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Ethical and Scientific Concerns about the MRC PACE Trial

West Midlands MREC reference: MT/MREC/02/7/89

Chief Investigator: Professor Peter D White (Psychiatrist, St Bartholomew's Hospital, London)

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"PACE" is the acronym for **P**acing, **A**ctivity, and **C**ognitive behavioural therapy, a randomised **E**valuation (a randomised, controlled trial of adding cognitive behaviour therapy, graded exercise, or adaptive pacing to usual medical care, compared to usual medical care alone, for Chronic Fatigue Syndrome [ME]).

The Governance arrangements for NHS Research Ethics Committees, 2001, state:

"9.7 The primary task of a REC lies in the ethical review of research proposals and their supporting documents, with special attention given to the nature of any intervention and its safety for participants, to the informed consent process, documentation, and to the suitability and feasibility of the protocol".

In relation to the MRC PACE Trial on "CFS/ME", there are serious concerns about all these issues.

1. The Trial entry criteria

The re-submitted Application was reviewed at the West Midlands MREC meeting on 24th October 2002 and was APPROVED (letter dated 29th October 2002 to Dr [now Professor] Peter White from Maureen Thrupp, Administrator). The accompanying documentation states: *"MREC noted the importance of the study and wished to commend the researchers on the RCT design"*. However, the design of the

trial does not accord with the elementary scientific research requirement for as homogeneous a cohort as possible in a clinical trial. On the contrary, it intentionally includes as heterogeneous a cohort of "fatigued" people as possible yet claims to be studying a specific and formally classified neurological disorder (CFS/ME).

Entry to the Trial was contingent upon a participant meeting the 1991 Oxford criteria for CFS which were partially funded by the Chief Investigator himself (JRSM 1991:84:118-121) and which look at patients *"with a principal complaint of disabling fatigue"*. The Oxford criteria were described at the time by one of the co-authors: "*British investigators have put forward an alternative, less strict, operational definition* ***which is essentially chronic fatigue in the absence of neurological signs, (with) psychiatric symptoms…as common associated features***" (A.S. David; BMB 1991:47:4:966-988), thus the entry criteria for the PACE Trial expressly exclude those with neurological disturbance but specifically include those with psychiatric disorders.

The Oxford criteria have been stringently criticised for being too broad to be meaningful; they have no predictive validity, have rarely been adopted outside the Chief Investigator's own small group of colleagues and their use in scientific trials has recently been described as "*objectionable by current standards"* (http://www.cfids.org/xmrv/022510study.asp). One of the Principal Investigators (PIs) stated as long ago as 1997 that the Oxford criteria *"have been superseded by international consensus"* (Occup Med 1997:47:4:217-227), by which he meant the 1994 CDC criteria (Ann Intern Med 1994:121:953-959).

Of cardinal concern is that the Oxford criteria specifically exclude the pathognomonic symptom of CFS/ME (post-exertional fatigability and malaise) so cannot define the population the PIs purport to be studying because people with neurological disease are specifically excluded, yet ME/CFS has been classified by the WHO as a neurological disease since 1969 (ICD-10 G93.3).

The Chief Investigator failed to fully inform the MREC of this contradiction and thus denied the MREC the opportunity to discuss the issue.

ME is accepted by the Department of Health (one of the co-funders of the Trial) as a neurological disease and it is included within the UK National Service Framework for chronic neurological disorders.

The primary symptoms of ME are neurological, immunological, cardiovascular, respiratory, endocrinological/metabolic, gastrointestinal and musculoskeletal, for all of which there is a significant and substantial evidence-base dating back to 1938. For referenced illustrations of this evidence-base, see Section 2 of the 442-page Hooper Report of February 2010 "Magical Medicine: how to make a disease disappear" (http://www.meactionuk.org.uk/magical-medicine.htm).

If the favoured entry criteria were correctly applied, patients with ME should have been screened out of the PACE Trial, yet the Trial literature specifically states that CFS/ME equates to ME.

Furthermore, it was confirmed on 12th May 2004 by Parliamentary Under Secretary of State at the Department of Health, Dr Stephen Ladyman, at an All Party Parliamentary Group on Fibromyalgia, that doctors were being offered financial inducements to persuade patients with FM to attend a CFS Clinic to aid recruitment to the PACE Trial (EIF: Spring/Summer 2004, page 19), which means that the PACE Trial intentionally includes at least three distinct disorders -- CFS/ME (ICD-10 G93.3); fibromyalgia (ICD-10 M79.0) and psychiatric fatigue (ICD-10 F48.0). This is disturbing because CFS/ME and FM have distinct biological profiles, for example:

- levels of somatomedin C are lower in FM patients but are higher in CFS/ME patients (J psychiat Res 1997:31:1:91-96)
- levels of Substance P are elevated in patients with CFS/ME but not in patients with FM (Pain 1998:78:2:153-155)
- patients with FM are not acetylcholine sensitive (Rheumatology 2001:40:1097-1101) but patients with CFS/ME are acetylcholine sensitive (Prostaglandins, Leukotrienes and Essential Fatty Acids 2004:70:403-407)
- endothelin-1 is raised in fibromyalgia (Rheumatology 2003:42:493-494) but is normal in CFS /ME (Rheumatology 2004:43:252-253).

Because it is unclear which disorder is being studied in the PACE Trial, it will not be possible to draw any meaningful conclusions from the data, which calls into question the purpose of the Trial.

2. Dilution of the Trial cohort

Once the Trial was underway, the Chief Investigator made numerous applications to the MREC for the protocol to be amended and he changed the

design as he went along. This undermines the reliability of the conclusions, not least because the first 75 participants recruited met different entry criteria from those who were recruited later:

- the Trial Identifier stated at section 3.6: "*The RN* (research nurse) *will use a standard psychiatric interview…to exclude those with…a chronic somatisation disorder"*, but the Minutes of the Joint Meeting of the Trial Steering Committee and Data Monitoring and Ethics Committee held on 27th September 2004 record at point 12: "*Professor White noted that there were… changes already planned…Under medical history, patients with…somatisation disorder would not be excluded".* Intentionally to include those with somatisation disorder in a Trial that purports to be studying those with a classified neurological disorder does not meet the required standards of scientific rigour, yet this was approved by the MREC

- the Chief Investigator further diluted the entry criteria by moving the SF-36 (physical function score) goalposts and by including people who had previously undergone the interventions being assessed in the Trial (CBT/GET). Originally, the SF-36 cut off point was set at 75 (Trial Identifier: 3.6) and those who had previously undertaken CBT/GET were excluded from the PACE Trial. However, on 9th February 2006 the Chief Investigator wrote to the MREC seeking permission to implement changes that had the specific aim of increasing recruitment (the SF-36 cut off point had been changed from 75 to 60 but was then changed yet again to 65). Up to December 2005 (when the changes took place), the Investigators had excluded 65 people from 140 applicants. Thirty-six people had scored too highly on the SF-36 (so were deemed too well to take part in the Trial) and twenty-nine people had previously undertaken CBT/GET; thus 46.43% of 140 applicants had originally been rejected, but such people were then to be invited to take part in the PACE Trial, and this was approved by the MREC

- despite the Trial Identifier stating at section 2.5 "*We will not recruit directly from primary care because we wish to compare the efficacy of these treatments in patients whom GPs regard as requiring additional help and who are likely to have a worse prognosis"*, in apparent desperation to reach their recruitment target, on 14th July 2006 the Chief Investigator sought approval from the MREC to advertise his trial to GPs, abandoning the protocol by which he intended to recruit "*consecutive new patients"* attending CFS clinics and instead seeking patients directly from primary care. In his letter, Peter

White virtually begged GPs to send anyone who suffered from "*chronic fatigue (or a synonym)*" to a PACE Trial Centre. This means the Investigators are likely to have included people who are "tired all the time" (TATT), which bears no relationship to ME, yet this significant dilution of the Trial cohort was approved by the MREC. Just how scientifically rigorous the inclusion of patients with "*fatigue (or a synonym)*" might be is a matter for speculation. Quite certainly, such broad canvassing has resulted in people who had shingles (herpes zoster) being included in the PACE Trial on CFS/ME even though post-herpetic fatigue is not the same disorder as CFS/ME. Such lack of exactitude means that the results of the PACE Trial are likely to be evidentially meaningless.

Given the overly-inclusive entry criteria and the numerous dilutions of the study cohort, the results of the Trial cannot credibly be taken to apply to those with the discrete disorder CFS/ME and will thus be devoid of scientific meaning and applicability.

3. <u>Participants were unable to give fully informed consent</u>

The MREC failed to ensure that participants were in a position to give fully informed consent, which is a serious ethical issue. For example:

- participants were to be treated throughout the Trial as though they were not physically but mentally ill
- the fact that the PACE Trial was predicated on the Chief Investigator's assumption that participants had no organic disease (merely an "aberrant belief" that they were physically sick) was intentionally withheld from them
- some of the Manuals (all of which were approved by the MREC) advise therapists actively to dissuade participants from seeking medical advice about their symptoms and (in the CBT arm) to convince participants that the symptoms do not result from a physical disease (something the therapists cannot know), a potentially dangerous situation which in some cases might even result in death
- the Chief Investigator's unproven beliefs and assumptions are presented as fact (for example, that CBT and GET are curative), which misleads participants
- Trial therapists were trained to provide participants with misinformation (for example, that the symptoms are merely the result of wrong beliefs

and behaviour); for NHS staff deliberately to mislead and misinform sick people is unethical

- the vested interests of the PIs were not made clear to participants (thus breaching the Declaration of Helsinki B22), ie. their financial involvement with the medical and Permanent Health Insurance industry -- a matter of serious concern to the 2006 Gibson Inquiry, a committee of Parliamentarians that included the former Chairman of a House of Commons Science and Technology Select Committee and former Dean of Biology; a member of the Home Affairs Select Committee; a Minister of State for the Environment; a former President of the Royal College of Physicians; the Deputy Speaker of the House of Lords, and a former Health Minister and Honorary Fellow of the Royal College of Physicians
- participants' confidential data was not kept securely and was stolen (thus breaching the Declaration of Helsinki B21) but participants were not informed that confidential information about them had been stolen; the crime number is 3010018-06
- the PIs' role as advisors to UK Departments of State whose known aim is to remove people with CFS/ME from benefits was withheld from participants (the Chief Investigator is lead advisor on CFS/ME to the DWP and the DWP was to have unrestricted access to participants' medical records).

Had participants been informed of these facts, some might have declined to enter the Trial.

4. <u>The existing evidence-base about the disorder was entirely ignored</u>

The Chief Investigator entirely ignored the existing biomedical evidence-base about the disorder (thus breaching the Declaration of Helsinki B11), despite the fact that the PACE Trial is co-funded by the Department of Health, whose own Research Governance Framework for Health and Social Care, Second Edition, stipulates: ***"2.3.1: All existing sources of evidence…must be considered carefully before undertaking research"*** and ***"It is essential that existing sources of evidence…are considered carefully prior to undertaking research. Research which…is not of sufficient quality to contribute something useful to existing knowledge is in itself unethical"***, which is exactly the situation that pertains in the PACE Trial.

The fact that the Chief Investigator rejects the extensive biomedical evidence and persists in asserting that CFS/ME is a behavioural disorder is insufficient justification to predicate a clinical trial on a false premise that aims to re-categorise a neurological disorder as a behavioural disorder (which would be to the advantage not only of the DWP, which would be saved from paying the higher rate of Disability Living Allowance because those with a mental disorder are ineligible, but also of the Chief Investigator's Permanent Health Insurance employers, since mental disorders are excluded from benefit, a conflict of interest on the part of all the Principal Investigators that breaches the Declaration of Helsinki B22).

5. Misinformation in the Trial Manuals

The West Midlands MREC approved the Manuals used in the Trial, but the Manuals are grossly misleading if not deceptive, badly and carelessly written and are internally inconsistent.

5.1 The Manuals fail to mention the significant body of evidence showing that incremental aerobic exercise is potentially harmful to some people with CFS/ME. Trial therapists ought to have been made aware of this in order to meet the ethical requirement to ensure that all research staff are competent. Therapists needed to know they were delivering an intervention which, however skilfully administered, could cause significant harm to some participants, a serious ethical issue about which the MREC apparently failed to exercise due diligence, alternatively, about which it was misled by the Chief Investigator. Equally, it is unethical for the Chief Investigator to have misled the therapists, thereby subjecting them unwittingly to committing potential professional misconduct.

5.2 The Manuals mislead participants in that they fail to mention that mainstream medicine, including the Department of Health, accepts that ME is a neurological disease. The Manuals are entirely based on the Chief Investigator's own model of CFS/ME (this being his assumption that CFS/ME is a behavioural disorder that is amenable to cognitive restructuring and incremental exercise).
That CFS/ME is a behavioural disorder has been repudiated in writing by the WHO, which has also provided written confirmation that it has no plans to reclassify ME as a behavioural disorder.

Notwithstanding, the PACE Trial is specifically intended and designed to alter the way participants think about their illness by re-structuring their thoughts and

challenging their "negative thought patterns" by persuading them to believe that they are not sick (indeed, according to the Chief Investigator, one of the aims of the Trial is *"Health economics and societal costs"* -- Bergen, October 2009), yet there is no evidence to show that the many pathophysiological abnormalities that have been demonstrated in CFS/ME are caused by wrong beliefs or behaviour, whereas there are over 5,000 published papers confirming the organic abnormalities. Indeed, the MRC has compiled a 351-page document review of research papers (some papers dating from before the PACE Trial began recruiting) and sent it to its CFS/ME Expert Group (http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC006509).

This proves that the MRC is fully aware that CFS/ME is not a somatoform disorder, yet the MRC is contemporaneously co-funding and backing the PACE Trial which is entirely predicated on the Chief Investigator's erroneous assumption that CFS/ME is a somatoform disorder, an unethical situation in itself.

5.3 The Manuals play down the fact that the interventions used in the Trial were already known to be ineffective (thus breaching the Declaration of Helsinki B19): it was already established that the interventions are *"not remotely curative"* and that *"These interventions are not the answer to CFS"* (Editorial: Simon Wessely JAMA 19th September 2001:286:11).

Lilford et al (JRSM 1995:88:552-559) are clear about such a situation:

"Members of ethics committees should proceed on the basis that the question to be investigated has not already been answered…. ***Under these circumstances the trial would be unethical".***

Even though the interventions were known to be at best unhelpful and at worst to be harmful, over £5 million of public money has now been spent on the PACE Trial.

5.4 It should never be suggested to participants in a clinical trial that the intervention they are undertaking is a cure unless it is certain that it is indeed curative, in which case there would be no need for an expensive trial to prove the efficacy of the intervention. It is a basic rule of any clinical trial that participants are not told during the trial how effective is the intervention that they are receiving, yet the Manuals in two arms of the Trial do exactly this and promise recovery from the disorder if participants are compliant with CBT and GET. To

mislead patients by promising a cure when there is no such certainty is clearly unethical and is in breach of the General Medical Council (GMC) Regulations as set out in "Good Medical Practice":

"Providing and publishing information about your services – paragraphs 60-62

> *60. If you publish information about your medical services, you must make sure the information is factual and verifiable.*
>
> *61. You must not make unjustifiable claims about the quality or outcomes of your services in any information you provide to patients.* ***It must not offer guarantees of cures****, nor exploit patients' vulnerability or lack of medical knowledge".*

The NICE Clinical Guideline on CFS/ME (CG53, August 2007) did not support the Chief Investigator's promises of recovery: "***The Guideline Development Group did not regard CBT or other behavioural therapies as curative***" (Full Guideline, page 252).

5.5 In clinical trials there is an ethical requirement for equipoise, defined as *"the point where there is no preference between treatments, i.e. it is thought equally likely that treatment A or B will turn out to be superior"* (RJ Lilford et al. JRSM 1995:88:552-559). The Trial Protocol cites Lilford et al and furthermore it states: *"those recruiting and randomising participants will rigorously maintain a position of equipoise and employ explanations that are consistent with this. All the participating clinicians regard all four treatments as potentially effective"*. However, it is evident that not all the participating clinicians do believe all four treatments to be potentially effective, as the Manuals state that CBT and GET are curative, whereas no similar claim is made for APT (adaptive pacing therapy) or SSMC (Standardised Specialist Medical Care). Indeed, in 2002 two of the PACE Trial PIs (Professors Peter White and Trudie Chalder) resigned from the CMO's Working Group on CFS/ME because they opposed its support of pacing.

Given that the Investigators had already formed their belief that CFS/ME is a behavioural disorder, it is troubling to observe how they appear to have allowed their beliefs to undermine the objectivity of the Trial.

The MREC seems not to have addressed the issue of whether it is ethical for the Chief Investigator to be responsible for a trial that includes assessment of pacing when he is on public record as believing that pacing has the potential to harm

patients by maintaining them in a state of alleged deconditioning (Trial Identifier Section 2.3) even though in 2001 it was conclusively demonstrated that deconditioning is not a factor in CFS/ME (Bazelmans et al. Psychol Med 2001:31:107-114).

Of concern is the fact that the MREC approved such unethical weighting in two of the four arms of the MRC clinical trial, especially given the widely available published evidence that those particular arms of trial were known to be particularly favoured by the Chief Investigator and the other two PIs. The strict requirement for equipoise means that on this basis alone the PACE Trial is unethical, because there is known agreement between the three PIs (as well as psychiatrist Professor Simon Wessely, who is in charge of the PACE Clinical Trial Unit) that CBT and GET are superior to APT and to SSMC (about which the PIs are publicly dismissive), yet the MREC apparently failed to exercise due diligence over this crucial ethical issue.

5.6 The Trial literature and Manuals inform participants and therapists that there are no serious adverse side-effects from the interventions, but this is misleading and therefore unethical.

Even before the Trial began it was known that several thousand CFS/ME patients had suffered serious adverse effects from one of the interventions in particular: not only was it not helpful, it had made 50% of participants worse (Severely Neglected: M.E. in the UK. Action for ME, March 2001).

The Cochrane Review of CBT for CFS (Cochrane Database of Systematic Reviews, 2008, Issue 3) noted: *"For the treatment of CFS, CBT combines a rehabilitative approach of a graded increase in activity with a psychological approach addressing thoughts and beliefs about CFS that may impair recovery"* but repeatedly emphasised that scientific data on adverse events is completely lacking:

- *"Data referring to adverse effects of psychological treatment was not systematically presented by any study"*
- *"No studies examined side effects"*
- *"Dropout due to adverse effects: No studies contributed to this outcome at post treatment or follow-up"*
- *"Outcomes which are of high relevance to the individual with CFS, including adverse effects, were under-evaluated…."*.

Santhouse recently acknowledged the Cochrane finding that the known and adverse events associated with the CBT/GET combination have never been scientifically evaluated ("*researchers have never really looked"*: Evid Based Ment Health 2009:12:16), yet seven years previously the Chief Investigator had assured the MREC (and subsequently the participants) that these interventions were safe, an assurance for which there was/is no evidence as far as ME is concerned (thus breaching the Declaration of Helsinki A5, B20 and B22).

Indeed, it is the case that the MRC's own Neuroethics Committee expressed doubts over the use of CBT: *"…CBT aims to influence how a person thinks or behaves… there is increasing evidence that (it) can alter brain function. Further research is needed to …determine whether therapies are reversible or if there are persistent adverse effects. There is already evidence that in certain situations psychotherapy can do harm…There is also increasing public concern that psychological therapies could be used for brainwashing….How much information should patients be given about the possible effects of therapy on their brain?….How appropriate is this use of psychological therapy?"* (Report on MRC Neuroethics Workshop, 6th January 2005: Section 2: Altering the brain).

6. <u>The deliberate decision not to obtain objective evidence of efficacy of the Trial interventions</u>

The original protocol included the collection of actigraphy data from participants before and after the interventions as an objective outcome measure; however, once the Trial was underway, the MREC acquiesced with the Chief Investigator's decision that no post-intervention actigraphy data should be obtained.

The cardinal feature of CFS/ME is post-exertional relapse, often not experienced until some hours or even days after exercise (CMO's Working Group Report on CFS/ME, 2002), a fact of which the Chief Investigator was/is fully aware, as he himself published a paper before the PACE Trial started recruiting participants which demonstrated the adverse effect of exercise on CFS/ME patients lasting up to three days post-exercise (JCFS 2004:12 (2):51-66*):*

"Concentrations of plasma transforming growth factor-beta (TGF-β) (anti-inflammatory) and tumour necrosis factor-alpha (TNF-α) (pro-inflammatory) have both been shown to be raised… Altered cytokine levels, whatever their origin, could modify muscle and or neuronal function… Concentrations of TGF-

β1 were significantly elevated in CFS patients at all times before and after exercise testing…We found that exercise induced a sustained elevation in the concentration of TNF-α which was still present three days later, and this only occurred in the CFS patients… TGF-β was grossly elevated when compared to controls before exercise… The pro-inflammatory cytokine TNF-α is known to be a cause of acute sickness behaviour, characterised by reduced activity related to 'weakness, malaise, listlessness and inability to concentrate', symptoms also notable in CFS…These…data suggest that 'ordinary' activity (ie. that involved in getting up and travelling some distance) may induce anti-inflammatory cytokine release (TGF-β), whereas more intense exercise may induce pro-inflammatory cytokine release (TNF-α) in patients with CFS".

The Chief Investigator thus knew that a single six-minute level walking test (the allegedly "objective" outcome measure approved by the MREC) is inappropriate for people with CFS/ME.

In the light of this biomedical evidence which pre-dated the start of the PACE Trial recruitment, it is inexplicable that in his many applications to the West Midlands MREC for amendments to his original protocol, the Chief Investigator failed to seek permission to carry out objective post-exercise immunological testing of participants; had he done so, this would likely have provided incontrovertible substantiation of serious organic pathology in any participants who actually have CFS/ME as opposed to those with psychiatric "fatigue".

It is therefore a matter of serious concern that (a) the findings of the Chief Investigator's own study on post-exertional cytokine elevations were withheld from participants and therapists alike and (b) studies (some of which pre-dated the PACE Trial) have unequivocally demonstrated that even if participants report feeling better on subjective questionnaires such as those to be used as outcome measures in the PACE Trial, participants are actually less physically active than before the intervention when measured using objective actigraphy data.

It is disturbing that the Chief Investigator requested the abandoning of post-intervention actigraphy and that he did not inform the MREC of the known discrepancy between subjective and objective reports of physical capacity (Vercoulen JH et al. J Psychiat Res. 1997 Nov-Dec; 31(6):661-73): having evaluated whether physical activity levels <u>can</u> be adequately assessed by self-report measures by correlating seven outcome measures in relation to actometer readings, Vercoulen et al demonstrated that "*none of the self-report questionnaires*

had strong correlations with the Actometer". The study showed that *"self-report questionnaires are no perfect parallel tests for the Actometer"* and that subjective questionnaires *"do not measure actual behaviour"*.

Furthermore, a study on CFS/ME patients in the US by Friedberg et al that used CBT which also encouraged exercise found on actigraphy measurements that there was in fact a numerical decrease from the pre-treatment baseline (J Clin Psychol 2009, February 1).

Thus, by design, the PACE Trial is not capable of producing scientifically meaningful results and therefore cannot test the efficacy of the Trial interventions, an unacceptable outcome of which the MREC approved.

Subjecting people to an elaborately involved procedure that can have no constructive end result would seem to be in breach of the Declaration of Helsinki, the ensuring of adherence to which is the duty of the MREC.

7. Community implications of the Trial results

The PACE Trial Chief Investigator bears responsibility for the Trial's potential impact on those severely affected by ME and indeed the Governance requirements for NHS Research Ethics Committees, 2001, draw particular attention to:

" 9.18 Community considerations:

a. the impact and relevance of the research on the local community and on the concerned communities from which the research participants are drawn".

Given the content of the Manuals, the impact that the PACE Trial results are likely to have on people who are severely affected with ME/CFS required full consideration before ethical approval was given. The Trial appears to have selected participants who meet only the loosest criteria and who are not very incapacitated, but the effect of the research on other people with much more severe illness should have been robustly addressed by the MREC yet seemingly it failed to do so. This could place such seriously ill people in jeopardy.

Conclusion

It seems indisputable that, either through dereliction of duty or through being inadequately informed by the Chief Investigator, the West Midlands MREC failed to adhere to section 9.7 of the Governance arrangements for NHS Research Ethics Committees (2001) which were in place at the time it granted ethical approval for the MRC Trial.

Given the nature of these ethical concerns, there should be serious consideration given to the continuation of the Trial and the publication of any data.

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