Christie NHS Foundation Trust over a four-month period and is planned to end (last participant enrolled) by January 2022.

7.2 Participant identification

Stage 1 of the study will involve members of the clinical team identifying potential participants from the breast cancer clinic database at the Christie Hospital. Patient records will be used to assess inclusion and exclusion criteria to identify participants who are potentially eligible for the first stage of the study. These potentially eligible breast cancer participants will be invited to take part in the study. Recruitment will be complete when we reach the target sample size of 285 participants.

7.3 Stage 1

Participants will be recruited to Stage 1 of the study remotely and if required, in-person through attendance at the breast cancer clinic at the Christie NHS Foundation Trust.

7.3.1 Stage 1 Electronic Consent (eConsent)

Participants will be contacted by the clinical study team by text message. This text message will give some brief information about the study and an internet link to the study information including the Patient Information Sheet (PIS) and Informed Consent Form (ICF). If required, initial contact can also occur by email, telephone and/or online video conferencing. In these instances, the potentially eligible participant will be provided with the same internet link as above. Moreover, the initial contact can also be face to face in the clinic. The PIS and ICF to be used in the study will be approved by the Research Ethics Committee (REC) and follow GCP guidelines. These documents have been designed to be viewed and completed by patients on their smartphone. If required, these documents can also be accessed by a computer or tablet. Patients will be given time to consider taking part in the study and provided with contact details of the clinical study team to discuss any questions they may have regarding the study. If willing to participate, they will be asked to complete the ICF. At this stage the participant will be asked to provide their email address and mobile phone number for the purposes of sending study questionnaires and further study information. If no response has been received from potential participants within 3 days of the receiving the first text message, the initial text message will be sent again.

A proportionate approach to eConsent in guidance with the MHRA/HRA Joint Statement regarding seeking consent using electronic methods will be taken[22]. The HRA indicate that it is not necessary to include a PIS or ICF for online questionnaire-based research[23]. However, we have taken the decision to provide patients with these documents to ensure they have sufficient information to enable them to reach an informed decision to take part. As the study is observational and low risk, participants will confirm participation in the trial by simple e-signature on the ICF. Within the ICF, participants will be asked to consent to the use of their personal data for the purposes of sending online questionnaires and for the Sponsor to have access to this data for monitoring purposes. Participants will also be asked to consent to being contacted to take part in Stage 2 of the study. See Figure 1 for an outline of the eConsent process.

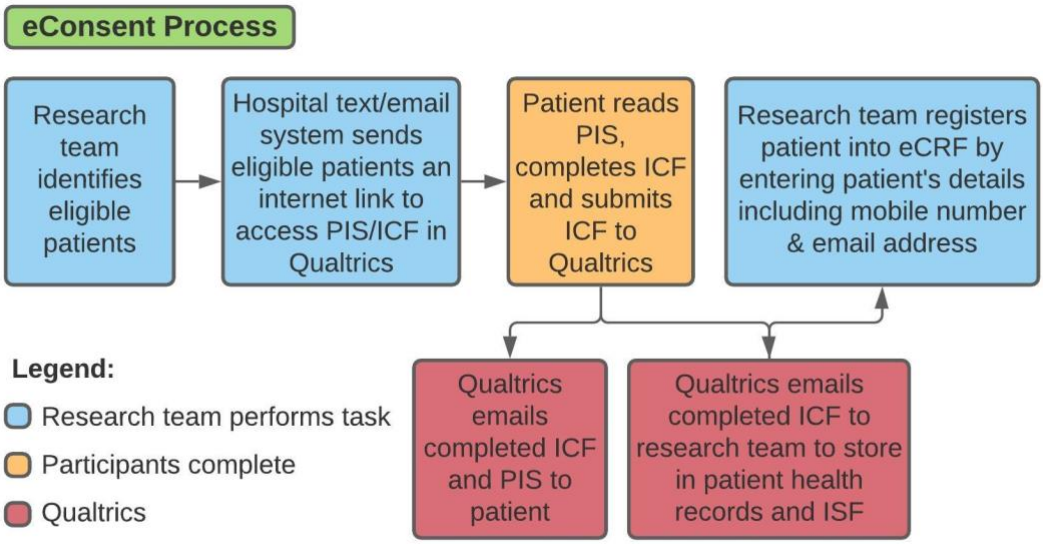


Figure 1. Outline of eConsent process using Qualtrics^{XM} platform.

Qualtrics^{XM} will be used as the online platform for providing patients with the study information, PIS and ICF, remotely. This platform is General Data Protection Regulation (GDPR) compliant and is ISO 27001 certified ensuring Qualtrics^{XM} meets the international standard defining requirements for Information Security Management System (ISMS). The clinical study team will be provided with a secure Clinical Study Team Qualtrics^{XM} User Account. This user account will be given a username and password for access only by authorised individuals in the clinical study team.

Once a participant completes and submits their online ICF, the information is saved within the Clinical Study Team Qualtrics^{XM} User Account. The Qualtrics^{XM} platform will be directed to send a copy of the PIS and completed ICF to the participant via email. A copy of the ICF will also be forwarded via email to the study team for downloading and storage in the Investigator Site File (ISF) and patient medical record.

As mentioned, the eConsent process can be performed face-to-face in clinic. Participants can complete the consent process directly online on their smartphone. If this is unavailable, a tablet can be provided, or paper documentation can be supplied. If completed on paper, clinic study staff will need to enter relevant data into Qualtrics^{XM} platform to activate downstream processes for Stage 2 of the study.

7.3.2 Participant Registration

The clinical study team will be notified of consenting participants through the delivery of completed ICFs via email from the Qualtrics^{XM} platform. Upon receiving an ICF, they will review ICF to ensure completeness and register the patient into the eCRF. This will include entering the patient's mobile number and email address into the eCRF for remote questionnaire delivery. An anonymous participant identification number (PIN) will be assigned to the patient by the Electronic Data Capture (EDC) system. This PIN will also be used as a unique identifier within the Qualtrics^{XM} platform. See Figure 2 for an outline of Stage 1 study procedures.

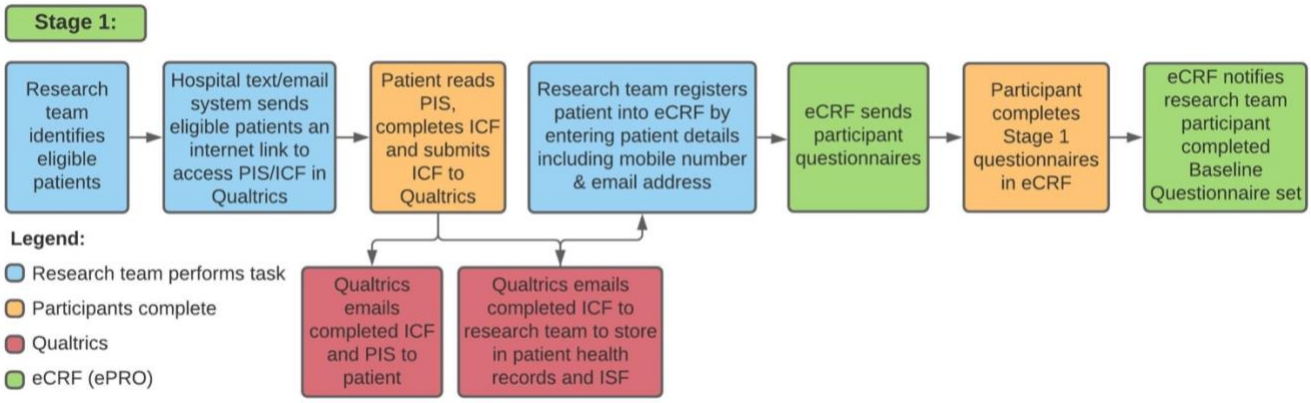


Figure 2. Outline of Stage 1 study procedures including informed consent.

Upon submission of a completed ICF, the Qualtrics^{XM} platform will store the participant's contact details within the Qualtrics^{XM} Directory which is securely located within the Clinical Study Team Qualtrics^{XM} User Account. These contact details will be used for sending Stage 2 specific-study information to participants who are eligible for the second stage of the study.

7.3.3 Questionnaire Completion

Following completion of patient registration into the eCRF, the electronic Patient Reported Outcomes (ePRO) module of the eCRF will be activated to send a text message (or email, if required) containing a link to the baseline questionnaire set to consenting participants. This questionnaire set consists of five short questionnaires including:

- Insomnia Severity Index: ISI
- Quality of life: EQ-5D-5L and FACT-ES
- Demographics and sleep history: age, gender, weight, height, ethnicity, marital status, educational level, current occupation, pregnancy, breastfeeding, menopausal status, shift-work/night-work and smartphone access. Sleep-related questions to determine if the patient has experienced sleep disturbance prior to the screening/baseline consultation with beginning or worsening of sleep disturbance since breast cancer diagnosis and if patient has suffered or currently suffering from sleep apnoea.

The participant can complete the questionnaires on their smartphone. It is estimated the participant will take 20-25 minutes to complete these questionnaires. If the participant does not complete the baseline questionnaire within 3 days, the eCRF will send a questionnaire reminder text message (or email, if required). This will be repeated on two subsequent occasions if the questionnaire remains uncompleted for the three preceding days. The eCRF can be configured to notify the clinical study team by email when a participant completes the questionnaire set. Questionnaires can also be completed on computer or tablet however smartphone completion is preferred.

The baseline questionnaire set can be completed on paper if the clinic, however clinic study staff will be required to subsequently enter the data recorded by the participant directly into eCRF.

7.4 Stage 2

Briefly, Stage 2 will run separately from Stage 1 to aid the timely recruitment and flow of participants through the study. Participants will be asked to consent to taking part in Stage 2, separately from the consent to take part in Stage 1. As participants in Stage 1 will have consented to the use of their contact details for the purposes of being invited to take part in Stage 2, all recruitment and procedures in Stage 2 will be carried out remotely. Figure 3 describes Stage 2 procedures.

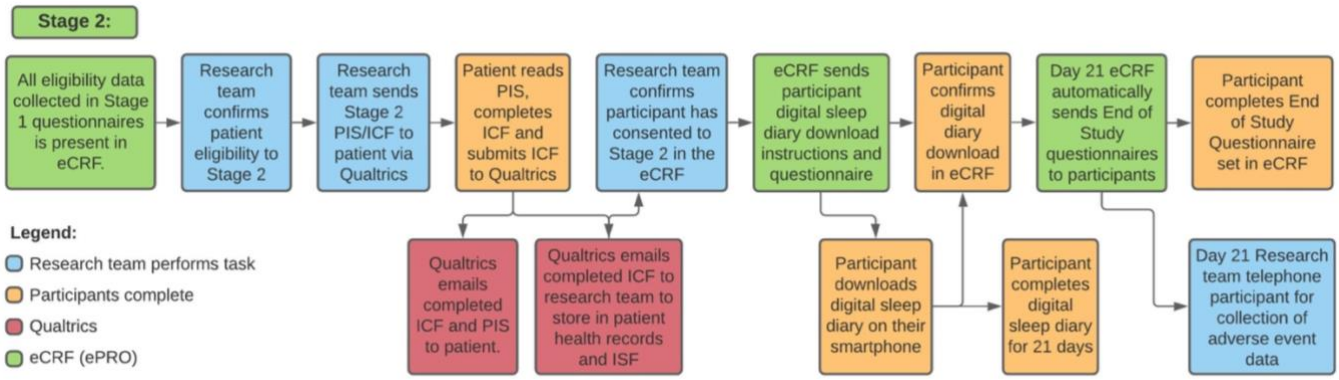


Figure 3. Outline of Stage 2 study procedures.

7.4.1 Stage 2 Eligibility Assessment

All questionnaire-derived eligibility-related data for each participant will be present within the eCRF. This will enable the clinical study team to populate the eligibility eCRF including ISI scores and data related to self-reported sleep history, sleep apnoea, shift-work or night-work, possession of smartphone and breast feeding. The EDC will be configured to automatically calculate the total ISI score required for assessment of eligibility to Stage 2. The clinical research team will be required to confirm from patient medical records the stage of breast cancer, any other diagnosis of cancer, not including basal cell carcinoma of the skin or cervical carcinoma in situ, within the previous 5 years, and any co-morbidities incompatible with study participation.

7.4.2 Stage 2 eConsent

Within 28 days of consenting to Stage 1 of the study and following confirmation of a participants' eligibility to Stage 2, a clinical study team member will activate the Qualtrics^{XM} platform to send a Stage 2-specific PIS and ICF to the eligible participant via text message (or email, if required). Again, the patient will be given time to consider taking part in the study and provided with contact details of the clinical study team to discuss any questions they may have regarding the study. Once a participant completes and submits their online Stage 2-specific ICF, the Qualtrics^{XM} platform will send a copy of the Stage 2 PIS and completed ICF to the participant via email and a copy of the ICF to the study team. If no response has been received from potential participants within 3 days of the receiving the Stage 2 invite text message, this text message will be sent again. This will be repeated once more, 3 days later if no response has been received.

7.4.3 Digital Sleep Diary

Upon receiving and reviewing completed Stage 2-specific ICF, the study team will assign a participant-specific digital sleep diary code to the participant provided by Closed Loop Medicine and enter this code into the eCRF. Within the eCRF the study team will confirm consent for Stage 2 has been obtained and then instruct the ePRO module of the eCRF to send the participant via text message (or email if required) instructions for downloading, enrolling, and using the digital sleep diary app on their smartphone. The participant will also be asked to complete a short questionnaire to confirm they have downloaded and enrolled into the app. This is required for the automation of delivery of End of Study Questionnaire Set by the eCRF at day 21. If the short questionnaire is not completed by the participant within 3 days, the eCRF will send a questionnaire reminder email or text message. This will be repeated again 3 days later if the if the download and enrolment procedure is not confirmed. If after 9 days the questionnaire still remains unanswered, a member of the research team will call the participant to determine if they are experiencing any issues with downloading the digital sleep diary app and provide assistance.

The participant will then complete the digital sleep diary each day for three weeks. Participants will be provided with contact information if they require assistance with downloading or using the app during the study period. This will be a study-specific email address to be received by members of the clinical study team. Participants requiring assistance will be contacted by a clinical study team member either by email or telephone. Where required, the clinical study team will access technical support directly from Closed Loop Medicine.

7.4.4 Clinical Data Capture

Upon receiving and reviewing completed Stage 2-specific ICF, the study team will review patient medical records and capture required data for the following eCRFs:

Cancer Medical History: capturing data regarding, time since cancer diagnosis, cancer stage, primary or secondary cancer, surgery type, neoadjuvant or adjuvant treatment, and positivity for oestrogen receptors (ER), progesterone receptors (PR) or human epidermal growth factor receptor 2 (HER2).

Cancer Treatment: current breast cancer treatment broken down by chemotherapy, radiotherapy, and hormonal therapy and information regarding current medication cycle.

Current Co-morbidities: current co-morbidities and whether each co-morbidity is being treated with medication.

7.4.5 End of Study Procedures

At day 21 of follow up, the ePRO module of the eCRF will automatically send by text message (or email, if required) each participant in Stage 2 of the study the End of Study Questionnaire set consisting of:

- ISI
- EQ-5D-5L
- FACT-ES
- User experience questionnaire (UEQ)

The participant can complete the questionnaires on their smartphone. It is estimated the participant will take 20-25 minutes to complete these questionnaires. If the questionnaire set is not completed by the participant within 3 days, the eCRF will send a questionnaire reminder email or text message. This will be repeated on two subsequent occasions if the questionnaire remains uncompleted within the three preceding days. Questionnaires can also be completed on computer or tablet however smartphone completion is preferred.

On day 21 (+8 days), a member of the clinical study team will phone each participant and record any AEs and SAEs that the participants have experienced in the previous 3 weeks. AE's and SAEs will be entered into the eCRF and patient health records. Prior to the phone call, the eCRF will be checked to determine if the participant has completed the End of Study Questionnaire set. If this has not been completed, the staff member will remind the participant to complete these questionnaires. The clinical study team will attempt to telephone the participants on three occasions. If unsuccessful, this will be recorded as a missed visit in the site protocol deviation log.

7.5 Withdrawal criteria

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study for any reason. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Efforts will be made to continue to obtain 3-week follow-up data, even if the participant did not complete their sleep diary and with the permission of the patient. Participants who withdraw from the study will be offered the User Experience Questionnaire.

Should a patient decide to withdraw from follow up data collection, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Participants who discontinue from the study will not be replaced. Clinical study team will complete the withdrawal form in the eCRF when participants chose to discontinue. Data already collected from a participant prior to withdrawal will be retained and used in the study.

7.6 Storage and Analysis of Clinical Samples

No biological samples will be collected in this study.

7.7 End of Study Definition

End of study will be defined as the last participant to complete their end of study visit (remote).

8 DIGITAL SLEEP DIARY

8.1 Description of digital sleep diary

The digital sleep diary has been designed by Closed Loop Medicine Ltd. This diary will be hosted, monitored, and managed by the digital sleep diary designers at Closed Loop Medicine. The digital sleep diary comes in the form of a patient-facing mobile phone application intended to be installed on the participant's smartphone. The application will be available in both iOS and Android, and we will establish a list of supported operating systems. A risk-based approach will be taken for supporting updates to these versions over the course of the study. All sleep data will be collected in the app. The sleep diary question set is consistent with previously published sleep diaries[24-28] and will collect the following data daily from each participant:

- what time the patient got into bed last night
- what time did the patient try to go to sleep last night
- how long it took the patient to fall asleep
- how many times the patient woke up last night
- in total, how long the patient was awake during the night
- what was the patient's final wake-up time that morning
- how long the patient stayed in bed after waking up
- how did the patient rate their quality of sleep last night
- did something in particular affect the patient's sleep

No recommendations regarding diagnosis, intervention, treatment, or care planning will be made by the app.

8.2 Regulatory status of the digital sleep diary

The digital sleep diary used in this study is not a medical device.

8.3 Concomitant medication

Participants are permitted to continue taking existing concomitant medication, including sleep medication. During the three-week study period introduction of new sleep medication is not permitted.

8.4 Trial restrictions

There are no study restrictions.

8.5 Adherence to the digital sleep diary and study questionnaires

As compliance of data entry into the digital sleep diary is a secondary outcome, adherence to the digital sleep diary will not be monitored during the three-week study period. Adherence to the enrolment procedure required for downloading and setting up the digital sleep dairy on participants smartphones will be assessed remotely by Closed Loop Medicine. If digital sleep diary has not been downloaded within three days of the participant receiving instructions to do so, the eCRF will send a reminder by email or text. If after another three days, the digital sleep diary has not been downloaded the clinical study team will attempt to call the participant to remind participant to download the app and determine if they require any assistance doing so. Compliance of data entry into the digital sleep diary during three-week study period will be assessed at the end of the three-week study period by Closed Loop Medicine.

Questionnaire adherence will be monitored by the clinical study team throughout the study period. Questionnaire reminders, at baseline and end of study, will be sent by email or text message to participants by the Qualtrics^{XM} platform. Reminder email or text messages will be sent up to three times, three days apart. If the end of study questionnaire set remains uncompleted, the clinical research team will remind the participant to complete the questionnaire during remote telephone consultation at day 21.

Non-compliance to the protocol study procedures will be documented by the investigator in the participant study files and site deviation log.

9 SAFTEY REPORTING

9.1 Definitions

Term	Definition
Adverse Event	Any untoward medical occurrence in a study participant which does not necessarily have a causal relationship with the procedure involved.
Serious Adverse Event	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.2 Operational definitions for (S)AEs

The risks to participants enrolled in this observational study are considered very low.

All AEs and SAEs experienced during the three-week study period by participants enrolled in Stage 2 will be recorded in the eCRF and in the patients' medical records. AEs and SAEs can either be volunteered by the participant or detected by the clinical research team through physical examination or in the patients' medical notes.

Only SAEs that the Principal Investigator (PI) considers to be directly related to the digital sleep diary will be reported to the Sponsor via the EDC system.

9.3 Recording and reporting of SAEs

For each AE, the investigator must pursue and collect information to adequately determine the outcome of the AE and to assess whether it meets the classification criteria of an SAE. All SAEs considered to be directly related to the digital sleep diary, occurring from the time of participant consent to Stage 2 of the study to the conclusion of the 3-week observation period, must be reported to the Sponsor within 24 hours of awareness of the event by the PI. In the rare situation that the PI does not become immediately aware of the occurrence of a safety event, the PI must report the event within 24 hours of learning about it and record the time of awareness of the event.

For each SAE, the following information will be collected: full details in medical terms and case description, event duration (start and end dates, if applicable), action taken, outcome, seriousness criteria, and causality (i.e. relatedness to the digital sleep diary), in the opinion of the PI. Any change of condition or other follow-up information should be updated in the EDC system. The Sponsor should be notified as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

9.4 Site Investigator Assessment

The PI is responsible for the care of the participant, or in his/ her absence an authorised clinician within the research team is responsible for assessment of any event for:

- Seriousness: assessing whether the event is serious according to above definitions (Section 9.1).
- Causality: assessing the causality of all serious adverse events/reactions in relation to use of the digital sleep diary according to the definition given.
- Severity: assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.
    - Mild: Some discomfort noted but without disruption of daily life
    - Moderate: Discomfort enough to affect/reduce normal activity
    - Severe: Complete inability to perform daily activities and lead a normal life.

The PI will ensure all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

9.5 Sponsor Medical Assessment

The Sponsor's Chief Medical Officer (CMO) will oversee medical assessment of all reported SAEs. The CMO review all SAEs within 24 hours of receipt. This review will encompass seriousness and relatedness and be in accordance with the trial risk assessment and protocol as detailed in the Safety Monitoring Plan. As this observational study was deemed not to require Data Monitoring Committee

and / or Trial Steering Committee, the CMO is not required to report safety information to the independent oversight committees.

9.6 Notification of deaths

Only deaths that are assessed to be caused by use of the digital sleep diary app will be reported to the Sponsor. This report will be immediate from the point the assessment is made.

9.7 Pregnancy reporting

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The sample size required for Stage 1 is based on an assumed prevalence of insomnia of 44% in breast cancer patients (midway point of insomnia prevalence range found in breast cancer patients 19-69%)[4-10]. A sample size of 267 participants is required for estimating the expected prevalence rate with 5% absolute precision and 90% confidence or 6% absolute precision and 95% confidence[29].

The target for Stage 2 is for approximately 100 participants to complete the study, to provide sufficient data to assess the secondary objectives. With an assumed prevalence of 44% and a 20% drop out rate, then 285 participants in Stage 1 would give an expected 125 eligible participants for Stage 2 with 100 participants assumed to complete the 3-week observation period.

Therefore, the study will aim to recruit a minimum of 285 patients into Stage 1 to cover the sample size requirements for Stage 1 and Stage 2.

10.2 Planned recruitment rate

Recruitment will take place over a four-month period and is planned to end (last participant enrolled) by January 2022. Expected recruitment rate for Stage 1 is aimed at 15 participants per week with approximately half of these (7-8 participants per week) being eligible for Stage 2 of the study.

10.3 Statistical analysis plan

The analyses will be carried out according to the statistical analysis plan (SAP) which will be prepared prior to database lock. The SAP will describe the statistical methods to be used in the analysis and reporting of study data.

10.3.1 Summary of baseline data

Baseline demographic data will be summarised for all participants enrolled in Stage 1, and separately for those in Stage 2. In general, continuous variables will be summarised using the following standard descriptive summary statistics: number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarised as the number and percentage of participants in each category.

10.3.2 Primary outcome analysis

The prevalence estimates for insomnia in the breast cancer cohort studied will be reported as the number and percentage of screened patients in Stage 1 determined as having insomnia by the ISI (total score of 8 or more) and accompanied with exact 95% confidence intervals. Prevalence rates and 95% confidence intervals will also be reported by breast cancer stage (Stages I, II and III) and type of breast cancer treatment.

10.3.3 Secondary outcome analysis

Insomnia severity will be assessed by calculating proportions (number and percentage) of participants within each of the ISI categories:

- no clinically significant insomnia (ISI score 0-7)
- subthreshold insomnia, (ISI score 8-14)
- clinical insomnia of moderate severity (ISI score 15-21)
- severe clinical insomnia (ISI score 22-28).

Percentage of participants in each severity category at baseline/screening will be derived and summarised based on all screened patients from data obtained during stage 1 (baseline/screening assessment). In addition, percentage of patient in each severity category will also be assessed only in those patients determined to have insomnia (i.e. enrolled patient in Stage 2) at both screening/baseline and day 21.

To determine sleep efficiency, the % of time a participant is asleep whilst in bed will be derived based on total time asleep relative to total time in bed. Sleep efficiency will be derived and assessed over the last 2 weeks of the 3-week observation period to correspond with the insomnia severity assessment which is also based on the last 2 weeks. Other timepoints may also be assessed (e.g. weekly).

Quality of Life Data from the EQ-5D-5L self-classifier, which includes five dimensions (mobility, self-care, daily activities, pain/discomfort, and anxiety/depression), will be used to calculate an index value as a measure of the participant's health, both at screening/baseline (all screened patients; Stage 1) and following the observational period (all enrolled patients; Stage 2). Data will be summarised descriptively.

Quality of Life Data from the FACT-ES self-report measure, which includes five subscale domains (physical well-being, social/family well-being, emotional well-being, functional well-being, and endocrine symptom subscale), will be used to calculate an index value as a measure of the participant's health, both at screening/baseline (all screened patients; Stage 1) and following the observational period (all enrolled patients; Stage 2). Data will be summarised descriptively.

Compliance of entry into the digital sleep diary will be assessed as the proportion of participants completing the digital sleep diary on at least 17 out of 21 days and summarised descriptively.

Reporting of user experience data collected from the UEQ at Day 21 will be descriptive.

All Reported AEs and SAEs will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and presented by SOC and PT. In addition, any AEs/SAE considered related to the usage of the sleep diary will be summarised separately (or listed if numbers are low).

To assess any association with treatment/clinical characteristics and insomnia prevalence, insomnia severity, sleep efficiency and Quality of Life, data will be reported and summarised by breast cancer stage, treatment regimen and baseline insomnia severity. Other clinical or treatment groups may also be explored. Full details of the characteristics to be assessed will be provided in the SAP.

10.4 Procedure(s) to account for missing or spurious data

The amount and type of missing data will be reviewed and if necessary, imputation methods for missing data may be implemented.

10.5 Other Statistical Considerations
Any changes made to the original analysis plan will be recorded in the Statistical Analysis Plan along with dates, updated SAP version number and description and reason for the changes. If a participant withdraws from the study, they will not be replaced.

10.6 Economic Evaluation
Not applicable.

11 DATA MANAGEMENT

11.1 Data collection tools
There are two datasets in the study: the SMART-Trial EDC system dataset and the Closed Loop Medicine digital sleep diary dataset. The Sponsor will act as custodian for the study data. SMART-TRIAL will be used as the primary Electronic Data Capture tool in this study. SMART-TRIAL is designed and developed in compliance with the PIC/S Guidance, PI-011-3 Good Practices for Computerised Systems in Regulated "GxP" Environments, with software validation based on IEC 62304. SMART-TRIAL is designed to enable its users to comply with Good Clinical Practice (such as the ISO 14155:2020 standard), ICH GCP, and other industry requirements, such as FDA 21 CFR Part 11, HIPAA and the EU GDPR. All data in SMART-TRIAL is collected, transferred, and stored encrypted in databases, which are hosted on ISO certified servers that are managed by SMART-TRIAL within the European Union (Ireland and the Netherlands).

11.2 Data Entry
Authorised staff at the clinical site will transcribe baseline and follow up data directly from electronic patient records into the eCRF in the EDC system. This will be performed by going to https://app.smart-trial.co/#/authentication/login and entering username and password to access the study database. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system. Authorised users delegated by the PI at the investigational site will have access to the eCRF and each user will be assigned specific user roles and rights. This will be reflected on the delegation log.

Patient-reported data will be entered into the eCRF by participants submitting completed questionnaires as described in throughout Section 7. Four validated questionnaires will be used for self-reported data collection and include:

- ISI: a validated self-report instrument for detection of insomnia[19].
- EQ-5D-5L: a validated self-report instrument for health-related quality of life data[30].
- FACT-ES: a validated self-report measure for health-related quality of life data in breast cancer patients[31].
- UEQ: a validated self-report instrument for measurement of usability aspects (efficiency and dependability) and user experience aspects (originality and stimulation)[32].

Closed Loop Medicine will be responsible for creating the digital sleep diary database and preparing and an enrolment code list. Closed Loop Medicine will provide a unique enrolment code for the digital sleep diary for each participant and monitor the use of these codes. Following the downloading and enrolment into the digital sleep diary, each participant will enter their sleep data into the diary every day for three weeks. Data collected in the digital sleep diary will be hosted, monitored, and managed by the digital designers at Closed Loop Medicine. This data will be linked to each participant by a unique identifier code. No patient identifiable data will be collected in this dataset. Closed Loop

Medicine designers of the digital sleep diary will only have read-only access to the database to ensure accurate data transfer and can request downloads intermittently, when required. Closed Loop Medicine designers will also be responsible for withdrawing participants, where necessary, from the digital sleep diary during the study and preventing access at the completion of the three-week observational period.

11.3 Security for EDC

Clinical site staff will request usernames and passwords for the EDC from the Sponsor. Systems access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested and a request for access to be revoked must be requested when staff members leave the project.

Participant initials and date of birth will be entered into the study database. Participant mobile phone number and email address will also be entered into the study database for the purpose of remote questionnaire delivery. All other patient identifiable information such as hospital number, names and addresses, and full postcodes will not be entered. The study site will maintain a master patient log linking full participant identifiers to study numbers. No data will be entered into the eCRF unless a participant has signed a consent form to participate in the trial.

11.4 Data Quality Processes

At the database design stage, validations will be programmed into the systems to minimise data entry errors by querying the data entered in real time with sites. The Sponsor will undertake appropriate reviews of the entered data, where appropriate for the purpose of data cleaning and will request amendments to the EDC system data as required. No data will be amended independently of the study site responsible for entering the data.

The Sponsor will prepare a Data Management Plan for EDC system once the system is made live. This plan will be filed in the Trial Master File (TMF). Using this Data Management Plan a Sponsor-delegate will raise Data Clarification Requests (DCRs) with the site in the eCRF. The study site will periodically review raised DCR's and respond to the queries raised. During site monitoring visits, monitor will raise any queries with sites via the Source Data Verification (SDV) function.

11.5 Database Lock

The site PI's will review participant data held in EDC system and provide sign-off to verify that all the data are complete and correct at the end of the study. The Sponsor will confirm all data checks are complete and all monitors queries have been resolved prior to database lock. At this point, with the agreement of the statistician, data will be formally locked for analysis. The Sponsor will remove all data entry user access whilst retaining only 'monitor' access for the investigational site PI. The dataset will be exported, the site will receive a copy of their site-specific dataset and confirm receipt.

The dataset from the EDC system will be reconciled with the Closed Loop Medicine digital sleep diary dataset prior to analysis. Closed Loop Medicine will be responsible for the final data export from the digital sleep diary database. A copy of the complete dataset will be stored in the TMF.

11.6 Direct access to Data, Source Data and Documents

Direct access will be granted to authorised representatives from the Sponsor, host institution and regulatory authorities to permit study-related monitoring, audits and inspections.

11.7 Archiving

Archiving will be authorised by the Sponsor following submission of the end of trial report. The PI will be responsible for archiving the ISF at site. The Sponsor will be responsible for archiving the TMF, associated documents and the trial dataset. All essential documents will be archived for 25 years after completion of trial. Destruction of essential documents will require authorisation from the Sponsor.

12 MONITORING, AUDIT & INSPECTION

Monitoring of this study to ensure compliance with applicable provisions of GCP will be managed by Closed Loop Medicine. The PI will permit trial-related monitoring, audits, REC review, and inspections by providing the Sponsor(s) and REC with direct access to source data and other documents (e.g. patients' case sheets, blood results, imaging reports, study protocol, statistical code, and etc).

Closed Loop Medicine will prepare a monitoring plan. The recruiting study site will have a Site Initiation Visit prior to recruitment of the first participant and regular site visits thereafter to verify the data. These visits may be performed remotely, if required.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review, amendments & reports

Before the start of the study, approval will be sought from a REC for the study protocol, ICFs, PISs and other relevant documents. Amendments to the protocol that require Health Research Authority (HRA) and REC review will not be implemented until the REC grants a favourable opinion for the trial. Closed Loop Medicine will be responsible for preparing and submitting protocol amendments to the HRA and REC and circulating updated document versions to the study site. Where required, site PI will be responsible for communicating relevant information to study participants.

All correspondence with the HRA and REC will be retained in the TMF/ISF. An Annual Progress Report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

13.2 Public and Patient Involvement

Patients and public will be involved in reviewing the study design, protocol, and patient-facing documentation. They will also have a role in the dissemination of findings of the study.

13.3 Protocol compliance

Protocol non-compliances are departures from the approved protocol. Accidental protocol deviations can happen at any time. They must be adequately documented in the site deviation log and reported to the Sponsor, on a regular basis. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.4 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the participants of the study, or the scientific value of the study. As this is an observational study, we believe the risk of a serious breach to be very minimal. However, the Sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The Sponsor will notify the REC were required of any serious breach of the conditions and principles of GCP in connection with the study or the study protocol relating within 7 days of becoming aware of the breach.

13.5 Data protection and patient confidentiality

All study data will be stored in line with GCP, UK GDPR and UK Data Protection Act 2018. All participant data will be pseudo-anonymised.

When consent forms are signed, a copy will be provided to the patient, a copy will be filed in the medical records and the original will be retained in the ISF. This ISF will be maintained by the site PI. No data will be entered into the EDC system or Qualtrics^{XM} database unless a participant has signed a consent form to participate in the trial. Participants will be asked to consent to the use of their contact details including name, email address and mobile phone number in the Qualtrics^{XM} platform and eCRF for the purpose of remote consent and subsequent questionnaire delivery. The eCRF and Qualtrics^{XM} Directory will be accessed only by authorised clinical study team members. Participants will also be asked to consent to the Sponsor representative having access to these platforms for monitoring and audit purposes.

When the study is complete, a data sharing dataset will be created from the raw data by the study analyst, which will not include patient initials, date of birth or any other identifiable data and study ID will be altered so that individuals are not recognisable from the dataset.

13.6 Indemnity

Closed Loop Medicine provides no fault liability insurance in the event of harm arising from the study design. UK NHS recruiting sites provide indemnity in the event of clinical negligence.

13.7 Access to the final study dataset

Data will be available for sharing upon request for future research, subject to approval by the Sponsor.

14 DISSEMINIATION POLICY

The outcomes form the study will be published in a peer reviewed open-source medical journal as early as possible. The study site will be informed of the results and will be asked to disseminate the findings to participants. Patient groups will be informed of the results for dissemination among their members.

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16. APPENDICIES

Appendix 16.1 – Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = _____ your total score

Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

Appendix 16.2 – Quality of Life Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

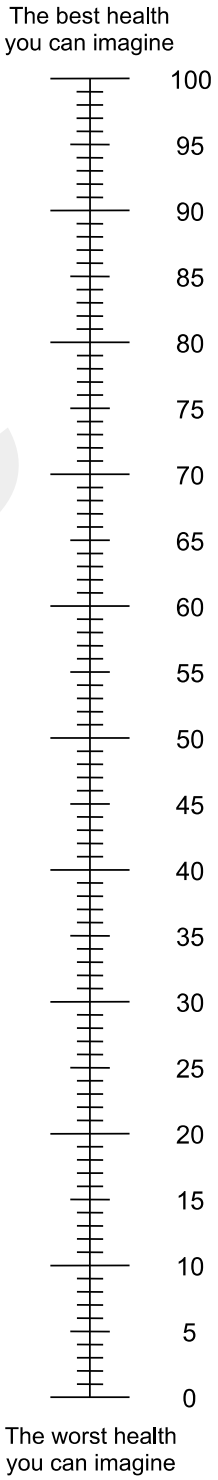
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 16.3 – Breast Cancer-Specific Quality of Life Questionnaire (FACT-ES)

FACT-ES (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-ES (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-ES (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix 16.4 – User Experience Questionnaire

CLINICAL TRIAL USABILITY QUESTIONNAIRE

Please make your evaluation now.

For the assessment of the product, please fill out the following questionnaire. The questionnaire consists of pairs of contrasting attributes that may apply to the product. The circles between the attributes represent gradations between the opposites. You can express your agreement with the attributes by ticking the circle that most closely reflects your impression.

Example:

attractive	O	®	O	O	O	O	O	unattractive

This response would mean that you rate the application as more attractive than unattractive.

Please decide spontaneously. Don't think too long about your decision to make sure that you convey your original impression.

Sometimes you may not be completely sure about your agreement with a particular attribute or you may find that the attribute does not apply completely to the particular product. Nevertheless, please tick a circle in every line.

It is your personal opinion that counts. Please remember: there is no wrong or right answer!

Please assess the product now by ticking one circle per line.

	1	2	3	4	5	6	7		
annoying	O	O	O	O	O	O	O	enjoyable	1
not understandable	O	O	O	O	O	O	O	understandable	2
creative	O	O	O	O	O	O	O	dull	3
easy to learn	O	O	O	O	O	O	O	difficult to learn	4
valuable	O	O	O	O	O	O	O	inferior	5
boring	O	O	O	O	O	O	O	exciting	6
not interesting	O	O	O	O	O	O	O	interesting	7
unpredictable	O	O	O	O	O	O	O	predictable	8
fast	O	O	O	O	O	O	O	slow	9
inventive	O	O	O	O	O	O	O	conventional	10
obstructive	O	O	O	O	O	O	O	supportive	11
good	O	O	O	O	O	O	O	bad	12
complicated	O	O	O	O	O	O	O	easy	13
unlikable	O	O	O	O	O	O	O	pleasing	14
usual	O	O	O	O	O	O	O	leading edge	15
unpleasant	O	O	O	O	O	O	O	pleasant	16
secure	O	O	O	O	O	O	O	not secure	17
motivating	O	O	O	O	O	O	O	demotivating	18
meets expectations	O	O	O	O	O	O	O	does not meet expectations	19
inefficient	O	O	O	O	O	O	O	efficient	20
clear	O	O	O	O	O	O	O	confusing	21
impractical	O	O	O	O	O	O	O	practical	22
organized	O	O	O	O	O	O	O	cluttered	23
attractive	O	O	O	O	O	O	O	unattractive	24
friendly	O	O	O	O	O	O	O	unfriendly	25
conservative	O	O	O	O	O	O	O	innovative	26

Please tell us about your experience using the product.

What is the one thing you liked most about the application?

What is the one thing you liked least about the application?

Which parts of the task did you find the most cumbersome / problematic?

Is there something else that comes to mind regarding the application you would like to share?

Appendix 16.4 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.