Home-based Brainwave Entrainment Technology (hBET) for management of chronic pain and sleep disturbance. A feasibility study.

EEG Extension – Statistical Analysis Plan

Clinicaltrials.gov ID: NHS001542(2)

HRA IRAS ID: 261462

Background: Participant flow and outcome measures schedule

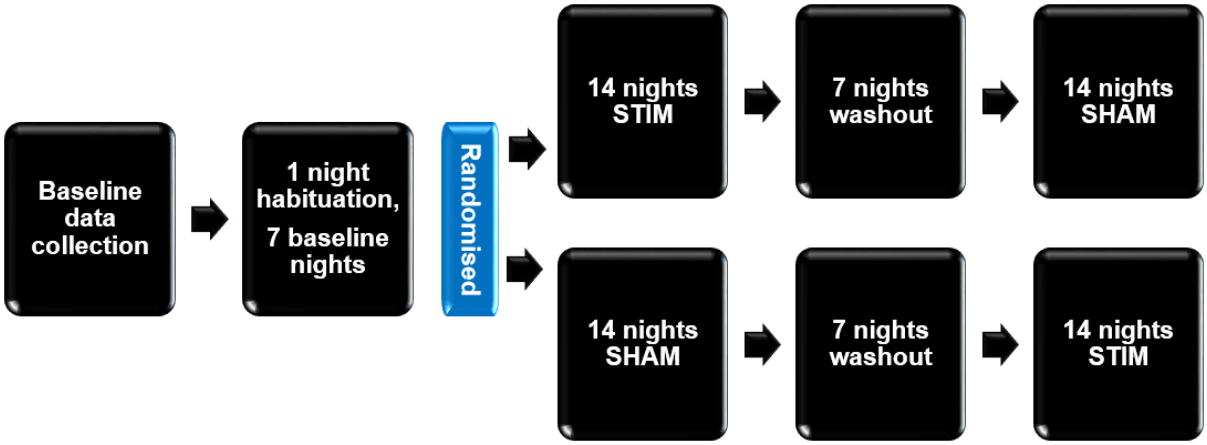

Figure 1 Participant flow diagram; two arm crossover design

	Baseline		**During hBET use and washout period**	
	Start of baseline week	Daily for baseline week	Daily	After each hBET use period (STIM and SHAM)
Pain and sleep diary		√	√	
Actigraphy		√	√	
Sleep Headband		√	√	
BPI	√			√ (weekly throughout)
PSQI	√			√
HADS	√			√
MFI	√			√
EQ5D	√			√

Table 1. Outcome measures schedule summary

Outcome measures

Primary Outcome measures:
1. Alpha entrainment effect
Alpha spectral power during active stimulation use periods compared to sham stimulation use periods and baseline equivalent periods.
Time Frame: Baseline (1 week) vs active stimulation (2 weeks) vs sham stimulation (2 weeks)

2. Sleep Quality, measured with Pittsburgh Sleep Quality Index
0-21 score of sleep quality. Within participant change, comparing active stimulation period with baseline and sham stimulation period with baseline.
Time Frame: Measured at Baseline (1 week), at completion of active stimulation, and at completion of sham stimulation (each in reference to the previous 2 weeks sleep).

Secondary Outcome Measures:
3. Sleep and Pain diary
Diary report of pain at night and over 24 hours (0-10 NRS), sleep parameters (total sleep time, sleep onset latency, wake after sleep onset, sleep efficiency) and quality (0-5 NRS) and refreshed (0-5 NRS).
Time Frame: Baseline (1 week) vs active stimulation (2 weeks) vs sham stimulation (2 weeks)

4. DREEM headband derived Sleep architecture
Sleep architecture (temporal parameters, continuity, stages) as measured by Dreem 3 headband
Time Frame: Baseline (1 week) vs active stimulation (2 weeks) vs sham stimulation (2 weeks)

5. Brief Pain Inventory Pain Interference score, gives a 0-10 score for pain interference.
Time Frame: Measured weekly through Baseline (1 week) active stimulation (2 weeks), washout (1 week) and sham stimulation (2 weeks).

6. Actigraphy
Wrist actigraphy measures of sleep temporal parameters (total sleep time, sleep latency, wake after sleep onset, sleep efficiency).
Time Frame: Baseline (1 week) vs active stimulation (2 weeks) vs sham stimulation (2 weeks)

7. Brief Pain Inventory Severity score
0-10 NRS for pain severity
Time Frame: Measured weekly through Baseline (1 week) active stimulation (2 weeks), washout (1 week) and sham stimulation (2 weeks)

8. Hospital Anxiety and Depression Scale
Scores of 0-21 for anxiety, 0-21 for depression
Time Frame: Measured at Baseline (1 week), at completion of active stimulation, and at completion of sham stimulation

9. Multidimensional Fatigue Inventory
Score of 20-100
Time Frame: Measured at Baseline (1 week), at completion of active stimulation, and at completion of sham stimulation

10. EuroQol 5 Dimensions (EQ-5D-5L)
0-1 global index score, 0-100 VAS score of health related quality of life
Time Frame: Measured at Baseline (1 week), at completion of active stimulation, and at completion of sham stimulation

Pre-specified Analyses

Hypothesis testing analyses:

1. Linear Mixed Effects Modelling

To explore the within-participant effect of active stimulation compared to baseline and to sham stimulation, making use of repeated measures. Testing the hypothesis that active stimulation results in greater improvement from baseline than sham stimulation.

2. Within-participant comparison of clinical outcomes

Comparing change from individual baseline in active vs sham phases, using paired tests, (e.g. paired T-tests or Wilcoxon sign rank tests). Testing the hypothesis that active stimulation results in greater improvement from baseline than sham stimulation.

3. Within participant analysis of electrophysiological effect

Comparing alpha spectral power during the period of active stimulation use with the equivalent period of baseline and sham stimulation use, testing the hypothesis that hBET entrains alpha and this can be detected with DREEM headband.

4. Correlation of alpha entrainment to clinical outcomes

To examine whether sleep, pain and other symptoms improve particularly in those who achieve alpha entrainment. Including: diary report of pain and sleep symptoms, symptoms reported on standardised questionnaires, actigraphy measures of sleep, DREEM headband measures of sleep.

5. Adherence to the protocol

Proportion of nights correct programme used and degree of data completeness, to test whether participants can feasibly follow the protocol and use the intervention

Hypothesis generating analyses:

6. Subgroup analysis by Responder category

Response categories pre-specified as improvement with active stimulation, compared to baseline of at least 1 point on BPI pain interference score (the MCID), partial response being improvement of less than 1 point, non-response being no improvement.

7. Analysis of order effect

Comparison of STIM-> SHAM vs SHAM->STIM, to explore order effect and sufficiency of 1 week washout period

8. Agreement between actigraphy, diary and Dreem EEG headband on sleep parameters

Exploring the level of agreement, regression exploring characteristics which predict good and poor agreement