

Two and a half year follow up

We have now received research ethics committee approval to ask how everybody is some two and a half years after coming into the PACE trial. This will allow us to know whether treatments have sustained effects or not. We will analyse outcomes in two ways; firstly on the basis of the original PACE trial treatment received, and secondly, on the basis of all treatments received including any received after participation in the trial. This will allow us to know whether treatments continue to work long-term or whether participants have recurrences after treatment. Research

nurse/assistants from the first wave centres have started to collect data from participants who finished the trial some 18 months ago, 2.5 years after randomisation. These outcome data are much less than normal follow-up assessments and are collected by post, with a telephone call follow up to check any uncertain or missing data. There is no need to visit the hospital for this follow up. We hope that all participants will contribute to this follow-up, which is important if we are to learn whether treatments last. We are most grateful to those who have already sent back their questionnaires.

Medical Research Council grants further funds

The Medical Research Council (MRC) has granted the PACE trial team further funding to allow the study to continue recruiting until the end of November 2008. This will allow the team to achieve the aim set out in the protocol of recruiting 600 participants. The ethics committee has also agreed to allow the team to recruit over the 600 mark if possible by this end date.

The trigger to increase time to the trial came when it was noticed that recruitment had begun to slow down. This came about for a number of reasons. One of these was the establishment of the CFS Clinical Network Coordinating Centres (CNCC) which has allowed greater local access to services for CFS/ME to participants in England. This has allowed people to seek services closer to home where previously they may have had to travel to a secondary care centre such as those hospitals participating in the PACE trial.

Another possible cause of slowed recruitment may have been as a consequence of the release of the NICE guidelines for CFS/ME. The

document detailed the review of previous research for treatments for CFS/ME. This has allowed people to make more informed choices about what treatments they may wish to try based on the available research evidence.

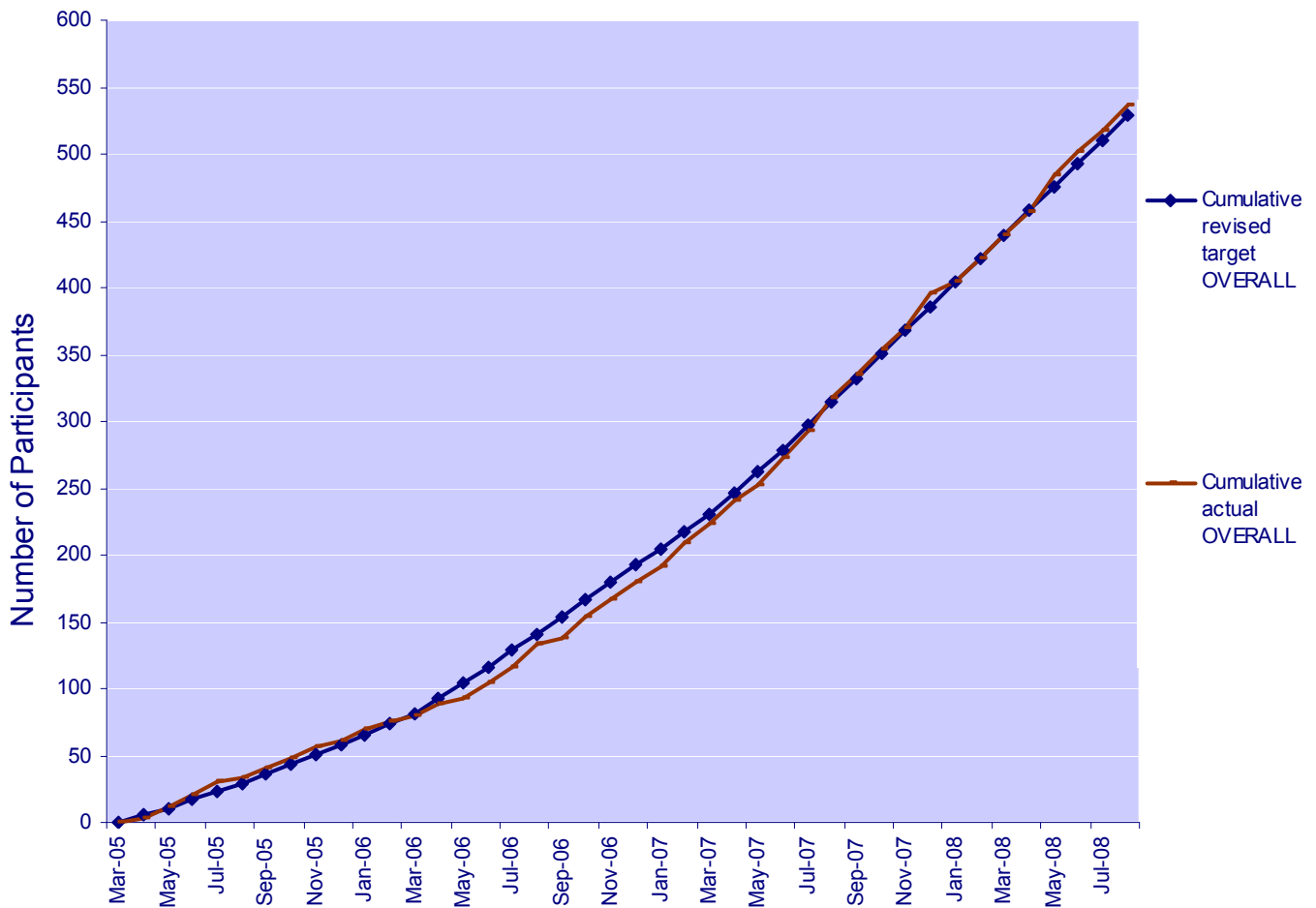
The PACE trial retains a significant role as the largest trial ever for comparison of rehabilitative therapies for CFS/ME and the results will add important new information to the pool of previous studies.

As well as increasing time and funding to PACE, we also increased the number of our centres. As announced in the last newsletter a sixth hospital was invited to join the PACE trial and Bristol Frenchay have been successfully recruiting since April of 2007. We are very excited to be able to welcome staff and participants from the South West to take part.

With all of these extensions, the PACE trial is now well on course to achieve the target of 600 participants by the end of November 2008, and the ethics committee have also granted us permission to recruit more by this date if we can.

Recruitment update for July 2008

Recruitment to the PACE trial continues to progress at a steady rate as may be seen from the graph below.



All six hospital centres combined have not only managed to meet the revised recruitment targets, but also to exceed them. This is a fantastic achievement for the trial team.

None of these successes would be possible without every volunteer who has opted in to the study and we would like to thank you and those who support you for your time and commitment to this research. Together we strive to increase the knowledge about this often very misunderstood condition and hope that we will deliver strong evidence for treatments that will have meaningful benefit for all with the condition.

Please do remain in contact with the trial. We would love to hear more of your feedback and see more contributions to this newsletter from participants of PACE. Thank you.



Feedback

What Number 10 Downing Street think about the PACE Trial

“As with all serious illnesses, it is important that patients, their families and the healthcare professionals looking after them have the best scientific information available and the PACE trial has been designed to help them decide for themselves what treatment is likely to be best from them.”

(<http://www.number-10.gov.uk/output/Page14656.asp>).

A doctor's feedback

We have received a copy of a letter from a doctor, of a patient attending the Bristol centre, to a PACE therapist. He kindly authorized us to publish the letter.

“I just wanted to feed back to you positive changes I have seen in (patient) since participating in your trial. I know the (therapy) is recommended (...) for CFS, but this is the first time I have seen such a well thought out programme put into practice. (The patient) attended today with the plan and I think even the layout of it, is with the programme moving to more positive colours, has clearly been very carefully thought about. I would strongly support any extension of the trial, which clearly has the potential to transform lives of many people suffering with this debilitating disease. Congratulations to yourself and your colleagues in such a successful programme.”

Some participants' feedback

“Being included in this trial has helped me tremendously. (The treatment) is now a way of life for me, I can't imagine functioning fully without it. I have nothing but praise and thanks for everyone involved in this trial”.

“The therapy was excellent and very helpful. (...) I found the trial to be very professionally run and the Research Nurse was very understanding and empathetic.”

“(The therapist) is very helpful and gives me very useful advice and also motivates me.”

“I really enjoyed being a part of the PACE Trial. It helped me to learn more about myself, especially (treatment), and control factors in my life that were damaging. It is difficult for me to gauge just how effective the treatment was because 2007 was a particularly strained, strange and difficult year for me but I feel I survived and that the trial armed me with the necessary aids to get me through. It was also hugely beneficial being part of something where people understand the symptoms and illness and I really enjoyed this aspect.”

“Found (the treatment) extremely useful. Would have liked more help with muscle pain. Found both therapist and research nurse very pleasant, approachable and professional.”

“I am so happy that this treatment/trial has greatly changed my sleeping! I can sleep throughout the night (6-7hrs) and even have a nap! Thank you.”

Recent Research into CFS

Update on the FINE Trial

The FINE Trial was funded by the MRC and the Department of Health at the same time as PACE, and has been running since April 2004 in the North West of England. The principal investigator is Dr Alison Wearden of the University of Manchester, with other members of the research team drawn from the Universities of Manchester, Liverpool and York.

The treatments which have been tested in FINE are pragmatic rehabilitation, a treatment which aims to restore sleep patterns, gradually increase activity levels, and encourage efficient use of rest and relaxation; and supportive listening, a non-directive counselling treatment in which the patient sets the agenda for therapy sessions. These treatments will be compared with each other and with treatment as usual by the patient's general practitioner.

Patients with CFS/ME have been recruited to the FINE trial using similar criteria to those used by PACE, but FINE differs from PACE in that patients have been referred by their GPs and are treated in their own homes by three specially trained nurse therapists. Recruitment to the FINE trial ended in October 2007, with 296 patients recruited, and the research team are currently carrying out the final batch of one-year follow up assessments. We plan to analyse the findings from the trial early in 2009, and the results will be available later in the year.

Dr Alison Wearden

For more information about the FINE Trial please visit the website at

<http://www.fine-trial.net/>



FINE Trial
Fatigue Intervention by Nurses Evaluation

What research into CSF/ME is the MRC currently funding?

Apart from its investment in the PACE and FINE trials, the MRC is currently funding the following research projects:

- ▶ A preliminary epidemiological project to test the feasibility of identifying the risk factors for persistent symptoms of fatigue and abdominal and widespread pain. (Manchester University, led by Professor Francis Creed).
- ▶ An epidemiological study to assess ethnic variations of the prevalence of a CFS-like illness, associations with potential risk factors, and coping behaviours. (Barts and the London Medical School, led by Professor Kam Bhui). This study is proceeding well, the first two papers being currently submitted for publication. It seems as though CFS is more rather than less common in ethnic minorities in English speaking countries, and the investigators are now looking into why this might be.
- ▶ Indirect support through one trial exploring the management of patients with persistent unexplained symptoms. (Manchester University, led by Professor Richard Morriss).
- ▶ General and specific risk markers and preventive factors for chronic fatigue and irritable bowel syndromes in a birth cohort. (Barts and the London, led by Dr Charlotte Clark). This study has only just started so no results are yet available. The investigators will examine risks and preventative factors for CFS and irritable bowel syndrome in many thousands of people born in one week in the UK in 1958.

For more details visit the MRC website:

http://www.mrc.ac.uk/OurResearch/Impact/CFS-ME/MRC002029#P27_2052

Worldwide Conferences on CFS

Professor Peter White, one of the PACE trial principal investigators, recently attended and gave presentations at two international conferences in USA and Japan.

HHV6 in Baltimore, USA

This conference was on the relationship between viruses in general, and human Herpes virus type 6 (HHV6) in particular, and CFS, in Baltimore in June.

There were two presentations that were particularly important. One was the first report of an RCT of the antiviral drug, valganciclovir (Valcyte), and the other reported findings of Coxsackie virus in the stomachs of patients with CFS.

Dr Jose Montoya presented data from 20 patients given six months of valganciclovir compared to 10 patients given placebo. Patients met CDC criteria for CFS, but also had to have “elevated” antibody titres against either Epstein-Barr virus or HHV6 – which may simply mean that they had had these infections at some time in their past. There was no significant difference in the primary outcome of the total Multidimensional Fatigue Inventory (MFI) score either three months after treatment or immediately after treatment. The MFI is a 20 item self-rated inventory measuring five aspects of fatigue. Proportions of patients improving by greater than 10% from baseline, in one or two MFI sub-scale scores, were statistically significantly different at different times, particularly self-rated cognitive ability. Dr Montoya explained that these analyses were preliminary.

Dr John Chia reported his interesting case control study finding Coxsackie viral RNA in the stomachs of the large majority of patients with CFS, collected over many years. The laboratory work looked convincing, but many patients had significant gastro-intestinal symptoms and even signs, casting some doubt on the diagnoses of CFS being the correct or sole diagnosis in these patients.

Fatigue in Japan

The International Conference on Fatigue Science was held in Okinawa, Japan in September 2008.

The most remarkable presentations reported how common fatigue is in Japan. In a recent national survey, 55% of Japanese people reported fatigue, 37% reported chronic fatigue lasting six months or longer; half of whom found the fatigue disabling. This is about two or three times the prevalence rates found in the UK. Two of the reasons suggested at the conference included significant sleep deprivation, even in children, and overwork. The Japanese are set to introduce public health programmes to emphasize the importance of adequate good quality sleep and work-life balance.

The Japanese are particularly interested in understanding how stress causes these health problems. Two particular studies, by Dr Kouzi Yamaguti, Dr Jun-ichi Koizumi and colleagues, found that people with reduced variation in the time between heart beats (suggesting sympathetic nervous system overactivity) was associated both with more severe chronic fatigue syndrome and overwork, but taking breaks during work reduced the effects of the latter problem.

One of the most interesting studies, carried out by Dr Floris P. de Lange and colleagues in the Netherlands, showed that cognitive behaviour therapy was associated with an increase in grey matter of the brain and this increase was associated with improved cognitive function.

PACE Trial research results

Since the first participant was recruited in March 2005, many people would like to know how long it will take before results are released.

We finish recruiting patients into the trial at the end of November 2008. They have to be followed for a year, until November 2009. During that period, we will be analysing some of the data collected in the first two visits, before treatment, and hope to submit this for publication by the summer of 2009. We will be very busy analysing the main results of the trial in the spring of 2010, with a view to rapid publication in the summer of 2010.

PACE protocol online

A shortened version of the PACE trial protocol (or outline) has been published online by Biomed and Pubmed. It can be found at:

<http://www.biomedcentral.com/1471-2377/7/6>.

The link has also been added to the PACE trial website (<http://www.pacetrials.net>).

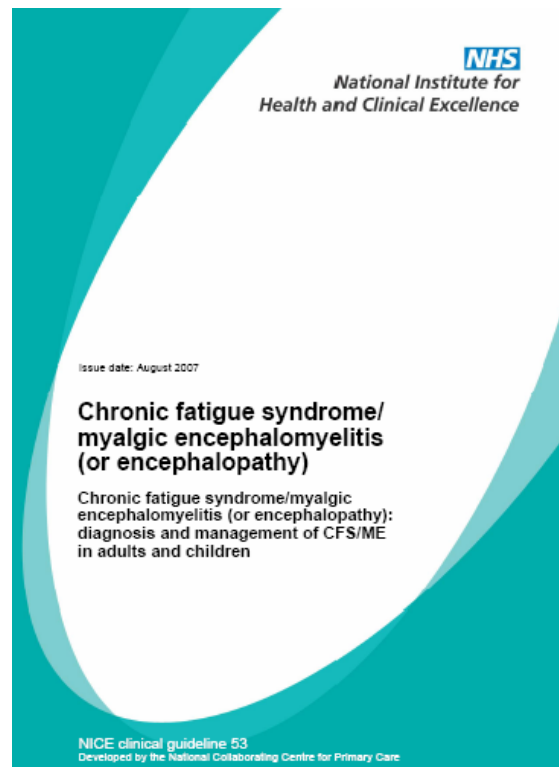
We are delighted to say that the PACE website has been accessed over 2,000 times since its launch last year.

NICE Guidelines

After several years of hard work from the guideline development group and stakeholders, the final version of the NICE clinical guidelines about the treatment and care of people with CFS/ME in England and Wales, were published in August 2007.

The guidelines intend to provide a framework for healthcare services working with people with CFS/ME to ensure effective diagnosis and management. They are based on the best available evidence and consensus where evidence is sparse, and can be accessed via the NICE website (<http://www.nice.org.uk/CG053>). The guidelines are also written for people with CFS/ME, and parents or carers of people with the condition. It may also be useful for other family members or for anyone with an interest in CFS/ME. The guideline aims to help you understand the care and treatment options that should be available in the NHS. The guidelines emphasise the importance of joint decision making and informed choice and recommended therapies include Cognitive Behavioural Therapy, Graded Exercise Therapy and Activity Management.

Although the PACE trial outcome has not been incorporated into the guidelines, as it is still in progress, the good news is that the guidelines are reviewed two and four years after publication and we hope that the trial outcome will enrich the guidelines in 2009.



If you would like to contribute to the PACE Newsletter please send your news or contact the PACE Trial Administrator, email: pace@qmul.ac.uk.
Editor: Sylvie Fritche. Contributions from: Prof. Peter White, Julia DeCesare, Julie Richards, the Doctor from Bristol and six participants.

Pacing, graded Activity, and Cognitive behaviour therapy; a randomised Evaluation

PACE Trial Coordinating Centre, Queen Mary, University of London, Barts and The London, School of Medicine and Dentistry
Wolfson Institute of Preventive Medicine, Centre for Psychiatry, Dominion House, Suite 3.1, 59 Bartholomew Close, London EC1A 7ED
Telephones: PACE Trial Administrator, Sylvie Fritche 020 7601 8176.