PE1690/CC
MEAction Scotland submission of 8 March 2019

Response to oral and written evidence submitted by the Cabinet Secretary for Health and Sport, Chief Medical Officer and the Deputy Director, Planning and Quality Division

This document restates and lays out the evidence for #MEAction Scotland's position on the removal of Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) as primary treatments in Scotland:

1. The majority of people with ME find GET harmful
2. There is a lack of evidence that either CBT or GET is beneficial
3. Due to a lack of transparency regarding points one and two, it is not possible for people with ME to participate in these treatments with informed consent

We include in our submission a table that references abnormalities found in people with ME. We consider it irresponsible for any healthcare professional to ignore this evidence to make claims about the illness based on their personal beliefs. We conclude our submission with a summary of next steps.

Issue 1 - Do No Harm

Do no harm is one of the fundamental principles of medicine. It is a doctor's job to support the wellbeing of their patients. To continue to give treatments that the majority of patients find harmful and for which there is no evidence of long term benefit is unethical - *Why would we continue a treatment which the majority of patients find harmful?*

- **Documented exercise related physiological abnormalities in ME:** The main symptom of ME is Post Exertional Malaise (PEM)[1]: an exacerbation of symptoms following physical or cognitive exertion. It has been objectively demonstrated by exercise physiologists that people with ME have impaired aerobic energy metabolism, and muscle biopsies reveal ME patients have severe metabolic impairments (Brown et al 2015[2], Snell et al. 2013). The following changes have also been measured in people with ME during exercise:

Table 1: Comparison of the Effects of Exercise on People with ME and Healthy People

People with ME	Healthy people
Reduced blood flow to the brain and heart (Neary et al. 2008)	**Increased blood flow** to the brain and heart
Reduced oxygen uptake in red blood cells (Miller et al. 2015)	**Increased oxygen uptake** in red blood cells
Reduced oxygen utilisation (Vermeulen, R. C., & Vermeulen van Eck, I. W. 2014)	**Increased oxygen utilisation**

- **Patient reports of harm:** A 2018 survey with over 600 respondents found that most ME sufferers (89%) experienced worsened symptoms after increasing activity. Physician-led GET was also found to exacerbate symptoms in the majority of people with ME in a 2015 survey.

[1] The biggest literature review to date, by the National Academy of Medicine in 2015, concluded that PEM is the primary feature of ME, and can be used to distinguish ME from other diseases (NAS 2015)
[2] https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0122982

- **Precedent from other countries**: The US Agency for Healthcare Research and Quality (AHRQ) has downgraded its recommendation of GET and CBT in ME, and the US Centers for Disease Control and Prevention (CDC) has removed these treatment recommendations from its website.

Issue 2 - Lack of Evidence that CBT or GET Benefits People with ME

- **There is no evidence that the research used to recommend CBT and GET was conducted on people with ME.** The evidence for giving CBT or GET as primary treatments for people with ME comes from research using the Oxford Criteria. The main requirement for these criteria is 6 months of unexplained fatigue. Fatigue is a non-specific symptom of many illnesses. The criteria do not select for people who have post exertional malaise, the cardinal symptom of ME. This has led the US Agency for Healthcare Research and Quality to conclude that there is a high risk of patients with other fatiguing illness being included in any research undertaken using the Oxford Criteria, and for the National Institute of Health to state that the use of the Oxford Criteria "may impair progress and cause harm". The research that is used to justify the use of CBT and GET in people with ME does not use diagnostic criteria that identify people with ME, but rather individuals with a variety of chronic, fatiguing illnesses. 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.
- **The PACE trial,** the flagship study used to justify the prescription of CBT and GET for people with ME, has been debunked. It has been flagged with a letter of concern[3] by PLoS One (the Public Library of Science) and multiple critiques of the study's flaws have been released by academics and MPs. The trial contained uninterpretable anomalies such as overlapping entry and recovery criteria. The PACE trial has been used in academic coursework as an example of poor study design and unethical reporting practice[4]. Over a hundred international academics are calling for its retraction[5]. The PACE trial used the Oxford Criteria that encompass many chronically fatiguing illnesses. It appears that even for people with Oxford-diagnosed chronic fatigue, GET and CBT are not useful treatments.
- **Note:** The Lothian clinic evolved from the Scottish branch of the PACE trial. In NHS Lothian's submission to the Scottish Parliament, they stated they "do not accept" criticisms of the trial, but offered no explanation and did not address any of the problems with the trial. This is a highly unscientific and irresponsible approach to evidence based medicine by a Scottish health board.
- **Lack of evidence of benefit**: Objective measures – like actimeters/step-trackers, getting off benefits, and going back to work – are unaltered, or may even be worse after GET and CBT (Wiborg J., 2010). In medical practice, CBT has not yielded any long term benefits in people with ME, and the idea that CBT or graded activity can reverse or cure ME is not supported by post-intervention outcome data (Friedberg D and Adamowicz J., 2014, Price et al., 2008). Furthermore, in routine medical practice CBT has not yielded clinically significant long-term benefits in CFS/ME (Whitehead L and Campioin P., 2002, Huibers MJ et al, 2004).

[3] https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0177037
[4] http://www.virology.ws/2018/09/18/trial-by-error-bruce-levin-on-how-not-to-conduct-a-randomized-clinical-trial/
[5] http://www.virology.ws/2018/06/19/trial-by-error-an-open-letter-to-the-lancet-two-years-on/

Since the evidence base for CBT and GET is irreparably flawed and there is evidence of harm, there is no reason to continue these treatments.

Issue 3 - Without Informed Consent, Treatment is Unethical

According to the NHS the principle of consent is an important part of medical ethics and international human rights law. Informed consent requires choice without coercion, being treated as autonomous agents (respect for persons) and being informed of the risks and benefits of any treatment. People with ME are not given the opportunity to consent to CBT or GET. We lay out the evidence below:

- **Choice without coercion** - The ability to refuse treatment without consequence is essential for informed consent. Yet, treatment is often forced on children with ME using child protection laws. Parents of children with ME face false accusations of fabricated/induced illness and are told children must undertake the treatment or face child protection proceedings. If patients cannot refuse a treatment, then they cannot consent to it. The UK children's charity Tymes Trust has helped over 200 families in the UK affected by this, none of whom was found at fault.
- **People with ME are autonomous agents**[6] - People with ME should be treated as autonomous agents as they have the capacity to understand the information given and make an informed decision. People with ME have the right to choose what to do with their own bodies. As patients are not given the full information about CBT or GET, their autonomy is denied.
- **Informed of adverse consequences -** People with ME are not given details of potential harm. People with ME who are given GET are not told that the majority of patients find the treatments harm them, or that there is evidence of impaired aerobic metabolism in ME patients. If individuals are not told of adverse consequences then there is no informed consent.
- **Informed of likelihood of benefit** - People with ME are prescribed CBT and GET as a primary treatment with promise of "recovery", yet evidence demonstrates that there is no long-term benefit for these treatments. Being told there is evidence for efficacy when there is not is misleading, gives patients false hope, and renders informed consent impossible.

Full disclosure of treatment and treatment options is one of the main duties of healthcare professionals. All of the above components are required for informed consent, and are not being adhered to in Scotland. Unless healthcare professionals provide information that meets the requirements of informed consent, the treating people with ME with CBT and GET is unethical and breaches international human rights law.

Issue 4 - Evidence of Abnormalities in People with ME:

"To those people out there who still question whether there really is anything wrong in this illness, my advice to them would be try consulting the evidence." Professor Anthony Komaroff, Professor of Medicine at Harvard.[7]

It would be intellectually embarrassing and irresponsible for any healthcare professional to ignore the evidence and "believe" that ME does not exist. The table below gives a few examples of abnormalities found in ME patients. There was enough evidence in the 1960s for WHO to designate ME as a disease of the central nervous system and there is now over 35 years worth of

[6] Belmont report defines an autonomous person as an individual capable of deliberation of personal goals and capable of acting in direction of deliberation.

[7] Biennial International Association for CFS/ME Conference in Fort Lauderdale (October 2016)

research with consistent findings of abnormalities. This is not intended to be a comprehensive list of the research findings on ME: for a more comprehensive list see the ME Association or MEAction research summaries.

Table 2: Evidence of Abnormalities in ME Patients

System	Evidence in support of
Metabolism	Abnormalities in metabolic pathways, demonstrating **errors in cellular energy production** in patients (Armstrong et al., 2015; Fluge and Mella, 2016)
Microbiome	Altered composition of gut microbiome - **lack of good bacteria and proliferation of bad bacteria**, specifically associated with inflammation (Giloteaux et al., 2016)
Exercise Studies & Muscle research	**Low oxygen uptake by muscle cells** causes exercise intolerance- the evidence demonstrates it is not caused by deconditioning. (Vermeulen, R. C., & Vermeulen van Eck, I. W. 2014) Evidence for **muscle abnormalities** (Pietrangelo et al., 2009) and abnormal recovery from exercise (Jones et al., 2012, Paul et al., 1999) CONTINUED ON NEXT PAGE **2-day cardiopulmonary exercise tests** may be able to detect and quantify post-exertional malaise. People with ME exhibit significantly lower values for oxygen consumption and workload on the second day. (Potential biomarker) (Snell CR et al 2013).
Neurological	**Brain abnormalities** in both structure and function of brain- demonstrated by changes in white and grey matter and reduced cerebral blood flow (Puri et al., 2012, Shan et al., 2016). **Neuroinflammation** (Nakatomi et al 2014) **Increased cerebrospinal lactate** indicating reduced blood flow to brain (Mathew et al., 2008; 2010; 2012; 2017)
Immunological	Multiple studies have found evidence of **autoimmunity** (Maes M et al 2013,Loebel., 2016,) **Elevated inflammatory response.** (Lipkin and Hornig, 2015, Russell et al 2016). **Altered Natural Killer cellular function**- review of 17 studies found 88% of demonstrated ME patients have lower natural killer cell activity (Strayer et al,. 2015) (this is also a potential test to aid diagnosis).
Genetics	"Under and over-expression of certain genes and miRNAs (small molecules that regulate gene expression) may explain some symptoms and also account for an increased susceptibility to developing M.E. They also represent potential biomarkers for diagnosis and drug treatment targets." (ME Association 2018)

Sourced via ME Association and MEAction Research Summaries

Whilst there is evidence about the possible underlying pathophysiology of the disease, funding for research remains chronically low/inadequate. Investment in research is needed to fully understand the aetiology, disease process, and to identify potential treatments. Although we do not fully understand the disease, it is the responsibility of clinicians to follow the most up-to date evidence and not their beliefs.

5. Summary of Next Steps
Given the evidence above we reiterate our original petition demands and ask that:

1. **Research- the Scottish Chief Scientist Office** commits to a programme of investment in biomedical research proportional to disease burden.
2. **Education of healthcare professionals-** Can the Cabinet Secretary for Health and Sport and Chief Medical Officer provide assurances that they will work to urgently update and disseminate evidence-based information about ME to healthcare professionals?
   Immediate action: The Scottish Government issues a notice to health boards and other organisations with information about ME, explaining that it's a neurological condition and health care professionals should treat patients accordingly.
3. **Removal of CBT/GET** as primary treatment in Scotland:
   Immediate action: Ask Health Improvement Scotland to issue a Patient Safety Alert to primary health care practitioners about use of CBT/GET.
   Longer term: Update all guidelines to reflect the current evidence and remove CBT/GET

Furthermore, we ask the Committee to follow up our request in our initial evidence submission (PE01690/T) to ask the health boards to provide evidence for the following statements:

- NHS Borders to identify where its clinicians have sourced evidence that CBT/GET have the best evidence base for treatments (PE01690/D)
- NHS Lothian to provide clarification of its refutation of the criticism of the PACE trial in its evidence submission (PE1690/A). We would also like it noted that NHS Lothian received £165,055 funding whilst participating in PACE.

Factsheet on CBT/GET

Harmful treatment: Cognitive Behavioural Therapy and Graded Exercise Therapy

Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) are the only NHS recommended therapies for patients with ME in the U.K. These publicly funded therapies are based on an unsupportable theory of ME, and the majority of patients report finding them harmful.

The treatments of CBT/GET based on the biopsychosocial or CBT model of ME presumes the cause of the disease is a fear of exercise and deconditioning.[1] The researchers who promote this model have not described any underlying mechanisms, nor presented any evidence for the causation; however they refer to their hypotheses either as theories or models. This gives the impression of scientific support which in fact does not exist.[2]

A worsening of symptoms with exertion, termed post exertional malaise (PEM), is the cardinal feature of ME.[3] Mental and physical exertion, such as that encouraged by CBT/GET, can cause a worsening of symptoms which may be severe and last for days, weeks or, in some cases, cause a permanent relapse. Research has shown that PEM is not caused by patient beliefs or de-conditioning: exercise physiologists have demonstrated that people with ME have problems with aerobic energy metabolism and muscle biopsies reveal ME patients have severe metabolic impairments.[4] [5]

In patient surveys the majority of patients consistently report they find GET harmful. An analysis of over 18,000 patient responses to surveys on management of ME symptoms over a five year period reported that 57% deteriorated following GET and 48% reported no change following CBT. In contrast, pacing led to an improvement in symptoms for over 82% of patients.[6]

Further, the purported evidence for the efficacy of CBT/GET is scientifically unsound. The PACE research trial, which informed the widespread adoption of CBT/GET as a mainstream treatment for ME, has been discredited as an example of poor scientific practice. In a recent debate on the PACE trial in Westminster Carol Monaghan MP called the trial “one of the biggest medical scandals of the 21st Century.”[7] The flaws of this research included: changing outcome measures mid-trial with poor justification; the lack of blinding combined with the use of subjective, rather than objective, measures of recovery; having overlapping entry and recovery criteria, so that patients could be measured as ‘recovered’ despite getting worse; and the fact that researchers had undisclosed ties to the insurance industry.[8] [9] [10]

The American Centre for Disease Control has removed CBT/GET from its recommended therapies for ME.[11] It is vital that these treatments are removed from the Scottish Good Practice Guidelines immediately to stop any more patients being harmed.

The lack of scientific basis for the CBT Model, combined with the majority of patients finding the treatment harmful and developments in biomedical research are good reasons to urgently end CBT/GET as ‘treatment’ for ME in Scotland and the U.K as a whole.

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