
The PACE Trial: An Expression Of Concern

Douglas T Fraser

Tuesday 28th June 2011

On February 18th 2011 the Lancet published an article “PACE: a randomised trial” by P D White, A L Johnson, J Bavinton, T Chalder, and M Sharpe et al. [1].

Essentially an unblinded trial, it appears to be falsely registered as a RCT [1a], an example of “strawman design” [2], and published in breach of the Lancet's own requirements [3].

The article began by using the crutch of “linguistic spin” [4] to suggest a notion to Lancet readers that CBT and GET “can be effective treatments for chronic fatigue syndrome”.

Examination of the trial material, approved by an ethics committee, reveals how participants were being treated: “Patients often feel reassured when they are informed that CBT helps people with a wide range of health problems including cancer, chronic pain and diabetes” which “these days most people acknowledge that even for conditions such as cancer, heart disease or diabetes ... social, emotional, cognitive and behavioural factors play a part in causation and/or prognosis” [5].

The scientifically-driven journal impacting the health of millions, would be unlikely to entertain an article which claimed that CBT and GET “can be effective treatments” for cancer, diabetes chronic pain and diabetes, far less a disease that “is one of the most under-researched areas of clinical medicine” [6], and particularly when many apparently positive claims from psychosocial interventional trials in cancer have been exposed as exaggerated or “simply false” [7].

Following in the wake of an “international furore” [8] over the non-disclosure of trial results, revealed in a report published by the Lancet April 2004, which concluded : “Non-publication of trials, for whatever reason, or the omission of important data from published trials, can lead to erroneous recommendations for treatment” [9], trial registration has become a universal perquisite to publishing in reputable journals, leaving previous “Trial findings” [1] with uncertain status.

The ISRCTN Register advises that records are never removed or overwritten and that updated information will be added along with a date stamp to show when the changes were made to the trial record. It is stated that: “Although CCT does not ask for regular updates to any trial record in the ISRCTN register, sometimes it is necessary for trial record details to be updated. This can be due to many reasons, including a need to change the record once the ethics approval has been granted, updating the start and end dates of the trial to factor in delays to the start of the trial, and updating the funder and sponsor details if the trial has been extended, and the previous funding has run out Another reason for an update to a trial record can be due to an evolution in the WHO 20-item minimum dataset, and the ICMJE guidelines. In the case of an update to these guidelines, the principle investigator of a trial held in the ISRCTN register may wish to update their record to ensure that it is in line with these guidelines” [10].

The record for ISRCTN54285094 (PACE) is incomplete [11].

The changes to sponsors recorded earlier, from: 1) the “MRC Clinical Trials Unit” to: 2) the “Medical Research Council” to: 3) the “Queen Mary University of London (UK)” have not been recorded [12].

Change in previously recorded eligibility inclusion criteria i.e. from: “Chalder fatigue score of 4 or more and an SF36 physical function score of less than 75”, to: “6 or more” (Chalder) and “65 or less changed from 60 or less” (SF-36), have not been recorded [13].

The removal from the record of previous “Endpoints/primary outcome(s)” outcome measurement using bimodal scoring (0,0,1,1) i.e.: “The 11 item Chalder fatigue questionnaire, using categorical item scores to allow a categorical threshold measure of “abnormal” fatigue with a score of 4 having been previously shown to indicate abnormal fatigue”, has not been recorded [13].

The removal from the record of previous “Endpoints/primary outcome(s)” measurement: “The SF-36 physical function sub-scale, counting a score of 75 (out of a maximum of 100) or more as indicating normal function”, has not been recorded [13].

Changes in the previously recorded “Disease or condition” field, from: “Symptoms and General Pathology” to: “Neurosciences” to: “Symptoms and General Pathology”, have not been recorded [12-13].

The deletion of previously recorded: “Eligibility criteria exclusion - meet criteria for chronic somatisation disorder”, has not been recorded [13].

The change in “Anticipated end date” from 13/06/09 to 01/07/2011 is not recorded in the relevant field, making it difficult for the register user to easily identify a significant change of end date, involving a mere matter of two years [11].

An oblique comment under “Study hypothesis” reads: “As of 16/02/09 this record was updated to reflect an amendment to the anticipated end date. The initial information at the time of registration was 13/06/2009”.

Primary and secondary endpoints and the detailed means of measuring, and their descriptions, are missing [11].

In a field without space limitations, the requirement is to enter what is being measured, what instruments will be employed, a description of the scales involved, and at what time points in the trial measurements will be taken:

“Enter all primary [secondary] outcome measures in the trial as well as the method used to measure the outcome and any pre-specified timepoint(s) of primary interest. Be as specific as possible with the measure used e.g., Pain, measured using the Visual Analogue Scale (VAS) score (0 = no pain, 10 = unbearable pain) at baseline, one month and six months, as opposed to just "pain". No field limit” [10].

Study hypotheses or aims for ISRCTN54285094 are recorded as “Primary outcome measure(s)”, e.g.: “Study hypothesis: Are cognitive behaviour therapy [sic] (CBT) and/or graded exercise therapy (GET) more effective than pacing in reducing both fatigue and disability?” - “Primary outcome measure(s): Is APT and SSMC more effective than SSMC alone in reducing (i) fatigue, (ii) disability, or (iii) both?” - “Study hypothesis: What are the relative cost-effectiveness and cost-

utility of these treatments?”- “Primary outcome measure(s): What are the relative cost-effectiveness and cost-utility of these treatments?” [11].

No “lay summary” is entered, which “should answer the following questions: Background and study aims?, What does the study involve?, Who can take part?, When does the study take place?, Where does the study take place?, What are the risks to participants?, Who is funding the project?, Who is the main contact? ... No field limit” [10].

In a 2007 National Guideline (NICE CG53), the construction of which was informed by a team of academic reviewers (Bagnall et al. 15), who stated of level 1++ evidence that “by itself the RCT/controlled trial evidence base is not an adequate foundation of definitive guidelines” [14], one of the Lancet article authors (Bavinton J) endorsed a statement within that Guideline, clarifying that: “The GDG did not regard CBT or other behavioural therapies as curative or directed at the underlying disease process, which remains unknown” [15].

It was recorded that “the GDG does not state that ME/CFS is a behavioural disorder, a psychiatric illness, a somatic/functional disorder, an illness belief, depression or anxiety disorder” and “have recognised that CFS/ME is a physical illness”. A “recommendation that CFS/ME should be recognised as a physical illness had been made” [16]. The “recommendation” was subsequently removed from the Guideline [15].

A PACE trial “treatment leader” and co-author of the PACE GET Manuals [5], Bavinton listed under conflicts of interest: “JB was on the guideline development group of the National Institute for Health and Clinical Excellence guidelines for chronic fatigue syndrome and myalgic encephalomyelitis and has undertaken paid work for the insurance industry ” [1].

Within a GET manual, Bavinton J, Dyer N, White PD claimed that: “There is nothing to stop your body from gaining strength and fitness, as long as it is done in a carefully monitored way, relating directly with your own particular circumstances started and progressed at the right rate for you. Good luck! ” [5].

During an on-line Institute of Psychiatry Maudsley Video titled: “The treatment of chronic fatigue (“ME”) in primary care ... how not to get into arguments with the patient ... and how to carry out a plan of treatment aimed at the restoration of normal function” [17], tailored for GPs and featuring a non-medically qualified individual, (Dr) Trudy Chalder, introduced as “a specialist in chronic fatigue syndrome at the Institute of Psychiatry”, Professor Andre Tylee remarked: “It can be very frustrating working with patients with chronic fatigue syndrome, particularly as you can get into arguments based on their preset ideas about what causes the problem and what sort of treatment they want ... on that idea about alienation, this is something that we often find in primary care you know we're trying to tell this person that it's a psychological problem, they're trying to tell us it's a physical problem, how do we manage that situation? ... Chronic fatigue syndrome patients are difficult, we hope that you will persevere with them. It helps to arrange firm follow up and not to expect too much. Change often occurs over the long term. We've included with the package some guidance on using role plays to develop your skills in working with these patients, because we've found that it's only by rehearsing the skills that you need that you'll be able to use them when faced with the real situation. All that remains now is to wish you the very best of luck with it ! ” [18].

Ioannidis JP reported that: “The greater the financial and other interests and prejudices in a scientific field, the less likely the research findings are to be true. Conflicts of interest and prejudice may increase bias, u. Conflicts of interest are very common in biomedical research, and typically they are inadequately and sparsely reported. Prejudice may not necessarily have financial roots. Scientists in a given field may be prejudiced purely because of their belief in a scientific theory or

commitment to their own findings. Many otherwise seemingly independent, university-based studies may be conducted for no other reason than to give physicians and researchers qualifications for promotion or tenure. Such non-financial conflicts may also lead to distorted reported results and interpretations. Prestigious investigators may suppress via the peer review process the appearance and dissemination of findings that refute their findings, thus condemning their field to perpetuate false dogma. Empirical evidence on expert opinion shows that it is extremely unreliable” [19].

“Potential conflicts of interest (financial, corporate, academic, scientific, etc.) may lead to publication bias, time lag bias, selective outcome and analysis reporting bias, or even fraudulent results. While the latter category is probably uncommon, the other biases are likely to have a major common impact on the credibility of the available, visible randomized evidence. The problem with all these biases is that unless one pursues them with very elaborate detective work*, they largely remain invisible. Efforts have been undertaken to reduce the hiding places. Trial registration is a very important step in the direction of diminishing publication bias and raising awareness about the existence of unpublished data. However, registration alone does not address time lag bias, and it also does not currently protect from selective analysis and outcome reporting. Protocols are registered often with very minimal information on their analysis plans. This leaves a great deal of room for selection. Evaluation of large domains of randomized research suggests that, overall, there are more significant trials compared to what one would expect, even if the described effects were true. Selective reporting biases are probably greater in observational research, but its impact in randomized trials should not be underestimated. With prevailing conflicts of interest, biases may be very strong on some occasions. The problem is that it is very difficult to pinpoint where exactly these biases have operated more heavily and which particular interventions would be affected. With increasing awareness of the importance of detailed registration, one hopes that these biases will diminish in the future” [20] (* <http://tinyurl.com/64wmkfu>).

All three of the trial principal investigators (White PD, Chalder T, Sharpe M) declared conflicts of interest involving insurance companies.

Two principal investigators declared being in conflict over both “voluntary” and paid work for government and insurance.

It is possible that being in conflict over “voluntary” work for insurance and government points to graver issues, and in this instance the term “voluntary” may have been added after careful consideration.

In fairness to the taxpayer who paid 5-6 million pounds for the PACE Trial, and to the trial participants who have a right to know of these issues in detail, it might be ethical and prudent of the investigators to place all aspects and details of their interactions and influences in insurance and government on a dedicated web-site open for public scrutiny.

The main principal investigator (White PD) declared conflicts of unknown specification working for one of the trial funders, the UK Department and Work and Pensions, a Department that partly funded the trial anticipating that it would show: “that work is good for physical and mental well-being and that being out of work can lead to poor health and other negative outcomes” [21]. White PD also declared being conflicted in some manner over his interest in working for the reinsurance company “Swiss Re” - billed as a “Leading Global Reinsurer” [22].

Partly funded by the UK Medical Research Council, under the “Role of the funding source” it is reported in the Lancet that “The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report”.

It is not reported that during the life of the PACE trial, Sharpe M and Chalder T (including interested colleagues at the Department of Psychological Medicine at the Institute of Psychiatry London and elsewhere), were members of the MRC Advisory Board, and that White PD and Chalder T served on the MRC Neurosciences and Mental Health Board [23] (<http://tinyurl.com/6ld6m3q>).

The trial authors have stated that: “If participants are insistent that there is an ongoing "physical" problem, it is rarely helpful to directly challenge them on this point” [5].

At the All Party Parliamentary Group on M.E. on 16th February 2011, it is reported in the minutes that Professor Stephen Holgate, Chair of Medical Research Council (MRC) Expert Group on M.E. “explained that scientific peer reviews had tended in the past to involve mainly those with a background in neuroscience. This had led to research that did not reflect the views of those who believed that the condition has an organic cause” [24].

All three principal investigators were involved in a 2006 National Guideline (NHS Plus) in which a “key finding” stated that: “Cognitive behavioural therapy and graded exercise therapy have been shown to be effective in restoring the ability to work in those who are currently absent from work” [25].

In the Lancet PACE article the claim is made that CBT and GET “moderately improve” what is referred to as “outcomes” for chronic fatigue syndrome.

The trialists advised potential participants: ”You must be diagnosed by us as having CFS/ME...you will be helping others who get the same condition you have now” [5].

The trialists rejected two-and-a-half-thousand of three-thousand potential participants, and requested more tax-payers money and more time, in a country with hundreds of relevant support groups, many well organised charities, excellent communication systems, and something in the region of a quarter of a million sufferers.

Coyne JC observed that: “a large scale trial that produces null results is disappointing in biomedicine, but it does not threaten the legitimacy of biomedicine in quite the same way that it would health psychology” [7].

An insight into the nature of advice given to insurance and government is provided in “Trends in Health and Disability” the UnumProvident Chief Medical Officer’s Report of 2002, in a section titled “Functional Symptoms and Syndromes” crafted by PACE investigator Sharpe M. [26]

Introduced as being “particularly interested ... in how biological and psychological factors interact to cause symptoms and disability” and after declaring that: “social factors .. [which apparently include a respected charity that administers a scientific research Fund] ... are almost certainly of great importance in shaping functional illness ”, Sharpe M proceeds: “whatever their biological basis, there is strong evidence that symptoms and disability are shaped by psychological factors ...some persons appear to exaggerate symptoms but this is often hard to prove ... both State and private insurers pay people to remain ill ... patient’s beliefs may be become entrenched and be driven by anger and the need to explain continuing disability. The current system of state benefits, insurance payments and litigation remain potentially major obstacles to effective rehabilitation. It is often unrealistic to expect medical treatment alone to overcome these. Furthermore patient groups who champion the interest of individuals with functional complaints (particularly for chronic fatigue and fibromyalgia) are increasingly influential; they are extremely effective in lobbying politicians and have even been threatening towards individuals and organisations who question the

validity and permanence of the illness they champion. Again the ME lobby is the best example” .

In Sharpe's article for UnumProvident at “Table 1: Common medically defined functional syndromes listed by medical speciality”, Sharpe identifies “(Post-viral) fatigue syndrome (CFS)” as belonging under “infectious diseases”.

Although neurasthenia is recognised by ICD-10, but not by DSM-IV, nevertheless, in Sharpe's article for UnumProvident at “Table 2 : DSM-IV and ICD-10 categories for medically unexplained syndromes ”, a DSM-IV entry for neurasthenia appears, while the corresponding ICD-10 entry is left blank.

In ICD-10, 'Neurasthenia' excludes post-viral fatigue syndrome, myalgic encephalomyelitis and chronic fatigue syndrome.

Sharpe recommends: “Much could be gained from having an early biopsychosocial assessments of patients that ensured the identification of psychiatric as well as medical diagnoses”

Although the benign-sounding “biopsychosocial model” to which this refers appears to be a false top-down dogma with troubling authoritarian implications, it has been eagerly adopted in insurance and government, for obvious reasons (<http://tinyurl.com/6g8rmhy>):

“An example of a new Biopsychosocial assessment seen by Benefits and Work resulted in a claimant with Chronic Fatigue Syndrome losing his higher rate mobility component on the grounds that his condition was 60% “psychosocial”. The new system will be aimed particularly at claimants with “medically unexplained” conditions such as ME/CFS, fibromyalgia, low back pain and IBS ... The newsletter features an article by Mansel Aylward, former Chief Scientist at the DWP, self-effacingly entitled 'Professor Aylward endorses the Biopsychosocial Model of Disability' ...”.

PACE article author AL Johnson of the Medical Research Council Biostatistics Unit and the Medical Research Council Clinical Trials Unit, reported in 2006 that: “I have enabled a successful collaboration linking the research programmes of this Unit with the MRC Clinical Trials Unit (MRC CTU) in London, that has resulted in the establishment of a new Clinical Trials Unit dedicated to mental health and neurological sciences at the Institute of Psychiatry in London ...

The linkage has enabled my expertise in clinical trials to be extended to chronic fatigue syndrome and the setting-up of a major MRC study to evaluate the efficacy of four different interventions ...

My role within MRC changed radically in 2001, resulting in my switching from independent band 2 to core scientist, and with secondment (20%) to the Division Without Portfolio (DWP), now Division for Other Diseases, in MRC CTU, London (Director: Janet Darbyshire). My expertise in clinical trials was needed to expand the activities of DWP into areas such as mental health, dementia, chronic fatigue, and transfusion medicine, all currently the focus of government health policy.

The requirement to serve two MRC Units linking Cambridge and London has worked extremely well and I have not only fulfilled my expanded role within MRC CTU (as evidenced by their Unit review in 2004 and requests for an increased element of my time), but also through continuation and completion of the programme In this report I present activities within both Units under the main headings of epilepsy, dementia, psychiatry, chronic fatigue, and transfusion medicine, highlighting only the principal studies within each. Clinical Trials Unit (King's College London & Institute of Psychiatry at the Maudsley) (with S.Wessely, R. Kerwin, R. Walwyn, S. Lee, (Institute of Psychiatry, London)) A long needed Clinical Trials Unit (CTU) dedicated to RCTs in psychiatry

and the neurosciences has been established with an ambitious remit to advise, initiate, design, conduct, analyse, present and publish clinical trials in mental health. I have acted as a link between this CTU and MRC CTU, provided guidance as a member of its Steering and Management Committees, and provided supervision and management of its statisticians (Rebecca Walwyn & Sally Lee) on a monthly basis. I have attempted to guide the CTU towards critical mass and in addition to two statisticians it now has a Manager, Database Manager, and secretary. Difficulties with appointing a successor to Brian Everitt as Chair of Biostatistics or a senior lecturer within that department, posts that were intended to provide some management and supervision of statisticians within the CTU, have led management and supervision of statisticians within the CTU, have led to my fulfilling these roles as well as providing advice to grant applicants at the Institute of Psychiatry (IoP) and King's with inevitable requests, necessarily usually declined, to become a co-applicant. Mental Health Research Network (MHRN) Adoptions Committee (Chair: T. Wykes (Institute of Psychiatry, London)) In March 2005, I succeeded Janet Darbyshire as a member of this important independent subcommittee of MHRN that decides on the suitability of projects to run on the UK network provided that they have service user input, are in line with national mental health policy, are free of major ethical and design flaws, require multiple centres, and demonstrate feasibility to run on the network. I have guided the committee towards acceptance of larger studies, documentation and monitoring of load on the network within individual hubs, by disease areas, and by patient recruitment requirements. Depression R Bentall (Manchester), P Kinderman, R Morriss (Liverpool), J Scott (Newcastle, Glasgow, London)) Prior to 2001 we completed a RCT of the cost-effectiveness of cognitive therapy (CT) or usual treatment for people with residual (unipolar) depression followed up for 18 months in which I advised on design and supervised analysis.....

Chronic Fatigue Syndrome (CFS) (with P. White, T. Chalder (London), M. Sharpe (Edinburgh)) CFS is currently the most controversial area of medical research and characterised by vitriolic articles and websites maintained by the more extreme charities supported by some patient groups, journalists, Members of Parliament, and others, who have little time for research investigations. In response to a DH directive MRC called for grant proposals for investigations into CFS as a result of which two RCTs (PACE and FINE) were funded and have started despite active campaigns to halt them. I am part of the PACE study, a multi-centre RCT comparing cognitive behaviour therapy, graded exercise training, and pacing in addition to standardised specialist medical care (SSMC), with SSMD alone in 600 patients; it is funded by MRC, Chief Scientist's Office (Scotland), DH, and Department of Work and Pensions at an estimated cost of £2.7m. I have been fully engaged in providing advice about design of PACE and I am a member of both Trial Management Group and Trial Steering Committee. I am not a PI because of familial involvement with one of the charities, a perspective that has enabled me to play a vital role in ensuring that all involved in PACE maintain absolute neutrality to all trial treatments in presentation, documentation, and assessment.” [27].

Within material providing insight into the true nature of the trial, the authors state that: ”Evidence from research trials has indicated that patients who are in receipt of benefits or permanent health insurance do less well than those who are not in receipt of them ... For participants who are in receipt of IP, it can be worth discussing the advantages and disadvantages of being on it” [5].

The extent to which possible unnecessary suffering, hardship and distress may have resulted from the principal investigators secretive involvements with insurance and government over many years, is unknown, but such unusually serious conflicts of interest may in the end leave the PACE Trial and its publishers without any moral credibility.

In publishing the article, the Lancet appears to have breached its own conditions requiring formal Trial Registration without “missing fields or fields that contain uninformative terminology”, among other obligations [28].

Registration of trials allows everyone with an interest to freely access basic, meaningful and accurate information about a trial, without having to obtain the original protocol. It is also a public service that allows all interested parties to identify trials, in addition to tracking whether there have been any changes since the point of registration, which might suggest that investigators are deviating from the original plan. It serves various functions for scientists, not only that of reducing unnecessary duplication, but of alerting other investigators to the possible existence of unpublished data [20], data dredging and other irregularities. Precise details of endpoints and their measurement, entry and exclusion criteria, and other data required by the WHO 20-item minimum dataset [29], and any changes to any field, should be recorded.

Under “Updating an ISRCTN record” it is stated: “Please note that CCT does not remove information from a record, or overwrite previous information, but will instead add any updated information, along with a date stamp to show when the changes were made to the trial record”. [10]

Registration has been described as a “digital trail” [30], one part of the decades-long ongoing drive to eliminate selective and biased reporting in trials, among other forms of misconduct, and is part of an attempt to restore public confidence in research through greater transparency.

Fiona Godlee, now editor of the BMJ, was instrumental in the development of Current Controlled Trials Meta-Register, and in 2007 Godlee and Horton et al. noted of progress in the field: “Three years ago, trials registration was the exception; now it is the rule. Registration facilitates the dissemination of information among clinicians, researchers, and patients, and it helps to assure trial participants that the information that accrues as a result of their altruism will be come part of the public record. The WHO’s global efforts toward comprehensive trials registration and the ICMJE’s requirements for registration aim to increase public trust in medical science”. [32]

The information given for the PACE trial appears misleading and incomplete, thereby undermining the rationale of trial registration.

Although data on endpoints/primary outcomes and their measurement were partly recorded at a point in 2005 (now viewable only through externally archived public record), complete outcome measures and their mode of measurement, and changes in these are not recorded as required.

Changes in entry (inclusion criteria) are not fully detailed, nor are two changes in the trial's sponsor.

Changes which might alert users to possible problems within the conduct of the trial are not clearly recorded. Previously recorded as 13/06/2009, the anticipated end date is given as 01/07/2011.

Under “Study hypothesis” a note has been placed: “As of 16/02/09 this record was updated to reflect an amendment to the anticipated end date. The initial information at the time of registration was 13/06/2009”, making it difficult to quickly identify a two year extension, because of the page layout.

The instructions for registrants state: “We would expect the end date to be either the end of participant recruitment, or the end of the trial follow-up period” [10].

According to ISRCTN requirements, under the relevant field, changes should be clearly recorded e.g., rather than the above, something along the following lines might have been recorded:

Anticipated end date amended as of February 2009:	01/07/2011
Previous Anticipated end date provided at registration:	Not given
Previous Anticipated end date provided at 20 May 2005:	13/06/09

A significant two year change of anticipated end date appears to have become obscured.

The The UK Clinical Research Network Portfolio Database recorded ISRCTN54285094 (PACE) as: “Current Status Closed - follow-up complete - Closure Date 30/11/2008 - Sample Size 600” [33]

Of the five Directors at the International Standard Randomised Controlled Trial Number Register, (ISRCTN) three are based in the UK, Kate Law of Cancer Research UK, Marc Taylor on behalf of Department of Health, and Chris Watkins on behalf of Medical Research Council [34]. Watkins C authored the 2003 MRC “CFS/ME Research Strategy” [35] and acted as contact for Chronic fatigue syndrome/ME as Priority Area for the MRC (<http://tinyurl.com/68rbkh8> PDF document 390.8 KB).

The WHO International Clinical Trials Registry Platform requires that among the “Acceptability Criteria” for key Registers linked through the WHO ICTRP portal, including the major ISRCTN register where PACE is registered, they “Must not have conflicts of interest over which trials or trial information to register ” and must “Collect full Trial Registration Data Set” [36].

On 22 MAY 2003 the PACE trial was registered with the International Standard Randomised Controlled Trial Number Register (<http://www.controlled-trials.com/>) by “Mr Peter Denton White” as a “RCT of CBT, graded exercise, and pacing versus usual medical care for the chronic fatigue syndrome” [12] (the definite article being removed in May 2004):

The “disease or condition” was identified by White PD as “Symptoms and General Pathology”

The expanded MeSH entry for “Symptoms and General Pathology” consists of: “Abnormal anatomical or physiological conditions and objective or subjective manifestations of disease, not classified as disease or syndrome”[37].

The “disease/condition/study domain” for ISRCTN59388875 (“family focused CBT” ; Prof Trudie Chalder) is given as: “Chronic Fatigue Syndrome (CFS) otherwise known as Myalgic Encephalomyelitis (ME)” [38], and the “disease/condition/study domain” for ISRCTN74156610 (FINE; Dr Alison Wearden) is given as: “Chronic fatigue syndrome (CFS)” [39].

For ISRCTN54285094 (PACE) the corresponding entry in the UK Clinical Research Network Portfolio Database refers to: “Topic Neurological ... Disease(s) Nervous system disorders ” (UKCRN ID 4502) [33], and for ISRCTN74156610 (FINE) : “Topic Primary Care (co-adopted by Infection) ... Disease(s) Infectious diseases and microbiology All Diseases” (UKCRN ID 4248). [40]

According to the PACE Participants’ Newsletter , the FINE trial is a “sister” study to PACE for people “who are too unwell to attend a clinic ” [41].

The main result of the FINE intervention was reported as “not statistically significant at one year follow-up” [42]. After publication, the FINE authors, including a member of the PACE trial Group (Wearden A), reported they could demonstrate a clinically modest, but statistically significant “effect” when they changed a scoring method (from 0,0,1,1 to 0,1,2,3) for a four column questionnaire [43].

On this point the FINE trialists merely record under primary outcome measures: “The score on the 11-item Fatigue Scale”.

The ISRCTN register stipulates: “Primary outcome measure(s): Enter all primary outcome

measures in the trial as well as the method used to measure the outcome and any pre-specified timepoint(s) of primary interest. Be as specific as possible with the measure used e.g., Pain, measured using the Visual Analogue Scale (VAS) score (0 = no pain, 10 = unbearable pain) at baseline, one month and six months, as opposed to just "pain". No field limit" [44].

At the 22 MAY 2003 the original ISRCTN register PACE entry states [12]: "Participants - Sequential outpatients attending six chronic fatigue clinics in secondary care, who meet the Oxford criteria for chronic fatigue syndrome (CFS). We will operationalise CFS in terms of fatigue severity and disability as follows: a Chalder fatigue score of 4 or more and an SF36 physical function score of less than 75"

Also at the 2003 entry the Trial Sponsor is recorded as the "MRC Clinical Trials Unit" and changed to the "Medical Research Council" in May 2004. No start and end dates are recorded.

The National Research Register entry (ID: N0042140250) recorded: "Start date: 1 April 2002 End date: 31 March 2007" and stated that primary outcome measures or endpoints would consist of Chalder FQ (0,0,1,1) where: "The pre-specified criteria for good outcome will be a 50 % reduction from baseline fatigue score, or a score of 3 or less, this threshold having been previously shown to indicate a normal level of fatigue" and the SF-36 physical function sub-scale" where: "We will count a score of 75 (out of a maximum of 100) or more, or an increase of 50 % increase from baseline in SF-36 subscale score as indicating a good outcome". The Chalder FQ (0,1,2,3) was recorded as a secondary outcome "to better measure response to treatment"

In addition to the "endpoints" of the CFQ & SF-36 sub-scale measurements provided under "Outcome measure description", notice in the NRR was provided that: "We are therefore confident [sic] that recruitment, at an overall rate of 200 participants per year is feasible and that the trial will achieve 600 participants over three years. We will however closely monitor recruitment, especially in the first six months, and the trial management group, after advice from the TSC, will consider replacing those centres that either do not recruit sufficient participants, or fail to provide quality data ... MeSH terms not yet assigned" [45].

"National Research Register (NRR) returns provide the information required from the NHS to allow DH to: a) review performance; b) make decisions on future funding requirements. c) answer Parliamentary Questions, prepare briefings for Ministers and respond to other requests for information efficiently and effectively. Therefore, it is important that the information provided is accurate and consistent" [46].

At 23 February 2011 the ISRCTN PACE entry states: "The participant's Chalder Fatigue Questionnaire score is 6 or more The participant's SF-36 physical function sub-scale score is 65 or less (changed from '60 or less' in April 2006)" [11].

The Sponsor is given as "Queen Mary University of London (UK)".

"The sponsors of the study" are referred to in the Lancet as the Medical Research Council, the Scottish Chief Scientist's Office, the Department of Health in England and Wales and the Department for Work and Pensions .

It is recorded at 23 February 2011: "Anticipated start date 14/06/2004 - Anticipated end date 01/07/2011 - Status of trial Ongoing"

The The UK Clinical Research Network Portfolio Database recorded ISRCTN54285094 (PACE): "Current Status Closed - follow-up complete - Closure Date 30/11/2008 - Sample Size 600" [33].

In 2004 Richard Horton and colleagues from the International Committee of Medical Journal Editors issued a Statement that “The ICMJE member journals will require, as a condition of consideration for publication, registration in a public trials registry” [46].

In April 2005 the World Health Organization delineated a 20-item data set of minimal registration requirements, promptly adopted by the ICMJE, which require the precise recording of outcome or endpoint measurements, among other trial details comprising the data set [47].

Recorded as “Date live in mRCT 20 May 2005” (ISRCTN54285094), primary outcomes and exclusions, among other details, were recorded at mRCT (<http://www.controlled-trials.com/>) which “shows subsets (or views) from the ISRCTN Register”, including the following:

“Disease or condition - Neurosciences”

“Endpoints/primary outcome(s): 1. The 11 item Chalder fatigue questionnaire, using categorical item scores to allow a categorical threshold measure of “abnormal” fatigue with a score of 4 having been previously shown to indicate abnormal fatigue. 2. The SF-36 physical function sub-scale, counting a score of 75 (out of a maximum of 100) or more as indicating normal function”

“Eligibility criteria – exclusion - Patients who (a) are at significant risk of self-harm (b) meet criteria for chronic somatisation disorder (c) are unable to either speak or read English adequately (d) are unable to either attend hospital reliably or to do the therapies (e) are less than 18 years old ...Open to recruitment ... Trial start date 14/06/04 - Trial end date 13/06/09” [13].

At 9 November 2005 the ISRCTN register recorded projected start and finish times as:

“Anticipated start date 01/03/2005 - Anticipated end date 13/06/2009”

In the “2005 R&D annual reports” the National Research Register recorded start and finish dates as :

“Start date: 1 April 2002 End date: 31 March 2007 Project status: Ongoing” [45].

At 23 February 2011 the ISRCTN register reports: “Anticipated start date 14/06/2004 - Anticipated end date 01/07/2011 - Status of trial Ongoing .. last patient recruited 28/11/2008”

The ISRCT record “Last edited 23/02/2011” gives the “Anticipated start date” as 14/06/2004 and the “Anticipated end date” as 01/07/2011 and last patient recruited as 28/11/2008 .

Under “Study hypothesis” notice is given that “As of 16/02/09 this record was updated to reflect an amendment to the anticipated end date. The initial information at the time of registration was 13/06/2009”.

“Disease/condition /study domain Symptoms and general pathology ”

Eligibility includes: “The participant meets operationalised Oxford research diagnostic criteria for CFS 4. The participant's Chalder Fatigue Questionnaire score is 6 or more 5. The participant's SF-36 physical function sub-scale score is 65 or less (changed from '60 or less' in April 2006) ”

The Primary outcome measure(s) are listed as: “1. Is APT and SSMC more effective than SSMC alone in reducing (i) fatigue, (ii) disability, or (iii) both? 2. Is CBT and SSMC more effective than

APT and SSMC in reducing (i) fatigue, (ii) disability or (iii) both? 3. Is GET and SSMC more effective than APT and SSMC in reducing (i) fatigue, (ii) disability, or (iii) both? 4. Are the active rehabilitation therapies (of either CBT or GET) more effective than the adaptive approach of APT when each is added to SSMC, in reducing fatigue, in reducing physical disability? 5. What are the relative cost-effectiveness and cost-utility of these treatments? ”

Secondary outcome measure(s) are listed as: “1. Do different treatments have differential effects on outcomes (i.e. fatigue versus physical disability)? 2. What baseline factors (other than randomised treatment) predict a reduction in (i) fatigue, (ii) disability in all participants? 3. Are there differential predictors of response to APT, CBT, GET, and SSMC (i.e. treatment covariate interactions)? 4. Are there changes in factors (time- dependent covariates) during the earlier stages of treatment that (after controlling for baseline overall and differential predictors) are associated with outcome at 1 year from randomisation? 5. Are the differences across treatment groups in the primary outcomes associated with similar differences in secondary outcomes (e.g. in global change, mood, quality of life and objective measures of physical activity)? ”

In a series of trials funded by Cancer Research UK (e.g. ISRCTN84767225 SMaRT oncology 1) , Sharpe correctly identifies the "Disease/condition/study domain" as "Cancer and depression".

"Primary outcome measure(s)" are given as: "The principal outcome measure will be a 50% reduction in the SCL-20 depressive symptoms score from baseline" and under "Secondary outcome measure(s)" it is recorded that: "Secondary measures will be: 1. Mean depression scores from the SCL-20 2. Remission specified as an SCL-20 score of <0.75 3. The presence of major depressive disorder assessed by SCID diagnostic interview. Subsidiary outcome measures will be: 1. Quality of life measured on the World Health Organisation (WHO) EQ-5D 2. EORTC-QLQ-C30 3. Anxiety measured on the 10 anxiety items of the SCL-90 4. A measure of self-efficacy, coping and social support 5. An estimate of the direct health care costs measured by case note review and patient questionnaire The outcomes will be measured at 3, 6 and 12 months" [49].



It may well be the case that “the covenant between researcher and patient, indeed between ethical review boards and patients, is broken” in the case of PACE [31].

There may be resistance and defensive argument, but for the scientific record and in the interests of transparency, scientists, clinicians and other register users, out of respect for trial participants, and the taxpayer who paid the £5-6 Million PACE bill, out of respect for lay and professional activists who have fought long battles for trial registration, especially the early AIDS activists [48-48a] to whom all, including the trialists, should be grateful, the ISRCTN register should be updated to accurately record all changes since original registration, regardless of the timing of ethical approval and finalised protocol (the full 2006 version of which should be made publicly available), and all details should be entered as specified. The original intentions of the trialists should be clearly visible, and explanations of changes and omissions recorded, inaccuracies corrected, all clearly entered into each separate field.

It has been estimated there may be 17 million sufferers worldwide [50].

On an Australian Radio programme [51], the Editor of the Lancet Richard Horton commented: “But one sees a fairly small, but highly organised, very vocal and very damaging group of individuals who have, I would say, actually hijacked this agenda and distorted the debate so that it actually harms the overwhelming majority of patients”.

Dr Richard Horton may have misidentified that fairly small group.

DT Fraser 28-6-2011 The PACE Trial: An Expression Of Concern

Obviously, this has not been exposed to what sometimes passes as “peer review”.

Getting to grips with PACE would take a reviewer months, not a Fast-track couple of weeks.

All mistakes and misunderstandings are MINE.

Feel free to repost and use, or add to, or correct in any way that might be in the public interest.

For research papers, which will usually be randomised controlled trials, judged to warrant fast dissemination, The Lancet will publish a peer-reviewed manuscript within 4 weeks of receipt (see Fast-track publication). If you wish to discuss your proposed fast-track submission with an editor, please call one of the editorial offices in London (+44 [0] 20 7424 4943), New York (+1 212 633 3667), or Beijing (+86 10 852 08872).

Disclosure may aid readers interpretation of PACE

Sir,

Interpretation of this article (1) is a matter for individual readers.

Young and Solomon (2) point out: "Many journals now routinely require authors to declare any potential financial or other conflicts of interest when an article is submitted. The reader must then decide whether the declared factors are important and might have influenced the validity of the study's findings".

In 2002 the British Medical Journal reported (3): "Two psychiatrists, a public health doctor, and a nurse therapist have resigned, saying that the report plays down the psychological and social aspects of the condition and concentrates on a medical model ... One of the most contentious issues is the inclusion of "pacing" as one method for managing the condition ... Dr Peter White of St Bartholomew's Hospital, London [was] one of those who resigned from the group".

Without this information, readers may not be able to fairly assess the validity of the study's findings.

Yours faithfully,

Douglas T Fraser

(1) Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial

(2) "How to critically appraise an article" : Jane M Young and Michael J Solomon : Nature, Clinical Practice, Gastroenterology & Hepatology February 2009 vol 6 no 2

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Manuscript reference number: THELANCET-D-11-01476  
Title: Disclosure may aid interpretation of PACE Trial Results

Dear Mr. Fraser,

Thank you for submitting your letter. After in-house review, I'm afraid we have decided not to accept it for publication. We regret that we are unable to write a personal note for every letter we turn down, but the following common reasons for rejection may help you with future submissions: lateness (ie, more than 2 weeks after publication of the article on which you are commenting), inclusion of original research (the section is not peer reviewed, so we cannot publish such work here), submission of case reports (we have a separate section for these), reiteration of points made by another correspondent, and inappropriate length (limits are 250 words and 5 references). If none of these apply to your letter, please be assured that we have nevertheless considered it carefully and probably had to refuse it because we have simply received too much good material.

Yours sincerely

Zoë Mullan  
Senior Editor

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DOI:10.1016/S0140- 6736(11)60096-2 <http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2811%2960096-2/abstract>

[1a] "For controlled trials, the identity of the control arm should be clear. The control intervention(s) is/are the interventions against which the study intervention is evaluated (e.g. placebo, no treatment, active control). If an active control is used, be sure to enter in the name(s) of that intervention, or enter "placebo" or "no treatment" as applicable. For each intervention, describe other intervention details as applicable (dose, duration, mode of administration, etc)".
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Professor M Knapp HSPHRB Representative Centre for Analysis of Social Exclusion London School of Economics London
[http://web.archive.org/web/20030423052737/www.mrc.ac.uk/index/about/about-organisation/about-bodies_and_members/about-mrc_advisory_board_\(mab\)/about-mab_a-d.htm](http://web.archive.org/web/20030423052737/www.mrc.ac.uk/index/about/about-organisation/about-bodies_and_members/about-mrc_advisory_board_(mab)/about-mab_a-d.htm)
Dr D Bhugra HSPHRB Representative Department of Psychiatry Institute of Psychiatry London
Dr T Chalder HSPHRB Representative Department of Psychological Medicine Institute of Psychiatry London
Dr A Cleare NMHB Representative Department of Psychological Medicine Institute of Psychiatry London
Professor A David NMHB Representative Department of Psychological Medicine Institute of Psychiatry London
Professor C F Dowrick NMHB Representative Department of Primary Care University of Liverpool Liverpool
[http://web.archive.org/web/20030423051347/www.mrc.ac.uk/index/about/about-organisation/about-bodies_and_members/about-mrc_advisory_board_\(mab\)/about-mab_e-k.htm](http://web.archive.org/web/20030423051347/www.mrc.ac.uk/index/about/about-organisation/about-bodies_and_members/about-mrc_advisory_board_(mab)/about-mab_e-k.htm)
Professor A E Farmer Ordinary Member Social, Genetic & Developmental Psychiat Institute of Psychiatry London
Dr J R Geddes NMHB Representative Department of Psychiatry University of Oxford Oxford
Professor GM Goodwin MCMB Representative Department of Psychiatry University of Oxford Oxford
Professor A Haines Ordinary Member Public Health & Primary Care London School of Hygiene & Tropical Medicine London
Professor P W Halligan NMHB Representative Department of Psychology University of Wales College of Cardiff Cardiff
Dr M H Hotopf NMHB Representative Department of Psychological Medicine Institute of Psychiatry London
Professor A House Ordinary Member Academic Unit of Psychiatry & Behavioural Sciences

University of Leeds School of Medicine Leeds

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Dr S M Lawrie NMHB Representative Department of Psychiatry University of Edinburgh
Edinburgh

Professor R M Murray NMHB Representative Department of Psychological Medicine Institute of Psychiatry London

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Dr M C Sharpe Ordinary Member Department of Psychological Medicine University of
Edinburgh Edinburgh

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Dr S M Lawrie NMHB Representative Department of Psychiatry University of Edinburgh
Edinburgh

Professor R M Murray NMHB Representative Department of Psychological Medicine Institute of Psychiatry London

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Dr M C Sharpe Ordinary Member Department of Psychological Medicine University of
Edinburgh Edinburgh

Professor A Thapar Ordinary Member Department of Psychological Medicine University of Wales
College of Medicine Cardiff

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Members of the College of Experts affiliated to the
Neurosciences and Mental Health Board

Professor R P Bentall School of Psychological Sciences The University of Manchester Manchester

Professor T Chalder Department of Psychological Medicine Institute of Psychiatry London

Professor P Cowen Psychopharmacology Research Unit Warneford Hospital Oxford

Professor A E Farmer Social, Genetic & Developmental Psychiatry Institute of Psychiatry London

Professor J R Geddes Department of Psychiatry University of Oxford Oxford

Dr S M Lawrie Department of Psychiatry University of Edinburgh Edinburgh

Professor P D White Department of Psychological Medicine Medical College of St
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RCT of CBT, graded exercise, adaptive placing and usual medical care for the chronic fatigue syndrome Project record Publication ID: N0042140250 NRR data provider: South London and Maudsley NHS Trust Region: London Regional Office

Project description Title: RCT of CBT, graded exercise, adaptive placing and usual medical care for the chronic fatigue syndrome

Principal research question: The PACE trial is designed to answer the following questions:

- 1) Is CBT and/or GET more effective than APT when given added to SUSMC in reducing both fatigue and disability?
- (2) Is APT and SUSMC more effective than SUSMC alone?
- (3) Are there differential predictors of response to APT, GET and CBT and does the mechanism of change differ between them?
- (4) Do different treatments have differential effects on outcomes (i.e. disability versus symptoms)?
- (5) What factors predict a favourable response to treatment in general and to specific individual treatments?
- (6) What are the mechanisms of change with successful treatment?
- (7) What are the relative cost-effectiveness and cost-utility of these treatments?

Methodology description: A four arm, single blind, randomised parallel group controlled trial of patients who meet operationalised criteria for CFS, with follow-up for 12 months.

Sample group description: We will study 600 participants, recruited over three years in six centres, one of which is King's College London. Each centre will be expected to recruit a minimum of 33 new participants per annum.

All participants will be attending secondary care chronic fatigue clinics. The six trial centres are all staffed by clinicians and scientists with established experience of running chronic fatigue services. Each centre will receive regular visits by the TM and a PI or other centre leader and all aspects of the local operation will be audited. Each centre leader will receive and be asked to signify their understanding of their responsibilities as centre leaders. All centres have reported that they currently see a minimum of 100 new patients with chronic fatigue per year. We estimate that 50 will meet eligibility criteria, and a conservative estimate is that two thirds will agree to enter the trial. Only seven and 15% of eligible participants refused to participate in the previous GET trials^{15,16} and three, 10 and 26% of those eligible refused CBT.¹²⁻¹⁴ We are therefore confident that recruitment, at an overall rate of 200 participants per year is feasible and that the trial will achieve 600 participants over three years. We will however closely monitor recruitment, especially in the first six months, and the trial management group, after advice from the TSC, will consider replacing those centres that either do not recruit sufficient participants, or fail to provide quality data.

Outcome measure description: 4.4 Endpoints:

1. The 11-item Chalder fatigue questionnaire measures the severity of symptomatic fatigue,²³ and

has been the most frequently used measure of fatigue in most previous trials of these interventions. We will use the 0,0,1,1 item scores to allow a possible score of between 0 and 11. The pre-specified criteria for good outcome will be a 50 % reduction from baseline fatigue score, or a score of 3 or less, this threshold having been previously shown to indicate a normal level of fatigue.²³ A Likert scoring (0,1,2,3) will also be used, as a secondary outcome measure, to better measure response to treatment. 2. The SF-36 physical function sub-scale²⁴ measures physical function, and has been used as an outcome measure in previous trials of CBT and GET. We will count a score of 75 (out of a maximum of 100) or more, or an increase of 50 % increase from baseline in SF-36 subscale score as indicating a good outcome. A score of 75 is one standard deviation below the mean score (90) for the UK working age population.²⁹

Research results: Research results are not currently collected by the NRR

Project organisation This record refers to a multi-centre study led by another centre Lead centre name: St Bartholomew's Hospital, London Start date: 1 April 2002 End date: 31 March 2007

Project status: Ongoing Contact person: Prof Martin Knapp CEMH Institute of Psychiatry De Crespigny Park Denmark Hill London SE5 8AF Telephone: 020 7836 5454 E-mail: sptemrk@iop.kcl.ac.uk

Programme Identifier NHS organisation code: RV5 Title: Better treatments for Chronic Fatigue Syndrome Funding information Funding organisation name: Medical Research Council Funding reference number: G0200434 Funding amount: £31929 Funding organisation name: NHS R&D Support Funding reference number: 2005/06 Funding amount: £37167 MeSH index terms Primary keywords: MeSH terms not yet assigned

Direct link to this record:

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