Review: The SMILE trial – a lesson in how not to conduct clinical trials in people with ME/CFS

12th October 2017

Dr Charles Shepherd, Hon. Medical Adviser, ME Association:

"The SMILE trial is one of the worst examples of a clinical trial supposedly designed to assess the acceptability, effectiveness and safety of a treatment for ME/CFS that I have come across. In fact, in several ways it is a lesson in how not to conduct a clinical trial in people who have ME/CFS.

"There was no adequate control group, no attempt to properly measure the effectiveness of the Lightning Process® as a stand-alone intervention, and no mention of the likely placebo effect in an unblinded trial that involved comparing treatment A (i.e. specialist medical care) with treatment A + treatment B (i.e. specialist medical care plus the Lightning Process®).

"There was a serious lack of objective outcome measures (especially in relation to measuring physical activity levels), no explanation of the likely impact on self-report outcome questionnaires (where those receiving the Lightning Process® may well have been aware of the alleged benefits), and the specialist medical care 'control' seemed to involve a 'pick and mix' approach that was not at all standardised.

"It is very hard to understand why the Science Media Centre went all-out in their attempt to promote this trial. We were not therefore surprised to read of the negative scientific reaction to their coverage of it – or that one expert from their panel compared neurolinguistic programming (a key component of the Lightning Process) to 'pseudoscience'. However, we were surprised by the way in which the British and overseas media accepted the findings without question.

"The ME Association stands by its initial statement on the SMILE trial and does not recommend the Lightning Process® for people with ME/CFS. We have referred several Lightning Process® practitioners to the Advertising Standards Authority where therapeutic claims have been made that cannot be supported. We will continue to do so, if necessary.

"We welcome sound research into treatments that could produce better outcomes for children and adolescents with ME/CFS and any applications in this area made to the MEA Ramsay Research Fund."

Science media centre: Inconvenient Truths
Science media centre: Prof. Dorothy Bishop
Media reaction to SMILE trial: The SMILE trial is published
ME Association statement: Lightning Process and SMILE trial in young people with ME/CFS

Overview of the study

You can read the full SMILE trial – which is open access – here.
And the previously published feasibility study, here.

The SMILE Trial randomly assigned 100 children aged 12-18 with mild/moderate chronic fatigue syndrome (CFS) to either a specialist medical care group (SMC-only), which served as the 'control' group, or a specialist medical care and Lightning Process® group (SMC+LP).

'49 children were allocated to SMC-only, and 51 to SMC+LP. Participants' mean age was 14 years, 76 were female and all described themselves as British. Participants were disabled by their fatigue: only seven were attending full-time school and 47 described themselves as attending 2 days or less school a week.'

The primary outcome measure of the trial was the SF-36 physical function questionnaire, which was completed before treatment and then at 6 and 12 months after treatment.

Secondary outcome measures included the Chalder fatigue score, the Hospital Anxiety and Depression scale (HADS), the Spence Children's Anxiety Scale (SCAS), the visual analogue pain scale (VAS), and self-reported school attendance, measured as the number of days attended in the previous week.

Results revealed that both treatment arms improved physical function and decreased fatigue and anxiety, but that the SMC+LP group showed a greater improvement overall than the SMC-only group.

The trial also looked at the cost-effectiveness of SMC+LP by using quality-adjusted life years (QALYs), derived from the EQ-5D-Y questionnaires, but it did not appear to be more cost-effective than SMC-only, due in large part to the initial high cost of the Lightning Process® treatment, despite the concluding remarks.

The authors concluded:

'The LP is effective and is probably cost-effective when provided in addition to SMC for mild/moderately affected adolescents with CFS/ME.'

What is the Lightning Process® (LP)?

The exact content of the LP is not very clear; even the study protocol for the LP group is reasonably vague.

From the trial, the LP is described as using concepts from Neural Linguistic Programming (NLP), hypnotherapy, osteopathy and life coaching for a variety of conditions:

'clients read information, attend three group sessions and then receive follow-up phone calls'.

The Lightning Process® website describes it as:

"a training course that focuses on the science behind how the brain and body interact; it gives you powerful tools to use this brain-body link to influence your health and life. The tools involve gentle movement, meditation-like techniques and mental exercises."

The exact methods used remain secretive, and despite the published protocol we don't know how the LP was exactly applied in this trial. Was it different to that taught commercially, or the same? Had it been adapted for children and, if so, how?

It appears to be a form of intensive CBT (cognitive behavioural therapy), used to correct what are regarded as negative thinking patterns, teach stress-reducing techniques, and to set – and encourage people towards – personal goals of improvement.

But it remains unclear the extent to which NLP, osteopathy and hypnotherapy come into it, although anecdotal reports provide some worrying clues.

Recruitment

Children were eligible to participate in the trial if they were aged 12-18, spoke English and were not housebound.

They were diagnosed with ME/CFS after assessment by the Bath/Bristol paediatric ME/CFS service using the Royal College of Paediatrics and Child Health guidelines and the National Institute of Health and Care Excellence (NICE) ME/CFS guideline criteria.

The NICE guidelines are often seen as being not very specific and are currently pending a full review. Misdiagnosis rates can be quite high if criteria are not carefully applied (Newton 2010, Johnston 2014, Baraniuk 2017).

Most research studies for ME/CFS will use Fukuda/CDC or Canadian Consensus criteria, which are believed to reduce the amount of false-positive diagnoses.

In the SMILE trial, it was not clear if or how other comorbidities were ruled out and if cardinal symptoms such as post-exertional malaise were included.

Potential bias

There is some selection bias present because children were deemed ineligible if they were too far away from the study centre, resulting in proximity sampling bias.

Parents might have been motivated to get their child into the study if aware of the relatively high private cost for the intervention (£620), and so the parents that showed the most interest could be the ones with greatest expectations which may in turn have been passed on to their child.

4 children were deemed not eligible due to having previously received LP treatment. This tells us two things; the LP had not resulted in any significant improvement for these children as they were still being seen by the ME/CFS service, and that they may have been ruled out because they were considered unlikely to benefit from the LP.

310 (out of 631) children were determined eligible for the study, but only 100 were randomised to the two treatment arms, giving a recruitment rate of only 32%. The authors said:

'We do not know why the majority did not want to take part in the trial but it may be because they did not want to take part in groups or travel for three consecutive days'.

This may have been true (although similar reasons were given to explain the drop from 631 children), but it would have been useful if the authors had discovered the actual reasons for this low rate of acceptance.

It might reflect parental attitude towards the LP and could imply that those who remained in the trial were more positive about receiving it and this positivity may then have carried through to the self-reported outcomes.

Baseline characteristics

The study used a cut-off score for the HADS of >12 for anxiety, however, Bjelland *et al* (2002) identified a cut off point of >8 for the HADS anxiety scale to be the most sensitive.

The average score for participants was over 8 for both groups, meaning they had mild-moderate anxiety, which should be considered a comorbid factor.

The mean SCAS scores for the SMC-only group were above 39, classed as elevated levels of anxiety (Essau *et al* 2002), which was not the case for the SMCS+LP group.

Therefore, the SMC group had higher anxiety on average. However, the authors recognised this and state it was adjusted for in the statistical analysis of results.

Study design

One of the biggest flaws in the study design was that it was not blinded, meaning both the participants and the providers knew which treatment they were receiving, and this could have led to an over-estimate of outcome effectiveness.

It left room for bias as the control group (SMC-only) may have been disappointed with their eventual treatment allocation and the SMC+LP group may have been exposed to positive expectations.

Can such treatment trials be blinded? On the one hand, the SMILE trial randomised assessment of trial data so the assessors could not determine who received what treatment.

But on the other, SMILE did not adopt a 'sham' treatment arm either of CBT or LP to try and determine if participant outcomes are the result of any 'active' therapy application.

Such an approach could have been extremely useful and quite innovative as psychotherapy trials in ME/CFS, and more generally, appear reluctant to test the impact of placebo.

Other concerns:

1. In the feasibility study parental feedback suggested the benefits of the LP were emphasized, and most of the information given was about the LP, and that there was some disappointment when finally allocated to the SMC group.

   This could have influenced subsequent outcomes although we don't really know who completed the self-report outcome measures or the degree to which parents might be said to have influenced outcome measures.

2. Three of the participants allocated to the SMC-only arm went on to seek private LP.

   This may confirm that they only entered the study in the hopes of getting LP for free or could reflect how well LP was portrayed in the initial information given pre-randomisation.

   It is not clear whether the data from these 3 participants was then used in the SMC or SMC+LP data at the end, but it could have affected the results.

3. According to the diagram of the two study arms (Figure 1):

   - 9 of the 51 participants allocated to the SMC+LP arm appear to have received SMC-only
   - 39 of the 51 received the full LP course, yet there appears to be 44 participants included in the primary analysis

   The numbers here do not seem to add up and it is not clear whether SMC-only participants were included in the SMC+LP data analysis; which would be contamination of the treatment group, affecting the validity of the results.

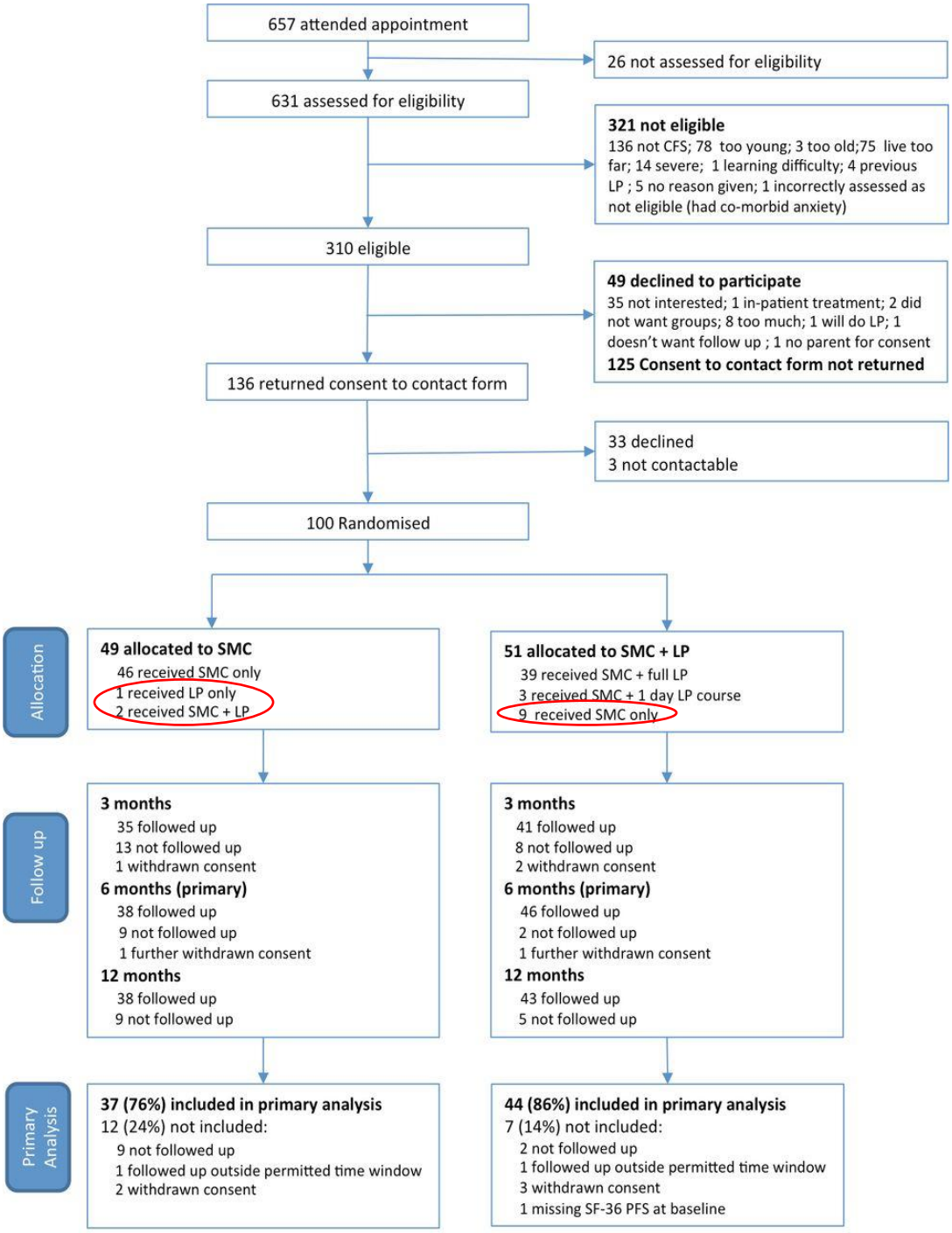
4. The authors said that, 'three participants in the SMC+LP arm received the LP course after completing the 6-month follow-up'.

   This would have affected the results if they were included in the data analysis as the 12-month results would in fact be less than 6 months after LP treatment.

   These areas of the study, largely confused by Figure 1 (below), are not very transparent so it is difficult to determine which participants were included in the final results.

5. The authors said that, 'Five participants withdrew from the study: two from the SMC-only and three from the SMC+LP arm'.

   There are no reasons given that might explain why this was the case and yet it would have been useful qualitative data to collect and might have given us a better idea of the acceptability of the treatment amongst participants.



CFS = Chronic fatigue syndrome; SMC = Specialist Medical Care; LP = Lightning Process

Treatment groups

Specialist Medical Care (SMC)

This group were essentially the control group.

The treatment provided was based on that currently provided by Bath/Bristol specialist service, and:

'focused on improving sleep and using activity management to establish a baseline of activity (school, exercise and social activity) which was gradually increased'.

The study says that the participants were 'offered a variety of treatment options' and that interventions such as CBT (cognitive behaviour therapy) and GET (graded exercise therapy) were 'offered if children needed it'.

This meant that the participants could 'pick and mix' the parts they felt they wanted to receive and so it was not consistent across all participants, making for a very un-controlled control group!

Also, the paper states that 'the number and timing of the sessions were agreed with the child and family, and varied depending on the needs and goals of the child', again adding to the variability of treatment and contact time received by each participant.

There is no information provided on the average number of sessions received or on how many participants received CBT or GET.

Similarly, we don't know how many contact hours in total each child or group received but it appears the children who were in the SMC+LP group received more attention and of course two treatment approaches compared to those in SMC-only.

Specialist Medical Care + Lightning Process®

The LP treatment comprised participants being given an information book to read before attending a three-day course, followed by 2 follow-up phone calls.

The course was run in groups of 3-4 children for around 4-hour sessions on 3 consecutive days. The course consisted of a theory session, a group discussion, and a practical session.

The study describes the protocol as:

"A theory session with taught elements on the stress response, how the mind and body interact, and how thought processes can be either helpful or negative. This was followed by group discussion where the language used was discussed and in some cases challenged, and where participants were encouraged to think about what they could take responsibility for and change. In the practical session, participants identified a goal they wished to achieve

(such as standing for longer) and were given different cognitive (thinking) strategies before and while the goal was attempted."

Problems

The SMC-only control group was not appropriately matched with the SMC+LP group as there was no equivalent 3-day intensive course. SMC-only was not delivered to groups of children but on an individual basis and participants had far less contact with providers than those in the SMC+LP group.

These are both issues that would have affected the results.

It would have been preferable if there had been a separate control group, such as children awaiting treatment i.e. those waiting to be seen by the ME/CFS specialist service. We might then have been able to better compare treatment effectiveness and determine if children improved naturally over time without any intervention.

But the authors felt that it would have been unethical to have a control group without treatment, and yet while they clearly considered this option, it is not clear if they consulted an ethical body about what is relatively standard practice in other clinical trials.

It would also have been better if this trial had compared treatments on a like-for-like basis, for example, one group received an intensive 3-day group standardised activity management course, measured against a similar group receiving just the Lightning Process.

As things stand it is impossible to determine if the LP on its own, or any of its constituent parts, is an effective intervention for ME/CFS in children and adolescents.

Data collection

There was no mention of placebo effects in the study. SMILE does not allow us to reach any informed decision about the effectiveness of SMC or LP.

The outcomes could certainly have been influenced by things like positive expectations and by the way in which both CBT and LP aim to change the way children perceived their symptoms.

In a trial where the participants (and their parents) knew what treatment they would receive (and where SMC was muddled and mixed with LP) the effects of placebo seem even more likely to have occurred.

Other concerns:

1. The use of only subjective outcome measures introduces the possibility of self-report bias, where participants may want to please the investigator – or their parents.

2. Due to the nature of LP, the perception of how participants viewed their symptoms may have changed, while their symptoms had not, which could lead to false-positive reporting.

3. Several studies on CBT have shown that subjective measures showed improvement while objective measures showed no change, or in some cases worsening in fatigue or cognitive ability (Knoop *et al.* 2007, Friedberg *et al.* 2009, Wiborg *et al.* 2010).

4. There are several objective measures which can be used in ME/CFS, such as CPET and cognitive testing (Twisk 2015). The trial could have also used an actometer to objectively measure physical function alongside the SF-36 questionnaires (St-Ogne *et al.* 2007) to increase the validity of the results.

5. The SF-36 questionnaire may not have been the most reliable primary outcome measure for improvement for ME/CFS.

   In a study of patient-reported outcome measures in ME/CFS, there were concerns over the reliability and validity of the SF-36 questionnaire and it was concluded that the DePaul symptom questionnaire was much more reliable (Murdock *et al.* 2017).

   Jason (2015) also found the DePaul questionnaire to be the most valid measure for ME/CFS symptomology. In addition, the SF-36 also does not contain a sleep variable, when sleep is a big part of ME/CFS.

6. School attendance was collected via self-report, based on the number of days attended in the last week. Due to the fluctuating nature of ME/CFS, this may not have been an accurate representation.

   It would have been better to take an objective measurement, for example, from an average attendance over a month taken from school records.

7. To improve follow up rates on questionnaire completion, there was a phone call to non-responder's two weeks after a reminder was sent, where a reduced set of questionnaires was completed over the phone.

   However, answering the questionnaires over the phone could have lead to prompted or rushed answering, producing inaccurate results.

   It is also not clear whether the children themselves completed the questionnaires or if the parents completed them on their behalf, which may have also affected the accuracy of the results.

Results

Physical function improved in both groups overall, however, mean SF-36 physical function improved more over time in participants allocated to the SMC+LP arm than those in SMC.

The differences in mean SF-36 scores at 6 and 12 months were 12.5 and 15.5 respectively, with a higher score in the SMC+LP group.

The authors had pre-defined a minimal clinically important difference as being >10, which these results are, by 2.5.

Those in the SMC+LP group also had reduced fatigue compared with SMC at 12 months (The Chalder Fatigue score was 3.2 lower on average) and greater improvement in anxiety at 12 months, according to both the HADS and SCAS scales (with differences of -12.1 and -2.8, respectively).

Participants allocated to the SMC+LP arm had better school attendance at 12 months than those allocated to SMC, with a mean increase of 0.9 days.

Concerns:

1. The size of the SMC+LP group was reasonably small, at 39, which lowers the validity of the results as low statistical power often leads to inflated effect size estimation and low reproducibility (Faber and Fonseca 2014).

2. We know that several children in the trial were not attending any school when it began. What we don't know is if those same children – because of SMC or SMC+LP – were able to attend any school at the end of the trial. It would have helped determine effectiveness if the authors had included a list of anonymised participants pre- and post-trial recording school attendance so that we could have seen individual outcomes and been better able to judge effectiveness.

3. In the feasibility study, one of the parents suggested that in the LP group you were encouraged to return to school; "now you don't need to do the pacing; you can just go back to school full time".

   This approach may have influenced the 1-day difference in school attendance as the LP group could have been encouraged to return to school, whereas the SMC group could have been encouraged to pace schooling.

   But the authors did not provide sufficient information on the content of these approaches to really draw any conclusions.

4. Published studies that have used CBT and psycho-education approaches, and relied on outcome measures such as the SF-36 questionnaire, claim to be just as effective at increasing school attendance as was determined by the SMILE trial for the Lightning Process® (Chalder *et al* 2010 and Stulemeijer *et al*. 2004).

5. We know that ME/CFS affects a much greater proportion of females than males (around 2:1), so it was interesting to note that males appeared to have a much more significant response to the LP+SMC than did females.

The mean difference in SF-36 scores between the two treatment arms was 26.6 in the males and only 9 in the females. However, the p-value for this association was 0.08 and a p-value of below 0.05 is needed for statistical significance.

The authors stated, 'There was weak evidence that the effect in males was greater than that in females', but this evidence could warrant greater investigation, as the effect in females was not 'clinically important'.

6. Despite the authors remarks about cost-effectiveness, the study is confusing in this regard and it's not at all clear how they arrived at their conclusion.

   For example: "The initial cost of LP *was not* fully offset by marginally lower costs of other care over the 12-month period. The incremental cost of SMC+LP *was higher* in both complete case and multiple imputation datasets".

7. During the study, there were no serious adverse events that could be attributed to either treatment arm in the trial. However, the authors reported, 'Physical function at 6 months deteriorated in nine participants, of whom eight were in the SMC arm'.

   No details were given to explain why this might have occurred which was unfortunate as it leaves us to speculate on what might have been the cause.

   We also don't know if these participants were included in the results - could the scores from these 9 participants (24%) have swayed the mean in a negative direction?

Problems with Studying children

The ME Association and many others had been opposed to this trial on children with ME/CFS because children represent a vulnerable group that would be subjected to a commercial product about which very little was known other than anecdotal reports and proprietorial promotions.

There are important considerations that should be considered before children are involved in research, and these formed the basis of our early protests in 2010 (GMC, Ethical Guidance). However, the feasibility study did identify some issues that were then changed in the main trial and the trial did receive ethical approval.

Children may be more impressionable than adults and may have a stronger desire to please their therapist (or their parents) or to answer questions in a way which reflects what they have been taught e.g. to misrepresent their symptoms, which was a particular concern with the Lightning Process®.

In addition, it has been shown that children are more likely to make a full recovery and recover more quickly than adults (Jordan *et al*. 2010, Burgess 2011, Norris *et al*. 2017).

The children in this study could have improved naturally, which may have contributed to their improved outcomes, however, any such improvement has been assumed to be the result of an intervention.

A proper control group – a non-treatment group – would have helped us to see if children had improved without intervention and we could have made appropriate comparisons.

Finally, it should be noted that the results of this study cannot be more widely applied to adults.

Conclusion

This trial determined that the Lightning Process® was effective when used in addition to specialist medical care in the treatment of ME/CFS in children.

However, it did not determine if the Lightning Process® is effective on its own or if it is any more effective than other treatment options, such as CBT or activity management and/or pacing.

The trial also failed to determine if the Lightning Process® and specialist medical care in their entirety are effective, or if it could have been component parts such as sleep hygiene, or the number of contact hours etc. that might have led to improved outcomes.

And it failed to consider placebo effects or try to address many of the biases associated with trials of this nature and with unblinded studies in general.

From the authors:

- The improvement in SF-36-PFS in those receiving SMC+LP is consistent with those receiving treatment in previous paediatric trials investigating both family based and individual CBT.
- The participants in our study who received SMC only did not improve as much as other trials investigating CBT, which may be because on average they had less than half the number of treatment sessions.
- As we did not compare LP with either a full course of only CBT or GET, we do not know if LP is more of less effective than either of these treatment approaches.
- Further research is needed to understand why LP improves outcomes at 6 and 12 months and which aspects of the LP contribute to its effectiveness.

Any trial that can demonstrate an effective treatment approach which can help improve the quality of children's lives is welcome, however this study should be viewed with caution and it should not be used as evidence of a psychological basis to ME/CFS.

Furthermore, there remains a concern about studies in ME/CFS that do not choose to use more stringent research criteria, or measures that can better definite patient cohorts.

We need to be sure that those being studied have ME/CFS and not 'chronic fatigue' which may be caused by something else or alleviated in ways that ME/CFS may not.

We do not know how the Lightning Process® was delivered in this trial. We don't know if, for example, the delivery replicated exactly how it is sold to members of the public or if it was adapted in some way to pass ethical approval in a trial aimed solely at children and adolescents.

The ME Association remain sceptical of neuro-linguistic programming and osteopathy and of the Lightning Process® in general and despite this clinical trial, we do not recommend this product as a treatment for ME/CFS.

Please help us continue our work

If you have found this review useful then please donate – whatever you can afford – to help us continue with our work to make the UK a better place for people with M.E. Just click the button below to visit our JustGiving page:

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