Health Research Authority

South West - Frenchay Research Ethics Committee
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22 November 2016

Professor Esther Crawley
Consultant Paediatrician, Reader in Child Health
University of Bristol
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Oakfield House, Oakfield Grove
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BS8 2PS

Dear Professor Crawley

Study title:	**The feasibility and acceptability of conducting a trial investigating the effectiveness and cost effectiveness of Graded Exercise Therapy compared to Activity Management for paediatric CFS/ME: A feasibility randomised controlled trial**
REC reference:	**15/SW/0124**
IRAS project ID:	**176764**

Thank you for your letter received 31st October 2016, responding to the Committee's request for further information following a request to re-review the application from a number of parties with concerns about the safety and validity of the study.

The further information has been considered by the Committee.

Summary of discussion at the meeting

The Committee noted that the main issues raised in the challenge to the favourable opinion were as follows;

Controversy surrounding the PACE trial

The PACE trial was a large trial of graded exercise therapy (GET) in adults. The challenge to the favourable opinion stated that the evidence from PACE was controversial, inadequate, flawed and that the protocol specified results did not justify the claim that GET is moderately effective and therefore did not justify a trial of GET in children. The challenge to the favourable opinion stated that the main findings from the PACE trial had now been overturned by its authors after reanalysis of the data.

You provided a written response to the above claims and advised that the recent re-analysis by the PACE authors of primary outcomes, as written in the original protocol were consistent with their original interpretations and that they concluded 'In summary, these results support our initial interpretation that CBT and GET can be safely added to the SMC to moderately improve outcomes for chronic fatigue syndrome, but APT is not an effective addition'.

Your response stated that results from PACE and the wider world literature show that patients are more likely to improve with exercise therapy compared to either medical care alone or medical care plus pacing as given as a therapy.

The Committee discussed the Cochrane review of the PACE trial which had concluded that there was no evidence that the trial would cause any harm to the participants. The Committee commented that the Cochrane review was the most stringent and rigorous review and noted that it stated that 'patients with CFS may generally benefit and feel less fatigued following exercise therapy, and no evidence suggests that exercise therapy may worsen outcomes.' The Committee commented that the exercise therapy used in MAGENTA is in NICE guidelines and does not solely rely on information from the PACE trial with other good research supporting its use. The Committee stated that the Cochrane report underpinned their decision that the MAGENTA trial was scientifically valid.

Risk of harm to the participants.

It was stated that there was evidence that GET carries a significant risk of long lasting harm and that adverse events were reported by hundreds of patients after GET, including children. The challenge to the favourable opinion stated that there was evidence that ME/CFS involved an unusual dysfunction of the aerobic system and the aerobic activity, the goal of GET, could pose a special danger for these patients including exercise induced relapses which could render a patient housebound or bedbound.

Your written response stated that there was no evidence of a significant risk of serious, long lasting harm and that the best quality evidence is from systematic reviews of high quality research which would be relied upon in preference to patient surveys in evidence based medicine. Your response stated that the largest systematic review to date was the Cochrane review which looked carefully at harm and side effects in 1518 patients and concluded that no evidence suggests that exercise therapy may worsen outcomes. Your response advised the Committee that the MAGENTA trial had an independent Data Safety Monitoring Committee (DMSC) appointed by the NIHR which funded the study. The DMSC had reviewed the accumulating data relevant to Magenta which included serious adverse events and all instances of deterioration in the SF-36-physical function subscale in either treatment arm and concluded that the data did not suggest evidence of any harm in MAGENTA.

The Committee discussed the risk of harm to the participants and noted that the PACE results had been interpreted to suggest that GET could be harmful in children. The Committee agreed that what happens with children with CFS/ME is not the same as what happens in adults with the same disease and noted that the PACE trial was carried out in adults which meant that simply carrying out the MAGENTA trial in adults first may not provide the evidence that it would be safe to carry out in children. The Committee agreed that there was no scientific evidence to support the reports of harm to the participants in the MAGENTA trial.

Inadequately informed consent.

The challenge to the favourable opinion stated that the ground for the controversy over the PACE trial reflected poorly on the justification for MAGENTA and also raised serious questions about whether patients, parents and carers gave adequately informed consent/assent. It was stated that the participants in the MAGENTA trial were not made aware of the serious flaws with PACE and the concerns about the risk of serious, long lasting harm from GET or the exercise physiology literature that indicates the potential dangers of aerobic activity.

You responded that informed consent is taken very seriously. It addition to patient information leaflets all participants discuss MAGENTA with the recruiting clinician with a further lengthy conversation with the research nurse to ensure that the information provided is balanced and considered. The information sheets are also discussed at length with a patient advisory group which included children and teenagers with CFS/ME, their parents, adults who developed CFS/ME as a child and the Chief Executive officer from the largest paediatric charity: The association for young children with ME. Your letter advised that you had used GET (as recommended by NICE) in your specialist paediatric CFS/ME service for nearly a decade and after over a year of running MAGENTA and a careful review of both the qualitative data and independent review by the DMSC you were more convinced that children and teenagers were not harmed by GET when delivered by specialist trained therapists.

The Committee discussed whether participants were provided with adequate information to give fully informed consent. The Committee agreed that the PIS allows informed consent to take place and is balanced. The Committee noted that the PIS contains important information that advises the participant that GET might help their condition, they might remain the same or it might make them feel worse. The Committee agreed that the information provided is well balanced and the possibility that this may not help was not hidden from the participant. The Committee agreed that the information provided allowed the participants to give full informed consent.

Confirmation of ethical opinion

On behalf of the Committee, I can confirm a favourable ethical opinion for the above research still stands.

After considering the evidence provided the Committee agreed there was no evidence to support the claim that the MAGENTA trial may not be scientifically valid.

The Committee agreed that based on the evidence provided and the review of the Cochrane report there was no evidence of risk of harm to the participants or to suggest that exercise therapy may worsen outcomes.

The Committee agreed that the PIS was well balanced and fair and provided all the required information to allow the participant's consent to be fully informed.

The Committee agreed that based on the information provided the favourable opinion of the study would still remain.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
GP/consultant information sheets or letters [Letter to participants GP]	d0.1	09 April 2015
Interview schedules or topic guides for participants [MAGENTA discussion topic guide]	d0.2	17 April 2015
IRAS Checklist XML [Checklist_23042015]		23 April 2015
IRAS Checklist XML [Checklist_02072015]		02 July 2015
Letter from funder [Confirmation of NIHR Award]		19 September 2013
Other [CFSActivityRestSleepdiary.]		
Participant consent form [8-15 assent to contact]		
Participant consent form [8-15 assent to record]	d0.6	16 April 2015
Participant consent form [8-15 assent to study]		
Participant consent form [8-15 assent to record treatment session]		
Participant consent form [16-17 consent to contact]	d0.5	09 March 2015
Participant consent form [16-17 consent to record]	d0.6	16 April 2015
Participant consent form [16-17 consent to study]	d.04	09 March 2015
Participant consent form [16-17 consent to record treatment session]	d0.5	09 March 2015
Participant consent form [Parent/Carer consent to contact]	d0.5	09 March 2015
Participant consent form [Parent/Carer consent to record]	d0.6	16 April 2015
Participant consent form [Parent/carer consent to study]	d0.4	09 March 2015
Participant consent form [MAGENTA 16-17 consent to study 17052015 d0.5]	d0.5	17 May 2015
Participant consent form [MAGENTA parent carer consent to study 17052015 d0.5]	d0.5	17 May 2015
Participant information sheet (PIS) [8-11]	v0.6	30 March 2015
Participant information sheet (PIS) [12-17]	v0.7	31 March 2015
Participant information sheet (PIS) [Parent/Carer]	v0.6	30 March 2015
Participant information sheet (PIS) [MAGENTA PIS 8-11 30032015 v0.6]	v0.6	30 March 2015

Participant information sheet (PIS) [MAGENTA PIS 12-17 17052015 v0.8]	v0.8	17 May 2015
Participant information sheet (PIS) [MAGENTA PIS Parent OR Carer 17052015 v0.7]	v0.7	17 May 2015
REC Application Form [REC_Form_17042015]		17 April 2015
Referee's report or other scientific critique report [ECrawley Fellowship Review]		
Research protocol or project proposal	v.09	09 April 2015
Summary CV for Chief Investigator (CI)		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [MAGENTA Summary flowchart]		15 April 2015
Validated questionnaire [Sleep diary]	April 2015	
Validated questionnaire [Paediatrics follow-up postal assessment (under 12's)]		
Validated questionnaire [Paediatrics follow-up postal assessment (over 12's)]		
Validated questionnaire [MAGENTA Postal questionnaire pack over 12's v0.1 20042015]	v0.1	20 April 2015
Validated questionnaire [MAGENTA Postal questionnaire pack under 12's v0.1 20042015]	v0.1	20 April 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

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available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

15/SW/0124	**Please quote this number on all correspondence**

Yours sincerely

P.P. S Draper.

Mr Stephen Draper
Chair

Email: nrescommittee.southwest-frenchay@nhs.net

Copy to: *Dr Jane Carter, Royal United Hospital Foundation Trust- RNHRD*