



Centre for Child & Adolescent Health  
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<http://www.bristol.ac.uk/ccah/>

Dear Natasha

**RE: 15 SW 0124. The MAGENTA Trial**

Thank you for offering me, on behalf of the MAGENTA team, the opportunity to address these concerns. I have addressed each issue in turn and I have also enclosed copies of the relevant publications.

The REC is probably aware that there are always campaigns against CFS/ME research, particularly research into behavioural approaches to treatment. These have been well described in both the scientific and lay press and are alluded to by the complainant. The current campaigns are focussed on treatment trials but also extend into biological research. There is currently a campaign against the MAGENTA trial and I have therefore provided a summary (appendix 1) of what has happened to date with this campaign.

My patients and participants in MAGENTA want research and want access to the full range of treatment options. This is reflected in the consistently high recruitment and retention rates we have experienced with MAGENTA. As you know, we included integrated qualitative studies in MAGENTA and we asked participants and their parents about both the trial and their views on graded exercise therapy (GET). Patients and participants like GET and want to be able to have it. They also want more research and want to be involved in trials.

I feel that the patient voice is important but it is rarely heard when discussing CFS/ME research which saddens me. Given the trial is ongoing, we have not analysed the qualitative data yet, but given the relevance of this to the concerns raised I think that it may be informative to your committee in understanding the issues.

I have therefore attached the quotes relating to GET (appendix 2) and the quotes about being involved in this trial (appendix 3). I have included all available quotes, anonymised but not otherwise edited.

I am certain the REC will receive FOI requests for the information included in this response. I am sure that the REC is aware that the qualitative quotes included here are exempt under section 22 "information intended for future publication". I suggest that I post this response (as is our normal policy) on the MAGENTA website but withhold the qualitative quotes prior to publication, not least because the trial is still in progress and I would not wish to bias future participants. I would be grateful if you could let me know your thoughts on this.

My detailed response to the complainant's comments are below:

**MAGENTA's protocol<sup>3</sup> justifies a paediatric trial of GET on the grounds that a large trial of GET in adults, published in 2011 — the PACE trial<sup>4</sup> — showed that GET is moderately effective in adults.**

The complainants are correct that the evidence from PACE is important and we discuss this further in this response. However, PACE only provides a contribution to the evidence base that exercise therapy is helpful in adults. A recent Cochrane independent systematic review (attached) of 8 trials (1518 patients) concluded that: “exercise therapy was more effective than passive treatments or no treatment”, and had a “positive effect on people’s daily functioning”. It also found “exercise therapy was not found to worsen symptoms for people with CFS”. Prior to PACE, there were two systematic reviews, two meta-analyses and two other trials. These all concluded that Graded Exercise Therapy was moderately effective.

**However, the evidence from PACE is inadequate, flawed, and enormously controversial — and its main findings have now been overturned by its authors’ own reanalysis of the data.**

This is incorrect. The original findings about the effectiveness of PACE are not disputed by the complainant. The original paper is attached which demonstrates the effectiveness of GET and CBT compared to Specialist Medical Care with or without Pacing.

The recent re-analyses by the PACE authors of primary outcomes, as written in the original protocol, were consistent with their original interpretations and they concluded: ‘In summary, these results support our initial interpretation that “CBT and GET can safely be added to SMC to moderately improve outcomes for chronic fatigue syndrome, but APT is not an effective addition.” See: [http://www.wolfson.qmul.ac.uk/images/pdfs/pace/PACE\\_bimodal\\_CFQ\\_analysis\\_final\\_8\\_Sept\\_2016.pdf](http://www.wolfson.qmul.ac.uk/images/pdfs/pace/PACE_bimodal_CFQ_analysis_final_8_Sept_2016.pdf), [http://www.wolfson.qmul.ac.uk/images/pdfs/pace/PACE\\_published\\_protocol\\_based\\_analysis\\_final\\_8th\\_Sept\\_2016.pdf](http://www.wolfson.qmul.ac.uk/images/pdfs/pace/PACE_published_protocol_based_analysis_final_8th_Sept_2016.pdf)

Therefore the primary findings of effectiveness are not disputed.

**We bring the following facts to your attention.**

**(1) New findings**

The 640-patient PACE trial dominates the literature on GET for ME/CFS. However, when its results were published, the protocol-specified thresholds<sup>5</sup> for “improvement” (the original primary outcome) had been drastically lowered. 61% of the GET group and 45% of a no-therapy control group were classed as “improved”. Additional post-hoc analyses used disability and fatigue thresholds in which patients could *get worse during the trial and yet be classed as effectively treated*. Together, these analyses were the basis for the PACE authors’ claim that GET was “moderately effective”. A patient’s Freedom of Information request has now forced the release of the relevant anonymised individual patient data. The day before release, the PACE authors finally published the

protocol-specified “improvement” figures.<sup>6</sup> They show that only 21% of the GET group “improved”, and 10% of the no-therapy group. That is, improvement rates using the protocol-specified measure are *a third of what was reported* and only ten percentage points higher than the comparison group. Considering that these results are based on self-report measures in an open-label trial, this is a very poor outcome and consistent with GET having no genuine effects at all.

1. In the PACE study, the authors investigated and reported on the efficacy of CBT, GET and Pacing in addition to specialist medical care. The primary outcome was the efficacy of treatment which they analysed by comparing the primary outcome between groups. The results of this are demonstrated in their paper ((White, 2011), see figures 2, 3 and table 3). These results showed: “*When added to SMC, CBT and GET had greater success in reducing fatigue and improving physical function than did APT or SMC alone. APT was not better than SMC*”. The complainants do not discuss these important results.
2. The statement “**Additional post-hoc analyses used disability and fatigue thresholds in which patients could get worse during the trial and yet be classed as effectively treated. Together, these analyses were the basis for the PACE authors’ claim that GET was “moderately effective”**” is not correct. Neither is it “**new information**” as it relates to analyses published in 2011.

The authors performed an additional secondary post hoc analyses to give the proportions of participants in each treatment arm who were within the population normal range (mean +/- SD) for the primary outcomes of fatigue and SF36 physical function sub-scale: “*In another post-hoc analysis, we compared the proportions of participants who had scores of both primary outcomes within the normal range at 52 weeks.*” (White et al, 2011) Since these thresholds were entirely independent of trial thresholds for eligibility, there were some (13%) participants who were within normal range of one or both primary outcomes at baseline. However, White and colleagues never stated that being in the normal range for primary outcomes was the same as being effectively treated. Their analyses was based on improvement between baseline and follow up. For a clinically useful difference or effect, participants had to improve by 8 or more points in SF36 and/or 2 points in fatigue. Please see page 831 of the White paper.

3. The complainants are correct in saying the authors have published their own results using the outcomes stated in their original protocol. . They did this to ensure it was done properly and with all the data necessary to do this. Here are the links to these analyses, published on their website.  
[http://www.wolfson.qmul.ac.uk/images/pdfs/pace/PACE\\_bimodal\\_CFQ\\_analysis\\_final\\_8\\_Sept\\_2016.pdf](http://www.wolfson.qmul.ac.uk/images/pdfs/pace/PACE_bimodal_CFQ_analysis_final_8_Sept_2016.pdf)

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As you will see, these re-analyses made no difference to the original conclusions; *‘In summary, these results support our initial interpretation that “CBT and GET can safely be added to SMC to moderately improve outcomes for chronic fatigue syndrome, but APT is not an effective addition.” ‘*

**If these figures had been reported in 2011, it seems likely that NICE would have abandoned GET as a therapy for ME/CFS.**

The NICE guidance was published four years before PACE was published, based on previous literature with which PACE is consistent. Prior to PACE there were two systematic reviews, two meta-analyses and two other trials. These all concluded that Graded Exercise Therapy was moderately effective. The primary analyses from the PACE trial are undisputed. The authors’ re-analyses are consistent with the original results. Therefore it seems very unlikely that NICE would have abandoned GET as therapy for CFS/ME.

**The protocol-specified results clearly do not justify the claim that GET is “moderately effective”, and do not justify a trial of GET in children.**

We disagree. The 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 given as a therapy.

**Patients, working with professors of statistics Bruce Levin of Columbia University and Philip B. Stark of the University of California, Berkeley, have now analysed the recovery rates in PACE according to the original protocol. Instead of the 22% recovery rate reported for GET, with a 7% rate in the no-therapy group, they found rates of 4% and 3%, respectively (the difference between the groups in the new analysis is non-significant). These null results further undermine the case for GET.**

This re-analysis used more stringent thresholds to define recovery, so it is no surprise that proportions meeting these criteria are smaller. For instance the Levin analysis excludes participants who rated their overall health as “much better” after GET from counting towards being recovered. Furthermore this analysis has not been subject to peer review nor has it been published in a scientific journal. We do not believe that such an additional

analysis on a secondary outcome using a more stringent definition of recovery means that we should not continue to test GET in children.

## (2) Controversy

It is impossible to overstate the level of controversy now surrounding PACE. In October 2015, Dr. David Tuller, a public health specialist at the University of California, Berkeley, published an extensive critique of PACE online, which gathered widespread attention.<sup>7</sup> The problems in the study were so remarkable that in November, a group of scientists and clinicians — now numbering over 40 — signed an open letter requesting independent reanalysis. They stated that PACE “suffered from major flaws that have raised serious concerns about the validity, reliability and integrity of the findings.... Such flaws have no place in published research.”<sup>8</sup> (See Appendix 1). Shortly afterwards, over 12,000 patients signed a petition requesting reanalysis, and the retraction of misleading claims in PACE,<sup>9</sup> and in March this year, 24 ME/CFS organisations in 14 countries, representing tens of thousands of patients, wrote to demand the release of anonymised data from PACE to the patient who had requested it under the Freedom of Information Act, to allow independent reanalysis.<sup>10</sup> Coverage of the controversy has ranged from the Wall Street Journal<sup>11</sup> to the US’s largest statistical conference.<sup>12</sup>

Controversy is not a basis for not seeking better treatment for patients. The only answer to a controversy is to undertake properly designed and ethically approved trials and studies, in order to provide stakeholders with the highest quality of evidence to resolve the controversy; something that MAGENTA is well placed to do. The PACE trial was funded by the MRC after extensive peer review. It was published in the Lancet in 2011, after high quality peer review. The editor of The Lancet has stated that he has no intention of retracting the paper, having been asked to do so. PACE publications continue to be published in high impact journals after peer review. The re-analyses referred to by the complainants has not been published in a peer review journal.

## (3) Risk of harm

There is evidence that GET carries significant risk of serious, long-lasting harm. Outside of PACE, surveys<sup>13 14</sup> show adverse events being reported by hundreds of patients after GET, including children (see Appendix 2). In PACE, there was no apparent association between adverse events and GET, but GET patients also failed to increase their fitness,<sup>15</sup> which suggests that they were unable to increase their overall activity. Thus attempts at GET may be safe, but perhaps only if the therapists involved accept the failure of the treatment and do not push patients to increase activity.

The complainants are not correct that there is “**significant risk of serious, long-lasting harm**”. The best quality evidence is from systematic reviews of high quality research and in evidenced based medicine, we rely on this in preference to patient surveys. The largest systematic review to date (the

Cochrane review, attached), looked carefully at harm and side effects in 1518 patients. They concluded that: *“no evidence suggests that exercise therapy may worsen outcomes.”*

The main PACE trial paper examined five measures of harm, and concluded that *“CBT and GET can safely be added to SMC to moderately improve outcomes for chronic fatigue syndrome”* (White 2011, attached). A later paper has been published examining adverse events in PACE in more detail, and concluded that *“The numbers of adverse events did not differ significantly between trial treatments, but physical deterioration occurred most often after APT.”* (Dougall et al, 2014, attached).

There are many reasons why patient surveys describe different results to those described in well conducted randomised controlled trials and prospectively collected cohort studies. There are additional reasons for this in CFS/ME. For example, patients may believe they have received GET when in fact they have just been told to go and exercise. The reasons for this difference in opinion are discussed in paper by Mallet (attached) which describes the wide difference in opinion between medical authorities and patient support organisations.

I take the risk of harm in my patients very seriously. MAGENTA has an independent Data Safety Monitoring Committee (DSMC), appointed by the NIHR which funded the study, which carefully reviewed the risk of harm before MAGENTA moved from feasibility to full trial. The DSMC has reviewed the accumulating data relevant to MAGENTA. This not only includes Serious Adverse Events but Adverse Events and all instances of deterioration in the SF-36-physical function subscale in either treatment arm. The DSMC has concluded that the data do not suggest evidence of harm in MAGENTA.

**There is evidence that ME/CFS involves an unusual dysfunction of the aerobic system, and that aerobic activity — the goal of GET — could pose a special danger for these patients.<sup>16</sup> Exercise-induced relapses can render patients housebound or bedbound and can last indefinitely. The implications for children are extremely worrying.**

The studies investigating biological function in adults with CFS/ME are interesting. At the moment, they are based on small sample sizes and have not always used sedentary controls so it is difficult to know what is a primary biological problem or a secondary effect.

However, they underline the importance of careful assessment by a specialist before providing GET. As you will see from the MAGENTA protocol and from the qualitative quotes, the first step in GET is to convert the “boom-bust” approach (a lot of activity one day followed by little the next), common in children with CFS/ME, to a baseline of steady activity. Children have detailed physical assessments and are only asked to increase exercise very slowly when activity levels are stable. This usually means that children are asked to reduce bouts of aerobic

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activity at the start of treatment. Arguably, (if what the complainants say is true), this should reduce risks (if they exist). We would refer the REC to participant quotes about GET where it is clear that participants enjoy GET, with no suggestion of experiencing harm, and in fact, start to regulate activity and make improvements.

#### (4) Inadequately informed assent/consent

The grounds for the controversy over PACE reflect poorly on the justification for MAGENTA but also raise serious questions about whether patients, parents and carers gave adequately informed assent/consent in the feasibility trial, or could do so in the larger trial. The MAGENTA participation-information sheet for parents/carers merely states:

“Treatments for CFS/ME don’t help everybody and you may find the treatment your child has been offered does not help them.... Young people with CFS/ME can get worse with any intervention offered and we do not know how likely this is.... We have used [GET] in our service and we are not aware of side effects. Studies in adults have also not shown that there are any side effects of [GET].”<sup>17</sup>

We can find no publicly available MAGENTA documents that mention the serious flaws with PACE, or the long-running controversy surrounding it; or the concerns from survey data about the risk of serious, long-lasting harm from GET; or the exercise physiology literature that indicates the potential dangers of aerobic activity to ME/CFS patients.

We take informed consent very seriously. In addition to detailed patient information leaflets, all potential participants discuss MAGENTA with the recruiting clinician. They then have a further lengthy conversation with the research nurse where all aspects of the trial are discussed. These recruitment discussions are listened to by the research team to ensure that the information provided is balanced and considered. We ensure that participant questions are answered and that patient preference is determined.

All our patient information is discussed at length with our Patient Advisory Group. This group includes 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 people with ME. This group did not recommend making the changes suggested by the complainant.

We stand by our statement that “*we have used GET in our service and we are not aware of side effects*”. We have used GET (as recommended by NICE) in my specialist paediatric CFS/ME service for nearly a decade. After over a year of running MAGENTA, and careful review of both the qualitative data and independent review by the DSMC, we are even more convinced that children and teenagers are not harmed by GET when delivered by specialist trained therapists as in our service. The qualitative data shows how much children and teenagers in our service enjoy both GET and being involved in a trial.



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We stand by our statement that there is no evidence of harm. There is increasing evidence that GET is safe as long as it is delivered by the appropriate specialists. We would argue that providing patients with low quality evidence from patient surveys that is not consistent with higher quality evidence from systematic reviews may bias the trial because of a nocebo effect. We believe patients have the right to the highest quality of evidence when available (as it is in this case).

**All of the serious problems with PACE mentioned in the scientists' joint letter were in the literature for years before the MAGENTA feasibility study began, yet the study's protocol simply repeats the PACE authors' statement that GET is "moderately effective", with no critical assessment: but PACE's flaws are so serious that even a feasibility study for MAGENTA should never have been funded. Now that key protocol-specified analyses have been published, it is clear that PACE did not show GET to be "moderately effective" and that its results are insufficient to justify further trials — and even perhaps, continued use of GET within the NHS.**

Please see our answers above, specifically those relating to the extensive trial and independently assessed systematic review data refuting the complainant's allegation.

**We consider that there is no rationale for a trial of GET in children and that they are being put at unnecessary risk in MAGENTA; and we can see no evidence that patients, parents or carers have been — or will be — provided with a basis for adequately informed assent/consent.**

NICE guidance is clear that children and young people should be offered CBT, GET and Activity Management for CFS/ME. Children, teenagers and parents in our service want GET treatment. However, this recommendation is on the basis of expert opinion and there is a specific research recommendation regarding additional evidence for children in CFS/ME: there is currently no evidence for the effectiveness and cost effectiveness. It is therefore vital that this is studied in a well-run trial, with minimal bias, so that evidence-based decisions can be made.

There is no evidence of risk to children with CFS/ME. There was no evidence before we started the trial, and now after a successful year of recruitment and follow up, we can confirm that there is no evidence that participants who receive GET are at any increased risk of harm. In fact, our view is that our results to date are reassuring that children not only do not experience harm, but enjoy GET, like being part of a trial and are keen on further research.

**We therefore ask you to take what action you can within your remit to halt the new, larger MAGENTA trial. We also ask you to investigate what appears to have been a serious failure to give patients, parents and carers an adequate basis for informed consent in the feasibility trial.**





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Thousands of patients have already signed a petition to the UK Government requesting MAGENTA, and all GET trials, to be stopped. Given the level of public interest, and the well-founded concerns of research scientists, statisticians, clinicians — including paediatricians — we have published our letter to you online. We now ask you to act without delay to protect the patients in MAGENTA and we look forward to your quick attention to this urgent matter.

As the chief investigator of this trial, and the lead for the largest paediatric CFS/ME service in the UK. I ask that you listen to the patient voice. Patients and participants with CFS/ME want this trial to go ahead. Clinicians want to know whether they should offer GET. The NHS needs to know whether GET is safe, effective and cost effective for children and young people with CFS/ME. MAGENTA is a successful trial that will provide important answers for the NHS.

Yours sincerely

A handwritten signature in black ink, appearing to be 'E. Crawley', written in a cursive style.

Professor Esther Crawley  
BA (Hons), BM, BCh, FRCPCH, PhD