

<p>Institution: Queen Mary University of London (QMUL)</p>
<p>Unit of Assessment: A2 (Public Health, Health Services Research and Primary Care)</p>
<p>Title of case study: Chronic fatigue syndrome</p>
<p>1. Summary of the impact</p> <p>Chronic fatigue syndrome (CFS) is a disorder of unknown cause affecting 1% of people. Studies by Queen Mary researchers between 1993 and 2012 helped to characterise and demystify CFS and, in a series of randomised trials, showed that graded exercise therapy (GET) was effective and cost-effective, especially when costs to the patient and society were included. For impacts, GET was [a] recommended in NICE guidance; [b] offered as standard therapy in most UK centres managing CFS; [c] recommended and used internationally. The lead researchers have worked hard to build a dialogue with patient groups, including working with them to co-design the most recent trial, thereby increasing the chance of acceptance of findings by people affected by CFS.</p>
<p>2. Underpinning research</p> <p>The research studies described here were undertaken from 1993 to 2012 and published from 1995 to 2013. Back in 1993, CFS, sometimes called myalgic encephalomyelitis (ME), was far from an established condition and those who did believe in the condition thought it untreatable. In a series of studies at Queen Mary, Prof White led work that established the separate existence, incidence and prognosis of the syndrome after an infection, and also showed that physical deconditioning predicted it [1]. On that basis, White (with Fulcher, an exercise physiologist) designed graded exercise therapy (GET), based on the existing literature (Richard Edwards had already published an open study of exercise for “effort syndrome”). White then led the first randomised controlled trial (RCT) of GET to show that it was more effective than a non-specific therapy time-control intervention for patients with CFS, whether or not this followed an infection [2].</p> <p>This work has been successfully replicated four times; systematic reviews and meta-analyses of these studies have confirmed the efficacy of GET for CFS. White went on to show (unexpectedly) that the effect of GET on global improvement was not mediated by a physical training effect [2], a finding since replicated by others. However, increased exercise tolerance, measured objectively, was mediated by increased fitness after GET [3]. This suggested that GET works as much as a behavioural graded exposure therapy as a physical training programme; something that was incorporated into later designs of GET trials.</p> <p>In spite of this scientific support, several surveys by patient organisations claimed that GET was often damaging, and that “pacing” (living within the limits of the illness) was most helpful. White therefore approached a patient charity, <i>Action for ME</i>, who agreed to help him design and implement an RCT to compare specialist medical care (SMC) alone against such care supplemented by either adaptive pacing therapy (APT), GET or cognitive behaviour therapy (CBT), the last of which had also been shown to be effective and was recommended by NICE (www.pacetrials.org) [4].</p> <p>The PACE trial recruited 640 UK participants from secondary care [4]. Physiotherapists delivered GET, designed to increase exercise duration and then intensity in a gradual and symptom-contingent manner, based on the principles of behavioural graded exposure therapy (www.pacetrials.org). The primary outcomes of fatigue and physical disability were significantly improved in those who had received either GET or CBT, compared to those who had received either APT or SMC; effect size was moderate (between 0.4 and 0.8) with similar effect sizes for both GET and CBT [4]. The pacing approach of APT was no more effective than SMC. The patterns of results were similar however CFS or ME were defined, as well as in those with a comorbid depressive illness. Serious adverse events and reactions were uncommon and equally distributed across the four treatment arms. CBT was the most cost-effective, followed by GET [5]. At a societal level both GET and CBT paid for themselves due to reductions in informal social care. 22% of patients in the trial recovered their health after either of these treatments, compared to 7% following SMC alone [6].</p>

White *et al* concluded that individually delivered CBT and GET were safe, effective and cost-effective when added to SMC, and should be offered to all secondary care patients with CFS, however defined. In a nutshell, gradually doing more is better for CFS than staying within limits imposed by the illness. Consequent research includes an NIHR-funded RCT of guided self-help using GET for patients with CFS (White is the PI). The Cochrane Collaboration have a systematic review update of GET for CFS in review, and an individual patient data meta-analysis is due for submission this year (White is a co-author).

The trial was coordinated at Queen Mary and sponsored by them. White (QMUL) was the lead principal investigator (PI), supported by co-PIs Trudie Chalder (KCL) and Michael Sharpe (Oxford). Funding was from Medical Research Council, Department of Health for England, Department for Work and Pensions, and Scottish Chief Scientist's Office.

3. References to the research

1. **White PD**, Thomas JM, Kangro HO, Bruce-Jones WDA, Amess J, Crawford DH, Grover SA, Clare AW. Predictions and associations of fatigue syndromes and mood disorders that occur after infectious mononucleosis. *Lancet* 2001; 358: 1946-54. (Analysis of large Epstein-Barr virus infection cohort, showing independent prediction of low physical fitness for later development of CFS, but not depression. First papers from this cohort were published in 1995.)
2. Fulcher KY, **White PD**. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ* 1997; 314: 1647-52. (The first randomised controlled trial of graded exercise therapy for CFS, which also showed that increased fitness did not mediate *symptomatic relief*; >400 citations)
3. Fulcher KY, **White PD**. Strength and physiological response to exercise in patients with the chronic fatigue syndrome. *Journal of Neurology Neurosurgery and Psychiatry* 2000; 69: 302-7. (Case control study showing that deconditioning was a problem in CFS, and graded exercise therapy led to improved fitness, mediating improvement in *objectively measured disability*.)
4. **White PD**, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC *et al*, and on behalf of the PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011; 377: 823-36. (The largest and definitive trial of GET for CFS, showing its efficacy and safety, when compared to two other interventions, and its similar outcomes to cognitive behaviour therapy, suggesting both interventions are effective and safe.)
5. McCrone PM, Sharpe M, Chalder T, Knapp M, Johnson AJ, Goldsmith K, **White PD**. Adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome: cost-effectiveness analysis. *PLoS ONE* 2012; 7 :e40808. (GET is cost-effective, and pays for itself when costs of social care are considered.)
6. **White PD**, Johnson AL, Goldsmith K, Chalder T, Sharpe MC. Recovery from chronic fatigue syndrome after treatments given in the PACE trial. *Psychological Medicine*, 2013, 1-9. (Three times more patients recover their health after either GET or CBT than alternatives.)

4. Details of the impact

4a: Informed and affirmed NICE guidelines for CFS and ME

As a major recommendation within its guidelines, NICE recommends: “*Cognitive behavioural therapy and/or graded exercise therapy should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.*” (page 30) [7]. There have been no trials of GET in severe CFS/ME. However, partly because of an open study conducted at Queen Mary, showing that GET helps severely disabled patients (Essame CS *et al*. *Journal of Chronic Fatigue Syndrome* 1998; 4: 51-60), NICE recommend an activity management programme for such patients that “*draws on the principles of CBT and GET.*” Since publication of the PACE trial in 2011, NICE have publicly affirmed their recommendation of GET (and CBT) [8].

4b: Graded exercise therapy has been adopted as a standard treatment for CFS in the UK

The British Association for Chronic Fatigue Syndrome/ME (BACME) “*champions evidence-based approaches to the treatment of CFS/ME*” and represents clinicians of NHS specialist services in the UK [9]. BACME welcomed the findings of the PACE trial saying: “*The PACE trial ... provides convincing evidence that GET and CBT are safe and effective therapies and should be widely available for patients with CFS/ME.*”

BACME is supported by the National Outcomes Database [9], which holds clinical assessment and outcome data on ~9,000 NHS patients, to allow benchmarking of effectiveness. Crawley and colleagues compared patient outcomes across six of the largest NHS services against outcomes after both CBT and GET in the PACE trial. Three of the services used GET; three used activity management incorporating the principles of GET. Symptomatic improvement was similar to that achieved after GET provided within the PACE trial [10]. However, the mean improvement in physical disability was about a quarter of the size achieved by GET in the trial, which may be partly explained by the fidelity of the intervention not always being optimal when implemented outside a trial setting. One obvious difference is that some services deliver interventions in a group setting, rather than individually as in the trial [10].

4c: Graded exercise therapy has been adopted internationally as a treatment of CFS

Permission has been granted for both translation into German and the use of the PACE trial GET manuals for a trial in neuromuscular disease, and for use in an Australian trial of rehabilitation for patients with traumatic brain injuries. The PACE trial treatment manuals are free to download from the trial website: www.pacetrial.org/trialinfo. The site was accessed by 6,672 people between June 2012 and 21 August 2013, particularly from the UK, USA, Australia, Germany, and Canada (source – Google Analytics), this monitored period being more than a year after the main results were published [11].

4d: Graded exercise therapy is included in guidelines for treatment of CFS internationally

Guidelines published in other countries recommend GET. For example:

- In **USA**, the Mayo Clinic states: “*The most effective treatment for chronic fatigue syndrome appears to be a two-pronged approach that combines psychological counseling with a gentle exercise program.*” [12]
- Also in **USA**, the Centers for Disease Control recommend GET; specifically White’s clinical website: “*The GET Guide 2008 by Chronic Fatigue Syndrome/ME Service at St. Bartholomew’s Hospital can be helpful in structuring your graded exercise plan.*” [13]
- Australian clinical guidelines for ME/CFS recommend GET “*unless severely affected*” [14]
- The **Norwegian** Knowledge Centre for Health Services, commissioned by their government, concluded: “*Cognitive behavioural therapy and graded exercise therapy is likely to be effective for people with chronic fatigue syndrome.*” [15]

4c: Engagement with ‘lay epidemiology’ and improving public understanding of science

This research succeeded in spite of considerable opposition from activists. Some people in the CFS/ME community have developed a ‘lay epidemiology’ comprising purely organic explanations and hypotheses for the condition, and view psychological hypotheses as dismissive of patients’ ‘real’ experiences. A vocal minority has actively opposed any research into this condition with a psychological component and has even sought to sabotage such studies [16]. Pressure from such activists (including threats of violence) has led some researchers to pull out of researching CFS altogether. The approach taken at Queen Mary, as described in Section 2, has been to seek dialogue with patients, carers and the lay public, engage with their concerns, try to understand their explanations and seek as far as possible to work with them rather than against them.

CFS is so controversial that the House of Lords held a debate about the PACE trial in February 2013 [17]. One peer was critical, but seven others supported the trial. Baroness Northover replied for the Government, and later wrote to White: “*PACE was an example of a well conducted, robust research study. It is with thanks to you and your team that we now have some very good evidence*

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that CBT and GET are moderately effective when provided alongside specialist medical care.” [18]

As part of a public relations policy to disseminate the PACE trial results, The Science Media Centre hosted a press conference for the main paper [19]. This led to positive, world-wide coverage, including almost all UK national newspapers as well as the *New York Times*, *Wall Street Journal*, Sky, BBC, and ITV, and radio stations in the UK, USA and Australia.

5. Sources to corroborate the impact

7. NICE Guideline 2007 (updated 2011) on Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CG053). <http://guidance.nice.org.uk/CG53/Guidance/pdf/English>
8. NICE affirming support of GET. www.nice.org.uk/nicemedia/live/11824/53532/53532.pdf
9. British Association for Chronic fatigue syndrome/ME BACME endorsement of GET www.bacme.info/aboutcfsme/management/get.html and national outcomes database: <http://www.bacme.info/nod/>
10. Crawley E, Collin SM, White PD, Rimes K, Sterne JAC, May MT. (Treatment outcome in adults with chronic fatigue syndrome: a prospective study in England based on the CFS/ME National Outcomes Database. *Quarterly Journal of Medicine* 2013; 106: 555-565. doi:10.1093/qjmed/hct061
11. PACE trial website: www.pacetrials.org
12. Mayo Clinic guideline on CFS www.mayoclinic.com/health/chronic-fatigue-syndrome/DS00395/DSECTION=treatments-and-drugs
13. US Center for Disease Control guideline on CFS www.cdc.gov/cfs/toolkit/get.html
14. See for example Government of South Australia ME/CFS guidelines <http://sacfs.asn.au/download/guidelines.pdf>
15. Norwegian Knowledge Centre for Health Services rapid review on CFS (English summary): www.kunnskapssenteret.no/Publikasjoner/Behandling+av+kronisk+utmattelsessyndrom+CFSME.12742.cms?language=english&threepage=1
16. Hawkes N. Dangers of research into chronic fatigue syndrome. *BMJ* 2011; 342: d3780
17. House of Lords debate on PACE, HANSARD 6 February 2013 (see column GC65): www.publications.parliament.uk/pa/ld201213/ldhansrd/text/130206-gc0001.htm
18. Letter from Baroness Northover. www.pacetrials.org/docs/Northover.pdf
19. Science Media Centre hosted a press conference on PACE. www.sciencemediacentre.org/cfsme-trial/ & www.sciencemediacentre.org/expert-reaction-to-lancet-study-looking-at-treatments-for-chronic-fatigue-syndromeme-2-2/