Bristol Randomised Trials Collaboration (BRTC)

SMILE

Specialist Medical Intervention & Lightning Evaluation

Statistical Analysis Plan

Version 2 (13 March 2014)

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Daisy Gaunt and Chris Metcalfe	Authors	D. Gaunt Chris Metcalfe	31/3/14 27-03-2014
Alan Montgomery	Statistical Reviewer	A Montgomery	28/3/2014.
Esther Crawley	Chief Investigator	Crawley	27/3/2014

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Abbreviations

AYME	Association of Young people with ME
BRTC	Bristol Randomised Trials Collaboration
CBT	Cognitive Behavioural Therapy
CFS	Chronic Fatigue Syndrome
DMG	Data monitoring group
GET	Graded Exercise Therapy
HADS	Hospital Anxiety and Depression Scale
LP	Lightning Process
ME	Myalgic Encephalopathy
NICE	National Institute for Health and Clinical Excellence
NLP	Neuro-linguistic programming
PIS	Patient Information Sheet
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SCAS	Spence Childrens Anxiety Scale
SF36	Short Form (36) Health Survey
SMC	Specialist medical care

1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from SMILE.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.
2. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

The information in this section is extracted from the study protocol published in *Trials* on 26 December 2013 [1] in order to place the analysis plan within the context of the trial aims and methods.

2.1. Trial objectives and aims

2.1.1. Primary objective

To investigate the effectiveness and cost-effectiveness of specialist medical care (SMC) with specialist medical care plus the Lightning Process (LP) in treating CFS/ME in children.

2.1.2. Secondary objectives

1. To explore prior exposure, beliefs, expectations and preferences about specialist medical care and the Lightning Process intervention in the early stages of the trial, and experiences and acceptability of interventions and outcome later on.
2. To observe the delivery of both specialist medical care and the Lightning Process to provide data on setting, implementation and acceptability.

2.2. Trial design and configuration

This is a pragmatic randomised controlled trial comparing SMC plus the LP with SMC alone among children with CFS/ME.

2.6. Randomisation procedures

The researcher providing information and recruiting participants will telephone the Bristol Randomised Trials Collaboration for the intervention allocation.
Allocation will be minimised by age and gender, and retain a random component to reduce risk of prediction of allocation.

2.10. Outcome measures

2.10.1. Primary outcome

The self-completed SF-36 physical function subscale analysed as a continuous variable collected at six months post-randomisation.

2.10.2. Secondary outcomes

School attendance in the previous week, collected as a percentage (10, 20, 40, 60, 80 and 100 %), at 3 months, 6 months and 12 months ; the SF-36 (physical function) at 3 and 12 months; Chalder Fatigue Scale score at 3, 6 and 12 months and pain visual analogue scale at 6 months. We have obtained consent to check school attendance using school records at assessment, 3, 6 and 12 months.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1. Analysis populations

Primary

- As randomised, with primary outcome recorded.

Sensitivity

- As randomised, with missing primary outcome data imputed.
- Repeat the primary outcome as analysed, excluding those recruited and assessed up to 31 January 2011.

The sensitivity analysis excluding those recruited and assessed up to 31 January 2011 is included because of an amendment carried out to improve follow up after that date. Sensitivity analyses will be conducted for the primary outcome only both with and without imputed data.

3.2. Derived variables

The SF-36 scoring is included as reference [2, 3]. The HADS scoring is included as reference [4, 5]. The SCAS scoring is included as reference [6, 7]. The Chalder Fatigue scoring is included as reference [8] and the Likert version of the scoring will be used.

3.3. Procedures for missing data

Missing data will be imputed using multiple imputation.

3.4. Outliers

All the data is scaled, therefore outliers are unlikely.

3.5. Follow-up questionnaire windows

If both the full and reduced questionnaires are returned within 1 month of each other, the full questionnaire will be analysed, otherwise the questionnaire that is dated closest to the due date will be analysed for the primary outcome.

The variability of the follow-up questionnaire windows is as follows;

- Questionnaires returned up to 6 weeks after the 3 month time-point specified will be used for the 3 month follow-up.
- Questionnaires returned up to 6 weeks before or less than 3 months after the 6 month time-point specified will be used for the 6 month follow-up.
- Questionnaires returned up to 3 months before or after the 12 month time-point specified is allowable for the 12 month follow-up.

For each arm we will describe the mean and SD for time for follow-up between the two arms. We will include a variable in the model for time since randomisation for receipt of questionnaires.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1. Disposition

A flow of patients through the trial will be summarised in a CONSORT diagram that will include the eligibility, reasons for exclusion, numbers randomised to the treatment groups, losses to follow up and the numbers analysed.

4.2. Baseline characteristics

The study cohort will be described by the baseline measures in Table 1 (see Section 8).

Continuous data that are approximately normally distributed will be summarised in terms of the mean and standard deviation. Categorical data will be summarised in terms of frequency counts and percentages.

5. ASSESSMENT OF STUDY QUALITY

5.1. Study completion

The final follow-up is the questionnaire 12 months after initial (baseline) clinical assessment.

5.2. Compliance

The compliance of patients with the intervention (drop-out or cross-over) will be shown by the CONSORT chart.

5.3. Specify and justify changes made to the planned statistical analyses

The planned safety analysis was not conducted as the recruitment rate accelerated greatly in the later stages of recruitment, and was nearly closed by the time sufficient data (six month follow up of 50% participants) had accumulated for a formal analysis.

6. ANALYSIS OF EFFECTIVENESS

6.1. Summary of primary and secondary outcomes

The scales will be summarised as the mean (SD) by the randomised groups.

6.2. Primary analysis

The tested null hypothesis is that the addition of the Lightning Process to specialist medical care is no different to specialist medical care alone in its clinical and cost effectiveness.

The primary analysis will be:

- Multivariable linear regression adjusted for baseline value of the outcome and minimisation variables; age and gender. Residuals will be checked and bootstrap confidence intervals adopted if clearly non-normal in distribution.
- We will adjust for variables known to be associated with outcome (disability (Sf-36) , fatigue severity (Chalder fatigue), co-morbid mood disorders (HADS, SCAS).
- The estimated treatment effect will be presented as the adjusted difference in means between the two intervention groups with a 95% confidence interval and p-value.

6.3. Secondary analyses

Similar analyses to that for the primary will be carried out on the secondary outcomes, using appropriate regression models, for an initial paper focused on the six month assessment.

A second paper will be produced once 12 month data are available. This will include repeated measures analysis of the primary and secondary outcomes using random effects. Whether the treatment effect changed over follow-up will be investigated by adding a time by treatment interaction for the SF-36 physical function subscale.

6.4. Sensitivity analysis

The sensitivity of the results to assumptions about the missing data will be assessed using multiple imputation for missing primary outcome data.

6.6 Subgroup analysis

Subgroup analysis of the primary outcome will explore differences in the effect of intervention according to age (<14.99 versus 15.00 to 17.99), gender (male/female), severity (no school attendance versus some school attendance at baseline) and co-morbid anxiety (defined as more than 12 on the anxiety sub-scale of the HADS questionnaire). These subgroup analyses are exploratory and will be conducted by adding interaction terms to the regression models used for the primary analysis. We recognise there will be low power for the sub-group analyses.

7. ANALYSIS OF SAFETY

7.1. Adverse events

The data monitoring group (DMG) will receive notice of Serious Adverse Events (SAEs) for the sample as a whole. If the incidence of SAEs of a similar type is greater than would be expected in this population, it will be possible for the DMG to receive data according to trial arm to determine any evidence of excess in either arm.

8. FINAL REPORT TABLES AND FIGURES

8.1. Subject characteristics and background summaries

Table 1. Baseline Demographics and Clinical Characteristics of Eligible Patients

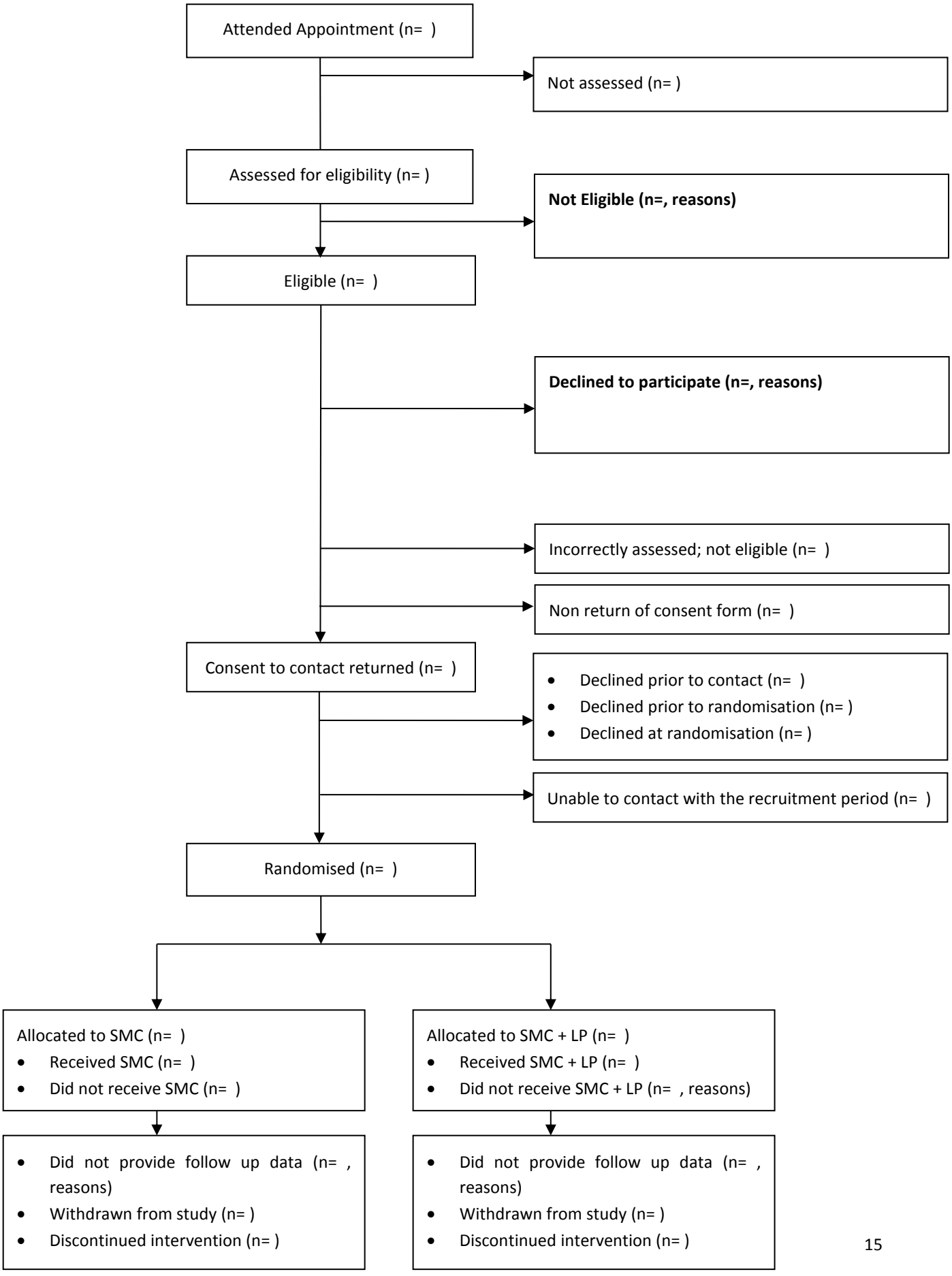
	Recruited (n=)	Eligible but not recruited (n=)
Demographic data		
Mean age (SD)		
Number female (%)		
Number British (%)		
Number English (%)		
Number Irish (%)		
Number Scottish (%)		
Number Welsh (%)		
Number Any other white background (%)		
Number White & black Caribbean (%)		
Number White & black African (%)		
Number White & Asian (%)		
Number Any other mixed background (%)		
Number Indian (%)		
Number Pakistani (%)		
Number Any other Asian background (%)		
Number Caribbean (%)		
Number African (%)		
Number Any other black background (%)		
Number Chinese (%)		
Median time from onset of illness to assessment (IQR)		
Clinical data		
Mean SF-36 Physical Function score (SD)		
Mean Chalder Fatigue score (SD)		
Mean pain VAS (SD)		
Mean SCAS (SD)		
Mean HADS Anxiety score (SD)		
Mean HADS Depression score (SD)		
School attendance in the previous week n (%):		
None		
0.5 day		
1 day		
2 days		
3 days		
4 days		
5 days		
Not applicable		

Table 2. Baseline Demographics and Clinical Characteristics of Recruited patients

	Intervention (n=)	Control (n=)
Demographic data		
Mean age (SD)		
Number female (%)		
Number British (%)		
Number English (%)		
Number Irish (%)		
Number Scottish (%)		
Number Welsh (%)		
Number Any other white background (%)		
Number White & black Caribbean (%)		
Number White & black African (%)		
Number White & Asian (%)		
Number Any other mixed background (%)		
Number Indian (%)		
Number Pakistani (%)		
Number Any other Asian background (%)		
Number Caribbean (%)		
Number African (%)		
Number Any other black background (%)		
Number Chinese (%)		
Median time from onset of illness to assessment (IQR)		
Clinical data		
Mean SF-36 Physical Function score (SD)		
Mean Chalder Fatigue score (SD)		
Mean pain VAS (SD)		
Mean SCAS (SD)		
Mean HADS Anxiety score (SD)		
Mean HADS Depression score (SD)		
School attendance in the previous week n (%):		
None		
0.5 day		
1 day		
2 days		
3 days		
4 days		
5 days		
Not applicable		

8.2. Study quality summary

Table 3. Consort Chart



8.3. Outcome summaries

Table 4. Summary statistics and treatment effect estimates at 6 month assessment (Paper 1)

	Intervention mean (SD)	Control mean (SD)	Adjusted difference in means	95% Confidence Interval	P-value
Primary					
SF-36 Physical Function					
Secondary					
Chalder Fatigue score					
Pain VAS					
SCAS					
HADS Anxiety score					
HADS Depression score					
School attendance in the previous week:					
None					
0.5 day					
1 day					
2 days					
3 days					
4 days					
5 days					
Not applicable					

Table 5. Summary statistics and treatment effect estimates at 12 month assessment (Paper 2)

	Intervention mean (SD)	Control mean (SD)	Adjusted difference in means	95% Confidence Interval	P-value
Primary					
SF-36 Physical Function					
Secondary					
Chalder Fatigue score					
Pain VAS					
SCAS					
HADS Anxiety score					
HADS Depression score					
School attendance in the previous week:					
None					
0.5 day					
1 day					
2 days					
3 days					
4 days					
5 days					
Not applicable					

8.4. Sensitivity analysis for primary endpoint

Table 6. Sensitivity analysis primary endpoint results (Paper 1)

	Intervention mean (SD)	Control mean (SD)	Adjusted mean difference	95% Confidence Interval	P-value
Children recruited from 1 February 2011: SF-36 Physical Function					
All children recruited, missing imputed: SF-36 Physical Function					

8.5. Exploratory/other analysis results

Table 7. Subgroup analysis results of primary outcome (Paper 1)

SF-36 Physical Function at 6 months	Intervention mean (SD)	Control mean (SD)	Interaction Coefficient	95% Confidence Interval	P-value
Children <14.99 years					
Children 15.00-17.99 years					
Children female					
Children male					
Children no school attendance (baseline)					
Children some school attendance (baseline)					

8.6. Safety results

Table 8. Adverse events (Paper 1 and Paper 2)

Serious Adverse event	Intervention	Control

9. APPENDICES

9.1. Details of standard assessment tools

1. *RAND 36-item Health Survey 1.0 scoring* 03/02/2014]; Available from: http://www.rand.org/content/dam/rand/www/external/health/surveys_tools/mos/mos_core_36item_scoring.pdf.
2. Ware, J. and C. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473 - 483.
3. *Hospital Anxiety and Depression Scale FAQs*. 06/02/2014]; Available from: http://www.gl-assessment.co.uk/products/hospital-anxiety-and-depression-scale/hospital-anxiety-and-depression-scale-faqs.
4. Jorngarden, A., L. Wettergen, and L. von Essen, *Measuring health-related quality of life in adolescents and young adults: Swedish normative data for the SF-36 and the HADS, and the influence of age, gender, and method of administration.* Health Qual Life Outcomes, 2006. **4**: p. 91.
5. *Spence Children's Anxiety Scale* 06/02/2014]; Available from: http://www.scaswebsite.com/1_1_.html.
6. Spence, S., P. Barrett, and C. Turner, *Psychometric properties of the Spence children's anxiety scale with young adolescents.* J Anxiety Disord, 2003. **17**(6): p. 605 - 625.
7. Chalder, T., et al., *Development of a fatigue scale.* J Psychosom Res, 1993. **37**(2): p. 147 - 153.

10. REFERENCES

1. Crawley, E., et al., *Comparing specialist medical care with specialist medical care plus the Lightning Process(R) for chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME): study protocol for a randomised controlled trial (SMILE Trial).* Trials, 2013. **14**(1): p. 444.
2. *RAND 36-item Health Survey 1.0 scoring* 03/02/2014]; Available from: http://www.rand.org/content/dam/rand/www/external/health/surveys_tools/mos/mos_core_36item_scoring.pdf.
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4. *Hospital Anxiety and Depression Scale FAQs*. 06/02/2014]; Available from: http://www.gl-assessment.co.uk/products/hospital-anxiety-and-depression-scale/hospital-anxiety-and-depression-scale-faqs.
5. Jorngarden, A., L. Wettergen, and L. von Essen, *Measuring health-related quality of life in adolescents and young adults: Swedish normative data for the SF-36 and the HADS, and the influence of age, gender, and method of administration.* Health Qual Life Outcomes, 2006. **4**: p. 91.
6. *Spence Children's Anxiety Scale* 06/02/2014]; Available from: http://www.scaswebsite.com/1_1_.html.
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8. Chalder, T., et al., *Development of a fatigue scale.* J Psychosom Res, 1993. **37**(2): p. 147 - 153.