PE1690/QQ
Petitioner submission of 11 November 2019

Responding to NHS Lothian submission of 23 August 2019

The NHS Lothian submission was titled "What was the PACE trial?". It defended the use of the PACE trial as evidence for the efficacy and continued use of Graded Exercise Therapy (GET) and Cognitive Behavioural Therapy (CBT) as treatments for people with Myalgic Encephalomyelitis (ME). #MEAction Scotland were surprised and disappointed by the tone and contents of the NHS Lothian submission. We are concerned that this response demonstrates the level of misinformation surrounding ME, the mis-reporting and lack of understanding regarding the evidence around GET and CBT. We, ME stakeholders and academics have previously submitted evidence to the Committee on this subject (1,2,3,4,5,6,7,8,). We have chosen to provide a comprehensive response to NHS Lothian because people with ME consistently report deteriorating health during GET in patient surveys, and urgently need care and support based on the best available evidence.
We have have bolded and italicised all quoted statements from NHS Lothian, our comments are below each statement.

"A substantial proportion of participants met an ME definition."
The diagnostic criteria for entering the PACE trial was the Oxford criteria for chronic fatigue syndrome (CFS). We detailed the problems with using this criteria in page 2 of our previous submission. "The result is that findings from research conducted on a group of people, many of whom do not have ME, are being applied to all people with ME."
In the PACE trial, they did assess patients on whether they met a criteria of ME, but the assessment was not a criterion for entry into the trial.

"The study looked very carefully for harms and found no excess of harms with the rehabilitative-type treatments."
When the Cochrane Library published their updated systematic review of exercise therapy in adults with 'CFS' in October 2019, which included the PACE trial, their conclusion was: "We are uncertain about the risk of serious adverse reactions because the certainty of the evidence is very low." (Cochrane Systematic Review)

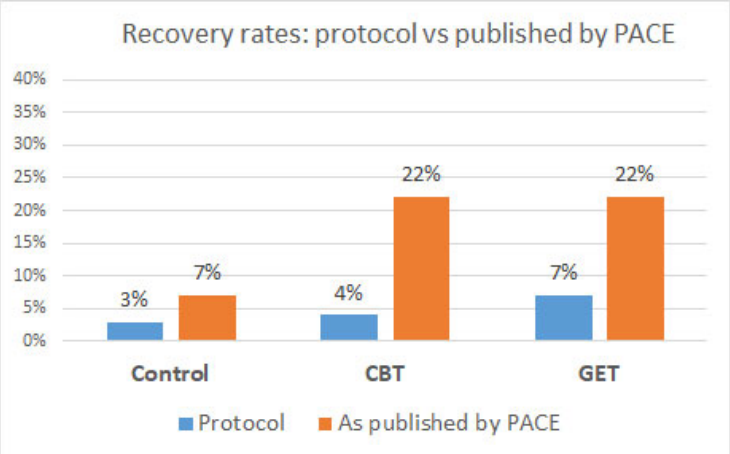
NHS Lothian states a main criticism of the trial is:
"The trial finding that CBT and GET are superior to APT and standard medical care is false because it used patient rated outcomes."
This appears to mis-represent one of the main criticisms of the trial which was:

- The trial was unblinded combined with subjective outcomes: Professor Edwards details the problem with conducting unblinded trials with subjective outcomes in his June 2018 evidence: "*the treatment deliberately induces subjective bias of exactly the sort that proper trial design is designed to avoid.*"

"*Bias in patient-rated outcomes is a risk.. This is a problem for all trials of therapies of which the patient must be aware of used for a condition, which is defined in subjective terms."* Later on they conversely state: *"It is very hard to see that even if anyone had wanted to bias the results or to commit fraud, how they would have been able to do so"*
Acknowledging the potential for bias in patient rated outcomes, and the fact that this is a problem for all trials, does not make the bias disappear. It just means that there is a general problem of reliability in research using such outcomes.

Allegations about the Trial?
"The investigators changed the trial outcomes to make CBT and GET look better."
"The trialists used the originally registered primary outcomes to report the trial findings. There was no 'outcome-switching'." "The precise way the outcomes were used in the analysis was changed from the initial protocol following statistical advice."
Before trials are published investigators publish a 'trial protocol', in which they explain how they will measure improvement and recovery. In the case of the PACE trial, after the results had been collected the investigators weakened their standards of improvement and recovery. Publishing a trial protocol before analysing collected data is intended to prevent any such alteration in measurement of improvement or recovery to favour the study hypotheses. Below we provide evidence of how "the precise way the outcomes were used" worked to produce results that favoured the PACE investigators' hypothesis.

Comparing recovery rates analysed according to trial protocol vs final published report.
A comparison table of the difference between how improvement and recovery was measured in the trial protocol and how it was measured in the final report is available on (Wilshire et el. 2018. pg 3***)*** and summarised in the chart below***.***



Source: Simon McGrath, MECFS Review

- These changes meant that the number of people defined as “recovered” after CBT and GET tripled from 4% and 7% respectively to 22% for each (Wilshire et al. 2018). If the original trial protocol had been adhered to the results would have been statistically insignificant.
- In the investigators’ revised analysis, the trial had overlapping recovery and entry criteria. This means that their threshold of recovery was lower than their threshold for significant illness. It also meant that patients could meet the criteria for recovery even if their health had worsened during the trial. Entry criteria for the trial included a score of 65 or below on the Short-Form 36 physical function subscale (PACE trial protocol. pg 35) . The investigators later changed it so that participants were considered recovered at 60 or above on the subscale (White et al. 2013).

“The definition of recovery is contentious”

The common definition of recovery is a return to a normal state of health. Wilshire et al (2016) noted that “the lowered threshold of measuring recovery was so low that it was similar to the mean score of those with rheumatoid arthritis, and Class II congestive heart failure.” We ask the committee if they consider this an appropriate definition of recovery?

“A secondary paper exploring definitions of recovery found about twice as many people could be considered recovered with CBT and GET vs APT and SMC.”

According to the PACE investigators’ own research, there was no difference between the four treatments at long term follow up i.e there is no evidence that CBT/GET is better than adaptive pacing therapy (APT) or specialised medical care (SMC) (Sharpe et al. 2015).

“The allegation that people could be recovered when starting the trial is simply nonsense.”

When the trial data were made publicly available, an analysis revealed that 13% of the participants were qualified as recovered before the trial began, according to the investigators’ own revised physical function subscale recovery criteria. For three of these cases physical function was lower at the end of the trial than at the beginning. (Wilshire et al. 2016)

“The precise way the outcomes were used in the analysis was changed from the initial protocol following statistical advice.”

Although statistical analysis can change in research as new information is presented from a trial, the changes must be transparent, sensitivity analyses published and a reasonable explanation given - none of these took place.

Reason for change 1: The original protocol states that one of the criteria for recovery was a score of 85 or above on the SF-36 physical function scale (PACE trial protocol. pg 51). In a 2013 paper (White et al.) the investigators explained their reason for deviating from the analysis in their original protocol. They state that the

threshold needed to be lowered as the original aim of 85 meant that half the general working age population would not meet this criterion i.e that it was too high. However, the data they then referenced to evidence this included people above working age and those with long term health problems (Bowling et al 1999, pg 264, table 3), invalidating their revised definition of recovery.

Reason for change 2: Investigators have stated:
"We prefer the definitions of recovery we used to those used by Wilshire et al. as they give absolute rates more consistent both with the literature, and with our clinical experience." (Sharpe et al. 2019).

Research is intended to interrogate the truth of previous results - outcome criteria should not be changed to bring results them in line with previous research.

"The PACE trial data has been shared with a number of other scientists, including a Cochrane Collaboration Review group."
A principal investigator of the PACE trial stated that "disclosure to the Cochrane Review does not count as disclosure to independent scientists as all three of the PACE principal investigators sat on the review panel" (First-tier Information Rights Tribunal. pg 31).

"This released data has been used to "reanalyse" the trial results, with a claim that the published results were misleading. The reanalysis was flawed and consequently misleading."
The re-analysis was done according to the PACE investigators' own protocol: if it was flawed and misleading, the investigators have not explained why.

"Many lengthy critiques have been produced alleging myriad flaws in the trial. Some of these quotes from scientists, none of whom are experts in clinical trials."
We detailed in our last submission that the flaws of the trial have been debated in multiple peer- reviewed journals and that the PACE trial has been used in academic coursework as an example of poor study design and unethical reporting practices. Over a hundred international academics are calling for its retraction.

"The PACE trial has been replicated many times. There are Cochrane reviews of these multiples studies."
The PACE trial has not been replicated. The most recently published Cochrane review of exercise therapy "*now places more emphasis on the limited applicability of the evidence to definitions of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) used in the included studies, the long-term effects of exercise on symptoms of fatigue, and acknowledges the limitations of the evidence about harms that may occur."* (Cochrane, 2019)

Conclusions

"It is most unfortunate that hostility to such treatments and associated misconceptions have led activist groups (not patients in general) to reject these treatments and to also to seek to discredit the science supporting them"

This sets up a false dichotomy between patients and 'activists', effectively silencing patients as anyone who speaks out about a negative experience or talks about issues with trial methodology is accused of hostility. As patients who have received these treatments, we are trying to advocate for ourselves and other patients, and make the patient voice heard. Thousands of us have reported being worse after receiving GET. This has been ignored. Ultimately, this narrative does have a negative impact on patients and we are saddened that it continues to be perpetuated.

Many researchers have spoken about how valuable the patient activist-researcher relationship is. Professor Ponting of Edinburgh University said earlier this year: "*Can I state categorically that ME scientists are not being harassed by the ME community. We are listening to legitimate questions and concerns about science."*

We thank the Petitions Committee for their time and hope that our responses and conduct throughout this process goes some way towards rebutting the suggestion of hostility on the part of patients.

Action

We ask the Petitions Committee to request that Healthcare Improvement Scotland issue a Patient Safety Alert about GET for ME patients to primary healthcare practitioners. We reiterate our ask that GET and PACE-style CBT is withdrawn from the Scottish Good Practice Statement and the Statement is updated.

People with ME urgently need appropriate advice and care. If the guidelines were updated, we could roll out education and invest in care for ME, and patients in Scotland would get the care they need.