Statistical Analysis Plan

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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2.0	9th September 2022	Sarah Lockwood	Amended definition of analysis sets to only include patient eligible for the study and added that baseline BMI would be reported

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ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
eConsent	Electronic Consent
ePRO	Electronic Patient Reported Outcomes
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FACT-ES	Functional Assessment of Cancer Therapy-Endocrine Symptoms
HER2	Human Epidermal Growth Factor Receptor 2
ICF	Informed Consent Form
ISI	Insomnia Severity Index
NHS	National Health Service
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
UEQ	User Experience Questionnaire

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide detailed descriptions of the planned analysis and reporting of the data from the study CLM-INS-004 (Protocol version 1.0 dated 28th September 2021).

1.1. Study Objectives

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 for all participants enrolled in Stage 1.
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 for all participants enrolled in Stage 2.
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 all participants 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 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, prior chemotherapy, and baseline insomnia severity.	Performed on data collected at Stage 1 and Stage 2.

1.2. Study 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).

The digital sleep diary comes in the form of a patient-facing mobile phone application. All daily sleep diary data will be collected in the app.

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.

1.2.1. Sample Size Considerations

The sample size required for Stage 1 is based on an assumed prevalence of insomnia of 44% in breast cancer patients. 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.

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.

If the actual prevalence rate is higher than the assumed rate or the drop-out rate is lower, then the study may recruit less patients to achieve the desired 100 patients in stage 2 or the study could continue to the original recruitment target of 285 and achieve > 100 patients in stage 2. This decision will be driven by availability of patients and desired study reporting timelines ensuring the minimum target is reached.

2. ANALYSIS AND REPORTING CONSIDERATIONS

2.1. General Considerations

Statistical analysis will be performed using SAS® software. Continuous variables will be summarized using the mean, the standard deviation [SD], median, 25th and 75th percentiles, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

Where applicable, 95% confidence intervals (CIs) will be presented.

The tables, listing and figures will be developed as a separate standalone document from the SAP. The document will provide templates of the outputs to be provided following database lock based on the summaries detailed in the SAP. All data will be listed, in addition to the summaries outlined in the SAP

2.2. Definitions of Analysis Sets

The following analysis sets will be used in the statistical analyses and reporting of study data.

- Stage 1 analysis set will include all participants who consented to stage 1, are eligible for the study and have evaluable data for at least one of the questionnaires (ISI, EQ-5D-5L or FACT-ES).

- Stage 2 analysis set will be a subset of the Stage 1 analysis set and will include eligible Stage 1 participants who scored ≥8 on their baseline ISI questionnaire and consented to stage 2. Note if a patient consents to Stage 2 but does not provide **any** stage 2 data (e.g., questionnaire/sleep data) then they will be excluded from the stage 2 analysis set.

Note, listings will generally be based on the stage 1 analysis set with an indicator for patients who also entered into stage 2, with the exception of the cancer history, cancer treatment, co-morbidities, sleep diary, AE and UEQ listings which will be based on the stage 2 analysis set since these are only completed for stage 2 patients.

If a participant does not enroll in the digital diary (i.e., does not even download the app) but completes the UEQ, then data from the UEQ will not be included in the reporting of the data.

Percentages will generally be derived based on the analysis set N as the denominator, unless stated otherwise. Where there is missing data, % may be derived based on those within the analysis set who have evaluable data. Where applicable missing categories will be included to show the number of patients with missing data for the relevant endpoint.

2.3. Baseline Definition

In general, for questionnaire data, baseline is defined as the assessment completed during Stage 1 of the study on Day 0 (as indicated in Table 1).

For the sleep diary, baseline will be considered the assessment completed on Day 0 of Stage 2 (as indicated in Table 1).

Change from baseline variables will be calculated as:

- post-treatment value minus the value at baseline.

If applicable, % change from baseline will be calculated as:

- (post-baseline value - baseline value)/baseline value x 100.

2.4. Study Day

For Stage 1, Study Day 0 will be defined as the day that the questionnaires (ISI, EQ-E5-DL, FACT-ES) are completed. This will be referred to as S1D0, for Stage 1 day 0. All questionnaires are expected to be completed on the same day but if any are completed after day 0 then they will be labelled accordingly relative to day 0 (e.g. S1D2, if done 2 days after the initial day 0).

For Stage 2, Study Day 1 will be defined as the first day the sleep diary is completed in Stage 2 and will be referred to as S2D1. All subsequent assessment will then follow in sequence as S2D2, S2D3, S2D4 etc.

2.5. Missing Data Handling Rules

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. Where applicable, outcomes may still be derived for questionnaire data based

on missing data rules. For example, FACT scores can still be derived provides <50% of data is missing. Any missing data rules are provided in the relevant derivation sections.

Where applicable missing categories will be presented to show the number of patients with missing data for the relevant endpoint.

Imputation of partial dates

Initial diagnosis date:

- If year is missing, do not impute.
- If only day is missing, impute day as 15th of the month.
- If day and month are missing, impute as July 1st.

3. ANALYSIS AND REPORTING OUTPUTS

All data collected will be listed and summarized as follows:

- Demographics and sleep history– Stage 1 and Stage 2 analysis sets
- Cancer history, medical treatment, co-morbidities – Stage 2 analysis set only
- ISI, EQ-5D-5L, FACT-ES – Stage 1 (day 0) and Stage 2 (day 0 and day 21) analysis sets
- Sleep diary, UEQ, AEs – Stage 2 analysis set only

3.1. Patient Information

3.1.1. Disposition of Patients

The number of participants who signed consent for each stage will be summarised as well as the number of patients within each analysis set (i.e. Stage 1 and 2 analysis set). In addition, the number of patients withdrawing early from the study and the reason why will also be summarised.

3.1.2. Protocol Deviations

Any protocol deviations recorded on the eCRF will be listed and summarised for each analysis set. Any deviations with a start date after the consent date for Stage 1 but prior to the consent date of Stage 2 will be considered as a deviation for Stage 1 of the study and summarised based on the Stage 1 analysis set. Any deviation reported on or after the consent date for stage 2 will be regarded as a Stage 2 deviation and summarised based on the stage 2 analysis set.

For summary purposes, deviations will be categorised as relating to:

- Informed consent
- Inclusion/exclusion criteria
- Study procedures
- Other

3.1.3. Demographics

Baseline demographic data and sleep history will be summarised for each analysis set

The following will be summarised:

Demography

- Age
- Gender (Male/Female)
- Height
- Weight
- BMI categorised as:
    - 18.5 or less = Underweight
    - 18.5 to 24.9 = Normal Weight
    - 25.0 to 29.9 = Overweight
    - 30.0 to 39.9 = Obese
    - 40 and above = Morbidly Obese
- Ethnicity(White, Mixed/multiple ethnic backgrounds, Asian/Asian British, Black/ African/ Black British, Other)
- Marital status (Married or living with partner, Single, Separated or divorced, Widowed, Rather not say)
- Education level (Primary school, Secondary school, College, University)
- Employment status (Full-time work, Part-time work, Unemployed, Retired, Student)
- Breast feeding (Y/N)
- Menopausal status (Pre-menopause, Peri-menopause, Post-menopause, Don't know)
- Shift work (Y/N)

Sleep history

- Sleep difficulties (Y/N)
- Started/worsened since diagnosis of breast cancer (Y/N)
- Medications prescribed by doctor for sleep issues (Y/N)
- Sleep apnoea (Y/N)
- Access to smartphone (Y/N)

3.1.4. Medical History of Breast Cancer

The following will be summarized for the stage 2 analysis set only.

- Time since breast cancer diagnosis (derived as consent date-diagnosis date+1)
- Stage of disease (Stage I to Stage III)
- Tumor staging (T1, T2, T3, T4, DCIS)
- Nodes staging (N0, N1, N2, N3)
- Surgery type (Lumpectomy, Mastectomy, Double Mastectomy, No surgery, Not available)

- Time since surgery (derived as consent date-surgery date+1, for applicable patients)
- Neoadjuvant treatment (Y/N)
- Oestrogen receptors (Y/N)
- Progesterone receptors (Y/N)
- HER2 receptors (Y/N)

3.1.5. Breast Cancer treatments

Previous and current Breast cancer treatment will be summarized for the stage 2 analysis set only based on the following:

- Current systemic anti-cancer therapy
- Time since start of current systemic anti-cancer therapy
- Number of cycles of current systemic anti-cancer therapy
- Dexamethasone treatment (Y/N)
- Time since start of dexamethasone treatment (for applicable patients)
- Radiation therapy? (Y/N)
- Time since start of radiation therapy
- Hormonal treatment? (Y/N)
- Current hormonal treatment (for applicable patients)
- Time since start of hormonal treatment (for applicable patients)
- Targeted therapy for HER2 positive breast cancer? (Y/N)
- Current targeted therapy (for applicable patients)
- Time since start of targeted therapy (for applicable patients)

3.1.6. Co-morbidities

Any co-morbidities will be summarised for the stage 2 analysis set only based on the number and % of patients with any of the following conditions and the number and % of patients receiving medication for each relevant condition:

- Cardiovascular disease
- Chronic pulmonary disease (not asthma)
- Asthma
- Chronic kidney disease
- Gastrointestinal disease
- Genitourinary disorder
- Liver disease
- Chronic neurological disorder
- Psychiatric disorder
- Chronic hematologic disease
- Rhematologic disorder
- Immunological disorder
- Endocrine (including diabetes) disorder

- Musculo-skeletal disorder
- Other

3.2. Questionnaire data

3.2.1. ISI

The primary outcome of Stage 1, the prevalence estimate for insomnia in the breast cancer cohort studied, will be reported as the number and percentage of patients in the Stage 1 analysis set determined as having insomnia by the ISI assessment. Insomnia will be defined as a total score of 8 or more. Exact Clopper-Pearson 95% confidence intervals for the prevalence rates will also be reported.

Note, if any patients in the stage 1 analysis set do not have evaluable ISI data (i.e., total score) then the prevalence rate and 95% confidence interval will also be derived based on evaluable patients only.

Insomnia severity will be assessed by calculating the 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).
- missing (if applicable)

For Stage 2, severity categories will be summarized at baseline and day 21 and a shift table will also be presented to show any change in severity since baseline.

Severity categories will also be graphically displayed in the form of bar charts for the relevant timepoints for each stage.

3.2.2. EQ-5D-5L

The EQ-5D-5L descriptive system consists of five health dimensions: mobility, self care, usual activities, pain/discomfort and anxiety/depression. Patient's rate each of the dimensions on five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems and these are scored 1 to 5 to give an overall 5-digit health state. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression

The EQ-5D-5L also uses a visual analog scale (VAS) where patients rate their health on a vertical scale from 0-100. The data from the VAS can be used as a quantitative measure of health as judged by the individual patients.

For each of the 5 dimensions, data will be reported descriptively as the number and % of patient reporting each level within the 5 dimensions. In addition, a bar chart will also be produced to graphically represent the data.

Data from the VAS will be summarised descriptively as a continuous variable (N, mean, median, min max etc).

The above EQ-5D-5L summaries will also be presented for the Stage 1 analysis set split by those with no insomnia (scores ≥7) versus those with insomnia (score ≥8).

3.2.3. FACT-ES

Quality of Life Data will be reported based on the FACT-ES self-report measure, which includes five subscale domains:

- physical well-being (PWB, 7 items, score of 0-28)
- social/family well-being (SWB, 7 items, score of 0-28)
- emotional well-being (EWB, 6 items, score of 0-24)
- functional well-being (FWB, 7 items, score of 0-28)
- endocrine symptom subscale (ES,19 items, score of 0-76)

Scores will be derived as follows:

- If >50% of items have been answered within a subscale, then multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered.
- If <50% of items within a subscale have been answered, then the subscale will be reported as NE/missing.

It was discovered during the trial that a single question from the EWB subscale (GE4 "I feel Nervous") was missing from the questionnaire. This was added in part way through the trial so some patients will not have available data for this specific question. EWB scores will still be derived (as described above) provided at least 50% of the EWB items are available at the time of data reporting.

Note, a higher score reflects a better QoL. Some scores need to be reversed by subtracting the score from 4 (see appendix A for details on reverse scoring for individual items)

Subscales scores as well as an overall FACT-ES total score (total of all 5 subscale scores, PWB+SWB+EWB+FWB)+ES) will be reported for the relevant timepoints. FACT-G scores will also be presented (total of PWB+SWB+EWB+FWB).

Boxplots of the subscale scores and total scores will be presented for each analysis set for the relevant time points.

The above FACT summaries will also be presented for the Stage 1 analysis set split by those with no insomnia (scores ≥7) versus those with insomnia (score ≥8).

3.3. Daily Sleep diary data

The sleep diary will collect the following data daily from each participant in the stage 2 analysis set:

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

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, derived as:

- (Number of hours asleep/number of hours in bed)*100%
    - Number of hours in bed will be derived as:
        - (Wake up time – time participant got into bed) + time in bed after waking
    - Number of hours asleep will be derived as :
        - (Wake up time – time participant got into bed)-(time to fall asleep + total time patient was awake in the night)

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.

For each patient, a daily % will be derived and then this will be averaged over the 2 weeks. The average scores will then be summarised over time for patients in the stage 2 analysis set. Averages will be derived based on the number of days with evaluable sleep efficiency data within the 2-week period.

In addition, weekly averages will also be reported where each patient will have a weekly average derived over week 1-3 based on number of days with evaluable data within each weekly period.

Line plots of mean daily sleep efficiency (%) over time will also be presented with error bars, to allow each average daily change to be visualised.

In addition, the following information will be summarised from the sleep diary data over the last 2 weeks and also weekly for week 1-3 and plotted based on daily means across the patients:

- Time to get to sleep
- Total awake time
- Number of awakenings

- Quality of sleep rating (rated 1 (awful) to 10 (excellent))

Compliance of entry into the digital sleep diary will be assessed as follows:

- Entry compliance: Number and % of patients who used the diary at least once (i.e entered at least one data point into the diary)
- Completion compliance: Number and % of participants completing the digital sleep diary on at least 17 out of 21 days.
- Overall diary compliance rate derived as:
    - (number of days sleep diary completed/21)*100%

Sleep diary data will be listed and summarized based on the stage 2 analysis set only. If any sleep variables cannot be determined at a timepoint (due to partial/missing data) then relevant variables will be considered missing at the affected timepoint(s) and excluded from the relevant data summaries.

3.4. User Experience Questionnaire

Reporting of user experience data collected from the UEQ at Day 21 will be presented in the form of summary tables (n, mean, SD and 95% CI) and bar charts for the 26 individual items and the 6 domain scores.

Means will be derived for each domain (attractiveness, perspicuity, efficiency, dependability, stimulation and novelty) as described via the online help tool (https://www.ueq-online.org/). The means and 95% CIs will then be presented graphically in bar chart form for each domain and also for individual items.

UEQ values between -0.8 and 0.8 represent a more or less neutral evaluation of the corresponding scale, values > 0.8 represent a positive evaluation and values < -0.8 represent a negative evaluation.

Note: Individual response values for individual questions will either be subtracted from 4 or have 4 subtracted from them as per the online guidance depending on the whether the items starts as a positive/ negative scale. For example, items starting with a positive scale will be derived as (4-recorded score) and items starting with a negative scale will be derived as (recorded score-4).

Each participant will then have a score derived for each of the domains based on a subset of responses per domain. These will then be used to derive the domain means and CIs. CIs will be derived as follows using the mean, SD and n per domain:

$$\bar{x} \pm 1.96\left(\frac{\sigma}{\sqrt{n}}\right)$$

3.5. Adverse Events

The number of reported AEs in this study is expected to be low. Therefore, AE data will not be coded by MedDRA. Data will be listed as per the CRF entries.

The number and % of patient will be summarized for the following AE categories:

- Any AE
- Any SAE
- Any diary related AE (where "Possibly", "Likely", or "Definitely" is recorded for the AE relationship question on the eCRF)

AEs will be summarized based on the stage 2 analysis set only.

3.6. Association of breast cancer characteristics and sleep

To assess any association with treatment/clinical characteristics and insomnia severity, sleep efficiency and Quality of Life, data will be reported and summarized by the following characteristics for the stage 2 analysis set:

- Breast cancer stage
  - Stage I, II or III
- Treatment regime
  - Systemic, dexamethasone, radiotherapy, hormonal or targeted
- Prior chemotherapy
  - No prior chemotherapy
  - Prior chemotherapy started ≤ 3 months of study entry
  - Prior chemotherapy started >3 and ≤ 6 months of study entry
  - Prior chemotherapy started > 6 months of study entry
- Baseline insomnia severity
  - subthreshold, moderate, and severe
  - Note no patient should have category of "none" for the baseline assessment since they have to have insomnia to be eligible for Stage 2

The following summary tables will be presented for the above baseline/disease characteristics:

- Insomnia severity at baseline and day 21 (for breast cancer stage, treatment and prior chemotherapy only)
- Sleep efficiency % (average of last 2 weeks)
- EQ-5D-5L, summary of 5 dimensions and VAS at baseline and day 21
- FACT-ES subscale scores, FACT-G and total-ES score at baseline and day 21

In addition to tabular summarises the following plots will be produced

- Bar charts of insomnia severity (for stage, treatment and prior chemotherapy only)
- Line plots of mean daily sleep efficiency (%) over time

- Boxplots of FACT-ES subscale scores, FACT-G and total-ES score at baseline and day 21

4. CHANGES FROM THE PROTOCOL

- Clarification of analysis sets to be used to summarize Stage 1 and Stage 2 data.
- For EQ-5D-5L, individual health index values will not be derived since these are generally more relevant for treatment intervention studies that require quality-adjusted life years (QALYs) to be derived for use in informing economic evaluations of health care interventions. Instead, the data will be summarised descriptively based on the 5 level health states reported for each domain.
- Due to the expected low number of AEs, events will not be coded by MedDRA but will be reported as recorded on the CRF.
- Prior chemotherapy has been added for the secondary endpoint assessing associations between severity of insomnia and clinical or treatment characteristics of breast cancer patients.

5. APPENDICES

APPENDIX A

FACT-ES Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G, FACT-ES-19 and FACT-ES-23).
5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL WELL-BEING (PWB)	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY WELL-BEING (SWB)	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____=**EWB**

subscale score

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB**

subscale score

19 ITEM ENDOCRINE SYMPTOM SUBSCALE (ESS-19)	ES1	4	-	_____	=_____
	ES2	4	-	_____	=_____
	ES3	4	-	_____	=_____
	ES4	4	-	_____	=_____
	ES5	4	-	_____	=_____
Score range: 0-76	ES6	4	-	_____	=_____
	ES7	4	-	_____	=_____
	ES8	4	-	_____	=_____
	ES9	4	-	_____	=_____
	ES10	4	-	_____	=_____
	An9	4	-	_____	=_____
	O2	4	-	_____	=_____
	C5	4	-	_____	=_____
	An10	4	-	_____	=_____
	Tax1	4	-	_____	=_____
	ES11	4	-	_____	=_____
	ES12	4	-	_____	=_____
	ES13	4	-	_____	=_____
	BRM1	4	-	_____	=_____

Sum individual item scores:_____
Multiply by 19: _____
Divide by number of items answered: _____=**ES**

Subscale score

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____ =_____=**FACT-G**

Total score
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-ES total score:
Score range: 0-184

_____ + _____ + _____ + _____ + _____ =_____=**FACT-ES Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**ESS-19** score)

DocuSign

Certificate Of Completion

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Subject: Please DocuSign: CLM_INS-004_SAP_Final 2.0.pdf
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Cambridge, Cambridgeshire CB22 3AT
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Leanne Richardson leanne.richardson@closedloopmedicine.com DL Tutor Closed Loop Medicine Security Level: Email, Account Authentication (None)	DocuSigned by: Leanne Richardson 6996431975254D7... Signature Adoption: Pre-selected Style Using IP Address: 94.119.64.73	Sent: 13-Sep-2022 | 10:28 Viewed: 13-Sep-2022 | 10:29 Signed: 13-Sep-2022 | 10:29

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ID: 91058102-4a82-45e9-a163-ad6427b3a356

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	13-Sep-2022 | 10:28

Envelope Summary Events	Status	Timestamps
Certified Delivered	Security Checked	13-Sep-2022 I 10:40
Signing Complete	Security Checked	13-Sep-2022 I 10:40
Completed	Security Checked	13-Sep-2022 I 10:40

Payment Events	Status	Timestamps

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