FLEX ISRCTN SAP

A novel online program for fatigue; a feasibility study

Study Objectives

1) Determine the recruitment rate and retention rate of participants to follow-up assessments.
2) Explore the acceptability of interventions through self-report questions and adherence rates.
3) Assess the reliability and potential responsiveness of a range of outcome measures for a full-scale RCT in the future.
4) Explore the signal of efficacy for a key mechanistic outcome (i.e. whether the online training in CBM-I reduces negative interpretations relative to the control condition)/
5) Explore the signal of efficacy for treatment effects on self-report measures of fatigue, acceptance of fatigue, depression, anxiety, disability, illness-related cognitions, persistence in goal-directed behaviour and influence of thoughts on actions.

Analysis Plan

General considerations

All datasets will be cleaned. Continuous variables will be summarised using descriptive statistics (non-missing sample size, mean, standard deviation, median and range). Categorical variables will be summarised using frequency and percentages (of the non-missing sample).

Following general statistical conventions for reporting feasibility trials, P-values will not be reported, as the trial is not powered to detect effects. Frequencies will be reported to zero decimal places and percentages to one decimal place. Descriptive statistics will be reported to one decimal place greater than the original data, other than quantiles (e.g. median) and ranges, which will use the same number of decimal places as the original data. Estimated parameters (e.g. effect sizes) will be reported to 3 significant figures.

Descriptive statistics for the outcome measures will be reported separately for each of the long-term conditions (chronic fatigue syndrome/long COVID, multiple sclerosis, cancer) but not analysed.

Outcome analysis

1) Recruitment and retention. Using a consort chart to report: the number of participants who register for the online platform, the number and proportion (including 95% confidence interval) of participants who are eligible once screened, and the number and proportion (including 95% confidence interval) of eligible participants who consent to being randomised. Where possible, reasons for exclusion and drop-out at each stage will be reported. Frequency and percentages (including 95% confidence interval) of participants retained at each assessment timepoint will be reported, both separately for each condition and overall.
2) Acceptability and adherence. Frequencies and percentages (including 95% confidence interval) of participants who are classified as full (10-12 sessions), partial (4-9 sessions) and low (0-3 sessions) completers will be reported separately for active and control groups. Acceptability ratings will be summarised by reporting frequencies, percentages, and median scores (including 95% confidence intervals) separately for the active and control groups at both time points.
3) Reliability and potential responsiveness of self-report outcome measures. Each measure will be assessed for suitability by looking at number of missing items, proportion of scale scores at ceiling/floor, and internal consistency. These will be reported for the overall sample, for all measures at T0 and T1.
4) Signal of efficacy for mechanistic outcome. The treatment effect (interpretation bias) will be estimated using linear mixed-effect models that include post-randomisation interpretation bias scores (i.e. T1, T2 and T3) as the outcome variable. Condition and assessment timepoint will be included as dummy-coded variables and condition X timepoint as interaction terms. Baseline level interpretation bias score will be included as a covariate. Mean differences, confidence intervals of the mean differences, effect sizes and confidence intervals of the effect sizes will be reported.
5) Signal of efficacy for treatment effects on self-reported measures. Treatment effects on self-report outcome measures (fatigue, acceptance of fatigue, depression, anxiety, disability, illness-related cognitions, persistence in goal-directed behaviour and influence of thoughts on actions) will be estimated using linear mixed effect models. Condition and timepoint will be included as dummy-coded variables and condition X timepoint as interaction terms. Baseline levels of the outcomes will be included as a covariate. Mean differences, confidence intervals of the mean differences, effect sizes and confidence intervals of effect sizes will be reported.

To check that the analysis is feasible, all analyses will be repeated using the per protocol sample and reported in supplementary materials. This sample will be defined as those who completed at least 10 assignments and completed assessments at both T0 and T1. The proportion of participants in the per protocol sample will be reported.

Missing data

Missing at item level

Participants were allowed to skip items as per the protocol. If there are no more than 20% missing items, we will prorate by replacing missing item values with the mean value of the complete items for each participant. The total scale score will then be calculated using the complete values and the replacements. Where there are more than 20% missing items, the scale will be considered missing for that participant.

Missing at scale level

Missing outcome data at the scale level will be assessed using logistic regression models to see if any baseline variables predict missingness. If they do not, we will consider the data missing at random (MAR). If there are baseline variables that predict missingness, these will be included as covariates in the models used to examine the outcomes described above.

Progression criteria

Progression to a full-scale efficacy trial will be considered using the below criteria:

Measure	**Progress**	**Consider progressing**	**Do not progress**
Recruitment (% of target sample size)	100%	70-100%	<70%
Retention to T3 (% retained)	>70%	50-70%	<50%
Intervention Adherence	>70%	50-70%	<50%
Acceptability (mean scores)	T1 logic >2 T1 usefulness >2	T1 logic 1.5-2 T1 usefulness 1.5-2	T1 logic <1.5 T1 usefulness <1.5
Serious device-related adverse events	No serious adverse events attributed to the intervention	Rectifiable SAEs attributed to the intervention	Irremediable SAEs or SUSARs (unexpected serious adverse reactions) attributed to the intervention