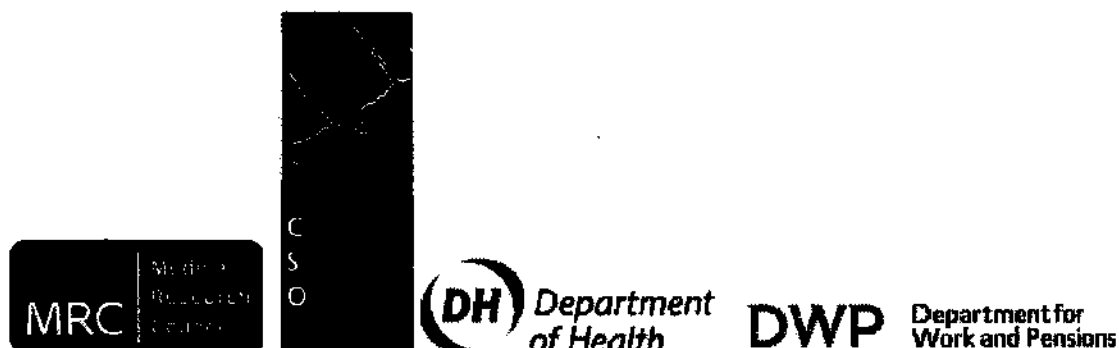




Pacing, graded **A**ctivity, and **C**ognitive behaviour therapy; a randomised **E**valuation

Final Protocol Version 5.0
01 February 2006
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The PACE trial

Short title of trial:

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

Long title of trial:

A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome / myalgic encephalomyelitis or encephalopathy

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1. General Information

1.1 Protocol information

This document describes the PACE trial, which is sponsored by Barts and the London, Queen Mary School of Medicine and Dentistry, designed in collaboration with Action for M.E. and funded by the MRC, the DH, the DWP and the Scottish CSO and provides information about procedures for entering patients into it. Neither the protocol nor the therapy manuals should be used as aide-memoires or guides for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact the trial manager at St Bartholomew's Hospital, London to confirm they have the most up to date version. Clinical problems relating to this study should be referred to the relevant centre leader or one of the investigators.

1.1.1 Compliance

The trial will be conducted in compliance with the protocol, MRC Good Clinical Practice (GCP) guidance, the Data Protection Act (1998), the Multi-centre Research Ethics Committee (MREC) and Local Research Ethics Committees (LREC) approvals and other regulatory requirements, as appropriate.

1.1.2 Sponsor

The main sponsor is Barts and the London, Queen Mary School of Medicine and Dentistry. Each participating centre will also have a local sponsor.

1.1.3 Name of person/s authorised to sign the final protocol and protocol amendments for the sponsor

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(Mr Shah replaces Mr Simon Menezes who worked on the PACE database until January 2005).

2. Glossary and Abbreviations

AE	Adverse Event
AfME	Action for M.E.
APT	Adaptive Pacing Therapy – in this protocol the abbreviation 'APT' refers to Adaptive Pacing Therapy given with Standardised Specialist Medical Care
CBT	Cognitive Behaviour Therapy– in this protocol the abbreviation 'CBT' refers to Cognitive Behaviour Therapy given with Standardised Specialist Medical Care
CFS	Chronic fatigue syndrome
CFS/ME	Chronic fatigue syndrome / myalgic encephalomyelitis or encephalopathy – Official term for the illness as described in the 'Working group report to the Chief Medical officer' (2002) and the MRC RAG report (2003)
CMO	Chief Medical Officer for England
CRF	Case Report Form
CSO	Chief Scientist's Office for Scotland
CTU	Clinical Trials Unit
DM	Data Manager
DMEC	Data Monitoring Ethics Committee
DH	Department of Health
DWP	Department for Work and Pensions
ELCHA	East London and City Health Authority
GCP	Good Clinical Practice
GET	Graded Exercise Therapy– in this protocol the abbreviation 'GET' refers to Graded Exercise Therapy given with Standardised Specialist Medical Care
ISD	Information and Statistics Division
ISRCTN	International Standard Randomised Controlled Trial Number
LREC	Local Research Ethics Committee

ME	Myalgic encephalomyelitis/encephalopathy
MRC	Medical Research Council
MREC	Multi-centre Research Ethics Committee
ONS	Office for National Statistics
PACE	Pacing, graded Activity and Cognitive behaviour therapy: a randomised Evaluation
PI	Principal Investigator
PCL	Patient Clinic Leaflet
PIN	Participant Identification Number
PIS	Participant Information Sheet
PTM	Participant Treatment Manual
R&D	Research & Development – also referred to as NHS R&D.
RN	Research Nurse
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SL&M	South London & Maudsley NHS Trust
SOP	Standard Operating Procedure
Sponsor	Individual/organisation responsible for the initiation, management/financing of a clinical trial
SSMC	Standardised Specialist Medical Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCMF	Trial Centre Master File
TMD	Trial Master Database
TMG	Trial Management Group
TSC	Trial Steering Committee

3. Summary

3.1 Abstract

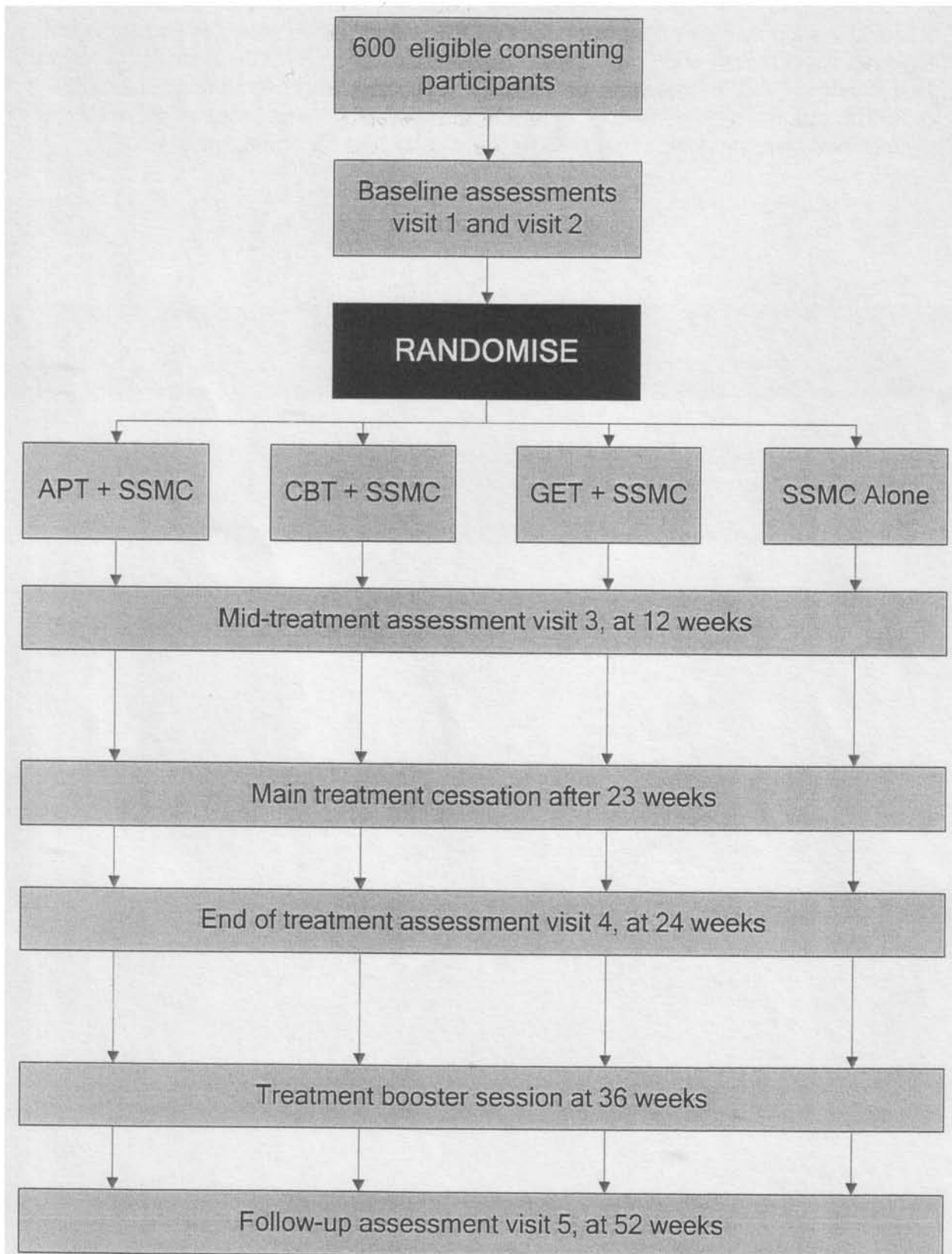
The chronic fatigue syndrome (CFS, sometimes called myalgic encephalomyelitis /encephalopathy or ME) is a debilitating condition which has a prevalence of between 0.4% and 2.5% in the population of the UK. It has major effects on the health and welfare of both patients and their families. There is no specific medical treatment and standard medical care consists of advice and treatment of symptoms. In addition to this basic medical care, patients may be referred for supplementary non-pharmacological therapies. One such supplementary therapy, called pacing, has been found to be helpful in chronic pain disorders. It is based in general on the principle of adapting to symptoms and in CFS in particular on the theory that people with CFS/ME have a fixed amount of available energy to which they must adapt. It is popular amongst CFS/ME patient organisations, but lacks empirical support. Two other supplementary therapies cognitive behaviour therapy (CBT) and graded exercise therapy (GET) have been found to be beneficial in small trials. Subsequent surveys of members of patient organisations have suggested that CBT and especially GET may make some patients worse when administered in routine practice. We do not know either how these supplementary therapies work or who responds best to each. The recent report to the CMO on the management of CFS/ME was unable to recommend one of these three treatments above the others. There is therefore a need for a trial that compares the relative effectiveness of supplementary therapies when added to standardised specialist medical care (SSMC) against SSMC alone, that seeks evidence of adverse effects, and that also examines predictors and mechanisms of response.

The proposed trial will compare the efficacy, adverse effects, and cost-effectiveness of adding adaptive pacing therapy (APT), CBT, or GET to SSMC and compare them to SSMC alone.

We aim to recruit 600 patients who meet operationalised diagnostic criteria for CFS, from six hospital clinics, into a randomised controlled trial of the four treatments. In three of the treatments fourteen sessions of each of the three supplementary therapies will be given over 24 weeks with the fifteenth 'booster session' being delivered at 36 weeks. The fourth treatment is SSMC with no supplementary therapy. Participants will be seen by their SSMC doctor a minimum of three times after randomisation, with the first SSMC appointment taking place as soon as possible after randomisation. Outcome will be assessed at 12, 24, and 52 weeks after randomisation. The two primary outcomes of self-rated fatigue and self-rated impairment of physical function will allow us to assess any differential effect of each treatment on fatigue and on function. Secondary outcomes will include other subjective measures of symptoms, mood, and function and objective measures of physical activity and fitness, as well as measures of cost-effectiveness and cost-utility. All participants who are assessed as requiring further treatment after their participation in the trial, will be offered it (as agreed between patient and clinician following final trial assessment 52 weeks after randomisation).

The results of the trial will: provide high quality information for patients, patient organisations, and healthcare professionals about the benefits and possible adverse effects of the main available treatments for CFS/ME; inform health services about the cost-effectiveness and cost-utility of these treatments for CFS/ME; provide a better understanding of the mechanisms of clinically significant improvement; and provide a basis for the rational development of more efficient therapies. Knowledge of predictors will allow informed choice of which treatment is likely to be best for an individual patient.

Figure 1: 3.1.1 Flowchart of trial design



4. Background

4.1 Introduction

The chronic fatigue syndrome (CFS) is a condition characterised by chronic disabling fatigue and other symptoms, which are not better explained by an alternative diagnosis.^[1-3] Myalgic encephalomyelitis/encephalopathy (ME) refers to a severe debilitating illness thought by some to be a separate illness, but by others to be synonymous with CFS.^[2-6] In keeping with the MRC Research Advisory Group report and the CMO's working group report, we will refer to the illness using both terms: CFS/ME.^[4, 6] The prevalence of CFS/ME in the population is between 0.4 and 2.5 %.^[3, 4, 6] A working group, reporting to the Chief Medical Officer (CMO) for England, recently concluded; "CFS/ME is a relatively common clinical condition, which can cause profound, often prolonged, illness and disability, and can have a substantial impact on the individual and the family."^[4] As many as half the patients with CFS/ME are unemployed,^[7] and they have 10 times the amount of sick-leave of other general medical outpatients.^[8] The prognosis is poor: in primary care only a third improve by one year, and of those referred to secondary care less than 10% return to pre-morbid functioning.^[3, 9] The management of patients with CFS/ME currently consumes significant resources in both primary and secondary care with uncertain benefit to patients.^[4, 5] CFS/ME patients use an annual average of 13 visits to their general practitioner and 5 visits to secondary care.^[7] There is now some evidence that specific treatments can improve these poor outcomes. The CMO's working group concluded; "Therapeutic strategies that can enable improvement include graded exercise/activity programmes, cognitive behaviour therapy, and pacing."^[4] However this positive statement was balanced in the report by other statements: first the concern of patient organisations that graded exercise therapy (GET) may worsen symptoms and disability, and second that pacing, although widely advocated by patients' organisations, is as yet unsupported by scientific evidence.

4.2 Population

We will study a sample of 600 new patients from those attending specialist chronic fatigue and CFS/ME clinics in UK secondary care with a diagnosis of CFS/ME made according to the Oxford research diagnostic criteria.

4.3 Investigational interventions

This is a four arm study. All participants will receive standardised specialist medical care (SSMC). Those allocated supplementary therapy will also receive one of the following: APT, CBT or GET.

4.4 Relevant studies/trials

4.4.1 Efficacy

Two independent systematic reviews have found that rehabilitative CBT and GET were the most promising treatments for CFS/ME in secondary care.^[5, 10-12] The published trials of these treatments were however also criticized for being too small, too selective, and for using different outcome measures. No other treatments for CFS/ME have so far been shown to be helpful in more than one RCT.^[5, 12] CBT is a more complex therapy than GET, requiring highly trained therapists, and is therefore less readily available. In contrast, surveys carried out by *Action for M.E.* of their members have indicated that CBT and GET can sometimes make people worse.^[13-15] Pacing and rest were reported to be more helpful.^[13] Pacing has been described in the scientific literature as a lifestyle management that allows optimal adaptation to the illness, including an appropriate balance of rest and activity.^[4, 16] It has been advocated by exponents of the "envelope theory" of CFS/ME, which states that a patient has a fixed and finite amount, or "envelope", of energy that they must adapt to by managing their activity.^[16] A non-randomised comparison of adaptive (rather than rehabilitative) CBT, which included adaptive pacing therapy (APT) based on this model, found that, although fatigue improved, this treatment was no more effective than the control condition of no treatment in reducing disability.^[17] A recent systematic review concluded that there was insufficient evidence to recommend APT at present.^[5, 10, 12] There is therefore an urgent need to: (a) compare the supplementary therapies of both CBT and GET with both APT and SSMC alone, seeking evidence of both benefit and harm (b) compare supplementary APT against SSMC alone and (c) compare the supplementary therapies of APT, CBT and GET in order to clarify differential predictors and mechanisms of change.

4.4.2 Differential outcomes

Because CBT and GET are based on a graded exposure to activity or exercise, they may preferentially reduce disability, whilst APT, being based on the theory that one must stay within the limits of a finite amount of "energy", may reduce symptoms, but at the expense of not reducing disability. By measuring both symptoms and disability as our primary outcomes, we will be able to test this secondary hypothesis.

4.4.3 Process of treatment

We do not know the mechanisms of successful rehabilitation for CFS/ME. Do illness beliefs or focusing of attention on symptoms (symptom focusing) need to be changed for CBT to be effective? Or do CBT and GET both work by improving tolerance to activity? Is increased physical fitness essential to recovery or not? How important is the alliance between therapist and patient? Is it necessary to adapt to the limitations imposed by the illness to reduce fatigue? A greater understanding of these processes will shed light on the nature of recovery from CFS/ME and allow the development of more efficient treatments.

4.4.4 Predictors of outcome

Predictors of a negative response to treatment found in previous studies include mood disorder, membership of a self-help group, being in receipt of a disability pension, focusing on physical symptoms, and pervasive inactivity.^[3, 18, 19] There is however no general agreement on which are the most important predictive factors.

4.4.5 Cost-effectiveness and cost utility

A recent study has suggested that there is little difference in the cost-effectiveness of CBT and GET for chronic fatigue in primary care, and both were more expensive *and* more effective than standard care.^[20] However, only one-third of patients in this study had CFS/ME and it was not powered to detect differences for this subgroup. There are currently only limited published data on the cost-effectiveness of treatments specifically for CFS/ME.

4.5 Risks and benefits

There is a discrepancy between reports of ME patient group members and published evidence from trials. Some ME charity members have reported that they feel worse after exercise therapy, and to a lesser extent CBT, whereas the trial evidence suggests minimal or no risk with these treatments. A further survey by *Action for M.E.* of their members suggests that reports of deterioration with therapy are related to either poorly administered treatment or lack of appropriate professional supervision.^[13-15] The individual treatment programmes used in PACE will minimise this risk by being mutually agreed between participant and therapist, carefully monitored and flexibly implemented. We will also carefully monitor all participants for any adverse effects of the treatments, and will undertake a detailed assessment, at home if necessary, of any participant who reports deterioration or who withdraws from treatment, following which they will be offered appropriate help.

4.6 Rationale

The results of this trial will: (a) allow people with CFS/ME, clinicians and health planners to choose treatment on the basis of both efficacy and cost; (b) provide evidence about the efficacy and possible negative effects of the four treatments (APT, CBT, GET and SSMC); (c) provide the first test of SSMC plus pacing against SSMC alone; (d) indicate which patient characteristics predict a successful outcome; (e) identify which patient characteristics predict response to which treatment and (f) define the essential aspects of effective treatment as a first step toward the development of more efficient therapies.

The trial will recruit new patients from secondary care clinics run by three different disciplines (immunology, infectious disease and psychiatry) in six different centres in both England and Scotland. This recruitment plan will ensure sufficient heterogeneity to allow generalisation of the findings. 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 (one of the recommendations CMO's report^[4]). Furthermore, direct recruitment from primary care has been found to be problematic in previous studies. Two recent trials of treatment for prolonged fatigue (not CFS/ME) using large and well established primary care research networks recruited only 46 patients with CFS/ME in three years^[21] and 44 patients in 2.5 years^[22].

5. Aims and Objectives

5.1 Aims

The main aim of this trial is to provide high quality evidence to inform choices made by patients, patient organisations, health services and health professionals about the relative benefits, cost-effectiveness, and cost-utility, as well as possible adverse effects, of the mostly widely advocated treatments for CFS/ME.

The secondary aims of this trial are to investigate the mechanisms and predictors of a successful outcome.

5.2 Objectives

The PACE trial is designed to answer the following questions:

5.2.1 Primary objectives

- (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?

NB For the sake of brevity, the rest of the protocol will refer to the four treatment arms as APT, CBT, GET and SSMC rather than APT plus SSMC, CBT plus SSMC, GET plus SSMC and SSMC alone.

5.2.2 Secondary objectives

The secondary analyses are exploratory but we will be guided by previously published findings.

- (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)?

5.3 Hypotheses of efficacy

- (1) APT plus SSMC is more effective than SSMC alone in reducing (i) fatigue, (ii) reducing physical disability and in reducing (iii) both.
- (2) CBT plus SSMC is more effective than APT and SSMC in reducing (i) fatigue, (ii) disability and in reducing (iii) both?
- (3) GET plus SSMC is more effective than APT and SSMC in reducing (i) fatigue, (ii) disability and in reducing (iii) both?
- (4) The *active* rehabilitation therapies (of either CBT or GET) are more effective than the *adaptive* approach of APT when each is added to SSMC, in reducing fatigue, in reducing physical disability and both.
- (5) CBT plus SSMC is more effective than SSMC in reducing (i) fatigue, (ii) disability and in reducing (iii) both?
- (6) GET plus SSMC is more effective than SSMC in reducing (i) fatigue, (ii) disability and in reducing (iii) both?

Other secondary hypotheses will be stated pre-hoc in the Analysis Strategy document.

6. Trial Design

6.1 Type of design

A four arm, randomised multi-centre parallel group controlled trial of patients who meet operationalised criteria for CFS/ME, with follow-up for 52 weeks.

6.2 Schematic trial flow diagram

See section 3.1.1.

6.3 Trial treatments - interventions and control

There are four treatment arms. SSMC is given to all participants. Three quarters will also receive one of the following supplementary therapies: APT, CBT or GET. These are described briefly in section 8, and in detail in the therapy manuals (see below and Appendix A2).

6.4 Duration

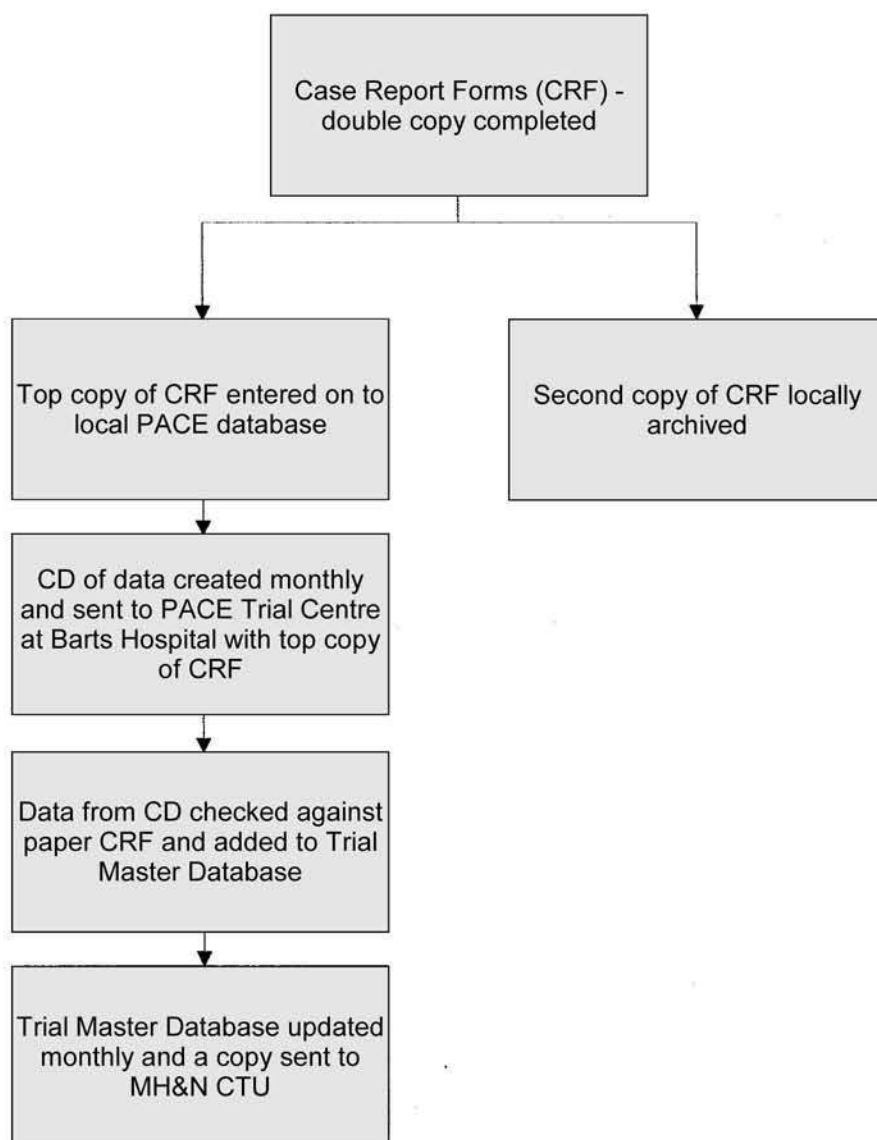
Each participant will be assessed, and those who give consent will be randomly allocated to one of the four treatments. Treatment will start as soon as possible after randomisation. The final outcome assessment will be at 52 weeks post randomisation.

6.5 Data recording and Case Report Forms

Data will be recorded on Case Report Forms (CRFs). These will be completed by the patient for the self-report measures, and all other data will be collected and completed by the RN. (See Appendix 6). The CRFs which will be checked by the RN, will consist of two non-carbon copy forms. The top copy will be given to the local data manager at each centre for data entry. The bottom copy will be kept in the participant's research case file to be kept in each local centre for archive purposes. Once data has been entered onto the local database, then the same top copy and a CD containing the data will be sent to the trial manager (TM) at Bart's for entry into the Trial Master Database (TMD) and for quality control purposes. The CDs will be created and sent to Bart's on a monthly basis. The Bart's centre data manager will then compare the hard copy with the database to check accuracy. S/he will check all the primary outcome variables and a randomly chosen 20 percent of the other variables. All case report forms (CRF) for the first ten patients randomised per centre will be double checked by the Bart's centre data manager. If there are any errors on primary outcomes, or greater than 1% errors of other variables, 100% data checks will be completed until the error rate ceases or drops. In order to ensure all relevant data are double checked, the TM will check the two Bart's centres relevant data.

A copy of the TMD will be sent to the CTU Trial Database Manager at KCH. The master database for PACE will be maintained at Bart's by the TM and DM but will not include the assigned treatments – these will be recorded in a separate database by the CTU data manager (and a non-statistician nominee in his/her absence), with a copy held by the TM. The type of data to be recorded is detailed in the Assessments and Procedures section (section 9). See SOP 12 & 13 for details of data recording, computer entry, checking, backup, and transmission.

Figure 2: 6.5.1 Flow diagram of data entry



7. Selection of Participants

7.1 Number and source of participants

We will study 600 participants, recruited from new patient attenders, over approximately three years in six centres. Each centre will be expected to recruit a *minimum* of 33 new participants per annum. Only three centres will recruit in the first year, all six will recruit in the second year with three centres aiming to recruit at the rate of 66 new participants in the third and final year of recruitment. Extra resources will be available to allow this to happen.

All participants will be attending secondary care chronic fatigue clinics. Certain secondary care CFS services, near to PACE centres, would be allowed to make a *clinical referral* to a PACE centre for clinical assessment, with one option for treatment being the PACE trial. If such a patient is either found to be ineligible or declines to give informed consent, they would be offered a choice of clinical treatment outside of the trial, at the PACE centre or referral back for clinical treatment at the original referring service. Such patients would only be recruited from localities that already refer patients to the clinical services based at the PACE centres. Therefore this proposal does not represent setting up of new PACE centres. The six trial centres are all staffed by clinicians and scientists with established experience of running chronic fatigue (CFS/ME) services. Each centre will receive regular visits by the TM and a PI or other centre leader and relevant aspects of the local operation will be audited. Each centre leader will receive a contract and be asked to signify their understanding of their responsibilities as centre leaders. (See SOP 11).

All centres have reported that they currently see a minimum of 100 new patients per year. We estimate that 60 will meet eligibility criteria, and a conservative estimate is that two thirds of these will agree to enter the trial, giving potentially a minimum of 40 participants per centre. In previous trials of both CBT and GET, only 7 and 15% of eligible participants refused to participate in GET trials^[23, 24] and 3, 10 and 26% of those eligible refused to participate in the three previous CBT trials.^[18, 25, 26] We are therefore confident that recruitment, at an overall rate of 100 participants in the first year (when only three centres will be recruiting), 200 in the second year (when all six centres will be recruiting), and 300 in the last year (when three of the six centres will be recruiting at twice the minimum rate) is feasible and that the trial will recruit 600 participants over three years. We will however closely monitor recruitment, especially in the first six months of each centre's start of recruitment. The TMG, after advice from the TSC, will consider replacing those centres that either do not recruit sufficient participants, or fail to provide quality data. It is recognised that a centre could demonstrate that they are able to increase recruitment at greater than the minimum rate before the final year of recruitment. In this instance, permission will be sought from the MRC to allocate more money at an earlier stage to facilitate increased recruitment.

Figure 3: 7.1.1 Graph of projected recruitment

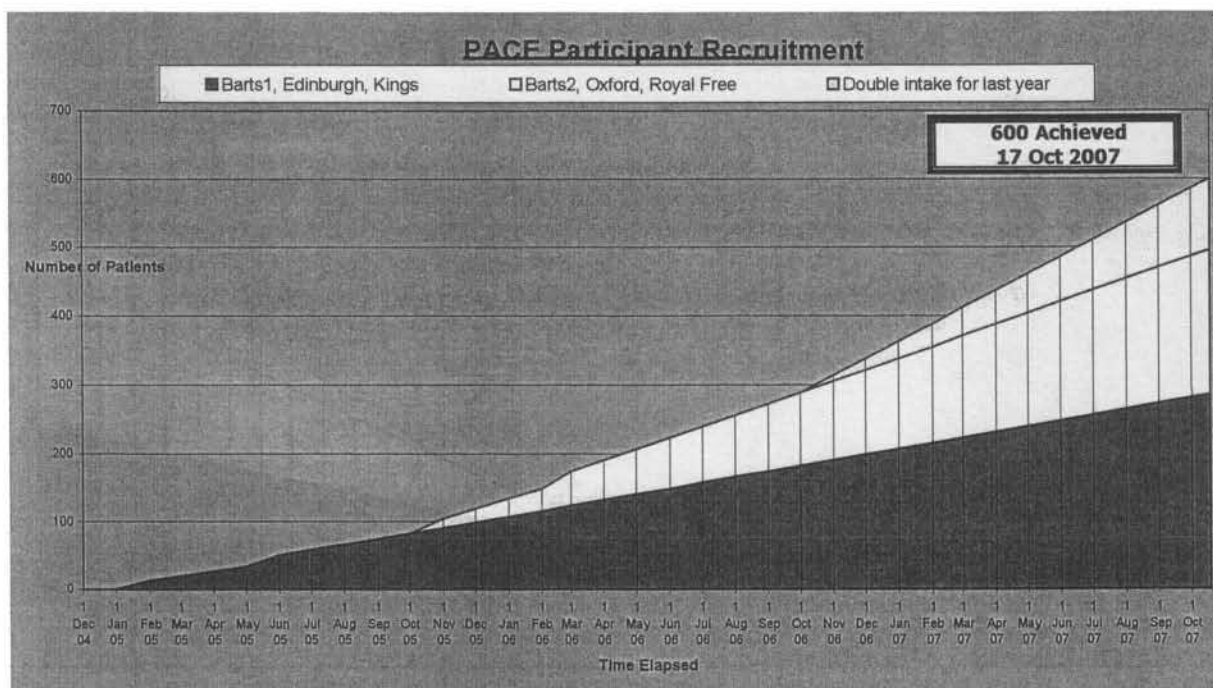


Figure 4: 7.1.2 Table of projected recruitment

Date	First recruiting centres: Barts I, Edinburgh & KCL	Second recruiting centres: Barts II, Oxford, Royal Free	Three centres recruiting at double rate in final year	Total recruitment
Dec 2004	0	0	0	0
June 2005	50	0	0	50
Dec 2005	99	20	0	119
June 2006	149	74	0	223
Dec 2006	198	124	17	339
June 2007	248	173	66	487
Oct 2007	285	211	104	600

Recruitment estimates based upon 80% efficiency for the first three months rising to 100% efficiency by six months.

The anticipated start date of recruitment was delayed and therefore the projected recruitment figures were revised accordingly altering the start date of the first wave centres to March of 2005 and the start date of the second wave centres to March 2006. Figures 5 and 6 depict these revisions.

Figure 5: 7.1.1 Graph of revised projected recruitment

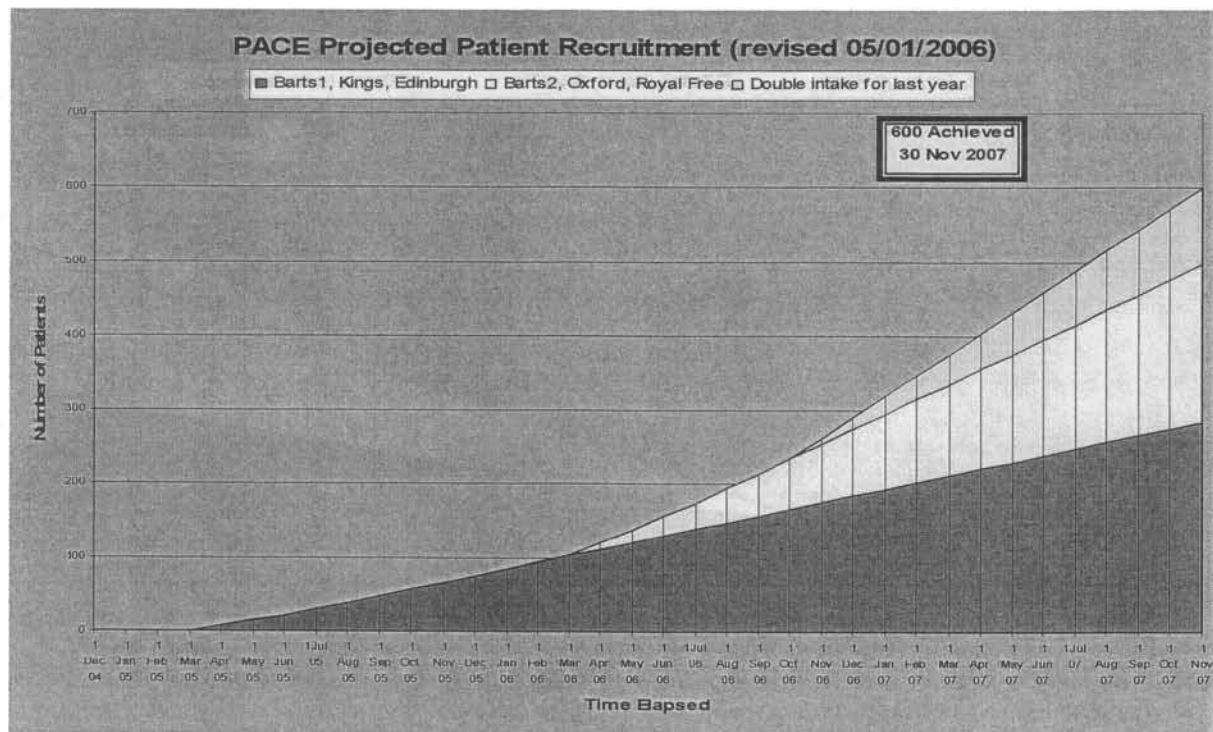


Figure 6: 7.1.2 Table of revised projected recruitment

Date	First recruiting centres: Barts I, Edinburgh & KCL	Second recruiting centres: Barts II, Oxford, Royal Free	Three centres recruiting at double rate in final year	Total recruitment
Dec 2004	0	0	0	0
June 2005	22	0	0	22
Dec 2005	75	0	0	75
June 2006	130	26	0	156
Dec 2006	185	90	16	291
June 2007	239	156	64	460
Nov 2007	285	211	104	600

7.2 Inclusion criteria

7.2.1 Consent given

- Both participant and clinician agree that randomisation is acceptable.
- The participant has given written informed consent.

7.2.2 Eligibility items

- The participant meets operationalised Oxford research diagnostic criteria for CFS.^[2]
- The participant's Chalder Fatigue Questionnaire score is 6 or more.^[27]

5. The participant's SF-36 physical function sub-scale score^[28] is 65 or less.
6. The participant will be aged at least 18 years old.

7.3 Exclusion criteria

1. All potential participants will be screened for medical exclusions, by history and physical examination.^[1, 2, 4, 29] Appropriate investigations^[4, 29] will be undertaken by either the referring doctor or the centre doctors (checked by the RN). Patients with a relevant alternative medical diagnosis will be excluded.^[2] Investigations will be those recommended by the Royal Colleges' Report on CFS/ME and the CMO's working group report.^[4, 29] These results will be collated by the RN, and will have been undertaken within six months of the baseline assessment. (See SOP 9 & 10).
2. The Research Nurse (RN) will use a standardised psychiatric interview (the Structured Clinical Interview for DSM-IV - SCID),^[30] under supervision by a participating centre PI or nominated deputy, to exclude those who are at significant risk of self-harm and those with psychiatric exclusions listed in the Oxford diagnostic criteria for CFS.^[2]
3. Patients who are considered by the RN in discussion with their centre leader to be unable to do one or more of the trial therapies or to complete all trial measures or for whom participation in the PACE trial would be inappropriate to their clinical needs (e.g. someone with significant post traumatic stress disorder or borderline personality disorder).
4. Patients who have previously attended a PACE centre specialist fatigue clinic and received a course of treatment from a specialist considered to be similar to SSMC or any of the supplementary therapies of CBT, GET or pacing therapy as delivered in the trial will be excluded from taking part in the trial.

7.4 Screening/Baseline Procedures

Written informed consent must be taken before any trials related procedure can take place, therefore PACE will utilise a two-stage consent/enrolment process. In the first stage the patient will consent to take part in the eligibility and baseline assessments and in the second stage the patient will consent to the full trial including randomisation, treatment and follow-up assessments.

7.4.1 Initial screening for eligibility – visit 0 (clinic doctor)

New referrals to the outpatient clinics may be received from GPs or any other appropriate medical practitioner. Each clinic doctor will ensure that all consecutive new outpatients with a clinical diagnosis of CFS/ME are considered for the trial (i.e. if thought to be eligible they are told about the trial). This will be monitored by the centre leader. Each centre leader will keep a trial log-book of every new chronic fatigue outpatient referral. This log book will detail each patient seen, whether or not they were referred for the trial and the reasons if not. (See SOP 9 & 10).

Where the patient is thought to be suitable by the clinic doctor (with a CFQ score of 6 or above and an SF-36 score of 65 or below), and the patient agrees to be assessed for

eligibility, the clinic doctor will forward the patient's contact details to the research nurse by encrypted email or telephone. The clinic doctor will give the patient the trial Participant Information Sheet and a copy of the Eligibility Assessment/Baseline Consent Form (see Appendix A1.3). The research nurse will contact the patient by telephone to discuss the trial and to arrange the first research visit (visit 1).

7.4.2 Telephone assessment

The RN will contact patients within 24 hours of receipt of referral, who have been referred by the clinic doctor for the PACE trial, by telephone. The RN will check that the patient has received a Participant Information Sheet from the clinic doctor, and if they express interest in the trial, will arrange a date for the patient to attend the first research assessment interview (visit 1) as soon as possible (within one week of referral).

7.4.3 Clinic new patient log book

A clinic new patient log book will be kept by the DM in each centre, documenting each and every attending new patient with a possible diagnosis of CFS/ME made by the referrer, giving the following details: date of attendance, full initials, whether sent for screening or not and reasons given. The data in the log-book will be coded on a monthly basis and sent to the TM. For audit purposes, the log-book will be kept in a secure place, to ensure confidentiality, and will be made available to appropriate trial colleagues (principal investigators and TM).

7.4.4 Informed consent for eligibility/baseline assessment (research nurse)

The research nurse will explain the trial and answer any queries by potential participants using the PIS as the template. The first consent form (see Appendix A1.3) will be completed at visit 1 to the RN when eligibility and some baseline assessments will be completed. In addition actigraphy monitoring will be initiated.

7.4.5 Eligibility assessment and consent for assessment – visit 1 (research nurse)

All of the following eligibility criteria must be fulfilled for the patient to participate:

1. The patient has a clinical diagnosis of CFS.^[2]
2. The patient does not have treatment needs that would make participation in the PACE trial inappropriate.
3. The patient is aged 18 years or above.
4. The patient can speak and read English at a level adequate for participation in the trial, as assessed by the RN. The reasons for this include the need to self-rate written primary and secondary outcomes using scales that have not been validated in non-English languages; the need to receive therapy that can be checked for quality and manual adherence; and the prohibitive cost of providing therapy in more than one language.
5. The Chalder Fatigue Questionnaire score is 6 or more.^[27]
6. The SF-36 physical function sub-scale score is 65 or less.^[28]
7. The Structured Clinical Interview for DSM-IV (SCID i/P; non-patient edition with psychotic screen).^[30] will be used to exclude patients with psychiatric exclusions.^[2] If a participant or patient is found to have a psychiatric diagnosis on the SCID, the

RN will inform the clinic doctor. All SCIDs will be audio-recorded for the purposes of quality control and RN supervision; the supervision being provided by the centre leader or their nominated deputy.

8. The patient is able to convince the RN that they will be able to attend hospital regularly and reliably for the duration of the trial (travel expenses will be given).
9. There is no contra-indication to any of the treatments that might be provided in the trial.
10. Permission has been obtained to review medical notes

At the end of this visit the research nurse will give the participant the further baseline self report questionnaires to complete at home and return at visit 2. S/he will also fit the actometer to the patient with an appropriate explanation and ask them to wear it until return on visit 2. After visit 1 the research nurse will discuss the patient's potential eligibility with the centre leader.

7.4.6 Eligibility assessment and consent for trial – visit 2 (research nurse)

At visit 2 to the RN (after one week) the patient will return the actometer (see section 7.4.6). If the patient understands the purpose of the trial and is willing to give informed consent to be randomised, treated and followed up, they will then sign the second consent form (see Appendix A1.4) to participate in the full trial.

7.4.7 Completion of baseline assessment

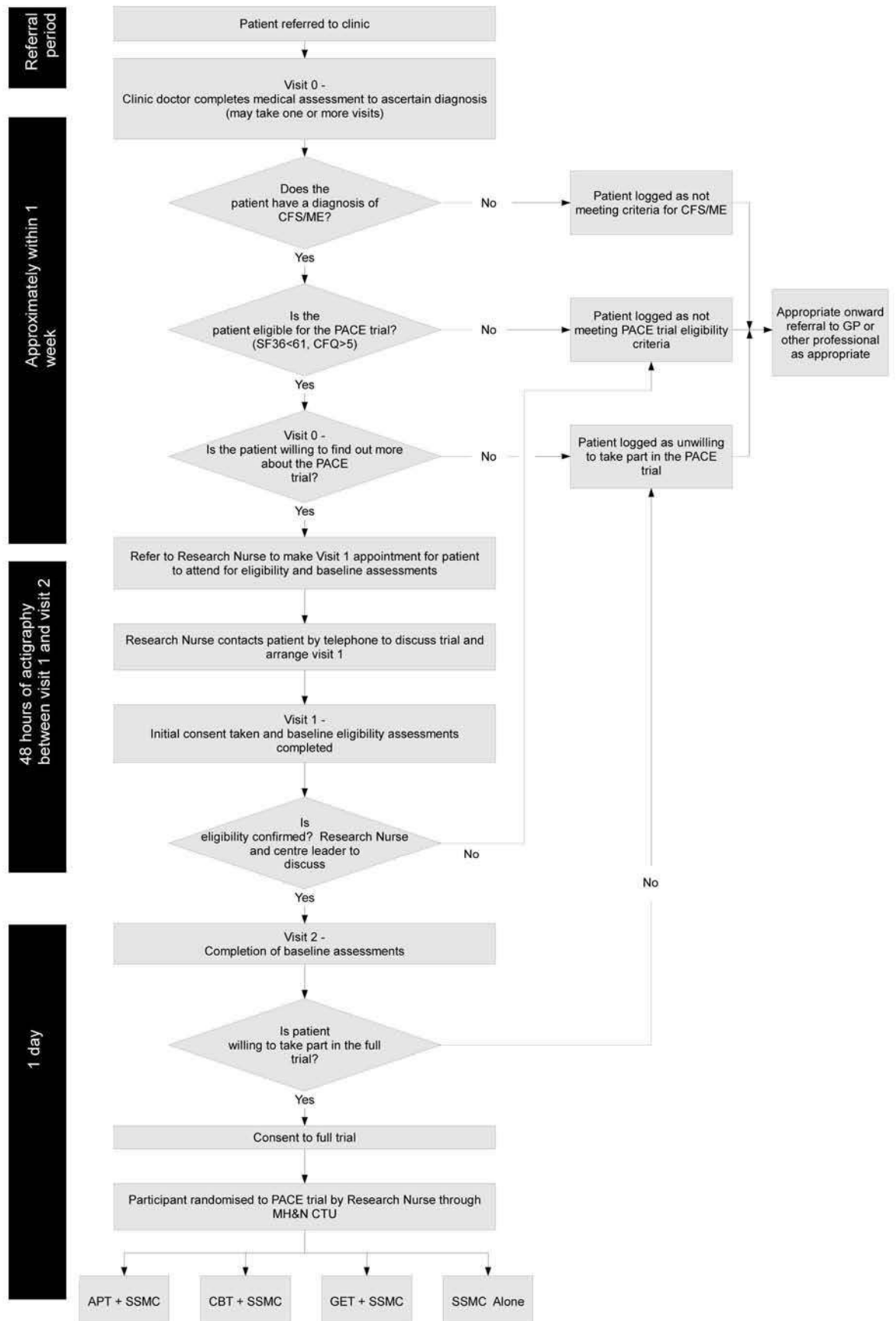
At visit 2, the following baseline assessments will be completed (see section 9 for more details):

1. Participant demographic details will be collected (including date of birth, age, sex, ethnicity, marital or partner status, years of education, occupation, partner's occupation)
2. Current medications and therapies (including complementary and alternative)
3. Co-morbid and current medical conditions
4. Duration of CFS/ME (months)
5. The CDC criteria for CFS (9 symptoms of CFS)^[1]
6. The London criteria for myalgic encephalomyelitis^[31]
7. Presence or absence of fibromyalgia (using chronic widespread pain criteria only and not tender points)^[32]
8. The Hospital Anxiety and Depression Scale (HADS)^[33]
9. Jenkins Sleep Scale of subjective sleep problems^[34]
10. The EuroQOL (EQ-5D)^[35]
11. The Work and Social Adjustment Scale^[36]
12. Exercise and Activity scale^[37]
13. Symptom Interpretation Questionnaire^[38]
14. Physical Symptoms (Patient Health Questionnaire; PHQ-15)^[39]
15. Preferred treatment group (single question)
16. The Chronic Disease Self-Efficacy measure^[40]
17. Current and specific membership of a self-help group (specific question)
18. The Client Service Receipt Inventory (CSRI), adapted for use in CFS/ME^[41]
19. In dispute/negotiation of benefits or pension

Section 7: Selection of Participants

20. The six-minute walking test^[42]
21. The self-paced step test of fitness^[43]
22. The Borg Scale of perceived physical exertion, scored once immediately after the step test^[44]
23. Body Mass Index (BMI) (measure weight in kg and height in metres)
24. One week of actigraphy^[18] (as initiated at visit 1 with the research nurse)

Figure 7: 7.4.7 Flow Diagram of patient/participant pathway



7.5 Randomisation and Enrolment procedure

Participants will be allocated to one of the four trial arms (ratio 1:1:1:1) by the Mental Health & Neuroscience Clinical Trials Unit (MH&N CTU) based at the Institute of Psychiatry. Allocation will be stratified by *centre* (Barts I, Barts II, Edinburgh, King's, Oxford or Royal Free), *CDC Criteria* (met or unmet), *London Criteria* (met or unmet) and *Depressive disorder* (present or absent) using minimisation with a random component.^[45] The first N cases (N will not be disclosed) will be allocated using simple randomisation to further enhance allocation concealment.

Once an eligible participant has completed the baseline assessment and given written informed consent, the Research Nurse will complete a "Randomisation Request Form" and contact the MH&N CTU via fax or phone for treatment allocation. A customised Microsoft Access database will be used to hold the basic details collected to facilitate subsequent verification and to generate the allocation. Within 24 hours of a request (Mondays to Fridays 9am to 5pm, excluding Bank Holidays) the MH&N CTU will complete a "Randomisation Notification Form" and send this via email or fax to the Research Nurse and the Trial Manager to notify them of the randomisation and inform them of the allocation. The Research Nurse will then complete an "Acknowledgement Form" and fax this to the MH&N CTU to confirm that they have the correct details.

The Research Nurse will on the same day inform the participant of his/her treatment group in person or by phone, and will also inform the SSMC doctor and appropriate therapist. The therapist will contact the participant to arrange the first treatment appointment as soon as possible. The SSMC doctor will also arrange to see the participant within one month of treatment allocation. The individual assignments will be available to the entire team on a need-to-know basis throughout the trial.

RANDOMISATIONS

Tel: 020 7848 0532

or

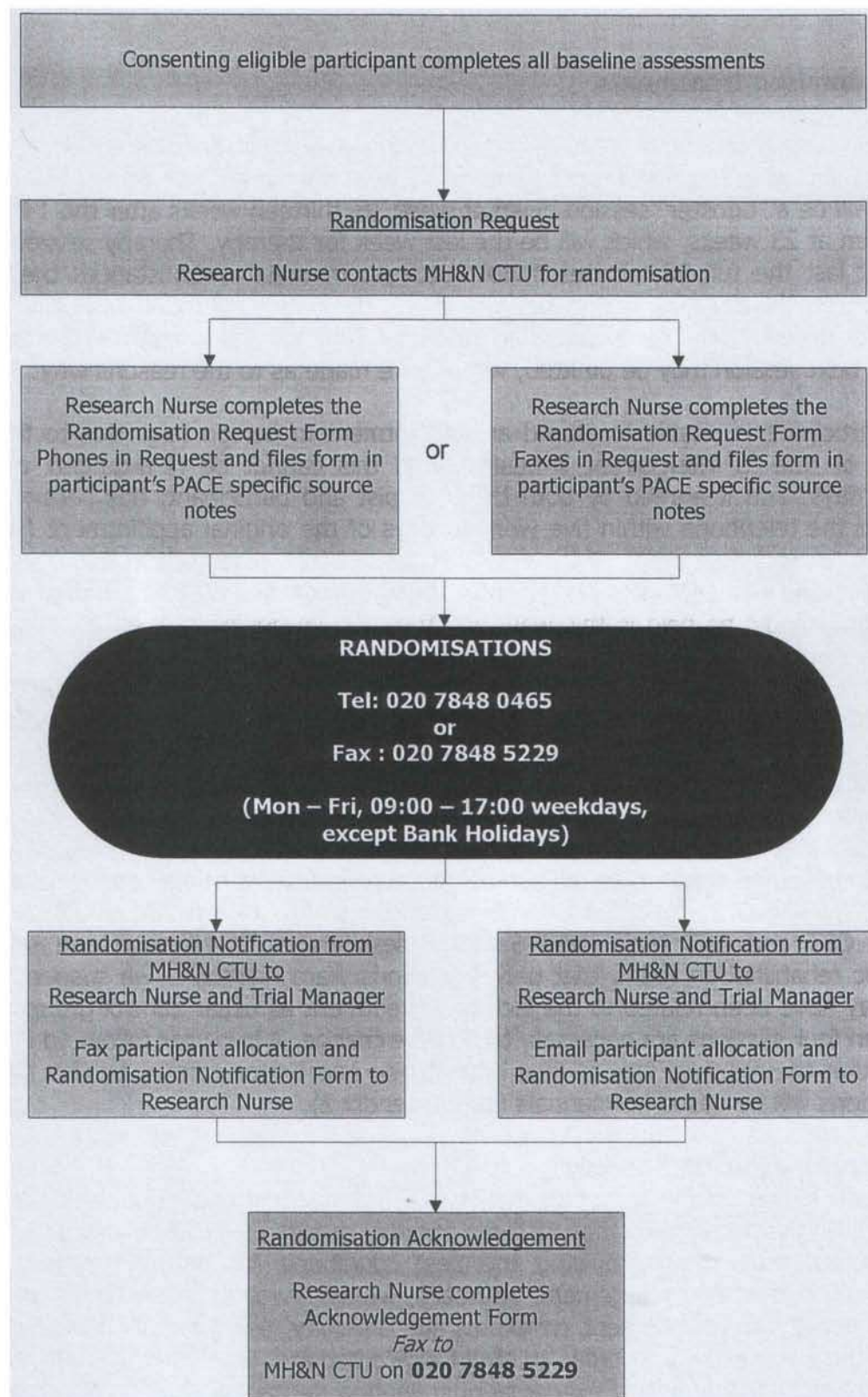
Fax : 020 7848 5229

(Mon - Fri, 09:00 – 17:00, except Bank Holidays)

7.5.1 Participant Identification Number

The participant identification number (PIN) will be a five digit number where by the first two digits denote the centre (01=Barts I, 02=Edinburgh, 03=Kings College London, 04=Barts II, 05=Oxford, and 06=Royal Free) and the remaining three denote the participant number by centre allocated in order of the patient entering the screening phase (e.g. the first patient seen at Barts I, will have the PIN 01001). Therefore every patient who consents to baseline and eligibility assessment will have a PIN, but not all will be randomised due to some being ineligible or not giving further consent.

Figure 8: 7.5.2 Flow diagram of randomisation process



8. Treatment of participants

8.1 Randomised treatments

Apart from those receiving SSMC alone, all participants will be offered equal therapist time; 90 minutes in the first session, and 14 subsequent sessions of 50 minutes. The 15th session will be a "booster" session given at week 36, thirteen weeks after the 14th session, itself given at 23 weeks, which will be the last week for therapy. Therapy sessions 2 to 15 need not last the full 50 minutes if not required. In these circumstances the therapist should record the duration of the session, giving the reasons why. If both therapist and participant believe that the next planned session is redundant because therapy is going so well, the next session may be omitted, with a note made as to the reasons why.

If the participant is unable to attend an appointment in person (e.g. due to feeling too disabled or due to intercurrent ill-health), and this cannot be re-arranged within five working days, and if agreed by both the therapist and participant, this session may be held over the telephone within five working days of the original appointment (with extra allowance for part-time staff). If the session does not take place within this time, the visit will be recorded as a DNA (Did Not Attend). Ideally, no more than four sessions of the first 14 sessions should be held in this way, and they should not be sequential. However, we believe it would be better that the participant receives some therapy rather than none at all and this will be judged on a per-participant basis. This policy is supported by the results of one trial having suggested that one of the therapies (GET) delivered by telephone works as well as face-to-face therapy. The fifteenth session should always be held face-to-face, if at all possible, but even this may be held by telephone if the alternative is non-attendance.

We have chosen 15 sessions for all supplementary treatments on the basis of the positive trials of CBT and GET,^[18, 23-26] as well as extensive clinical experience. RCTs of the least effective CBT and GET trials used 6 and 8 sessions.^[25, 46] Although one study of a pragmatic rehabilitation found that only 4 sessions were helpful,^[47] we suspect that this result may have been related to the lack of a 'treatment as usual' control group, and that more than four sessions are necessary to achieve change. A two year follow-up of this trial showed that the maximal face-to-face intervention had better efficacy by this time.^[19] All interventions will be based on manuals (see Appendix 2).

8.1.1 Adaptive Pacing Therapy

APT will be based on the illness model of CFS/ME as a currently undetermined organic disease, with the assumption that APT can improve quality of life, although not affect the core disease, other than providing the best conditions for natural recovery. APT is essentially an energy management approach, which involves assessment of the link between activity and subsequent symptoms and disability, using a daily diary, with advice to plan and pace activity in order to avoid exacerbations. Strategies include developing awareness of early warning of exacerbations; limiting demands; regular planned rest and relaxation, and alternating of different sorts of activities. The aim is to achieve optimal adaptation to the illness.^[4, 16, 17] *Action for M.E.* have helped in the design of the APT

manual and have endorsed this version of pacing, which is based on what is published and what patients and clinicians have reported as helpful (see appendices A2.1 and A2.2).

8.1.2 Cognitive Behaviour Therapy

CBT will be based on the illness model of fear avoidance, used in the three positive trials of CBT.^[18, 25, 26] There are three essential elements: (a) Assessment of illness beliefs and coping strategies, (b) Structuring of daily rest, sleep and activity, with a graduated return to normal activity, (c) Collaborative challenging of unhelpful beliefs about symptoms and activity (see appendices A2.3 and A2.4).

8.1.3 Graded Exercise Therapy

GET will be based on the illness model of deconditioning and exercise intolerance, used in the previous trials.^[23, 24, 47] Therapy involves an assessment of physical capacity, negotiation of an individually designed home exercise programme with set target heart rates and times, and participant feedback with mutual planning of the next fortnight's exercise programme (see appendices A2.5 and A2.6).

8.1.4 Standardised Specialist Medical Care

SSMC will be given to all participants. This will include visits to the clinic doctor with general, but not specific advice, regarding activity and rest management, such as advice to avoid the extremes of exercise and rest, as well as symptomatic pharmacotherapy. *SSMC* is standardised in the *SSMC Doctor's Manual* (see Appendix A2.7). As well as this, *SSMC* participants, like all other participants, will already have received the Patient Clinic Leaflet (PCL) (see Appendix A1.1). There will be no additional therapist involvement. In particular there will be no diary monitoring with consequent advice. The number of *SSMC* outpatient sessions will be recorded, along with any treatments given for each participant by the *SSMC* doctor. Participants will be seen by their *SSMC* doctor a minimum of three times after randomisation, with the first *SSMC* appointment taking place as soon as possible after randomisation, and within one month. Further sessions will be determined by clinical need.

8.2 Departures from randomised treatment

The centre RNs will be selected and trained to achieve positive relationships with participants. This will be especially important in the *SSMC* alone group. In addition to seeing them for a minimum of 5 times in 52 weeks, we will use techniques commonly employed in cohort studies to maintain participation, such as sending birthday cards, a trial web-site and regular trial newsletters in between these face-to-face meetings.

We will use the following strategies to minimise missing data in primary outcomes. Participants who drop out of treatment will be assessed as soon as possible, rather than waiting for the normal follow-up. Those who cannot attend clinic will be offered home assessments by the RN (or failing this assessment by telephone or by post), or centre leader as appropriate. If that is not achieved, we will seek to obtain outcome data by use of either postal or e-mail questionnaires, supplemented by telephone calls if necessary.

8.2.1 DNAs from treatment

The therapist (if they have one) or SSMC doctor will contact the participant by telephone in the first instance to ascertain the problem of attendance, and will discuss the appropriate solution with the participant. Choices include a telephone session or a re-arranged face-to-face session, so long as the latter is within five working days. Alternatively the session stays a DNA and is recorded as such. If the participant considers that they are deteriorating the standard policy for this problem will be enacted (see section 15.1.1).

8.2.2 Clinician/Researcher withdrawal of participant from treatment

The reason for this must be recorded. When this occurs, the centre-leader or nominee should assess the participant clinically within a week, and arrange appropriate care. Every effort must be made to obtain the two primary outcomes and the CGI (to assess illness progression), which should be scored in order to provide some outcome data (see section 10). Such participant's data should be included in the trial analysis. If the participant will still consent to research (RN) follow-up, this should continue as normal.

8.2.3 Participant withdrawal of consent to randomised treatment

In the first instance, the therapist (if they have one) or SSMC doctor will contact the participant by telephone in the first instance to ascertain the reason for drop-out, and will discuss the appropriate solution with the participant and then the centre leader. If the participant considers that they are deteriorating (see section 15.1.1), the standard policy for this problem will be enacted, as follows. If the participant does not wish to talk to the therapist or SSMC doctor, the centre leader or nominee should contact them themselves.

If possible, the reason for withdrawal (e.g. adverse events, inter-current illness, illness progression, inability to adhere, inability to attend regularly for treatment or assessment) should be ascertained. This information should be passed on to the other relevant members of the team and the TM. The centre leader should ensure that every effort must be made to obtain the primary outcome measures and the Clinical Global Impression (CGI) change score^[48] on participants who drop out of treatment as soon as this occurs, even if they are not dropping out of the trial follow-up itself.

The centre-leader or nominee will also ascertain whether consent is withdrawn from further trial treatment only or from both trial treatment and follow-up and in the latter case, whether the participant has given permission to retain data collected before treatment withdrawal for use at final analysis.

8.2.4 Participant withdrawal of consent to research follow-up

If a participant withdraws consent for research (RN) follow-up during the trial, the centre-leader or nominee should be informed on the same day, if possible. The centre-leader or nominee will then contact the participant to find out why the participant wishes to withdraw from research follow-up if they are happy to give a reason. The centre-leader or nominee will also determine whether the participant has given permission to retain data collected before withdrawal for use at final analysis, or whether this information should be destroyed. No data from the latter participant will be used in analysis.

8.2.5 Loss to follow-up

Permission will be sought from the Office of National Statistics (ONS) in England and the Information and Statistics Division (ISD) in Scotland, to track all participants randomised using NHS numbers. If a participant is lost to follow-up, the participant's GP will be contacted in the first instance, and if the participant has moved from the area, ONS (or ISD) will be contacted for details of the participant's new GP. This will only occur if the participant has given explicit consent (as detailed on the consent form) to allow this.

In all these situations the centre leader should inform the general practitioner and any referring doctor that their patient has withdrawn from either the trial or the trial treatment.

8.3 Measures of treatment compliance/adherence

The SSMC doctor will record how many clinic outpatient sessions were attended, and how many were not attended during the 52 weeks by reviewing the medical notes (see SOP 9, 10 & 11 and Appendix 6.6).

If the participant has been receiving supplementary therapy, the therapist will record how many sessions/part sessions out of 15 were attended; whether they were face-to-face or telephone consultations and the durations of each session attended. At the end of therapy, the therapist will also score how well the participant adhered to the general therapy approach (see SOP 10 & 11 and Appendix 6.6).

8.4 Modification of trial treatment

Trial treatments will only be modified with the advice of the TSC, having been advised by the DMEC that a particular treatment arm is causing a consistent pattern of deterioration, or if there is another obvious and significant clinical necessity.

8.5 Additional therapy after the trial

Participants who are judged to require further therapy after their involvement in the trial has been completed, will be offered additional therapy. The choice of additional therapy will be agreed by the participant, clinic doctor and relevant therapist, and will start after the final follow-up interview (52 weeks after randomisation into the trial).

8.6 Absence of a therapist

There will be occasions throughout the course of the trial when a therapist is absent due to annual leave, sickness, maternity or resignation. In these instances treatment delivery will be modified in order that a participant's therapy and the trial may continue

uninterrupted. Three contingency plans have been devised to allow for a flexible approach to tackling this situation when it arises.

8.6.1 Therapy from a nearby centre

Local centre cover is delivered by a PACE therapist of the same discipline working in a nearby PACE centre. This particularly applies to London and perhaps Oxford, whereby the appropriate PACE therapist from a nearby centre provides the therapy either at the original centre or their own, to be negotiated between therapist and participant.

8.6.2 Distant combined therapy

Distant therapy is delivered by a PACE therapist of the same discipline, whereby the therapist will conduct some visits face-to-face and the remainder by telephone. The participant will at the same time be also treated by a local cross-cover PACE therapist. This will be done for two reasons:

- Firstly, as well as building a rapport with the distant centre therapist who will be delivering the treatment, the participant will have a local therapist who may be contacted in an emergency.
- Secondly, this helps to ensure that the participant does not receive more than four sessions at home by telephone (see section 8.1). For those sessions where the distant centre therapist is unable to attend for a face-to-face interview, the participant will see the local cross-cover therapist at the hospital clinic who will sit in as an assistant to a telephone or video session conducted with the distant centre therapist.

8.6.3 Local cross-cover therapy

Cross-cover therapy is delivered by a PACE therapist of a different discipline, whereby the cross-cover therapist learns a second PACE therapy to a competent level. Competence will be judged independently by the treatment leader. The cross-cover therapist acts as an assistant therapist (e.g. a CB therapist learning GET becomes a physiotherapy assistant). They are supervised both by a distant centre PACE therapist of the appropriate discipline and a local one providing emergency assistance and assessment in case the patient has an intercurrent problem (e.g. pulls a muscle during GET).

8.6.4 Recruitment of a new therapist

In the case of resignation or maternity leave, the collaborating centre will seek to recruit a replacement therapist as quickly as possible.

It is recognised that there is a shortage of therapists working in the NHS and for this reason, the recruitment of staff of alternative appropriately qualified disciplines may also be considered. For example, an exercise physiologist may be recruited in place of a physiotherapist to deliver GET. There have been two randomised controlled trials of GET for CFS/ME provided by exercise physiologists, with positive outcomes.^[23, 49] In these instances the therapist will operate as a 'physiotherapy assistant' to a supervising physiotherapist. Similar alternative disciplines and supervision arrangements may also be considered for APT and CBT.

8.6.5 Changes to the therapy manuals

The treatment manuals for both therapists and participants state that APT will be given by an occupational therapist, CBT by a CB therapist, and that GET will be delivered by a physiotherapist. It is possible when allowing for contingency plans that this will not always be the case (e.g. GET may be delivered by a CB therapist, acting as a physiotherapy assistant who is trained to give GET as well). The manuals statement reflects 'usual practice' but where a participant is given treatment by a therapist of a different discipline, this will be fully explained to the participant before the start of the therapy.

8.6.6 Changes to consent process

If a participant is to receive treatment from a therapist of either a different centre or a different discipline, the participant will give consent once it is clear that they understand this and are willing to receive their treatment in this way. (See Appendix A1.7).

8.6.7 Contingency plan for planned annual leave

- *For leave of 3 weeks or less* the therapist will attempt to fit in the missed sessions within the five month treatment period but no more than one session will take place in any one week.
- *For leave periods of more than 3 weeks* another therapist trained to delivery the therapy will provide the therapy on a temporary basis.

8.6.8 Suspension of randomisation

There may be occasions of therapist absence where there is no available cover or more than one therapist is absent. In this situation, the TMG would seek approval from the Trial Steering Committee or its Chairperson to temporarily suspend randomisation in one treatment arm at the affected centre. In the case of two or more absent therapists it may be necessary to temporarily suspend randomisation to an entire centre.

9. Assessments and Procedures

9.1 Schedule for follow-up

See above Figure 1, section 3.1.1, and Figure 7, section 10.2.2.

9.2 Assessments

A participant's guide to completing their questionnaires will be given verbally to the participant by the RN. The questionnaires should be completed without conferring with friends or relatives and all questions should be answered even if the participant feels them to be irrelevant.

All participants will be re-assessed in clinic. Those participants who cannot attend clinic will be offered home assessments (or failing this assessment by telephone or by post). Before second and consequent RN assessments, self-rated measures will be posted to the participant prior to the visit and checked for completion at assessment by the RN. If the participant fails to bring them to the visit they should complete them at that visit. If a participant becomes too tired or ill to continue with the assessment, they will be offered the opportunity to complete the assessment on another day, within the next seven days.

Because we do not think it practically possible for the RN to remain blind to treatment group allocation, we will not attempt to achieve this. All our primary and secondary outcomes are therefore either self-rated or objective in order to minimise observer bias. Participants who drop out of treatment will be assessed for outcomes as soon as possible, rather than waiting for the normal follow-up.

When the participant does not attend a research interview, the RN will send the self-rated questionnaires to the participant's home address, with a stamped addressed envelope. If questionnaires are not received back within a week, the RN will arrange to visit the participant at home and oversee completion of the questionnaires. If necessary, only the primary outcomes and the CGI^[48] (to assess deterioration) should be the minimum completed.

9.2.1 Long term follow-up

Permission will be sought from the participant to be contacted annually for follow-up information regarding the participant's health and employment status. The participant will also be invited to remain in contact so that the results may be disseminated to them once published.

9.3 Premature trial closure

Premature trial closure is unlikely to be necessary in a trial that does not involve pharmaceutical or surgical trial treatments. If one treatment arm does show consistent and reliable evidence of causing serious adverse reactions in participants, then

consideration of closing that particular arm of the trial should be given by the TSC as advised by the DMEC.

10. Measures

10.1 Primary outcome measures

10.1.1 Primary efficacy measures

Since we are interested in changes in both symptoms and disability we have chosen to designate both the symptoms of fatigue and physical function as primary outcomes. This is because it is possible that a specific treatment may relieve symptoms without reducing disability, or vice versa. Both these measures will be self-rated.

The 11 item Chalder Fatigue Questionnaire measures the severity of symptomatic fatigue,^[27] 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. A positive outcome will be a 50 % reduction in fatigue score, or a score of 3 or less, this threshold having been previously shown to indicate normal fatigue.^[27]

The SF-36 physical function sub-scale^[28] measures physical function, and has often been used as a primary outcome measure in trials of CBT and GET. We will count a score of 75 (out of a maximum of 100) or more, or a 50 % increase from baseline in SF-36 sub-scale score as a positive outcome. A score of 70 is about one standard deviation below the mean score (about 85, depending on the study) for the UK adult population.^[50, 51]

Those participants who improve in both outcome measures will be regarded as overall improvers.

10.2 Secondary outcome measures

10.2.1 Secondary efficacy measures

1. The Chalder Fatigue Questionnaire Likert scoring (0,1,2,3) will be used to compare responses to treatment.^[27]
2. The self-rated Clinical Global Impression (CGI) change score (range 1 - 7) provides a self-rated global measure of change, and has been used in previous trials.^[45] As in previous trials, we will consider scores of 1 or 2 as a positive outcome ("very much better" and "much better") and the rest as non-improvement.^[23]
3. The CGI change scale will also be rated by the treating therapist at the end of session number 14, and by the SSMC doctor at the 52-week review.
4. "Recovery" will be defined by meeting all four of the following criteria: (i) a Chalder Fatigue Questionnaire score of 3 or less,^[27] (ii) SF 36 physical Function score of 85 or above,^[46, 47] (iii) a CGI score of 1,^[45] and (iv) the participant no longer meets Oxford criteria for CFS,^[2] CDC criteria for CFS^[1] or the London criteria for ME.^[31]
5. The Hospital Anxiety and Depression Scale scores in both anxiety and depression sub-scales.^[33]
6. The Work and Social Adjustment scale provides a more comprehensive measure of participation in occupational and domestic activities.^[36]

7. The EuroQOL (EQ-5D) provides a global measure of the quality of life.^[35]
8. The six-minute walking test will give an objective outcome measure of physical capacity.^[42]
9. The self-paced step test of fitness.^[43]
10. The Borg Scale of perceived physical exertion,^[44] to measure effort with exercise and completed immediately after the step test.
11. The Client Service Receipt Inventory (CSRI), adapted for use in CFS/ME,^[42] will measure hours of employment/study, wages and benefits received, allowing another more objective measure of function.
12. An operationalised Likert scale of the nine CDC symptoms of CFS.^[1]
13. The Physical Symptoms (Physical Health Questionnaire 15 items(PHQ15)).^[39]
14. A measurement of participant satisfaction with the trial will also be taken at 52 weeks.^[52]

Figure 9: 10.2.2 Table of research assessments by time point

	Completed by:	Pre-consent Visit 0	Baseline visit 1	Baseline visit 2 (& randomisation if appropriate)	12 weeks (mid-therapy)	24 weeks (end of therapy)	52 weeks (trial end)	Treatment discontinuation	Trial drop out
Eligibility assessment	RN & Doctor	X	X						
Consent to Baseline	RN / P		X						
Chalder Fatigue Questionnaire	P		X		X	X	X	X	X
SF-36 physical function sub-scale	P		X		X	X	X	X	X
Demographic details	RN		X						
Duration of CFS (months)	RN		X						
Medical History	RN		X						
Co-morbid active medical conditions	RN		X		X	X	X	X	
Self help group and/or CFS/ME patient organisation membership	RN		X				X		

	Completed by:	Pre-consent Visit 0	Baseline visit 1	Baseline visit 2 (& randomisation if appropriate)	12 weeks (mid-therapy)	24 weeks (end of therapy)	52 weeks (trial end)	Treatment discontinuation	Trial drop out
SCID	RN		X						
Oxford criteria	RN		X				X	X	
Body mass index	RN		X		X	X	X		
6 minute walking test	RN		X			X	X	X	
1 week actigraphy	RN		X						
Consent to full trial	RN / P			X					
CDC criteria for CFS	RN			X			X	X	
London criteria for ME	RN			X			X	X	
Presence or absence of fibromyalgia	RN			X			X	X	
CSRI	RN			X		X	X	X	
Preferred treatment group	P			X					
EuroQOL EQ-5D	P			X	X	X	X	X	
HADS	P			X	X	X	X	X	
Self-efficacy for managing chronic disease scale	P			X	X	X	X	X	
Work & Social Adjustment Scale	P			X	X	X	X	X	
Symptom interpretation questionnaire (short version)	P			X	X	X	X		

	Completed by:	Pre-consent Visit 0	Baseline visit 1	Baseline visit 2 (& randomisation if appropriate)	12 weeks (mid-therapy)	24 weeks (end of therapy)	52 weeks (trial end)	Treatment discontinuation	Trial drop out
Physical Symptoms (PHQ-15)	P			X	X	X	X	X	
Exercise and Activity Scale	P			X	X	X	X	X	
Jenkins sleep scale	P			X	X	X	X	X	
Concomitant medications & therapies	RN			X	X	X	X	X	
Step test of fitness	RN			X	X	X	X	X	
Borg Scale of perceived exertion	P			X	X	X	X	X	
Adverse events	RN				X	X	X	X	
CGI self-rated	P				X	X	X	X	X
Satisfaction scale	P					X	X		
Expectation of therapeutic outcome	P			X					
CGI SSMC doctor-rated	Doctor						X	X	X
CGI therapist-rated (2-part CRF)	Therapist					X CGI section of CRF	X No. of appt.s, DNAs, calls etc	X	X
Rating of homework compliance	Therapist				At every therapy session				

RN = Research Nurse; P = participant

10.3 Adverse outcomes

Adverse outcomes (score of 5-7 of the self-rated CGI) will be monitored by examining the CGI at all follow-up assessment interviews.^[48] An adverse outcome will be considered to have occurred if the physical function score of the SF-36^[28] has dropped by 20 points from the previous measurement. This deterioration score has been chosen since it represents approximately one standard deviation from the mean baseline scores (between 18 and 27) from previous trials using this measure.^[23, 25] Furthermore, the RN will enquire regarding specific adverse events at all follow-up assessment interviews (see section 14).

10.4 Predictors

1. Sex
2. Age
3. Duration of CFS/ME (months)
4. 1 week of actigraphy^[18] (as initiated at visit 1 with the research nurse)
5. Body mass index (measure weight in kg and height in metres)
6. The CDC criteria for CFS^[1]
7. The London criteria for myalgic encephalomyelitis^[31]
8. Presence or absence of "fibromyalgia" ^[32]
9. Jenkins sleep scale of subjective sleep problems^[34]
10. Symptom interpretation questionnaire^[38]
11. Preferred treatment group
12. Self-efficacy for managing chronic disease scale^[40]
13. Somatisation (from 15 item physical symptoms PHQ sub-scale)^[39]
14. Depressive disorder (major depressive disorder, dysthymia by DSMIV) (from SCID)^[30]
15. The Hospital Anxiety and Depression Scale (HADS)^[33] combined score
16. Receipt of ill-health benefits or pension
17. In dispute/negotiation of benefits or pension
18. Current and specific membership of a self-help group (specific question)

10.5 Process variables

1. Step test of fitness^[43]
2. Borg Scale of perceived physical exertion^[44]
3. Physical activity (by six-minute walking test)^[42]
4. The symptom interpretation questionnaire^[38]

10.6 Therapeutic input

1. At each RN assessment participants will be asked what other treatments they have been receiving (e.g. complementary and alternative therapies, prescribed and over-the-counter medicines).

2. The strength of the therapeutic alliance will be measured by the therapy integrity rating scale (Appendix 7) by an independent and blinded observer.^[52]
3. The differentiation of the supplementary therapies will be measured blind to treatment group by an independent observer.^[52]

10.7 Plausibility of therapy

After the first treatment session, all participants will be asked to fill in a brief measure of how plausible their treatment appears to them.

10.8 Economic costs

The CSRI^[41] will retrospectively record service utilisation for the six months prior to the baseline assessment, for the period between baseline and 24 weeks, and then for the period from 24 weeks to 52 weeks. A comprehensive range of services will be included so that in addition to being able to determine the resource implications to the NHS, we will also have information on the impact that treatment has on other parts of the care system as well as on informal carers. The ability to engage in employment, education and work in the home are frequently affected by CFS/ME and the CSRI will collect data on these activities. Service use will be valued by attaching appropriate unit costs from national sources (e.g. Netten et al, 2003^[53]) as well as intervention costs specifically calculated for the study.

11. Sample Size

11.1 Assumptions

At one year we assume that 60% will improve with CBT, 50% with GET, 25% with APT and 10% with SSMC. The existing evidence suggests that at one year follow up, 50 to 63% of participants with CFS/ME had a positive outcome, by intention to treat, in the three RCTs of rehabilitative CBT,^[18, 25, 26] with 69% improved after an educational rehabilitation that closely resembled CBT.^[43] This compares to 18 to 63% improved in the two RCTs of GET,^[23, 24] and 47% improvement in a clinical audit of GET.^[54] Having usual medical care allowed 6% to 17% to improve by one year in two RCTs.^[18, 25] There are no previous RCTs of APT to guide us,^[11, 12] but we estimate that APT will be at least as effective as the control treatments of relaxation and flexibility used in previous RCTs, with 26% to 27% improved on primary outcomes.^[23, 26] We propose that a clinically important difference would be between 2 and 3 times the improvement rate of SSMC.

11.2 Power analyses

Our planned intention to treat analyses will compare APT against SSMC alone, and both CBT and GET against APT. Assuming $\alpha = 5\%$ and a power of 90%, we require a minimum of 135 participants in the SSMC alone and APT groups, 80 participants in the GET group and 40 in the CBT group.^[55] However these last two numbers are insufficient to study predictors, process, or cost-effectiveness. We will not be able to get a precise estimate of the difference between CBT and GET, though our estimates will be useful in planning future trials. As an example, to detect a difference in response rates of 50% and 60%, with 90% power, would require 520 participants per group; numbers beyond a realistic two-arm trial. Therefore, we will study equal numbers of 135 participants in each of the four arms, which gives us greater than 90% power to study differences in efficacy between APT and both CBT and GET. We will adjust our numbers for dropouts, at the same time as designing the trial and its management to minimise dropouts. Dropout rates were 12 and 33% in the two studies of GET^[23, 24] and 3, 10, and 40% in the three studies of rehabilitative CBT.^[18, 25, 26] On the basis of our own previous trials, we estimate a dropout rate of 10%. We therefore require approximately 150 participants in each treatment group, or 600 participants in all. Calculation of the sample size required to detect economic differences between treatment groups requires data of cost per change in outcome, which is not currently available.

12. Analyses

12.1 Interim analyses

There are no planned interim analyses by the trial investigators.

The Data Monitoring and Ethics Committee (DMEC) will advise on the frequency of reviews of the data on the basis of accrual and event rates. If requested, interim analyses will be performed by the trial statistician and reported to the DMEC who will give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continued randomisation. We anticipate a decision to discontinue randomisation to one specific treatment will be made only if the evidence is likely to convince a broad range of clinicians, including those participating in the PACE trial, and the general clinical community. The DMEC will make recommendations to the Trial Steering Committee (TSC).

The role of the TSC is to provide overall supervision for the trial and safeguard its integrity. Executive authority for the continuation of the trial lies with the TSC.

12.2 Unblinding

All research and therapy staff and participants are unblinded to treatment allocation of individual participants. Therefore there will be no need for unblinding during the trial. The one exception is that the trial statisticians RW and TJ are blind to treatment allocation (coded A, B, C, D), as will be the DMEC, in order to take actions on the basis of the unblinded data alone.

12.3 Analysis plan (brief)

A full Analysis Strategy (modelled on that successfully employed within the recently completed, MRC-funded, trial of Cognitive Behaviour Therapy in Bipolar Affective Disorder), will be developed, independently of looking at the trial database, and before undertaking any analysis, about 6 months after the start of randomisation.

12.3.1 Primary analyses of efficacy

The primary analysis will be pragmatic, based on intention to treat, and will utilise all available follow-up data from all randomised participants. The primary binary outcomes of response on the fatigue and physical function sub-scales (comparing proportions with categorical adverse deterioration (see section 10.3) with this scale as well) and both will be analysed by logistic regression adjusted for centre with contrasts for:

- (1) APT vs. SSMC alone,
- (2) APT vs. CBT,
- (3) APT vs. GET,

- (4) Trend across SSMC alone, APT, and CBT/GET combined,
- (5) CBT vs. SSMC alone,
- (6) GET vs. SSMC alone,

Participants not followed to one year will be classed as non-responders unless they show a consistent pattern of outcome across assessments at 10, 24, and 39 weeks or whenever the last assessment is obtained.

12.3.2 Secondary analyses of efficacy

The secondary continuous outcomes will be analysed by repeated measures analysis of variance using a linear mixed model with AR(1) covariance structure, and including centre, depressive disorder, CDC and London criteria and baseline values as covariates. The same contrasts as those specified for the primary outcomes will be extracted. A summary measure, the area under the curve, will also be reported.

A secondary, per protocol, analysis restricted to participants who complete a minimum of 10 weeks of treatment will also be performed.

Further secondary sensitivity analyses will be used to assess the robustness of conclusions to missing primary outcomes; these will employ repeated binary outcomes, multiple imputation, and imputation analysing all possible outcomes.^[56]

Loss to follow-up, departures from randomised treatment protocols, and the prevalence of serious adverse events, will be reported at 13, 26, 39, and 52 weeks from randomisation.

Results from all analyses will be summarised as differences between percentages or means together with 95% confidence limits (CL). The significance level for all analyses of primary outcome variables will be $P=0.05$ (two-sided); for secondary outcome variables, $P=0.01$ (two-sided) unless profiles of response can be specified in advance.

[Prior to writing the Analysis Strategy a consensus will be reached on the profiles of response for each secondary outcome within each of the four treatment groups.]

12.3.3 Predictions and process of treatment

Associations between post-treatment outcomes and both predictor and process variables (including demographic, illness duration, and other putative clinical indicators) will be examined using multiple linear and logistic regression modelling techniques, including a limited examination of interactions both amongst pairs of predictors and between predictors and treatment groups. We anticipate that the sample size will be sufficient to identify important general predictors from a random-split, training set of two thirds (~400), with partial validation in the remainder, used as a test set. Shrinkage techniques (to allow for over-optimism in variable selection) will be applied in the development of a prognostic model to be applied to participants outside the trial.

12.3.4 Economic analyses

The main economic evaluation will be a cost-effectiveness analysis conducted from a societal perspective, examining comprehensive costs (treatment and service costs plus lost productivity) and the two primary efficacy measures (fatigue and physical function). Cost-effectiveness acceptability curves will be plotted as necessary. A supportive cost-consequences analysis will be conducted, examining comprehensive costs alongside all (primary and secondary) efficacy measures. To inform special interests, evaluations will also be conducted from the perspectives of the NHS, and also by using utility scores in the cost-effectiveness analysis (computed from either the EQ-5D^[35] or the WSAS,^[36] there being arguments for and against each as the basis for health-related quality of life measurement).

13. Monitoring

13.1 Direct access to data

The principal investigators, centre leaders and participants will permit trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents.

13.2 Confidentiality

No participant identification details will be used in any database. The one exception will be a separate database, held at the Bart's centre only, of name of participant, date of birth, PIN, and if relevant, allocated therapy, date of randomisation and NHS number for ONS tracing (England) or the Chi number for ISD (Scotland) to allow longer term follow-up for five years after the end of the trial. Participant names, addresses, and other contact details will be written in the CRF for identification and contact purposes. The CRFs will be regarded as confidential, and kept in locked filing cabinets in the local centre and the coordinating centre (St Bartholomew's Hospital).

13.3 Quality assurance and Quality control

A quality assurance and control policy will be written (see SOP 14).

13.3.1 Therapists' compliance with treatment manuals

Therapist compliance with treatment manuals will be monitored in two ways. 1) All therapists will receive a minimum of monthly telephone individual supervision and face-to-face group and individual supervision at least four times a year, depending on supervisory needs. All therapy sessions will be video/audio-recorded. Some recordings will be used by trainers/supervisors to provide feedback to therapists on competence and treatment fidelity, which will happen particularly in the first few months of a therapist starting to treat participants. Any significant deviations from the manual will be noted and feedback given to the therapist. Therapist competence will be measured by the relevant therapy leaders. Therapists will be allowed to treat trial participants once they have been approved as competent. 2) Two recorded sessions per therapist will be randomly chosen and assessed blindly and independently by an assessor to assess adherence to manual defined therapy.

13.3.2 SSMC doctors' adherence with SSMC manual

All SSMC doctors will receive training in use of the SSMC manual. All SSMC sessions will be audiorecorded. Some recordings will be used by centre leaders (using other centre leaders when the centre leader is providing SSMC) to provide feedback to doctors on competence and treatment fidelity, which will happen particularly in the first few months of a doctor starting to treat participants. Any significant deviations from the manual will be noted and feedback given to the doctor. Two recorded sessions per doctor will be randomly chosen

and assessed blindly and independently by an assessor to assess adherence to manual defined treatment. In addition, this will be particularly done for any doctor who routinely sees participants more than five times in the twelve months of the study.

13.3.3 Participant non-adherence with treatment

Participant non-adherence with treatment will be measured both by recording attendance and by therapist ratings of adherence to therapy.

13.3.4 Database quality

The TM and Bart's data manager will be responsible for checking the quality of the Trial Master Database (TMD), and will send local centre data managers query forms as necessary.

14. Adverse Events

14.1 Adverse events (AEs)

Adverse events (AE) are any clinical change, disease or disorder experienced by the participant during their participation in the trial, whether or not considered related to the use of treatments being studied in the trial.

14.1.1 Serious Adverse Events (SAEs)

An adverse event (AE) is defined as serious (an SAE) if it results in one of the following outcomes:

- a) Death,
- b) Life-threatening (i.e., with an immediate, not hypothetical, risk of death at the time of the event),
- c) Requires hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included),
- d) Increased severe and persistent disability, defined as:
 - severe = a significant deterioration in the participant's ability to carry out their important activities of daily living (e.g. employed person no longer able to work, caregiver no longer able to give care, ambulant participant becoming bed bound); and
 - persistent = 4 weeks continuous duration
- e) Any other important medical condition which, though not included in the above, may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed.
- f) Any episode of deliberate self-harm

If there is any doubt in the minds of the research nurse and the centre leader as to whether the AE is a serious AE, the centre leader will obtain a second opinion from one of the PIs.

14.1.2 Serious Adverse Reactions (SARs)

A Serious Adverse Reaction can be defined as:

A SAE considered to be a reaction to one of the supplementary therapies or a drug prescribed as part of SSMC.

14.1.3 Reporting serious adverse events and reactions (SAEs and SARs)

In the event of an adverse event (AE), the centre leader or nominee will judge the seriousness of the event, the relationship to a trial supplementary therapy or SSMC prescribed treatment, clinical severity and the expectedness of the event. All SAEs must be reported by the RN to the SSMC doctor (or SSMC doctor to the RN), centre leader or nominee (e.g. another centre leader), and the trial manager immediately the RN or SSMC doctor learns of the SAE, regardless of the relationship to trial treatment. The RN should also inform the local R&D office within fifteen working days. The trial manager must inform the MREC and the chair of the DMEC within fifteen working days. If the AE is

considered a Serious Adverse Reaction (SAR), the centre leader should inform their R&D office and the trial manager in the same timeframe as reporting of an SAE.

Where an event is determined by the centre leader or PIs to be a suspected unexpected serious adverse reaction (SUSAR) and is life threatening, the TM will report the event to the DMEC, MREC and R&D office within seven days.

Criteria include:
Definitely related
Probably related
Possibly related
Definitely unrelated
Uncertain

A summary of all SAEs and SARs will be reported to the MREC, the individual participating centre's R&D departments, and to the TSC via the DMEC through the usual annual reports (see SOP 10 & 11).

14.2 Non-serious adverse events and reactions

Non-serious adverse events or reactions will be assessed by the RN at each follow-up assessment interview (see 10 & 11). A risk assessment has been undertaken, and we have concluded that the therapies are of low risk to participants. Examples of expected non-serious adverse events have been identified, and these include:

- Development of new mood disorder
- Musculoskeletal injuries - e.g. ankle sprains etc.,
- Transient exacerbation of fatigue or pain, expected as a normal reaction to CBT or G ET in patients with CFS/ME, which does not have significant impact upon function (see 14.1.1 (a))
- Development of new sleep disturbance
- Falls (e.g. due to tripping, etc.)
- Worsening of anxiety - e.g. health anxiety, exacerbated by a transient increase in symptoms

Non-serious adverse events will be reported to the DMEC annually (or more frequently if requested) via the trial statistician and will be included in the safety reporting of the completed trial.

14.3 Follow-up after adverse events

After an SAE or SAR, a decision will be made by the centre leader, after advice from the relevant authorities and the participant's general practitioner, as to whether the participant should be withdrawn from either their randomised treatment or from the trial, or need an alteration in their SSMC. Arrangements will be made by the centre leader for further assessment and management as agreed with the relevant authorities, GP and participant. The RN will provide the centre leader and TM with a one month follow-up report on all

SAEs and SARs. Further monthly reports should be provided in the absence of resolution. These reports will be communicated to the DMEC and MREC via the TM or trial statistician, and by the RN to the local R&D office.

15. Ethical Considerations

15.1 Safety of participants

There is a discrepancy between patient organisation reports of the safety of CBT and GET and the published evidence of minimal risk from RCTs. Surveys by *Action for M.E.* of their members suggest that people becoming worse with these treatments is caused by either rigidly applied programmes that are not tailored to the patient's disability, or by improperly supervised programmes.^[13-15] PACE treatment manuals minimize this risk by being based on mutually agreed and flexible programmes that vary according to patient response. The RN will also carefully monitor for any adverse effects of the treatments.

15.1.1 Policy for deteriorating participant or one who drops out of treatment

The following policy will be enacted by the centre leader for any participant who is considered, or considers themselves, to be deteriorating, or has dropped out of treatment. The centre leader or delegated professional will undertake a detailed clinical assessment, at home if necessary, following which they will be offered appropriate help.

15.2 Recruitment, randomisation and retention

The patient's consent to participate in the trial should be obtained only after a full explanation has been given of the treatment options, including conventional and generally accepted methods of treatment. The patient information sheet and patient consent forms are attached. A copy of the LREC approval letter must be sent to the TM and PIs before a centre begins randomising participants.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinic doctor must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

Those recruiting and randomising participants will rigorously maintain a position of equipoise and employ explanations that are consistent with this.^[57] All the participating clinicians regard all the four treatments as potentially effective and are of the view that most patients seen will accept randomisation if it is fully and openly explained. Some patients are initially sceptical about treatment effectiveness but are willing to accept any recommended treatment as long it is appropriately explained and delivered. Therefore, we do not anticipate a difficulty either in acceptability of the proposed treatments, with recruitment into the trial, or acceptance of randomisation. We emphasise that we make this statement based on our having completed six trials of treatment for CFS/ME.

15.3 Standardised Specialist Medical Care (SSMC)

All 600 randomised participants will receive SSMD. This will be provided by a doctor with specialist experience in CFS/ME. SSMD is also the trial comparison intervention against which the three supplementary therapies will be judged. It is therefore important that this is similar in all centres, in order to avoid a centre effect, and in all four treatment conditions. Both a SSMD doctor's manual and a Patient Clinic Leaflet (PCL) have been written (see appendices A2.7 and A1.1). The SSMD manual gives guidance to the SSMD doctor regarding the standardised allowable interventions during the trial. The PCL will have already been given to the participant before entering the trial. This leaflet gives information about what CFS/ME is, its likely causes and the different approaches to management. It also gives guidance regarding activity management that is consistent with all four treatment arms of the trial.

SSMD will involve a minimum of three visits after randomisation, or more if clinically indicated (such as overseeing benefit/adverse effects of a prescribed medication). Allowed interventions include explaining the diagnosis, education about the illness, standardised advice on activity management (see PCL; Appendix A1.1), and prescription of symptomatic medications, such as antidepressants and hypnotics, as clinically indicated (see SSMD manual; Appendix A2.7). No added intervention is banned so long as the centre doctor considers that the intervention is indicated, and it is not already being provided as part of the trial.

All prescribed and non-prescribed medicines, and any complementary or alternative therapies or treatments will be recorded by the RN at assessment interviews.

16. Regulatory and Ethics Approval

16.1 Multi-centre Research Ethics Approval (MREC)

Ethical approval for the PACE trial was given by the West Midlands MREC (reference number MREC/02/7/89).

The initial application was approved on 24th October 2002 subject to clarifications. The following substantial amendments have been submitted:

Substantial Amendment 1 – approved 31.03.2003,
Substantial Amendment 2.1 – submitted 22.10.2004, approved 02.02.2005
Substantial Amendment 2.2 – submitted 24.11.2004, approved 02.02.2005
Substantial Amendment 2.3 – submitted 05.01.2005, approved 02.02.2005
Substantial Amendment 3.1 – submitted 06.12.2004, approved 02.02.2005

Study opens to recruitment March 2005.

Substantial Amendment 4.1 – submitted 05.08.2005, approved 30.08.2005

Minor Amendment 1 – submitted 11.02.2005, approved 25.02.2005 by phone
Minor Amendment 2 – submitted 05.08.2005, approved 02.09.2005
Minor Amendment 3 – submitted 05.08.2005, approved 02.09.2005
Minor Amendment 4 – submitted 10.10.2005, approved 10.11.2005
Minor Amendment 5 – submitted 06.01.2006
Substantial Amendment 5.1 – submitted 01.02.2006
Minor / Administrative Amendment 6 – submitted 01.02.2006
Minor / Administrative Amendment 7 – submitted 01.02.2006

16.2 Local Research Ethics Approval (LREC)

The trial has also been passed as ethical by the LRECs of the following participating centres:

- Edinburgh (reference number 04/S11/admin/79),
- Oxford (reference number 04/Q160S/83),
- SL&M (reference numbers not used by this LREC) and
- ELCHA (reference number P/99/068) LRECs.

We will approach the other two centres LRECs in late 2004/early 2005.

17. Indemnity

Each centre taking part in the trial will seek local approval and indemnity through their NHS R&D department. As an automatic consequence of this, local NHS indemnity will apply to the PACE trial. Details of local indemnity arrangements can be obtained through each centre's NHS R&D department.

18. Trial Committees

18.1 Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) is responsible for the independent oversight of the progress of the trial, investigation of serious adverse events, and determining the future progress of the trial in the light of regular reports from the DMEC. The TSC has the power to prematurely close the trial. MRC trials require an independent Chair for the TSC. The TSC is composed of:

Professor Janet Darbyshire (Chair),
Professor Jenny Butler (occupational therapist),
Professor Patrick Doherty (physiotherapist),
Dr Stella Harris (patient representative),
Dr Meirion Llewelyn (consultant physician in infectious diseases), and
Professor Tom Sensky (liaison psychiatrist and CBT therapist).

Observers include:

Professor Mansel Aylward (previously of DWP),
Mr Chris Clark (Action for M.E.),
Peter Craig (Scottish executive),
Dr. Moira Henderson (DWP)
Susan Lonsdale (DH) and
Dr Sarah Perkins (MRC),
Professor Stephen Stansfeld (centre lead for Psychiatry, Queen Mary University of London, on behalf of the sponsor).
Dr Alison Wearden (Principal Investigator of the FINE trial, a sister study of CFS/ME).

Other members include the three investigators, the trial statistician, and the trial manager (secretary to the committee).

Membership has been approved by the MRC.

Previous members/observers include:

Dr Robin Buckle (MRC)
Professor Clair Chilvers (R&D, DH)

18.2 Data Monitoring and Ethics Committee (DMEC)

The Data Monitoring and Ethics Committee (DMEC) are independent and responsible for monitoring progress of the trial and serious adverse events and reactions. The DMEC will meet annually or more often if the chair determines a reason for doing so, and provide a trial progress report at the end of each meeting which will be sent to the TSC.

Reports to DMEC and the main analysis itself (as far as possible) will be compiled blind to allocated treatment. DMEC reports will simply label treatments as A, B, C or D. DMEC may request unblinding only if they have serious concerns about any of the treatments. The unblinding would be handled by a third statistician independent of the TMG. The DMEC can recommend premature closure of the trial to the TSC. The circumstances for this need to be agreed by the DMEC and TSC, but we suggest the only likely scenario is if one of the trial treatments is shown to cause significant and consistent deterioration in a significant number of participants (to be quantified at the first meeting of the DMEC). If one treatment arm does show consistent and reliable evidence of causing serious adverse reactions in participants, then consideration of closing that particular arm of the trial should be given. The DMEC will be asked to keep a close eye on any consistent pattern of deterioration of participants.

The DMEC is composed of:

Professor Paul Dieppe (chair),
Dr Charlotte Feinmann (liaison psychiatrist) and
Professor Astrid Fletcher (epidemiologist).

18.3 Trial Management Group (TMG)

The Trial Management Group (TMG) will be responsible for the day-to-day running and management of the trial. It is composed of:

- The three principal investigators
- All centre leaders and co-leaders
- 4 treatment leaders (Jessica Bavinton, Mary Burgess, Diane Cox and Gabrielle Murphy)
- 2 health economists (Martin Knapp and Paul McCrone)
- Trial statisticians (Tony Johnson and Rebecca Walwyn)
- Chris Clark (for *Action for M.E.*) or a nominated deputy
- Julia DeCesare, Trial Manager
- Alison Wearden (observer for FINE trial)
- Sandy Smith, Data Manager/Senior Research Secretary for Bart's and secretary for the TMG
- Other PACE team members may attend as observers with the permission of one of the PIs
- The TMG is currently meeting every two months, but will meet less frequently in the future.

19. Publication

No report, either verbal or written, may be made without the approval of the Trial Steering Committee during the trial.

The results from different centres will be analysed together and presented first to a joint meeting of the TSC and DMEC for comment and discussion. Results will subsequently be published as soon as possible under the authorship of the writing committee on behalf of the "PACE Trial Management Group". The writing committee will consist of the three PIs, the TM and the two trial statisticians. Individual clinicians/centre leaders must not publish data concerning their participants that are directly relevant to questions posed by the study until the writing committee with the Trial Management Group has published its results. All publications pertaining to the PACE trial require the approval of the TMG.

All publications that result from the trial shall include a list of the members of the PACE TMG, TSC and DMEC. If there are named authors on the secondary papers, these will include the principal investigators, trial manager, and statisticians involved in the trial. The ISRCTN number (ISRCTN54285094) will be attached to any publications resulting from this trial.

20. Protocol Amendments

20.1 Protocol amendments to the previous versions

The main changes have been to provide more detail of what we will do, and we have made no significant changes to the goals or aims or design of the study.

Figure 10: 20.1.1 Table of submissions made to MREC

Date	Documentation details
13.09.2002	<ul style="list-style-type: none"> • Application Form 12.09.2002 • Protocol 19.06.2002 • Principal Researchers CV (undated)
20.03.2003	<ul style="list-style-type: none"> • Consent form • Information Sheet • Approval form • Letter to the MRC concerning reduction of questionnaires • Other trials
31.03.2003	Approval letter from MREC <ul style="list-style-type: none"> • MREC response form • Signed approval sheet • Membership list
22.10.2004	<p><u>Substantial Amendment 2.1, 22.10.2004</u></p> <ul style="list-style-type: none"> • Substantial amendment form 2 • Protocol version 2.1, 22 October 2004. <p>The main changes have been to provide more detail of what we will do, and we have made no significant changes to the goals or aims or design of the study. We have made some minor changes to the protocol with the addition of measures in order to: properly measure meaningful outcome (the addition of the Work and Social adjustment scale); to ensure we are measuring predictors that other studies have shown (self-efficacy) or that patient organisations believe are important (London criteria for myalgic encephalomyelitis); and to be sure that all likely mediators of change are measured (sleep disturbance scale).</p> <p>The CSRI now gives more accurate financial measures to enable us to accurately measure cost-utility of the different treatments. The symptoms interpretation questionnaire will give more pertinent information about the illness beliefs that may affect prognosis, and yet may change in the process of treatment.</p> <p>There have been changes to the initial protocol, considered by the MRC, and the version approved by MREC. These are listed below:</p> <ul style="list-style-type: none"> • A two stage consent to separate baseline assessment from full participation in the trial. We have done this in order to ensure participants are eligible before they are randomised. Otherwise

	<p>they may have given consent for randomisation before we know whether they are eligible.</p> <ul style="list-style-type: none"> • A two stage baseline assessment (with visits a week apart) in order to avoid unnecessary fatigue for participants by too long assessments. • Stratification for randomisation to ensure equal distribution of participants with mood disorders, and two different criteria for defining CFS/ME (the London and Centers for Disease Control criteria). • No research or therapeutic staff being blind to treatment allocation, in order to optimise clinical care, apart from the CTU staff. • A more detailed definition of adverse events and reactions, as well as operationalising clinical deterioration. This will ensure we are able to define and pick up adverse events quickly and efficiently. • A modification to the primary outcome, by the addition of a 50% reduction in fatigue and physical disability being a positive outcome, alongside the previously approved categorical outcome. • An additional primary outcome of needing both fatigue and physical disability to improve • Operationalised criteria for recovery • Audiorecording of the SSMC doctors' sessions • The addition of the following questionnaire measures: <ul style="list-style-type: none"> • Jenkins Sleep Questionnaire (4 items) • Self-efficacy (5 items) • Work and social adjustment scale (5 items) • Therapeutic plausibility (1 item) • The London criteria for ME (3 items) • The Symptom Interpretation Questionnaire (43 items) • Revision of the CSRI • Therapist and doctor rated CGIs (2 items) • The Physical Symptoms subscale of the Patient Health Questionnaire (15 items) (PHQ-15) instead of the somatoform section of the Standardised Clinical Interview for DSM-IV. • Therapy integrity rating scale to be filled in by blind independent assessor, not the participant <p>All these amendments (apart from # 9 and the PHQ-15) have been approved by the independent Trial Steering Committee (TSC) and the independent Data Monitoring and Ethics Committee at its joint meeting on 27th September 2004. Any future amendments to the protocol will be issued by the Trial Management Group after discussion with the TSC, and with the West Midlands MREC. Amendments were circulated to all centres and incorporated into a revised version of the protocol.</p> <p>This included the appendix which contains the following items: <u>Appendix 1: Patient/participant information</u></p>
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- A1.3 Participant Information Sheet, version 10,,22.10.2004
- A1.4 Eligibility Assessment / Baseline Consent Form, version 3.1 (eligibility/baseline),22.10.2004
- A1.5 Full trial Consent Form, version 3.2 (full trial),22.10.2004
- A1.6 Eligibility Assessment / Baseline Consent Form, version 3.3 (eligibility/baseline – missing therapy),22.10.2004
- A1.7 Full Trial Consent Form, version 3.1 (full trial – missing therapy),22.10.2004

Appendix 3: General Practitioner Letters

- Participant entry to trial, version 2,22.10.2004
- Participant completion of supplementary therapy, version 1, 22.10.2004
- Participant completion of trial, version 1, 22.10.2004
- Participant withdrawal from treatment, version 1, 22.10.2004
- Participant drop-out from trial, version 1, 22.10.2004

Appendix 4: Letters to the participant from the Research Nurse

- Participant initial letter from research nurse, version 1, 22.10.2004
- Participant follow-up appointments, version 1, 22.10.2004
- Participant letter for final follow-up visit, version 1, 22.10.2004
- Participant withdrawal from treatment, version 1, 22.10.2004
- Participant drop-out from trial, version 1, 22.10.2004

Appendix 5: Medical Screening Standard Operating Procedure

- Version1, 22.10.2004

Appendix 6: Case Report forms (all version 1, 22.10.2004, unless indicated)

- Actigraphy instructions
- Borg Scale
- Centers for Disease Control criteria for Chronic Fatigue Syndrome (CFS) (*previous version (Fukuda et al, 1994) MREC approved; no change made to symptoms, but more detailed update (Reeves et al, 2003) to be used*)
- Clinical Global Impression change scale (CGI) for participants (*previously MREC approved; formatting changes only*)
- CGI for therapists and doctors (*previously MREC approved; now filled in by both therapist and doctor*)
- Chalder Fatigue Questionnaire (*previously MREC approved; formatting changes only*)
- Co morbid medical conditions
- Concomitant medications
- Client Service Receipt Inventory (CSRI) (*previous version MREC approved*)
- Demographic information including self-help group and patient organisation membership

	<ul style="list-style-type: none"> • Eligibility criteria • Euroqol EQ5d (<i>previously MREC approved; formatting changes only</i>) • Exercise and Activity Scale • Expectation of therapeutic outcome • Fibromyalgia assessment • Hospital and Depression Scale (HADS) (<i>previously MREC approved; formatting changes only</i>) • Jenkins Sleep Scale • London criteria for ME • Oxford criteria for CFS (<i>previous use agreed by MREC; formatting changes only</i>) • Past medical history • Preferred treatment group • Therapy satisfaction scale (<i>previously MREC approved; formatting changes only</i>) • Self-efficacy scale • Standardised Clinical Interview for DSM (SCID) summary form (<i>previously MREC approved; formatting changes only</i>) • SF-36 physical function sub-scale (<i>previously MREC approved; formatting changes only</i>) • Self paced step test of fitness • Symptom Interpretation Questionnaire • Six minute walking test • SSMC monitoring interview • Work and Social Adjustment Scale • Adverse Event report form • Drop-out report form <p>This submission also included the following items for information only:</p> <ul style="list-style-type: none"> • Appendix 7: PACE policy on ancillary studies, version 1, 22.10.2004 • Appendix 8: Consort Diagram, version 1, 22.10.2004
24.11.2004	<p><u>Substantial Amendment 2.2, 24.11.2004</u></p> <ul style="list-style-type: none"> • Participant Information Sheet version 15, 22 November 2004 • Substantial Amendment Form 2.2
06.12.2004	<p><u>Substantial Amendment 3.1, 06.12.2004</u></p> <ul style="list-style-type: none"> • 'Adaptive Pacing Therapy (APT) Manual for Therapists', Version 2, 11.2004 • 'Adaptive Pacing Therapy (APT) Manual for Participants', Version 2, 11.2004 • 'Cognitive Behaviour Therapy (CBT) Manual for Therapists', Version 2, 11.2004 • 'Cognitive Behaviour Therapy (CBT) Manual for Participants', Version 2, 11.2004 • 'Graded Exercise Therapy (GET) Manual for Therapists', Version 2, 16.11.2004

	<ul style="list-style-type: none"> • 'Graded Exercise Therapy (GET) Manual for Participants', Version 1, 16.11.2004 • 'Standardise Specialist Medical Care (SSMC) Manual', Version 1, 02.12.2004 • Protocol version 3, 02.12.2004, which includes further minor amendments to the study design (detailed in 'tracked changes' format). The significant alterations to this document are listed in the Notice of Substantial Amendment Form.
05.01.2005	<u>Substantial Amendment 2.3, 05.01.2005</u> <ul style="list-style-type: none"> • Participant Information Sheet, Version 16, 5th January 2005 • Patient Clinic Leaflet, Version 9, 5th January 2005
02.02.2005	<u>Approval letter from MREC</u> <i>Approval of all items submitted to the committee since October 2004. (NB only the most recently submitted PIS and PCL are approved for use).</i> <ul style="list-style-type: none"> • Membership list
11.02.2005	<u>Minor / Administrative Amendment 1, 11.02.2005</u> <ul style="list-style-type: none"> • Affecting Protocol Version 3.1, 11th February 2005
25.02.2005	Anne McCullough (MREC administrator) confirmed that the Chairman of the committee agreed that the last submitted amendments were minor and the trial could begin.
05.08.2005	<u>Substantial Amendment 4.1, 05.08.2005</u> <ul style="list-style-type: none"> • Substantial Amendment form 4.1, 05.08.2005 • Proposed amendment to protocol section 8 (as an appendix to the above), 05.08.2005 • Consent form version 4.2 (pre-randomisation – missing therapist), 05.08.2005 • Initial consent form used in Edinburgh to cover the immediate situation of a therapist leaving version 4.1, 29.04.2005 • A tracked changes version of the Participant Information Sheet version 17, 05.08.2005 <u>Minor / Administrative Amendment 2, (therapy manuals), 05.08.2005</u> <ul style="list-style-type: none"> • Affecting Protocol Version 3.1, 11th February 2005 <u>Minor / Administrative Amendment 3, (protocol), 05.08.2005</u> <ul style="list-style-type: none"> • Affecting Protocol Version 3.1, 11th February 2005
30.08.2005	<u>Approval letter from MREC</u> <i>Approval letter of all items submitted to the committee for consideration under substantial amendment 4.1</i> <ul style="list-style-type: none"> • Membership list
02.09.2005	<u>Approval letter from MREC</u> <i>Approval of non-substantial items (duplication of items approved under previous letter)</i>
20.10.2005	<u>Minor / Administrative Amendment 4, (protocol), 26.09.2005</u> <ul style="list-style-type: none"> • Affecting Protocol Version 3.1, 11th February 2005 including an alteration to the Randomisation & Notification CRF, a new CRF for therapists and minor administrative changes to the protocol.

10.11.2005	<p>Approval letter from MREC <i>Approval letter of all items submitted to the committee for consideration under minor / administrative amendment 4</i></p>
10.01.2006	<p><u>Minor / Administrative Amendment 5. (protocol), 06.01.2006</u> <u>And protocol version 4 incorporating all amendments</u></p> <ul style="list-style-type: none"> • The protocol has been updated to include all items added via previously approved amendments. • Section 18, the Trial Committees of the protocol has been amended to reflect the fact that Clair Chilvers has now left the Trial Steering Committee. • Figure 11: 10.2.2 Table of research assessments by time point, has been amended to include the Therapist Rating of Homework Compliance case report form (version 1, 23.09.2005), approved under Administrative Amendment 4 (10.11.2005) • The Non-serious adverse events log has been added as item A6.35 in the appendix. This is the form on to which the research nurse/assistant records all events reported by the participant at each visit that are not serious. A6.36 has been re-titled to clarify that this form is to be used for serious events only. This form has been issued with a new version number accordingly (version 3, 05.01.2005). • Section 16.1 has been updated to list all submissions to MREC including those submitted since the last version of the protocol. • Under Substantial Amendment 4.1 (05 August 2005) the MREC approved the use of Participant Information Sheet (PIS) version 17. All consent forms in the protocol have been updated to refer to this revised PIS. This can be viewed in Appendices A1.3 – A1.7. • The PACE Trial Coordinating Centre fax number has been changed and page 16 has been amended to reflect this. • Section 7.1 of the protocol has been updated to present the revised target recruitment rate figures for the trial. These figures have been revised due to the trial opening for randomisation later than was originally anticipated. • The Actigraphy Diary (Appendix A6.1) has been modified slightly to alter 'Date completed' to 'Date issued'. This form has been issued with a new version number accordingly (version 2, 09.11.2005). • The SOPs for doctors have been expanded and amended. A5.1, one of these SOPs which was included in the original trial protocol, has been slightly amended to qualify the fact that examinations should be conducted by a qualified doctor. A new version number and date of release has been assigned to this document (version 3, 16.11.2005).
01.02.2006	<p><u>Substantial Amendment 5.1, 01.02.2006</u></p> <ul style="list-style-type: none"> • Substantial Amendment form 5.1, 01.02.2006 to alter eligibility for entry to the PACE trial

	<p><u>Minor / Administrative Amendment 6, (protocol), 06.01.2006</u></p> <ul style="list-style-type: none">• To make a minor correction to the APT manual <p><u>Minor / Administrative Amendment 7, (protocol), 06.01.2006</u></p> <ul style="list-style-type: none">• To make minor corrections to the trial protocol <p><u>And protocol version 5 incorporating all amendments</u></p>
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20.2 Ancillary studies

No ancillary studies currently have MREC approval. Any application for these must be approved by the TMG (see Appendix 8). There are currently a number of applications being discussed by the TMG and TSC before development for submission for funding and ethics approval.

21. References

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A1 Participant Information

A1.1 Participant Clinic Leaflet

Patient Clinic Leaflet

Notes for staff

**TEXT FOR PAGE SEVEN IF YOU HAVE ADDITIONAL TREATMENTS
(paragraph entitled 'Which treatments are available in this clinic?')**

We offer specialist medical care, as described above. We may also offer you these therapies as well as specialist medical care:

occupational therapy; cognitive behaviour therapy; physiotherapy; and other psychological therapies. <<< please add other available or subtract unavailable therapies to match what is on offer at your clinic >>> These options may include pacing and graded exercise therapy.

You also have the option in this clinic of putting yourself forward for the PACE Study, which is described below.

**TEXT FOR PAGE SEVEN IF YOU HAVE NO ADDITIONAL TREATMENTS
(paragraph entitled 'Which treatments are available in this clinic?')**

We offer specialist medical care, as described above. None of the other treatments described above are currently offered by this clinic, but we may recommend that your general practitioner refers you to another local service for one of these treatments.

You also have the option in this clinic of putting yourself forward for the PACE Study, which is described below.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

BEFORE PRINTING

Open up this PDF file

Type in therapies offered by your clinic
in the space provided on page six

WHEN PRINTING

print on HEADED PAPER from your CLINIC

Print page one on main letterhead
Print all other pages on follow-on letterhead

please do not use UNHEADED PAPER

[REDACTED]

Patient Clinic Leaflet

***Basic information on your illness
and the treatments we can offer you for***

**chronic fatigue syndrome
(CFS)**

also known as

**myalgic encephalomyelitis
or myalgic encephalopathy
(ME)**

Chronic fatigue syndrome (CFS) is an illness with a recognisable pattern of symptoms. The main symptom is fatigue – which you feel as tiredness, exhaustion or lack of energy. It is common to have muscle and joint pain, memory and concentration problems, disturbed sleep, headaches, and sore throats, and sometimes sufferers have tender lymph glands. Symptoms often get worse if you exert yourself.

This illness is also known as post-viral fatigue syndrome, myalgic encephalomyelitis (ME), and myalgic encephalopathy (ME).

Medical authorities are not certain that CFS is exactly the same illness as ME, but until scientific evidence shows they are different they have decided to treat CFS and ME as if they are one illness. We do the same at this clinic, and in this leaflet we will be calling this illness CFS/ME for short.

People with CFS/ME are sometimes afraid that people will not believe that their symptoms are real. In this clinic we believe CFS/ME is a real illness.

How is CFS/ME diagnosed?

There are several descriptions of the typical symptoms. Doctors call them case definitions, and all these definitions agree that people with CFS/ME:

- have the main symptom of fatigue that is often made worse by exertion
- often have other symptoms – including headaches, sleep disturbance, sore throat, muscle or joint aches and pain, and tender lymph glands
- have usually had these symptoms for more than six months
- cannot lead a normal life because of these symptoms.

When doctors recognise this pattern of symptoms, and when they can rule out all other causes, then they diagnose CFS/ME.

What causes CFS/ME?

We don't know what causes CFS/ME, although there are various theories – well-informed scientific ideas that have yet to be proved or disproved.

However, we do know that most illnesses have a number of causes that are often interlinked in complicated ways – and this is probably true for CFS/ME. This complexity means doctors prefer not to talk of causes in the everyday sense. They use the more accurate term 'factors', and they divide up factors into three types.

- Factors that make someone more likely to get the illness. An example might be their sex, as more women than men develop CFS/ME. Doctors call this a **PREDISPOSITION**
- Factors that bring on the illness in the first place. An example might be an infection. Doctors call this a **TRIGGER**
- Factors that stop people recovering from the illness. Sleep disturbance might be an example. Doctors call this a **MAINTAINING** factor.

What is a factor for one person may not be a factor for somebody else. For instance, sleep disturbance may be a maintaining factor in one person and not in another person.

What are these theories you mentioned?

These are the main theories about factors that trigger or maintain CFS/ME.

Infection

People often say their CFS/ME started after a flu-like illness. There is evidence that CFS/ME can be triggered by certain infections, most of them viral. There is no strong evidence that these infections are maintaining factors in CFS/ME.

The immune system

Minor abnormalities of the immune system are commonly found in people with CFS/ME. These abnormalities may be a factor in CFS/ME, or they may be an effect of having the illness. We don't know for sure.

Stress hormones and the hypothalamic-pituitary-adrenal (HPA) axis

The hypothalamus and the pituitary gland are organs at the lowest part of your brain that work with your adrenal glands as an 'axis' to control your reaction to stress. For instance, they control how much of the stress hormone cortisol is produced by your adrenal glands. Some research suggests that this axis works less well in people with CFS/ME. However, we don't know whether problems with the HPA axis predispose you to developing CFS/ME, maintain CFS/ME or are just an effect of the illness.

Stress

Stress may predispose you to all sorts of illness, and stress plus an acute infection can probably trigger CFS/ME. Once you have CFS/ME, this in itself will add to your stress, because you have to cope with disability, and other people may not understand or believe that you really are ill. Modern life doesn't give people much time to recover from illness, either, which may add to your stress.

Sleep disturbance

Many people with CFS/ME have problems sleeping. They may find it hard to fall asleep or stay asleep, and they can wake up unrefreshed. Poor sleep may delay your recovery from CFS/ME.

Doing too much and doing too little

People with CFS/ME often do too much and then feel ill – which forces them to do less. Alternating between too much and too little activity is called a 'boom-and-bust' pattern. This pattern may delay your recovery.

Loss of physical fitness and strength

After a period of being less physically active than usual, your body will become less fit. This can make it more difficult for you to do things you could once do easily. This loss of fitness may delay your recovery.

Food intolerance

Some people with CFS/ME say certain foods make them worse. But there is no good evidence that food intolerance triggers or maintains CFS/ME.

Other possible factors

Many other things are said to be linked to CFS/ME, and some get a lot of publicity – even though nobody has *proved* they are factors in CFS/ME. These include magnesium deficiency, overgrowth of the yeast *Candida* in the bowel, and low blood sugar (hypoglycaemia).

Is it true that CFS/ME leads to other illnesses?

Other illnesses often go together with CFS/ME – but we don't know that people get them *because* they've got CFS/ME. The main three such illnesses are described below.

Fibromyalgia

Fibromyalgia is like CFS/ME, but with more muscular pain and tenderness.

Irritable bowel syndrome

If you have bloating, cramps, and constipation alternating with diarrhoea you may be diagnosed as having irritable bowel syndrome (IBS).

Anxiety and depression

People with chronic illnesses such as CFS/ME often become understandably anxious or depressed.

How do you make or confirm a diagnosis?

We ask about your symptoms, how your illness started, and how it developed. We may give you a physical examination. We automatically do a set of standard blood and urine tests to make sure nothing else could be causing your symptoms – unless another doctor has done these tests recently. We also do specialist tests if they are necessary.

How soon will I get better?

Most people with CFS/ME improve over time with treatment, but we can't predict how long this will take.

What treatments are there for CFS/ME?

There is no agreed treatment for CFS/ME, and no drug has been found that is generally effective. There are various treatments that may help people to cope better, and they may help some people to recover. These treatments are usually given as *well* as specialist medical care. However, advice and support from a specialist CFS/ME doctor on its own may be just as good. Here are brief descriptions of the main treatments that are used in the NHS to treat CFS/ME.

Specialist Medical Care

Specialist medical care is the most usual treatment for CFS/ME, and it helps many people improve. You get a confirmed diagnosis, an explanation of why you are ill, and general advice about managing your illness. Your specialist might either prescribe medicine to help you manage troublesome symptoms such as insomnia and pain or advise your GP about what medicine is appropriate.

Here is some of the advice you may get as part of specialist medical care.

- *Avoid extremes of activity.* Many people with CFS/ME get into a pattern of being very active and then very inactive. It is better to give yourself a pattern of activity that you can keep going. This may be a lower level of activity you are used to.
- *Set a daily level of activity.* It will help to set a simple level of activity that you do every day. Stretching exercises, for example, will minimise the weakening effects that creep up if you don't use your muscles for a time.
- *Make only gradual changes to your activity level.* If you feel you can increase your level

of activity, and not everyone does, make changes carefully and gradually. A sudden increase in activity may make your symptoms worse.

- *Try to reduce stress in your life.* When we are ill, stresses such as excessive work demands don't help us. If you can reduce these stresses, it will help you recover.

Pacing – Adaptive Pacing Therapy

This approach is about pacing yourself – matching your activity level very carefully to the amount of energy you have. Usually, an occupational therapist works with you, helping you monitor your activity and symptoms so that together you work out just how much activity you can manage without making your condition worse. The aim of this therapy is to improve your quality of life and give you the chance of a natural recovery.

Cognitive Behaviour Therapy

Cognitive behaviour therapy is about examining how your thoughts, behaviour and CFS/ME symptoms relate to one another. Usually you see a cognitive behaviour therapist, who helps you to understand your illness and change the way you manage it. In between sessions you would try out new ways of managing your CFS/ME. The aim of this therapy is to help you manage your symptoms more effectively and do more.

Graded Exercise Therapy

Graded exercise therapy is about gradually increasing your physical activity. Usually, you see a physiotherapist who helps you work out a basic activity routine, then together you plan to gradually increase the amount of physical activity or exercise you do. The gradual increase takes into account your symptoms, fitness, and current activity levels. The aim of this therapy is to help you do more and feel better.

Self-help guides

There are self-help guide books available that you might choose to read.

Complementary and alternative therapies

Some people take complementary or alternative therapies that are not available from the NHS – and some say they benefit from them. Yoga and aromatherapy are two examples. However, we cannot recommend these therapies, because there is no scientific evidence that they are effective.

Which treatments are available in this clinic?

The PACE trial

This clinic is helping with a study of different treatments for CFS/ME called the PACE trial. The formal title of this trial is: *Pacing, graded Activity and Cognitive behaviour therapy – a randomised Evaluation*.

The PACE trial will tell us about the benefits and possible drawbacks of various treatments for CFS/ME. It could also tell us why successful treatments work and whether different people need different treatments. It may lead to a more effective treatment for CFS/ME.

Patients who join the PACE trial will get one of the following treatments.

- Specialist medical care
- Specialist medical care *plus* adaptive pacing therapy
- Specialist medical care *plus* cognitive behaviour therapy
- Specialist medical care *plus* graded exercise therapy

If you would like to know more, please ask your clinic doctor for a leaflet.

What if I have more questions?

If you have questions about this leaflet or your attendance at this clinic, we will be happy to answer them when we see you next.

=====

A1.2 Participant Information Sheet

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

BEFORE PRINTING

Open up this PDF file

Type in contact details on page one for
Research Nurse and Centre Leader

Type in contact details on page nine for
Research Nurse, Centre Leader, Independent Doctor

WHEN PRINTING

print on HEADED PAPER from the PACE TRIAL

Print page one on main letterhead
Print all other pages on follow-on letterhead

UNHEADED PAPER IS NEVER ACCEPTABLE

[REDACTED]

invitation to join

the PACE trial

*a randomised controlled trial
of treatments for*

**chronic fatigue syndrome
(CFS)**

also known as

**myalgic encephalomyelitis
or myalgic encephalopathy
(ME)**

We are inviting you to help us with our research. But before you decide whether or not you want to join our study, you will want to know what we are doing, why we are doing it – and what we would be asking you to do.

This leaflet will answer most of your questions. Please take it away and read it carefully. Talk over your decision with other people if you want to. And if something in this leaflet isn't clear, or if you want to know more, you can ask us.

Take as much time as you need to decide whether or not you want to help us. If you don't want to join our study, this will not affect your NHS care.

Thank you for taking time to read about our work.

Research Nurse

<Insert name and address>

Centre Leader

<Insert name and address>

Telephone:

Fax:

Email:

Telephone:

Fax:

Why are you asking me?

We have invited you to join our study because you have chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis or myalgic encephalopathy (ME).

In the rest of this leaflet we will be calling this condition CFS/ME for short.

What is your study for?

There are different treatments for CFS/ME, and we want to know which are the most helpful. To find this out, we are asking people like you who suffer from CFS/ME to join our study – which is a randomised controlled trial.

We hope our study will tell us about the benefits and possible drawbacks of each of these treatments. We also hope to learn why successful treatments work and whether different people need different treatments. Finally, the study will compare how much these treatments cost, to see if they are a good way of spending NHS money.

Whichever treatments are shown to be the best, we expect they will become more widely available across the country. This study may lead to a more effective treatment.

What are these different treatments you want to study?

Specialist medical care and three extra therapies are being tested in our study. Everyone joining our study will get specialist medical care from a hospital specialist. You might also get an extra therapy *as well as specialist medical care*. The specialist medical care and the three extra therapies being tested in our study are all described below.

Specialist Medical Care

Specialist medical care is the most usual treatment for CFS/ME, and it helps many people improve. In our study, you would get a confirmed diagnosis, an explanation of why you are ill, and general advice about managing your illness. Your specialist would either prescribe medicine to help you manage troublesome symptoms such as insomnia and pain or they would tell your GP what medicine is appropriate. Specialist medical care will be given by an appropriately trained doctor in the hospital clinic.

Adaptive Pacing Therapy (APT)

APT is about pacing yourself – matching your activity level very carefully to the amount of energy you have. In our study, an appropriately trained therapist would work with you regularly, helping you monitor your activity and symptoms so that together you work out just how much activity you can manage without making your condition worse. The aim of this therapy is to improve your quality of life and give you the best chance of a natural recovery. APT is usually given by an occupational therapist but may be given by an appropriately trained therapist of another appropriate healthcare discipline. You will be informed of the qualification and discipline of your therapist if you are randomised to receive APT.

Cognitive Behaviour Therapy (CBT)

CBT is about examining how your thoughts, behaviour and CFS/ME symptoms relate to

one another. With this treatment you would regularly see a CBT therapist, who would help you better understand your illness and change the way you cope with it. In CBT you would see a therapist, and in between sessions you would try out new ways of coping with your CFS/ME. The aim of this therapy is to help you find out which ways of coping work best for you. CBT is given by an appropriately trained cognitive behavioural therapist, such as a nurse specialist, psychologist or occupational therapist. You will be informed of the qualification and discipline of your therapist if you are randomised to receive GET.

Graded Exercise Therapy (GET)

GET is about gradually increasing your physical activity to make you fitter and get your body used to exercise again. In our study you would regularly see an appropriately trained therapist. They would help you work out a basic activity routine then gradually increase the amount of exercise you do. The gradual increase would take into account your symptoms, fitness, and your normal activity levels. This therapy aims to help you do more, without making you worse. GET is usually given by a physiotherapist but may be given by an appropriately trained therapist of another appropriate healthcare discipline. You will be informed of the qualification and discipline of your therapist if you are randomised to receive GET.

Do I have to join your study?

No. You decide whether or not you want to help us. We ask you to go away and think about what you want to do. If you decide to help us, we will ask you to sign two consent forms and give you copies. Even if you sign the forms, you can still leave the trial at any time – and you won't even have to give us a reason if you don't want to.

If you decide not to join our study, or if you leave our study after you have joined, this will not affect the usual NHS care you get for your condition. Your clinic can tell you what the usual NHS care would be for you, as this does vary between clinics.

What will happen if I join your study?

If you agree to join our study, this is what will happen.

1. We ask you questions and measure your fitness

You will meet your local study nurse, who will explain our study to you in more detail and answer any questions you have. Then we ask you to sign the first consent form, to let us find out if you are eligible for our study. This involves you filling out some questionnaires about your symptoms and how CFS/ME affects your ability to do things. Your nurse will also ask you about any emotional or psychological symptoms you might have.

A six-minute walking test will tell us how physically able you are. Your nurse will give you a movement monitor – it looks a bit like a wristwatch – and ask you to wear it on your ankle for one week. This will tell us how physically active you are. You will also get some questionnaires to take away and complete in your own time.

2. You find out whether you are suited to our study

A week later, you will bring back the movement monitor and the questionnaires. Your

nurse will ask you more questions, including how CFS/ME has affected you financially, and ask you to do a two-minute step test to tell us more about how fit you are. If we decide you should not be in our study, your nurse will refer you back to your clinic doctor. Otherwise, your nurse will ask if you still want to help us. This is when we ask you to sign the second consent form – which says you agree to take one of the treatments in our study. You don't have to sign, and if you do you will still be free to leave our study at any time.

3. A computer randomly allocates a treatment for you

If you decide you still want to help us, you will be randomly allocated a treatment. We use a computer to do this, because it is important that your treatment is chosen *by chance*. This is the computer equivalent of tossing a coin to decide which treatment you will get. We have to decide at random because this is the only way to compare the treatments fairly. This means you won't know what treatment you will get until *after* your fitness is assessed and *after* you have decided to join our study.

You will get one of these four treatments:

- Specialist medical care
- Specialist medical care *plus* APT
- Specialist medical care *plus* CBT
- Specialist medical care *plus* GET

4. Everyone sees their research nurse three more times

You will see your research nurse three more times so we can see how you are doing. These meetings will be 12 weeks, 24 weeks and a year after you find out which treatment you will get. We will post you our questionnaires, so you can fill them in at home, at your own pace, and bring them with you. Filling them in will take about an hour. In the meetings, your nurse will ask you some questions and measure your fitness with the step and walking tests. You won't need to wear the movement monitor again.

5. If you get APT or CBT or GET you meet your therapist as well

If you get a treatment that includes APT or CBT or GET, then you will meet your therapist up to 15 times. The meetings will happen in the five months after you find out which treatment you are getting. At first they will be every week, then every fortnight. The first meeting will last an hour and a half so your therapist can explain the treatment to you, answer your queries, listen to any concerns you may have, and plan how the therapy will work for you. The rest of the sessions will last 50 minutes each. If you can't get to all of your sessions, some of them could be done over the phone.

You will still see the clinic doctor and get the normal care they would give, including any prescribed medicines that you need.

We record the interview with the nurse and the treatment sessions

We will audio- or video-record the interview when the nurse asks about your emotional and psychological symptoms. We do this to supervise the nurse and to make sure the interview is done properly and the right interpretations are made.

We will also audio- or video-record your treatment sessions. We do this to make sure your sessions follow the manual we have written for our study, because that is the only fair way to compare these treatments. Only the research team will listen to these recordings, which will be kept safe in computerised form at the hospital for 20 years. After that time, all files of the recordings will be permanently deleted and all CDs of recordings destroyed.

Will I have to do anything after the study?

We will ask if you mind us contacting you once a year after you leave our study, so we can find out how you are getting on. We may need follow-up information for up to five years after you leave our study.

If you join our study, we will ask if we can use your (English) NHS number or your (Scottish) CHI to register you with the (English) Office for National Statistics or the (Scottish) Information and Statistics Division. This will help us contact you, perhaps through your GP, if you move house after you leave our study.

How many appointments would that be altogether?

Here's a summary of all the things you would be asked to do.

Attend five research interviews over 12 months

- At the first interview you fill in some questionnaires, talk to your nurse, do the walking test, and take away the movement monitor and questionnaires
- At the second interview you bring back the questionnaires and movement monitor, talk to your nurse, do the step test, and decide whether to join
- For the other three interviews, we will post you questionnaires so you can fill them in at home and bring them with you. You will talk to your nurse, and there will be a two-minute step test and a six-minute walking test

Attend at least three appointments with your clinic doctor

- You may get more if you and your clinic doctor feel they are needed

Attend 15 therapy sessions IF you are getting APT or CBT or GET

- The first 14 of these therapy sessions will be in the first five months
- The final, 15th, therapy session will be after a three-month gap

Who will pay for my extra travel to these appointments?

We will pay for your travel to the hospital for the research interviews. We can also contribute to your travel costs for trips you make to see your clinic doctor or therapist.

Will I still be free to take other treatments?

If you already get other treatment, you may not be able to join our study.

Before you join our study, we will ask you not to start any other treatments for CFS/ME for the 12 months you are in our study – unless your clinic doctor or your GP advises you to take them. If you still decide to start another treatment we will understand, but we would like you to tell your research nurse so we know what is happening and can check to see whether your other treatment affects our study results.

Will my treatment suddenly stop at the end of the trial?

When you leave our study, you will see your clinic doctor to discuss whether you need more treatment. If you do, your clinic doctor will discuss which of the three extra therapies would suit you best. The study therapists give you this treatment. Your research nurse can give you more details.

How do I qualify for your study?

You must be diagnosed by us as having CFS/ME. Fatigue or lack of energy must be your main problem, and it must be sufficiently severe and disabling. You must be at least 18 years old and be able to read and understand English.

What could exclude me from your study?

You could have CFS/ME but still not qualify for our study. For instance, if:

- another condition, apart from CFS/ME, might also be causing your fatigue
- you have tried one of the treatments in another fatigue clinic
- you have another health problem that would not be helped in the trial
- you would not be able to get to the hospital regularly for your treatment.

Other reasons may make it sensible to exclude you from our study. For instance, pregnant women and women who are trying to get pregnant should not join our study. And we will be asking women who could get pregnant to use an effective contraceptive *and* to tell their GP and their clinic doctor if they do get pregnant. Our study would not harm a pregnant woman or her baby, but we would want to adjust their treatment and check whether they are taking any new medication.

If you think there may be a reason why you should not join our study, it is very important that you tell us. We will let you know if it is safe for you to join our study.

Will there be any disadvantages or risks if I join?

If you join the study, then over one year you will need to go to the hospital five more times than you would have otherwise. And if you are given an extra therapy you will need to go to 15 therapy sessions over the year.

It is possible that a therapy we are studying may not be available at your clinic – for instance, if a therapist is sick for a long time. If this happens before you join us, we will tell you. And if this happens when you are already in our study, we will do our best to find you an alternative therapist.

Are there any benefits to joining your study?

We hope the treatment you get in our study will help you, even though this can't be guaranteed. And at the end of our study, you will get the chance to opt for one of the other treatments if you and your clinic doctor agree it could help you.

Our study should also lead to better treatment for people with CFS/ME, so you will be helping others who get the same condition you have now.

What treatments can I get if I *don't* join your study?

All the treatments we are testing are available *outside* our study in NHS centres in the UK. So you could get specialist medical care, pacing with an occupational therapist, cognitive behaviour therapy, or graded exercise therapy. However, your local NHS clinic may not offer all these therapies. There are also other, more general, treatments available for CFS/ME with clinical psychologists, physiotherapists and occupational therapists.

Could joining your study make my condition worse?

Patient surveys say APT helps many patients and does not cause harm. Research studies say CBT and GET appear to be safe when applied properly by trained staff, as will happen in our study. Some patient surveys suggest CBT and GET can make symptoms worse – but experts believe this happens when the therapy is not used properly or when there isn't good professional supervision.

Whatever treatment you get in our study, we will carefully monitor your progress. If you feel your condition is made worse by being in our study, we will give you a detailed reassessment and offer whatever help is appropriate.

The two-minute fitness test was designed for people of below average fitness. There is no evidence that it makes CFS/ME worse, but some people find that their legs ache for a day or so.

What about compensation if something goes wrong?

We will be monitoring your progress closely, so we don't expect to see any harmful effects caused by our study. However, you need to know that there are no special compensation arrangements if you are harmed because you have taken part. If you are harmed by someone's negligence you may be able to take legal action – but you may have to pay for it. The usual NHS complaints system will be available if you have any concerns about the way we have approached or treated you.

What if new information turns up while I'm in your study?

If we find any new information about the treatments we are studying, your research nurse or clinic doctor will tell you about it and ask if you want to stay in the study. If you want to leave our study, your clinic doctor will make sure your care continues. If you decide to stay in our study, we might ask you to sign an updated consent form that takes the new information into account. If your clinic doctor thinks the new information means that you should leave our study, they will tell you why and then make sure your care continues outside our study.

Will you keep my details confidential?

Yes. All your details and all recordings will be kept strictly confidential and held in a locked filing cabinet or on a secure computer. People on our research team will only see your records if they need to for the research.

Your GP and any other doctors you are consulting will be told you are joining our study.

And occasionally, other researchers will need to see your notes so they can audit the quality of our work. An audit might be run by one of the universities helping with our study or hospital regulatory authorities, or by one of the organisations funding our study.

The data and recordings we collect will be securely stored for 20 years after the end of the trial, for your protection and to follow good clinical practice (GCP). The same applies to other records gathered for our study, including your medical notes and the database holding the collected data for this trial.

Your name, address, and telephone number will be on only one database. This will be held securely at St Bartholomew's Hospital, in London, and it will be used only to monitor recruitment. You will not be named in any published results from our study.

What will happen to the results of your study?

Our results will be presented at national and international conferences and published in medical journals. Our study will run for five years, even though you will only be part of it for one year. This means you can expect to see the results around 2009. The results won't say who took part or give any details that lead to people being recognised or identified.

Who is paying for your study?

Our study is funded by the Medical Research Council (MRC), the Scottish Chief Scientist's Office (CSO), the Department of Health (DoH) and the Department of Work and Pensions (DWP). Nobody gets paid a fee for signing you up with our study.

Has anybody reviewed your study?

The West Midland Multicentre Research Ethics Committee has given national approval for our study. Our study has also been reviewed by the Local Research Ethics Committee (LREC) for your local NHS Trust, and the local NHS Research and Development office.

Is this study local or across the country?

This is a national study. Here is a full list of the participating NHS centres.

- Astley Ainsley Hospital, Edinburgh, working with the Regional Infectious Diseases Unit, Western General Hospital, Edinburgh, both of NHS Lothian
- Bart's and the London NHS Trust, East London
- East London and the City Mental Health NHS Trust
- Oxfordshire Mental Healthcare NHS Trust working with the Oxford Radcliffe Hospitals Trust
- The Royal Free Hampstead NHS Trust
- Guy's, King's & St Thomas' School of Medicine

Where can I get more information?

You can contact the research nurse or the centre leader listed below for more information

about our study. We have also listed an independent doctor who understands CFS/ME but has no connection with our study, in case you decide you need more independent advice.

Research Nurse

Centre Leader

<Insert name and address>

<Insert name and address>

Telephone:

Telephone: 020 7601 8108

Fax:

Fax: 020 7601 7097

Email:

Independent Doctor

<Insert name and address>

Telephone:

Fax:

You can also read about joining research trials like ours at:

Consumers for Ethics in Research www.ceres.org.uk

National Electronic Library for Health www.nelh.nhs.uk/clinicaltrials

Thank you for your interest in our work

Version 17, 05 August 2005

A1.3 Eligibility Assessment/Baseline Consent Form

(Form to be on headed paper)

(Form to be on headed paper)

Version 3.2 (eligibility/baseline), 05.08.2005

Centre Number:

Study Number:

Patient Identification Number for this trial:

CONSENT FORM 1 for eligibility/baseline assessment

Title of Project:

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

Full title:

A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome / myalgic encephalomyelitis/encephalopathy

Name of Researcher:.....

**Please
initial box**

1. I confirm that I have read and understand the information sheet dated 05 August 2005 (version 17), for the above study and have had the opportunity to ask questions. []
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. []
3. I understand that any of my medical notes may be looked at by responsible individuals from either the trial or regulatory authorities where it is relevant to my taking part in research. []
4. I give permission for these individuals to have access to my records. []
5. I understand that the standardised psychiatric screening interview and that any therapy sessions that I take part in will be video/audio-recorded and may be used for supervision, quality control, and research purposes, and that the recordings will be securely stored. []
6. I understand that my GP and other relevant health care professionals involved in my care will be contacted and informed of my participation in the trial. I agree for

- this to happen and for trial information to be recorded in my medical notes maintained by these professionals. []
7. I understand that in accordance with good practice guidelines, all of my records, notes and audio-recordings will be securely stored for twenty years after the end of this study. After this all recordings will be destroyed or permanently deleted. []
8. I understand that my eligibility for the trial must be confirmed before I can take part in the full trial. If I am found to be ineligible for the trial, I understand that my clinic doctor and GP will be informed in order to provide further care. []
9. If found to be ineligible for the full trial, I agree for the information gathered can be used and published for research purposes with my name or address being kept confidential. []
10. I agree to attend for the two baseline assessment interviews. []
11. If I have moved or lost contact with the clinic and vice versa, I agree that my GP or a relative may be contacted to provide contact details. []
12. I give permission for my NHS number to be recorded to allow my GP to be found through the Office for National Statistics (England) or for my Chi number to be collected for the Information and Statistics Division (Scotland) to allow follow-up information to be obtained for up to five years after the end of the trial, and for the researchers to have access to my paper and electronic records for this purpose. []
13. I agree to take part in the above study. []
14. I understand that information collected about me for the trial, including my personal details, a copy of this consent form and all of the questionnaires I complete for the trial, will be held securely by the local trial staff and at the PACE trial centre at Queen Mary, University of London. I give permission for this to happen. []

_____ Name of Patient	_____ Date	_____ Signature
_____ Name of Person taking consent (if different from researcher)	_____ Date	_____ Signature
_____ Researcher	_____ Date	_____ Signature

Appendix 1: Participant Information

1 for patient; 1 for research nurse in the trial specific source notes; 1 copy to GP, 1 copy to be kept with hospital notes, 1 copy to go to the PACE trial centre and original stored in Trial Centre Master File

A1.4 Full Trial Consent Form

(Form to be on headed paper)

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

Version 3.3 (full trial), 05.08.2005

Centre Number:

Study Number:

Patient Identification Number for this trial:

Title of Project:

Full title:

A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome / myalgic encephalomyelitis/encephalopathy

Name of Researcher:.....

**Please
initial box**

1. I confirm that I have read and understand the information sheet dated 05 August 2005 (version 17), for the above study and have had the opportunity to ask questions. []
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. []
3. I understand that any of my medical notes may be looked at by responsible individuals from either the trial or regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. []
4. I understand that my GP and other relevant health care professionals involved in my care will be contacted and informed of my participation in the trial and given follow-up information of my progress. I agree for this to happen and for trial information to be recorded in my medical notes maintained by these professionals. []
5. I understand that any therapy sessions that I take part in will be video/audio-recorded and may be used for supervision, quality control, and research purposes, and that the recordings will be securely stored. []
6. I understand that in accordance with good practice guidelines, all of my records, notes and video/audio-recordings will be securely stored for twenty years after the

end of this study. After this all recordings will be destroyed or permanently deleted.
[]

7. I agree to researchers contacting me after the trial is over for further follow-up, so long as further follow up has received research ethics committee approval.[]

8. I agree to attend for all the treatment and assessment interviews for the duration of the study. []

9. I agree not to be referred for a different therapy, or to a non-PACE therapist for the duration of my involvement in the study unless arranged by a treating doctor. []

10.If I have moved or lost contact with the clinic and vice versa, I agree that my GP or a relative may be contacted to provide contact details. []

11.I give permission for my NHS number to be recorded to allow my GP to be found through the Office for National Statistics (England) or for my Chi number to be collected for the Information and Statistics Division (Scotland) to allow follow-up information to be obtained for up to five years after the end of the trial, and for the researchers to have access to my paper and electronic records for this purpose. []

12.I agree to take part in the above study, and understand this may involve 15 attendances for a therapy, 3 follow-up research assessment visits and at least 3 attendances with the clinic doctor over the year of the study. []

13.I understand that information collected about me for the trial, including my personal details, a copy of this consent form and all of the questionnaires I complete for the trial, will be held securely by the local trial staff and at the PACE trial centre at Queen Mary, University of London. I give permission for this to happen. []

_____ Name of Patient	_____ Date	_____ Signature
_____ Name of Person taking consent (if different from researcher)	_____ Date	_____ Signature
_____ Researcher	_____ Date	_____ Signature

1 for patient; 1 for research nurse in the trial specific source notes; 1 copy to GP, 1 copy to be kept with hospital notes, 1 copy to go to the PACE trial centre and original stored in Trial Centre Master File

A1.5 Eligibility Assessment/Baseline Consent Form with missing therapist and no cover

Only for use when one therapist is unavailable at a centre for an extended period

(Form to be on headed paper)

Version 3.4 (eligibility/baseline – missing therapy), 05.08.2005

Centre Number:

Study Number:

Patient Identification Number for this trial:

CONSENT FORM 1 for eligibility/baseline assessment

Title of Project:

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

Full title:

A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome / myalgic encephalomyelitis/encephalopathy

Name of Researcher:.....

**Please
initial box**

1. I confirm that I have read and understand the information sheet dated 05 August 2005 (version 17) for the above study and have had the opportunity to ask questions. []
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. []
3. I understand that any of my medical notes may be looked at by responsible individuals from either the trial or regulatory authorities where it is relevant to my taking part in research. []
4. I give permission for these individuals to have access to my records. []
5. I understand that the standardised psychiatric screening interview and that any therapy sessions that I take part in will be video/audio-recorded and may be used for supervision, quality control, and research purposes, and that the recordings will be securely stored. []

6. I understand that my GP and other relevant health care professionals involved in my care will be contacted and informed of my participation in the trial. I agree for this to happen and for trial information to be recorded in my medical notes maintained by these professionals. []
7. I understand that in accordance with good practice guidelines, all of my records, notes and video/audio-recordings will be securely stored for twenty years after the end of this study. After this all recordings will be destroyed or permanently deleted. []
8. I understand that my eligibility for the trial must be confirmed before I can take part in the full trial. If I am found to be ineligible for the trial, I understand that my clinic doctor and GP will be informed in order to provide further care. []
9. If found to be ineligible for the full trial, I agree for the information gathered can be used and published for research purposes with my name or address being kept confidential. []
10. I agree to attend for the two baseline assessment interviews. []
11. If I have moved or lost contact with the clinic and vice versa, I agree that my GP or a relative may be contacted to provide contact details. []
12. I give permission for my NHS number to be recorded to allow my GP to be found through the Office for National Statistics (England) or for my Chi number to be collected for the Information and Statistics Division (Scotland) to allow follow-up information to be obtained for up to five years after the end of the trial, and for the researchers to have access to my paper and electronic records for this purpose. []
13. I agree to take part in the above study. []
14. I understand that information collected about me for the trial, including my personal details, a copy of this consent form and all of the questionnaires I complete for the trial, will be held securely by the local trial staff and at the PACE trial centre at Queen Mary, University of London. I give permission for this to happen. []
15. I understand that the graded exercise/adaptive pacing /cognitive behaviour therapy *[delete as applicable]* is not available at this time and the randomisation will not include this therapy []

Name of Patient

Date

Signature

Name of Person taking consent (if different from researcher)	Date	Signature
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_____ Researcher	_____ Date	_____ Signature
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1 for patient; 1 for research nurse in the trial specific source notes; 1 copy to GP, 1 copy to be kept with hospital notes, 1 copy to go to the PACE trial centre and original stored in Trial Centre Master File

A1.6 Full Trial Consent Form with Missing Therapist and No Cover

Only for use when one therapist is unavailable at a centre for an extended period

(Form to be on headed paper)

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

Version 3.5 (full trial – missing therapy), 05.08.2005

Centre Number:

Study Number:

Patient Identification Number for this trial:

Title of Project:

Full title:

A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome / myalgic encephalomyelitis/encephalopathy

Name of Researcher:.....

**Please
initial box**

1. I confirm that I have read and understand the information sheet dated 05 August 2005 (version 17), for the above study and have had the opportunity to ask questions. []
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. []
3. I understand that any of my medical notes may be looked at by responsible individuals from either the trial or regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. []
4. I understand that my GP and other relevant health care professionals involved in my care will be contacted and informed of my participation in the trial and given follow-up information of my progress. I agree for this to happen and for trial information to be recorded in my medical notes maintained by these professionals. []

5. I understand that any therapy sessions that I take part in will be video/audio-recorded and may be used for supervision, quality control, and research purposes, and that the recordings will be securely stored. []
6. I understand that in accordance with good practice guidelines, all of my records, notes and video/audio-recordings will be securely stored for twenty years after the end of this study. After this all recordings will be destroyed or permanently deleted. []
7. I agree to researchers contacting me after the trial is over for further follow-up, so long as further follow up has received research ethics committee approval.[]
8. I agree to attend for all the treatment and assessment interviews for the duration of the study. []
9. I agree not to be referred for a different therapy, or to a non-PACE therapist for the duration of my involvement in the study unless arranged by a treating doctor. []
- 10.If I have moved or lost contact with the clinic and vice versa, I agree that my GP or a relative may be contacted to provide contact details. []
- 11.I give permission for my NHS number to be recorded to allow my GP to be found through the Office for National Statistics (England) or for my Chi number to be collected for the Information and Statistics Division (Scotland) to allow follow-up information to be obtained for up to five years after the end of the trial, and for the researchers to have access to my paper and electronic records for this purpose. []
- 12.I agree to take part in the above study, and understand this may involve 15 attendances for a therapy, 3 follow-up research assessment visits and at least 3 attendances with the clinic doctor over the year of the study. []
- 13.I understand that information collected about me for the trial, including my personal details, a copy of this consent form and all of the questionnaires I complete for the trial, will be held securely by the local trial staff and at the PACE trial centre at Queen Mary, University of London. I give permission for this to happen. []
- 14.I understand that the graded exercise/adaptive pacing /cognitive behaviour therapy *[delete as applicable]* is not available at this time and the randomisation will not include this therapy []

Name of Patient

Date

Signature

Name of Person taking consent (if different from researcher)	Date	Signature
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_____ Researcher	_____ Date	_____ Signature
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1 for patient; 1 for research nurse in the trial specific source notes; 1 copy to GP, 1 copy to be kept with hospital notes, 1 copy to go to the PACE trial centre and original stored in Trial Centre Master File

A1.7 Full Trial Consent Form with Alternative Therapist Providing Cover

Only for use when one therapist is unavailable at a centre for an extended period but cover will be provided by a different therapist

(Form to be on headed paper)

Version 4.2 (pre-randomisation – missing therapist), 05.08.2005

Centre Number:

Study Number: ISRCTN54285094 MREC/02/7/89

CONSENT FORM 2 pre-randomisation (missing therapy)

Title of Project:

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

Full title:

A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome / myalgic encephalomyelitis/encephalopathy

PIN:

Name of Researcher.....

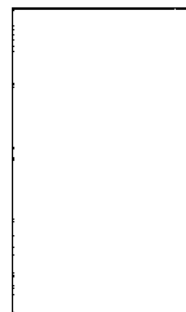
**Please
initial box**

- 1 I confirm that I have read and understand the information sheet dated 05 August 2005 (version 17), for the above study and have had the opportunity to ask questions.
- 2 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3 I understand that any of my medical notes may be looked at by responsible individuals from either the trial or regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
- 4 I understand that my GP and other relevant health care professionals involved in my care will be contacted and informed of my participation in the trial and given follow-up information of my progress. I agree for this to happen and for trial information to be recorded in my medical notes maintained by these

	professionals.	
5	I understand that any therapy sessions that I take part in will be video/audio-recorded and may be used for supervision, quality control, and research purposes, and that the recordings will be securely stored.	
6	I understand that in accordance with good practice guidelines, all of my records, notes and video/audio-recordings will be securely stored for twenty years after the end of this study. After this all recordings will be destroyed or permanently deleted.	
7	I agree to researchers contacting me after the trial is over for further follow-up, so long as further follow up has received research ethics committee approval.	
8	I agree to attend for all the treatment and assessment interviews for the duration of the study.	
9	I agree not to be referred for a different therapy, or to a non-PACE therapist for the duration of my involvement in the study unless arranged by a treating doctor.	
10	If I have moved or lost contact with the clinic and vice versa, I agree that my GP or a relative may be contacted to provide contact details.	
11	I give permission for my NHS number to be recorded to allow my GP to be found through the Office for National Statistics (England) or for my Chi number to be collected for the Information and Statistics Division (Scotland) to allow follow-up information to be obtained for up to five years after the end of the trial, and for the researchers to have access to my paper and electronic records for this purpose.	
12	I agree to take part in the above study, and understand this may involve 15 attendances for a therapy, 3 follow-up research assessment visits and at least 3 attendances with the clinic doctor over the year of the study.	
13	I understand that information collected about me for the trial, including my personal details, a copy of this consent form and all of the questionnaires I complete for the trial, will be held securely by the local trial staff and at the PACE trial centre at Queen Mary, University of London. I give permission for this to happen.	
14	I understand that the usual adaptive pacing/ cognitive behaviour/ graded exercise therapist <i>[delete as applicable]</i> is not available at this time. I understand that if I am randomised to receive adaptive pacing/ graded exercise/ cognitive behaviour therapy <i>[delete as applicable]</i> I will either: <ul style="list-style-type: none"> • receive my therapy from another local PACE therapist who has been trained to provide the missing therapy. 	

or if no other therapist locally is available to cover,

- receive my therapy from a therapist from a different PACE trial centre (some sessions by phone and some face-to-face), alongside face-to-face sessions with a local PACE therapist, who would provide therapy assistance, particularly during the telephone sessions



_____ Name of Patient	_____ Date	_____ Signature
--------------------------	---------------	--------------------

_____ Name of Person taking consent (if different from researcher)	_____ Date	_____ Signature
--	---------------	--------------------

_____ Researcher	_____ Date	_____ Signature
---------------------	---------------	--------------------

1 for patient; 1 for research nurse in the trial specific source notes; 1 copy to GP, 1 copy to be kept with hospital notes, 1 copy to go to the PACE trial centre and original stored in Trial Centre Master File

A2 Therapy Manuals

Please see separate manuals for full details.

The current versions of the manuals in use are summarised in the table below.

Appendix item	Manual	Version	Date
A2.1	APT Manual for Therapists	MREC Version 3	27.01.2006
A2.2	APT Manual for Patients	MREC version 2	November 2004
A2.3	CBT Manual for Therapists	MREC Version 2	November 2004
A2.4	CBT Manual for Patients	MREC Version 2	November 2004
A2.5	GET Manual for Therapists	MREC Version 2	16.11.2004
A2.6	GET Manual for Patients	MREC version 1	16.11.2004
A2.7	SSMC Manual for Doctors	MREC version 1	02/12/2004

A2.8 Administrative Amendment 2: 05 August 2005

Trial title: *The PACE trial – A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome / myalgic encephalomyelitis or encephalopathy (CFS/ME)*

MREC Number: MRE/02/7/89

Trial Identifier: ISRCTN54285094

Protocol version and date: Protocol version 3.1, 11 February 2005

Purpose of amendment: To widen the disciplines of the therapists that may give treatment in the PACE trial.

Amendment: This amendment applies to the GET and APT treatment manuals. The APT manual was originally written with the intention that the therapy would be delivered by an occupational therapist and the GET manual assumes that the treatment will be delivered by a physiotherapist. It has been decided that these treatments could be effectively delivered by trained professionals from other disciplines such as exercise physiologists or nurse specialists. (The CBT manuals do not state which discipline will provide the treatment, so no amendment is necessary.)

The following statement should be considered alongside the current versions of the therapist and participant GET manuals:

"This manual has been written with the assumption that this therapy will be given by a physiotherapist. However any appropriately qualified, trained and supervised therapist is able to give this therapy. You will be told the qualification, training and discipline of the therapist who will be giving you your therapy, which may or may not be a physiotherapist."

The following statement should be considered alongside the current versions of the therapist and participant APT manuals:

"This manual has been written with the assumption that this therapy will be given by an occupational therapist. However any appropriately qualified, trained and supervised therapist is able to give this therapy. You will be told the qualification, training and discipline of the therapist who will be giving you your therapy, which may or may not be an occupational therapist."

The Participant Information Sheet will be modified to reflect this change to ensure that all participants are fully informed.

A2.9 Administrative Amendment 6: 27 January 2006

Trial title: *The PACE trial – A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome / myalgic encephalomyelitis or encephalopathy (CFS/ME)*

MREC Number: MRE/02/7/89

Trial Identifier: ISRCTN54285094

Protocol version and date: Protocol version 5, 01 February 2006

Purpose of amendment: To amend the APT manual to be compliant with the trial protocol.

Minor amendment to the APT manual for therapists

It has been noticed that there is a minor error in the APT therapist manual. The Trial management group would like to amend this manual to be compliant with the trial protocol. The manual implied that a session 3 of APT could exceed the standard 50 minute session length. We would therefore like to alter the wording on page 56 from:

NB: *This session may need to be longer in order to incorporate the relaxation session. The relaxation session may be taped for the participants' home use.*

To:

NB: *In this session you can incorporate a relaxation session if required. The relaxation session may be taped for the participants' home use.*

The amended page to APT manual for therapists MREC version 3, 27.01.2006 will be circulated to all therapists.

A3 GP Letters

A3.1 Participant entry to trial

(Letter to be on PACE centre headed paper)

Address

Date

Dear Dr,

PIN	Name	DoB	Address
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Re: The PACE trial - Pacing, graded Activity, and Cognitive behaviour therapy; a randomised Evaluation; MREC/02/7/89

This letter is to inform you that your patient has consented to participate in this study. Your patient has been diagnosed as suffering from chronic fatigue syndrome / myalgic encephalomyelitis/encephalopathy (CFS/ME) and has agreed to enter this study.

The purpose of the study is to compare the efficacy and adverse effects of four different treatments. These include: standardised specialist medical care (SSMC) from the fatigue clinic doctor, SSMC plus adaptive pacing therapy (APT), SSMC plus cognitive behaviour therapy (CBT) or SSMC plus graded exercise therapy (GET). We will also study individual predictors of a good response, the mechanisms of change with treatment and cost-effectiveness.

Your patient has been allocated to receive XXXX.

If your patient has been allocated to one of the supplementary therapies, this means that they will receive 15 sessions of APT, CBT or GET plus standardised specialist medical care. If your patient has been allocated SSMC alone, they will be reviewed by the clinic doctor no less than three times in the next twelve months with advice given and appropriate medications prescribed or advised. Your patient will continue to remain under the consultant care of Dr _____ throughout the trial.

At the end of their participation in the trial, patients who remain unwell, will in discussion with their clinic doctor be offered additional treatment by the trial therapists.

There will be five research interviews with a research nurse over the next 12 months of the study. These include questionnaires, a psychiatric interview, assessments of fitness, and a measure of activity over 1 week.

The study has been funded by the Medical Research Council (MRC), the Scottish Chief Scientist's Office (CSO), the Department of Health (DH) and the Department of Work and

Pensions (DWP). The study has been passed as ethically satisfactory by the West Midlands MREC.

If you have any concerns or queries, please contact Dr _____ on *[telephone number]*. For your information, we enclose the Patient Clinic Leaflet and the summary/abstract of the trial.

Yours sincerely,

[Name]
Research Nurse

Enc: Copy of the patient consent
Reply slip requesting NHS/Chi number (*if patient has given permission*)

A3.2 Participant completion of supplementary therapy

(Letter to be on PACE centre headed paper)

Address

Date

Dear Dr,

PIN	Name	Address	DOB
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RE: The PACE trial – Pacing, graded Activity, and Cognitive behaviour therapy; a randomised Evaluation MREC/02/7/89

This letter is to inform you that your patient has completed their treatment arm of the PACE trial.

Your patient was randomised to receive standardised specialist medical care *[delete as appropriate]* [plus adaptive pacing therapy (APT) / graded exercise therapy (GET) / cognitive behaviour therapy (CBT) arm of the study] and has completed XX therapy sessions out of the planned 15 sessions. They will continue to be followed-up by the research nurse, and clinic doctor where appropriate, for a further sixteen weeks as part of the PACE trial.

Please do not refer your patient for any other treatment or therapies for CFS/ME during this period. If you would like to discuss this, please contact Dr..... on

If you have any queries or concerns please do not hesitate to contact me.

Yours sincerely,

[Name]
Research Nurse

Footer:

Version 1, 22.10.2004

GP letter completion of supplementary therapy

page number

ISRCTN54285094

A3.3 Participant completion of trial

(Letter to be on PACE centre headed paper)

Address

Date

Dear Dr,

PIN	Name	Address	DOB
-----	------	---------	-----

RE: The PACE trial – Pacing, graded Activity, and Cognitive behaviour therapy; a randomized Evaluation MREC/02/7/89

This letter is to inform you that your patient has completed their participation in the PACE trial.

[Select appropriate sentence of the following four:]

- a) Your patient was randomised to receive adaptive pacing therapy (APT) and standardised specialist medical care (SSMC), and has been under the supervision of the chronic fatigue clinic for one year. Of the fifteen therapy sessions, your patient completed XX.
- b) Your patient was randomised to receive graded exercise therapy (GET) and standardised specialist medical care (SSMC), and has been under the supervision of the chronic fatigue clinic for one year. Of the fifteen therapy sessions, your patient completed XX.
- c) Your patient was randomised to receive cognitive behaviour therapy (CBT) and standardised specialist medical care (SSMC), and has been under the supervision of the chronic fatigue clinic for one year. Of the fifteen therapy sessions, your patient completed XX.
- d) Your patient was randomised to receive standardised specialist medical care (SSMC), and has been under the supervision of the chronic fatigue clinic for one year and has attended XX appointments.

At the end of the trial your patient was assessed by Dr. _____ and has been discharged from the chronic fatigue clinic / will continue to be seen at the chronic fatigue clinic / has been referred for further therapy.

If you have any concerns or queries please contact Dr. _____

Yours sincerely,

[Name]

Research Nurse

Footer:

Version 1, 22.10.2004
GP letter 52 weeks

page number

ISRCTN54285094

A3.4 Participant withdrawal from treatment

(Letter to be on PACE centre headed paper)

Address

Date

Dear Dr,

PIN	Name	Address	DOB
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RE: The PACE trial – Pacing, graded Activity, and Cognitive behaviour therapy; a randomised Evaluation MREC/02/7/89

[Select appropriate sentence of the following two:]

- a) This letter is to inform you that your patient has chosen to withdraw from receiving treatment in the PACE trial. *[Specify reason if appropriate].*
- b) This letter is to inform you that your patient has been withdrawn from receiving treatment in the PACE trial by their therapist/clinic doctor. *[Specify reason].*

Your patient was randomised to receive standardised specialist medical care *[delete as appropriate]* [plus adaptive pacing therapy / graded exercise therapy / cognitive behaviour therapy, and has completed XX therapy sessions out of the planned 15 sessions] and has attended XX chronic fatigue clinic appointments.

Your patient has withdrawn from the treatment arm only and has agreed to continue in the PACE trial for follow-up and will continue to be seen by the research nurse. Please do not refer your patient for any new treatment or therapies until their involvement in the PACE trial is completed. If you would like to discuss this, please contact Dr _____ on _____.

If you have any concerns or queries please do not hesitate to contact me.

Yours sincerely,

[Name]
Research Nurse

Footer:

Version 1, 22.10.2004
GP letter withdrawal from treatment

page number

ISRCTN54285094

A3.5 Participant drop-out from trial

(Letter to be on PACE centre headed paper)

Address

Date

Dear Dr,

PIN	Name	Address	DOB
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RE: The PACE trial – Pacing, graded Activity, and Cognitive behaviour therapy; a randomised Evaluation MREC/02/7/89

This letter is to inform you that your patient has withdrawn from both treatment and follow-up for the PACE trial. *[Specify reason if appropriate]*.

Your patient was randomised to receive standardised specialist medical care *[delete as appropriate]* [plus adaptive pacing therapy / graded exercise therapy / cognitive behaviour therapy and has completed XX therapy sessions out of the planned 15 sessions] and has attended XX chronic fatigue clinic appointments.

Your patient has been assessed by Dr. _____ and *[delete as appropriate]* will continue to be seen at the chronic fatigue clinic /has been discharged from the chronic fatigue clinic / has been referred to _____.

If you have any queries or concerns please contact Dr. _____

Yours sincerely,

[Name]
Research Nurse

Footer:

Version 1, 22.10.2004

GP letter withdrawal from whole trial

.page number

ISRCTN54285094

A4 Letters to the Participant from the Research Nurse

A4.1 Participant initial letter from research nurse

(Letter to be on PACE headed note paper)

Address

Date

Dear ,

RE: Your first visit to the PACE trial nurse

Following our telephone conversation on *[insert date]*, I am very pleased to learn that you are interested in finding out more about the trial and consider undertaking the initial screening. This is to confirm that your appointment to visit me will be at *[insert time and date]* at *[insert name of hospital/institution]*.

During this visit I will answer any questions you may have about the trial and explain what will be involved if you agree to take part.

Please bring with you a list of any medications that you are taking, including any vitamin supplements and alternative or homeopathic medications.

I have enclosed another copy of the participant information sheet and consent form, which you may have already been given by the doctor at your recent chronic fatigue clinic appointment.

If you are unable to attend this appointment please contact me on *[insert telephone number]*.

Yours sincerely,

Name
Research Nurse

Enc: Participant Information Sheet
Consent form

Footer:

Version 1, 22.10.2004
Participant initial letter

page number

ISRCTN54285094

A4.2 Participant follow-up appointments

(Letter to be on PACE headed note paper)

Address

Date

Dear ,

RE: Your next visit to the PACE trial nurse

I am writing to you regarding your next visit to see me (the PACE trial nurse). As we previously arranged, your next visit for the PACE trial is planned for *[insert time and date]* at *[insert name of hospital/institution]*.

I have enclosed a questionnaire booklet for you. I would be very grateful if you would complete this at home ***in the week before you come and see me***. Please answer all the questions that you can, even if you think they don't apply to you. I would be happy to explain any questions that don't make sense when you come and see me, although it is important that your answers are your own. Please remember to bring it with you when you come to see me.

Please remember to bring with you a list of any medications that you are taking, including any vitamins or alternative / homeopathic medications.

If you are unable to attend this appointment please contact me on *[insert telephone number]*.

Yours sincerely,

Name
Research Nurse

Footer:

Version 1, 22.10.2004
Participant follow-up letter

page number

ISRCTN54285094

A4.3 Participant letter for final follow-up visit

(Letter to be on PACE headed note paper)

Address

Date

Dear ,

RE: Your final visit to the PACE trial nurse

I am writing to you regarding your last visit to see me (the PACE trial nurse). As we previously arranged, this is planned for *[insert time and date]* at *[insert name of hospital/institution]*.

I have enclosed a questionnaire booklet for you. I would be very grateful if you would complete this at home ***in the week before you come and see me***. Please answer all the questions that you can, even if you think they don't apply to you. I would be happy to explain any questions that don't make sense when you come and see me, although it is important that your answers are your own. Please remember to bring it with you when you come to see me.

Please remember to bring with you a list of any medications that you are taking, including any vitamins or alternative /homeopathic medications.

If you are unable to attend this appointment please contact me on *[insert telephone number]*.

Yours sincerely,

Name
Research Nurse

Enc: Questionnaire booklet

Footer:

Version 1, 22.10.2004
Participant final follow-up letter

page number

ISRCTN54285094

A4.4 Participant withdrawal from treatment

(Letter to be on PACE headed note paper)

Address

Date

Dear ,

RE: Your [next/final] visit to the PACE trial nurse

Following our telephone conversation on *[insert date]*, I am writing to you regarding stopping the treatment you receive as part of the PACE trial.

As we discussed on the telephone although you no longer wish to receive the treatment to which you were allocated, I understand you are willing to attend for *[follow-up assessment visits/ a final assessment visit]*.

I am pleased to confirm that your *[next/final]* visit to see me (PACE trial nurse) is arranged for *[insert time and date]* at *[insert name of hospital/institution]*

I have enclosed a questionnaire booklet for you. I would be very grateful if you would complete this at home ***in the week before you come and see me***. Please answer all the questions that you can, even if you think they don't apply to you. I would be happy to explain any questions that don't make sense when you come and see me, although it is important that your answers are your own. Please remember to bring it with you when you come to see me.

Please remember to bring with you a list of any medications that you are taking, including any vitamins or alternative /homeopathic medications.

If you are unable to attend this appointment please contact me on *[insert telephone number]*.

Yours sincerely,

Name
Research Nurse

Enc: Questionnaire booklet

Footer:

Version 1, 22.10.2004

page number

ISRCTN54285094

Participant withdrawal from treatment letter

A4.5 Participant drop-out from trial

(Letter to be on PACE headed note paper)

Address

Date

Dear ,

RE: Your final visit to the PACE trial nurse

Following our telephone conversation on *[insert date]*, I am writing to you regarding stopping your involvement in the PACE trial.

As we discussed on the telephone although I understand that you no longer wish to participate in the PACE trial you have kindly agreed to attend for a final assessment visit.

I am pleased to confirm that your final PACE assessment visit is arranged for *[insert time and date]* at *[insert name of hospital/institution]*

I have enclosed a questionnaire booklet for you. I would be very grateful if you would complete this at home ***in the week before you come and see me***. Please answer all the questions that you can, even if you think they don't apply to you. I would be happy to explain any questions that don't make sense when you come and see me, although it is important that your answers are your own. Please remember to bring it with you when you come to see me.

Please remember to bring with you a list of any medications that you are taking, including any vitamins or alternative /homeopathic medications.

If you are unable to attend this appointment please contact me on *[insert telephone number]*.

Yours sincerely,

Name
Research Nurse

Enc: Questionnaire booklet

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Participant drop-out letter

page number

ISRCTN54285094

A5 Medical Screening & Contraindications

A5.1 Medical screening SOP

Part of trial SOP chapter 9.

9.4.1 Assessment

9.4.1.1 All patients will be assessed by clinicians experienced in the diagnosis and management of CFS/ME. The assessment process is intended to determine:

- Whether the diagnosis of CFS/ME is appropriate
- Whether the patient is eligible for referral to the Research Nurse/Assistant for screening for the PACE trial.

Medical assessment will include:

9.4.2 History

9.4.2.1 Particular emphasis should be placed on:

- 1) History of present complaint
- 2) Current activity level/pattern
- 3) Mood disorder and illness beliefs
- 4) Sleep pattern
- 5) Severe personality disorder
- 6) Exclusion of patients in whom medical or psychiatric conditions are excluded by the Oxford criteria (see below and Oxford criteria)^[2] in trial protocol

9.4.3 Examination

9.4.3.1 All patients will undergo a physical examination prior to randomisation by a qualified doctor. The extent of this examination and the degree to which it includes a full neurological assessment is at the discretion of the examining doctor, and will be influenced by the history and the extent to which physical examination has been performed by the referring clinician (See SOP9.3).

9.4.3.2 All patients for whom there is any doubt about cognitive function should undergo a mental state examination. A useful guide to the use of the Mini Mental State Examination (MMSE) scale may be found here:

<http://www.hartfordign.org/publications/trythis/issue03.pdf> (correct at time of producing this SOP).

9.4.4 Investigations

9.4.4.1 All patients will have the following investigations performed in the previous six months:

- Full blood count,
- ESR and C-reactive protein,
- urea and electrolytes,
- liver function tests,
- calcium,
- albumin,
- creatine kinase,
- thyroid function (TSH and free T4),
- local coeliac screen (e.g. IgA endomysial or tissue transglutaminase autoantibodies),
- random blood glucose,
- urinalysis for blood,
- sugar and protein.

9.4.4.2 These tests must have been carried out no more than six months prior to assessment and the laboratory reports, or copies, must be reviewed by the assessing doctor.

9.4.4.3 The history may suggest the need for other tests (e.g. ANA, Lyme serology) but in the absence of a suggestive history no further tests are mandatory for trial entry. Medical exclusions are made from the history, relevant examination and investigations.

9.4.5 Common medical exclusions (taken from reference 1 in trial protocol)

9.4.5.1 Permanent medical exclusions include the following:

- 1) Organ failure (e.g., emphysema, cirrhosis, cardiac failure, chronic renal failure);
- 2) Chronic infections (e.g., AIDS, hepatitis B or C);
- 3) Rheumatic and chronic inflammatory diseases (e.g., systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, inflammatory bowel disease, chronic pancreatitis);
- 4) Major neurologic diseases (e.g., multiple sclerosis, neuromuscular diseases, epilepsy or other diseases requiring ongoing medication that could cause fatigue, stroke, head injury with residual neurologic deficits);
- 5) Diseases requiring systemic treatment (e.g., organ or bone marrow transplantation, systemic chemotherapy, radiation of brain, thorax, abdomen, or pelvis);
- 6) Major endocrine diseases (e.g., hypopituitarism, adrenal insufficiency);
- 7) Primary sleep disorders (e.g., sleep apnea, narcolepsy).

These medical exclusions have been selected in order to comply with the 1994 CDC criteria which state exclusions are "any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatiguing illness. Such conditions may include previously treated malignancies.....". As such patients with a history of malignancy successfully treated in the distant past are not excluded *so long as condition 5 (above) is not fulfilled*.

9.4.5.2 Temporary medical exclusions include treatable conditions that require evaluation over time to determine the extent to which they contribute to the fatiguing illness. These encompass four general categories:

- 1) Conditions discovered at onset or initial evaluation (e.g., effects of medications, sleep deprivation, untreated hypothyroidism, untreated or unstable diabetes mellitus, active infection);
- 2) Conditions that resolve (e.g., pregnancy until 3 months post-partum, breast feeding, major surgeries until 6 months post-operation, minor surgery until 3 months post-operation, and major infections such as sepsis or pneumonia until 3 months post-resolution; sleep disorders such as restless leg syndrome and periodic limb movement should be considered temporary exclusions for research criteria, if they are severe, but not if the degree of the sleep problem is insufficient to explain the severity of the fatigue);
- 3) Major conditions whose resolution may be unclear for at least 5 years (e.g., myocardial infarction, heart failure);
- 4) Morbid obesity (body mass index [BMI] > 40).

9.4.6 Psychiatric exclusions (taken from reference 2 in trial protocol)

9.4.6.1 A current diagnosis of:

- 1) Schizophrenia of any subtype,
- 2) Bipolar (manic depressive) mood disorder
- 3) An eating disorder
- 4) Alcohol or substance abuse as determined by DSM IV criteria, as laid out in the SCID
- 5) Proven organic brain disorder

Version	Final Draft Version 3
Date	16.11.2005
Author	GM, PDW & MM

A5.2 Contraindications and cautions for trial treatments

Certain co-morbid medical or psychiatric conditions may either be a contraindication or require specialist assessment or advice from the centre leader before participating in the trial. These mainly concern GET, but some conditions may affect other treatment groups.

Absolute Contraindications to the PACE trial:

Oxford criteria will have excluded some of the following conditions. However, please note that the following conditions may either be definite clinical exclusions for a trial treatment, or else be excluded on the grounds of difficulty in participating in a manual derived, time-limited version of a therapy:

- Uncontrolled hypertension
- Poorly controlled/unstable respiratory conditions, e.g. asthma
- Unstable musculoskeletal conditions, e.g. recent or poorly healed fracture, recent or unstable back injury or current back disease/disorder
- Pregnancy: would usually not be contraindicated to exercise in particular. However, the time limitations of the trial would not allow for a suitable break prior to and after birth.

Potentially allowable conditions (To be discussed with Centre Leader and Physiotherapist)

Cardiac conditions

- Pacemakers may affect heart rate monitors and target heart rate, therefore needs highlighting and advice
- Those on beta-blockers/ other cardiovascular medication that may affect heart rate / BP: will need guidance from doctors re: target heart rate

Musculoskeletal disorders:

Conditions that may affect *current* exercise ability -

- Significant arthritic conditions
- Significant previous injury / fractures
- Significant previous surgery
- Significant loss of range of movement, especially lower limb

NB previous major injuries or surgery are only relevant if they *currently* exclude a participant from actively participating in exercise

Psychiatric conditions

- Psychiatric disorders that may affect engagement or attendance, e.g. severe depressive or anxiety disorders

Respiratory conditions:

Well controlled conditions can be considered, although may limit exercise capacity and progress.

Significant regional pain

Any other condition that is thought to affect the participant's *current* ability to engage or participate in exercise.

Version 1, 22.10.2004

A6.2 Actigraphy instructions

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Please note which day of the week that the actigraphy started: _____

Actigraphy records the movement of the non-dominant ankle over a period of approximately 7 days and nights, apart from periods when the participant is immersed in water, such as having a bath or shower. All the data will be analysed by the Research Nurse to provide derived summary data, which will itself be used in the trial database. This derived summary data is described below.

Daytime

- Mean and standard deviation, median and interquartile range of activity (accelerations per one minute) for each complete day not attending hospital = 6 separate days

DAY	Mean	Median	Standard Deviation	Interquartile Range
2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
6	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
7	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

- Peak activity per day (highest measure of activity in one minute)

DAY	Peak Activity
2	<input type="text"/>
3	<input type="text"/>
4	<input type="text"/>
5	<input type="text"/>
6	<input type="text"/>
7	<input type="text"/>

3. Trough inactivity per day (lowest measure of activity in one minute)

DAY Trough Inactivity

2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
6	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
7	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

4. Total duration of activity per day (hours) x 6 days

DAY Activity Duration

2	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
6	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
7	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>

5. Total duration of inactivity per day (hours) x 6 days

DAY Inactivity Duration

2	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
6	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
7	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>

Night-time

1. Mean and standard deviation, median and interquartile range of activity (accelerations per one minute) for each complete night not attending hospital = 6 separate nights

NIGHT	Mean	Median	Standard Deviation	Interquartile Range
2	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
3	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
4	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
5	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
6	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
7	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

2. Peak activity per night (highest measure of activity in one minute)

NIGHT	Peak Activity
2	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
3	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
4	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
5	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
6	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
7	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

3. Trough inactivity per night (lowest measure of activity in one minute)

NIGHT Trough Inactivity

2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
6	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
7	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

4. Total duration of activity per night (hours) x 6 days

NIGHT Activity Duration

2	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
6	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
7	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>

5. Total duration of inactivity per night (hours) x 6 days

NIGHT Inactivity Duration

2	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
6	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
7	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>

A6.3 Borg Scale

Step Test of Fitness with Borg scale (laminated card)

Please ask the participant to choose a rating number that best indicates what effort they felt the exercise had taken at the end of the step test.

Intensity	Please indicate one number
	6
Very, Very Light	7
	8
Very Light	9
	10
Fairly Light	11
	12
Somewhat Hard	13
	14
Hard	15
	16
Very Hard	17
	18
Very, Very Hard	19
	20

A6.4 CDC

CDC

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Please score whether you have had any of the following symptoms in the last week:

Score each symptom by putting a circle round the number that most closely resembles the frequency and intensity of that particular symptom.

Symptoms	Not at all present	Present a little	Present more often than not	Present most of the time	Present all the time
Impaired memory or concentration	0	1	2	3	4
Sore throat	0	1	2	3	4
Tender lymph nodes (glands) in your neck or under your arms	0	1	2	3	4
Muscle pain	0	1	2	3	4
Joint pain in several joints without swelling or redness	0	1	2	3	4
New headache	0	1	2	3	4
Unrefreshing sleep	0	1	2	3	4
Feeling ill after exertion	0	1	2	3	4

Version 2, 26.11.2004

A6.5 CGI for participants

CGI

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Overall, how much do you feel your health has changed since the start of the study? Please tick the one box below that most closely corresponds to how you feel now.

Very much better	
Much better	
A little better	
No change	
A little worse	
Much Worse	
Very much worse	

Version 2, 26.11.2004

A6.6 CGI and treatment adherence for SSMC doctors

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

The following is a global impression of change scale. Please rate this scale including all of the various therapeutic factors.

1. Overall, how much has the participant changed since the start of the study (please tick only one box)?				
Very much better				
Much better				
A little better				
No change				
A little worse				
Much Worse				
Very much worse				
2. How well has the participant adhered to both medical management and advice – did the participant actually implement what had been negotiated in the sessions (please tick only one box)?				
Completely	Very well	Moderately well	Slightly	Not at all
3. To what extent did the participant accept the principles underlying the management advice they were given (please tick only one box)?				
Completely	Very well	Moderately well	Slightly	Not at all

4. Sessions received

- a. How many treatment sessions with you **in total** has the participant received (include face-to-face sessions and telephone sessions, but not administrative calls i.e. to re-arrange appointments)?

<input type="text"/>	<input type="text"/>
----------------------	----------------------

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

- b. Of these, how many were conducted over the telephone (do not include administrative calls)?

- c. How many hours and minutes in total of treatment were given (do not include administrative calls)?

 Hours

 minutes

5. How many planned sessions did NOT occur?

Of these:

- d. How many were cancelled because of your being unable to attend?

- e. How many cancellations or DNAs were instigated by the participant (e.g. travel problems, sickness, family commitments)?

- f. How many sessions were cancelled by mutual consent (i.e. both you and the participant agreed that the session was unnecessary)?

6. How many unplanned phone calls took place (phone calls regarding treatment issues, do not include administrative calls)?

7. How many sessions were attended by a relative (not partner) of the participant?

8. How many sessions were attended by a friend of the participant?

9. How many sessions were attended by the participant's partner?

A6.7 CGI and treatment adherence for therapists

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

The following is a global impression of change scale. Please rate this scale including all of the various therapeutic factors.

1. Overall, how much has the participant changed since the start of the study (please tick only one box)?				
Very much better				
Much better				
A little better				
No change				
A little worse				
Much Worse				
Very much worse				
2. How well has the participant adhered to the treatment – did the participant actually implement what had been negotiated in the therapy sessions (please tick only one box)?				
Completely	Very well	Moderately well	Slightly	Not at all
3. To what extent did the participant accept the model of therapy? (Please tick only one box).				
Completely	Very well	Moderately well	Slightly	Not at all

4. Sessions received

- a. How many therapy sessions with you **in total** has the participant received (include face-to-face sessions and telephone sessions, but not administrative calls i.e. to re-arrange appointments)?

<input type="text"/>	<input type="text"/>
----------------------	----------------------

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

- b. Of these, how many were conducted over the telephone (do not include administrative calls)?

- c. How many hours and minutes in total of treatment were given (do not include administrative calls)?

 Hours

 minutes

5. How many planned sessions did NOT occur?

Of these:

- a. How many were cancelled because of your being unable to attend?

- b. How many cancellations or DNAs were instigated by the participant (e.g. travel problems, sickness, family commitments)?

- c. How many therapy sessions were cancelled by mutual consent (i.e. both you and the participant agreed that the session was unnecessary)?

6. How many unplanned phone calls took place (phone calls regarding treatment issues, do not include administrative calls)?

7. How many sessions were attended by a relative (not partner) of the participant?

8. How many sessions were attended by a friend of the participant?

9. How many sessions were attended by the participant's partner?

We would like to know more about any problems you have had with feeling tired, weak or lacking in energy in the last month. Please answer ALL the questions by ticking the answer which applies to you most closely. If you have been feeling tired for a long while, then compare yourself to how you felt when you were last well. (Please tick only one box per line).

PIN		Participant Initials			Date completed				
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year		
					Less than usual	No more than usual	More than usual	Much more than usual	
Do you have problems with tiredness?									
Do you need to rest more?									
Do you feel sleepy or drowsy?									
Do you have problems starting things?									
Do you lack energy?									
Do you have less strength in your muscles?									
Do you feel weak?									
Do you have difficulty concentrating?									
Do you make slips of the tongue when speaking?									
Do you find it more difficult to find the correct word?									
					Better than usual	No worse than usual	Worse than usual	Much worse than usual	
How is your memory?									

A6.9 Co-morbid medical conditions

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Include current illnesses, and record any other event that may be significant to the trial or that has resulted in a serious adverse event.

Medical condition	Are you taking any medication for this condition?	
	Yes	No

A6.11 CSRI

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

We are asking you the following questions because we would like to know the cost of your illness both to you, those looking after you and to society in general.

1 In the last 6 months, what face-to-face consultations have you had with these practitioners?

(Note: only record one-to-one contacts here; see next questions for inpatient care and investigations)

Care provider	Have you used this service? (Please circle one)		Number of contacts in last 6 months		Average duration of contact
	No	Yes	CFS/ME related	Other reasons	
A. General practitioner (GP)	No	Yes			
B. Neurologist	No	Yes			
C. Psychiatrist	No	Yes			
D. Other doctor 1 - state what type (e.g. cardiologist) _____	No	Yes			
E. Other doctor 2 - state what type (e.g. dentist) _____	No	Yes			
F. Practice nurse	No	Yes			
G. Pharmacist (for advice)	No	Yes			

PIN	Participant Initials	Date completed
<div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px;"></div>	<div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px;"></div>	<div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px; margin-right: 5px; text-align: center;">2</div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px; margin-right: 5px; text-align: center;">0</div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px;"></div> <div style="display: inline-block; border: 1px solid black; width: 20px; height: 20px;"></div>
Centre Participant	Fore. Midd. Sur.	Day Month Year

Care provider	Have you used this service? (Please circle one)		Number of contacts in last 6 months		Average duration of contact
	No	Yes	CFS/ME related	Other reasons	
H. Psychologist / therapist (other than in the PACE trial)					
I. Physiotherapist (other than in the PACE trial)					
J. Social worker					
K. Community mental health worker					
L. Acupuncturist					
M. Osteopath					
N. Homeopath / herbalist					
O. Occupational therapist (other than in the PACE trial)					
P. Other (please state): _____					

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

2 In the last 6 months have you spent time as a hospital inpatient?

<input type="checkbox"/>	<input type="checkbox"/>
Yes	No

If yes:

Admission	Hospital name, plus department or type of ward (e.g. King's, neurology)	Reason for admission	Dates		Total days
			Admission	Discharge	
1 st admission					
2 nd admission					
3 rd admission					

a) How many times have you been admitted to hospital and discharged in the same day?

3 In the last 6 months how many times have you attended A & E?

a) What was the reason?

Appendix 6: Case Report Forms

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

4 In the last 6 months, have you had any of the following investigations or diagnostic tests?

Type of test	Have you had this test? (Please circle one)		Number of investigations / tests in the last 6 months
A. Magnetic Resonance Image (MRI)	No	Yes	
B. CT / CAT scan	No	Yes	
C. Ultrasound	No	Yes	
D. X-ray	No	Yes	
E. Electroencephalogram (EEG)	No	Yes	
F. Blood test	No	Yes	
G. Other (please describe) _____	No	Yes	

5 In the last 6 months, have you received help from friends or relatives on any of the following tasks, as a consequence of your fatigue?

Type of help	(Please circle one)		Average number of hours help per week	Who provides this care?	Do they live in your house?
Child Care (circle 'No' if you have no children)	No	Yes			
Personal care (E.g. washing, dressing etc.)	No	Yes			
Help in / around the house (E.g. cooking, cleaning etc.)	No	Yes			
Help outside the home (E.g. shopping, transport etc.)	No	Yes			
Other _____	No	Yes			
Total hours					

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

6 What was your employment status immediately before your illness started?

Employment status	Please circle one
Employed full-time and working	1
Employed full-time but 'off-sick'	2
Employed part-time	3
Employed part-time but 'off-sick'	4
Unemployed	5
Self employed and working	6
Self-employed but 'off-sick'	7
Retired (because of age)	8
Retired (because of ill health)	9
Student	10
Student but interrupted due to illness	11
Housewife/husband	12
Other (please specify) _____	13

7 How many hours per week did you work at that time (if any)?

<input type="text"/>	<input type="text"/>	<input type="text"/>	.	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------	---	----------------------	----------------------

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

8 What is your current employment status?

Employment status	Please circle one
Employed full-time and working	1
Employed full-time but 'off-sick'	2
Employed part-time	3
Employed part-time but 'off-sick'	4
Unemployed	5
Self employed and working	6
Self-employed but 'off-sick'	7
Retired (because of age)	8
Retired (because of ill health)	9
Student	10
Student but interrupted due to illness	11
Housewife/husband	12
Other (please specify)	13

9 If you are currently working, what is your current job title (if not, go to question 11)?

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

10 What are your current wages / salary before tax?

£ .

Please indicate if this is: Weekly ☐ Monthly ☐ Annually ☐

If the participant chooses not to give an answer, please use the prompt card to show income brackets, and record the letter that corresponds to the participant's income.

11 What benefits (if any) do you currently receive?

Name of benefit	Please circle
Income Support	1
Incapacity Benefit	2
Disability Living Allowance	
- care component	3
- mobility component	4
Disabled Person's Tax Credit	5
Severe Disablement Allowance	6
Council Tax Benefit	7
Housing Benefit	8
Jobseeker's Allowance	9
Working Tax Credit	10
Statutory Sick Pay	11
State retirement pension	12
Other (please specify)	13

12 Do you currently receive income protection benefit (income protection or total and permanent disability)? ☐ ☐

[illegible]

If the participant chooses not to give an answer, please use the prompt card to show income brackets, and record the letter that corresponds to the participant's income.

--	--

14 Have you had to stop or reduce work/study due to your state of ill-health? ☐ ☐
Yes No

15 a) If yes: how many days in the last 6 months have you had off work/study because of your fatigue?

--	--	--

--	--	--

Days

OR

15 b) How many fewer hours per week have you worked because of your fatigue?

--	--	--

Hours

16 Do you currently receive a private medical / retirement pension? ☐ ☐

Yes No

17 If yes, how much weekly do you receive? £

--	--	--	--	--	--

 .

--	--

Or

If yes, how much monthly do you receive? £

--	--	--	--	--	--

 .

--	--

Or

If yes, how much annually do you receive? £

--	--	--	--	--	--

 .

--	--

If the participant chooses not to give an answer, please use the prompt card to show income brackets, and record the letter that corresponds to the participant's income.

--	--

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

18 In the past six months, have you received any one-off payments from income protection or insurance schemes as a result of your health?

<input type="checkbox"/>	<input type="checkbox"/>
Yes	No

19 If yes, how much weekly do you receive? £

Or

If yes, how much monthly do you receive? £

Or

If yes, how much annually do you receive? £

If the participant chooses not to give an answer, please use the prompt card to show income brackets, and record the letter that corresponds to the participant's income.

<input type="text"/>	<input type="text"/>
----------------------	----------------------

20 Are there any benefits that you don't receive but which are currently under negotiation or in dispute?

<input type="checkbox"/>	<input type="checkbox"/>
Yes	No

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

21 We are interested in all spells of employment that you have had in the past six months, if any. Please give details of all jobs you have had in the past six months.

Employment 1															
Occupation:															
Normal hours per week worked:															
Date started								Date finished							
	d	d	m	m	y	y	y								
Reason for end of employment:															
How many days (including part days) did you take off due to fatigue?															
Employment 2															
Occupation:															
Normal hours per week worked:															
Date started								Date finished							
	d	d	m	m	y	y	y								
Reason for end of employment:															
How many days (including part days) did you take off due to fatigue?															
Employment 3															
Occupation:															
Normal hours per week worked:															
Date started								Date finished							
	d	d	m	m	y	y	y								
Reason for end of employment:															
How many days (including part days) did you take off due to fatigue?															

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	

Year:

22 If you are unemployed / retired:

Do you intend to return to work?

<input type="checkbox"/>	<input type="checkbox"/>
Yes	No

How long have you been unemployed / retired?

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Years		Months	

Version 2, 26.11.2004

CSRI Laminated card

Weekly		Monthly		Annually	
Code	Sum	Code	Sum	Code	Sum
AS	Up to £100	AO	Up to £500	AZ	Up to £5000
AI	£101-£250	AJ	£501-£1000	AV	£5001-£10,000
BB	£251-£500	AP	£1001-£2000	AD	£10,001-£20,000
AC	£501-£750	BL	£2001-£3000	AK	£20,001-£30,000
AT	£751-£1000	AU	£3001-£4000	AQ	£30,001-£40,000
BF	£1001-£1250	AL	£4001-£5000	AE	£40,001-£50,000
BC	£1251-£1500	AA	£5001-£6000	BI	£50,001-£60,000
AF	£1501-£1750	BH	£6001-£7000	AR	£60,001-£70,000
BL	£1751-£2000	AM	£7001-£8000	BE	£70,001-£80,000
AW	£2001-£2250	BD	£8001-£9000	AB	£80,001-£90,000
AN	More than £2251	BK	£9001-£10,000	BG	£90,001-£100,000
		AG	£10,001-£11,000	AH	£100,001-£110,000
		BJ	£11,001-£12,000	AY	More than £110,001
		AX	More than £12,001		

Version 2, 26.11.2004

A6.12 Demographic information including self-help group and patient organisation membership

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

1. Date of birth **Age**

Day Month Year Years

2. Sex

☐ Male ☐ Female

3. Patient's ethnicity
With which ethnic group that you identify?

(Please circle one)

White	British	1
	Irish	2
	Other	3
Asian	Indian	4
	Pakistani	5
	Bangladeshi	6
	Other	7
Black	Caribbean	8
	African	9
	Other	10
Chinese		11
Other (please state)		12
Prefer not to have this recorded		13

4. Marital status (Please circle one)

Single	1
Married	2
Living together	3
Separated	4
Divorced	5
Widowed	6

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

5. Who does the patient live with? (Please circle one)

Husband/wife/steady partner	1
Spouse/partner and children	2
Parents	3
Alone	4
Other	5

6. Does the patient have any dependants? Please state number

1	Children under 5	
2	Children over 5	
3	Elderly relative	
4	Other	

7. Usual place of residence: (Please circle one)

Owner occupied flat/house	1
Privately rented flat/house	2
Flat/house rented from local authority	3
Other	4

8. Educational level: (Please circle one)

None	1
GCSE/O'level or equivalent	2
A' level or equivalent	3
Degree	4
Postgraduate	5
Other (describe)	6

9. When did the first symptoms of your current illness start?

<input type="text"/>	<input type="text"/>
Month	Year

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

10. When did your current episode affect you to the extent that you were not able to work or carry out your usual activities (e.g. work, studies, household chores)?

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------	----------------------

11. Membership of a self-help group:

Are you currently a member of a local self-help group for CFS/ME? ☐ ☐
Yes No

12. Membership of a national CFS/ME patient organisation:

Are you currently a member of a national CFS/ME patient organisation? ☐ ☐
Yes No

If yes:

To which organisation(s) do you belong?

13. BMI Height cms Weight kgs

14. Have you been seen in any other specialist fatigue clinics in the past?

<input type="checkbox"/>	<input type="checkbox"/>
Yes	No

If yes

a) Please can you tell me which, and its location?

b) Did you receive any of these treatments from a therapist?

Pacing therapy or advice on pacing or lifestyle self- management? ☐ ☐
Yes No

Cognitive Behaviour Therapy? ☐ ☐
Yes No

Graded Exercise Therapy? ☐ ☐
Yes No

A6.13 Eligibility criteria

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

(Please tick one box per line)

Criteria	Yes	No
The patient has given written informed consent to be assessed for the PACE trial	<input type="checkbox"/>	<input type="checkbox"/>
The patient has a clinical diagnosis of CFS	<input type="checkbox"/>	<input type="checkbox"/>
The patient does not have treatment needs that would make participation in the PACE trial inappropriate	<input type="checkbox"/>	<input type="checkbox"/>
The patient is aged 18 years or above	<input type="checkbox"/>	<input type="checkbox"/>
The patient can speak and read English at a level adequate for participation in the trial	<input type="checkbox"/>	<input type="checkbox"/>
The Chalder Fatigue Questionnaire score is 6 or more	<input type="checkbox"/>	<input type="checkbox"/>
The SF-36 physical function sub-scale score is 60 or less	<input type="checkbox"/>	<input type="checkbox"/>
The patient does not have a psychiatric diagnosis (identified with the SCID) that excludes them from the trial	<input type="checkbox"/>	<input type="checkbox"/>
The patient is able to convince the RN that they will be able to attend hospital regularly and reliably for the duration of the trial	<input type="checkbox"/>	<input type="checkbox"/>
There is no contra-indication to <u>any</u> of the treatments that might be provided in the trial	<input type="checkbox"/>	<input type="checkbox"/>
To confirm the patient's eligibility, all of the above must be ticked yes, and none may be ticked no. Is the patient eligible for the trial?	<input type="checkbox"/>	<input type="checkbox"/>

Version 2, 26.11.2004

[NB: protocol Substantial Amendment 5.1 altered the SF-36 from 60 to 65. These forms are pre-printed so cannot be altered but the Research Nurse/Assistant at each centre is asked to cross through 60, write 65 and initial and date the change.]

A6.14 Euroqol EQ5d

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

By placing a tick in one box in each group below, please indicate which statements best describe your own health today.

Mobility		Pain/Discomfort	
I have no problems in walking about		I have no pain or discomfort	
I have some problems in walking about		I have moderate pain or discomfort	
I am confined to bed		I have extreme pain or discomfort	
Self-Care		Anxiety/Depression	
I have no problems with self-care		I am not anxious or depressed	
I have some problems washing or dressing myself		I am moderately anxious or depressed	
I am unable to wash or dress myself		I am extremely anxious or depressed	
Usual Activities (e.g. work, study, housework, family or leisure activities)		Compared with my general level of health over the past 12 months, my health today is:	
I have no problems with performing my usual activities		Better	
I have some problems with performing my usual activities		Much the same	
I am unable to perform my usual activities		Worse	

Version 2, 26.11.2004

PIN		Participant Initials			Date completed					
<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>		
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year			

Best
imaginable
health state

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

Worst
imaginable
health state

100

90

80

70

60

50

40

30

20

10

0

A6.15 Exercise and Activity Scale

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Please indicate how much you agree with the following statements by ticking the appropriate box. (Please tick one only per line)

Beliefs	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I should avoid exercise when tired					
Doing less helps fatigue					
Exercise is harmful					
I should avoid physical activity					

Version 2, 26.11.2004

A6.16 Expectation of therapeutic outcome

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Please circle one answer for each question which best represents your feelings about the treatment outcome.

How logical does this type of treatment seem to you?				
Extremely	Moderately	Somewhat	Only slightly	Not at all
How confident are you that this treatment will help your illness?				
Extremely	Moderately	Somewhat	Only slightly	Not at all

Version 2, 26.11.2004

A6.17 Fibromyalgia assessment

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

(Please tick one box per line)

Criteria	Met	Not met
<i>Pain is considered widespread when all of the following are present:</i>		
1. Pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist.	<input type="checkbox"/>	<input type="checkbox"/>
2. In addition, axial skeletal pain (cervical spine <u>or</u> anterior chest <u>or</u> thoracic spine <u>or</u> low back) must be present.	<input type="checkbox"/>	<input type="checkbox"/>
3. Self-reported widespread pain in all four quadrants of their body for a minimum of three months.	<input type="checkbox"/>	<input type="checkbox"/>
Notes for the Research Nurse:		
<i>In this definition, shoulder and buttock pain is considered as pain for each involved side.</i>		
<i>"Low back" pain is considered lower segment pain</i>		
<i>For the purposes of the PACE trial, tender points are not necessary</i>		

Fibromyalgia criteria met?	Met	Not met
Meets all three of criteria for fibromyalgia	<input type="checkbox"/>	<input type="checkbox"/>

Version 2, 26.11.2004

A6.18 Hospital and Depression Scale (HADS)

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

Please read each item and tick the box which comes closest to how you have been feeling during the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response. (Please tick only one box per statement)

1. I feel tense or wound up: Most of the time A lot of the time From time to time, occasionally Not at all	8. I feel as if I am slowed down: Nearly all the time Very often Sometimes Not at all
2. I still enjoy the things I used to enjoy: Definitely as much Not quite as much Only a little Hardly at all	9. I get a sort of frightened feeling like butterflies in the stomach: Not at all Occasionally Quite often Very often
3. I get a sort of frightened feeling as if something awful is about to happen: Very definitely and quite badly Yes, but not too badly A little, but it doesn't worry me Not at all	10. I have lost interest in my appearance: Definitely I don't take as much care as I should I may not take quite as much care as ever I take just as much care as ever
4. I can laugh and see the funny side of things: As much as I always could Not quite as much now Definitely not so much now Not at all	11. I feel restless as if I have to be on the move: Very much indeed Quite a lot Not very much Not at all
5. Worrying thoughts go through my mind: A great deal of the time A lot of the time From time to time but not too often Only occasionally	12. I look forward with enjoyment to things: As much as I ever did Rather less than I used to Definitely less than I used to Hardly at all
6. I feel cheerful: Not at all Not often Sometimes Most of the time	13. I get sudden feelings of panic: Very often indeed Quite often Not very often Not at all
7. I can sit at ease and feel relaxed: Definitely Usually Not often Not at all	14. I can enjoy a good book or radio or TV programme Often Sometimes Not often Very seldom

Version 2, 26.11.2004

A6.19 Jenkins Sleep Scale

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

These questions are about sleep problems. For each question, please tick the box that applies to you. Please tick ONE box only for each question.

How many times in the past month did you	Not at all	1-3 days	4-7 days	8-14 days	15-21 days	22-31 days
1. Have trouble falling asleep?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Wake up several times each night?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Have trouble staying asleep (including waking too early)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Wake up after your usual amount of sleep feeling tired and worn out?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Version 2, 26.11.2004

A6.20 London criteria for ME

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Criteria	Present	Not present
Criteria 1 to 4 must be met for a diagnosis of ME to be made.		
1. Exercise-induced fatigue precipitated by trivially small exertion (physical or mental) relative to the patient's / participant's previous exercise intolerance		
2. Impairment of short-term memory <i>and</i> loss of powers of concentration,		
- usually coupled with other [neurological and psychological] disturbances such as: <i>[NB These should be asked for as symptoms, not tests, and do not have to be total or persistent for the whole period. These symptoms in (a - e) should be recorded, but are not necessary to make the diagnosis.]</i>		
a) emotional lability [feeling easily upset by things that would not normally upset the participant, but the upset is brief and has usually gone within a few hours, and certainly by the next day]		
b) nominal dysphasia [difficulty finding the right word]		
c) disturbed sleep patterns [of any sort]		
d) disequilibrium [A feeling of imbalance]		
e) tinnitus [ringing in the ears]		
3. Fluctuations of symptoms <i>[NB The usual precipitation by "physical or mental exercise" should be recorded, but is not necessary to meet criteria.]</i>		
usually precipitated by either physical or mental exercise.		
4. These symptoms should have been present for at least 6 months and should be ongoing.		
5. There is no primary depressive illness present and no anxiety disorder/neurosis. <i>[N.B. This means if any depressive or anxiety disorder is present, the London criteria are not met.]</i>		

Version 2, 26.11.2004

A6.21 Oxford criteria for CFS

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

All of the white boxes should be ticked, and none of the grey boxes, for the participant to meet the Oxford criteria.

Criteria (to be judged by RN)	Yes	No
Is your fatigue (or a synonym), the principal (main, primary) symptom (e.g. tiredness, lack of energy, weariness, exhaustion)?	<input type="checkbox"/>	<input type="checkbox"/>
For the Research Nurse to judge: Can the fatigue be distinguished from low mood, sleepiness and lack of motivation?	<input type="checkbox"/>	<input type="checkbox"/>
Is your fatigue out of proportion to what you would expect as normal for this level of exertion?	<input type="checkbox"/>	<input type="checkbox"/>
Is your fatigue a clear change from how you were previously?	<input type="checkbox"/>	<input type="checkbox"/>
Did your fatigue start with a definite onset (which may be gradual)?	<input type="checkbox"/>	<input type="checkbox"/>
Have you had this fatigue all your life, as far as you can remember?	<input type="checkbox"/>	<input type="checkbox"/>
Have you had your fatigue for the last 6 months, during which it was present for more than half of the time?	<input type="checkbox"/>	<input type="checkbox"/>
Does your illness affect both your physical ability and mental functioning (thinking, concentrating, talking, reading or remembering)?	<input type="checkbox"/>	<input type="checkbox"/>

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

Medical exclusions	Checked	Not checked
Established medical conditions known to produce chronic fatigue (see medical screening SOP). RN to check that this has been done and documented by the clinic doctor.	<input type="checkbox"/>	<input type="checkbox"/>
Psychiatric exclusions (taken from the SCID) <i>Current diagnoses of:</i>	Present	Absent
Schizophrenia	<input type="checkbox"/>	<input type="checkbox"/>
Manic depressive (bipolar) illness	<input type="checkbox"/>	<input type="checkbox"/>
Substance misuse	<input type="checkbox"/>	<input type="checkbox"/>
Eating disorder	<input type="checkbox"/>	<input type="checkbox"/>
Proven organic brain disease	<input type="checkbox"/>	<input type="checkbox"/>
Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not reasons for exclusion.		

Oxford criteria met?	Met	Not met
Meets all of the inclusion criteria and none of the exclusion criteria for CFS	<input type="checkbox"/>	<input type="checkbox"/>

Version 2, 26.11.2004

PIN		Participant Initials			Date completed				
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year		

[illegible]

A6.23 Physical Symptoms (PHQ-15)

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

During the past 4 weeks, how much have you been bothered by any of the following problems?

		Not bothered at all	Bothered a little	Bothered a lot
a	Stomach pain			
b	Back pain			
c	Pain in your arms, legs, or joints: knees, hips, etc.)			
d	Menstrual cramps or other problems with your periods [Women only]			
e	Headaches			
f	Chest pain			
g	Dizziness			
h	Fainting spells			
i	Feeling your heart pound or race			
j	Shortness of breath			
k	Pain or problems during sexual intercourse			
l	Constipation, loose bowels, or diarrhoea			
m	Nausea, gas, or indigestion			
n	Feeling tired or having low energy			
o	Trouble sleeping			

Version 2, 08.12.2004

A6.24 Preferred treatment group

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

As you know, neither you nor the research nurse can choose which treatment you will receive. That having been said, we would be interested to know which of the four treatments you would prefer if you had a choice. Please place a tick against the treatment you would prefer to receive. If there are two or more treatments that you would prefer, please choose only one.

Please tick one	
1	Adaptive Pacing Therapy
2	Cognitive Behavioural Therapy
3	Graded Exercise Therapy
4	Standardised Specialist Medical Care alone
5	Don't know

Version 2, 26.11.2004

A6.25 Satisfaction scale

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Overall, how satisfied are you with the treatment you received?

(Please tick only one)	
Very satisfied	<input type="checkbox"/>
Moderately satisfied	<input type="checkbox"/>
Slightly satisfied	<input type="checkbox"/>
Neither	<input type="checkbox"/>
Slightly dissatisfied	<input type="checkbox"/>
Moderately dissatisfied	<input type="checkbox"/>
Very dissatisfied	<input type="checkbox"/>

Please add any additional comments below:

A6.26 SCID summary form

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year

Please summarise the results of the SCID on this table.

Bold text = exclusion criteria <i>Grey box = ineligible for trial</i> <i>Hashed box = Not required to be asked</i>	None	Current	Lifetime	5 or 2 years before onset of CFS/ME
Bipolar Disorder				
Major Depressive Disorder				
Severe, without psychotic features (melancholia)				
Severe, with psychotic features				
Dysthymic disorder (300)				
Minor depressive disorder				
Alcohol misuse				
Other substance misuse				
Panic disorder with agoraphobia				
Panic disorder without agoraphobia				
Obsessive-compulsive disorder				
Posttraumatic stress disorder				
Agoraphobia without history of panic disorder				
Social phobia				
Specific phobia				
Generalized anxiety disorder				
Anorexia nervosa				
Bulimia nervosa				

Psychosis				
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Version 2, 26.11.2004

A6.27 Self-efficacy scale

PIN		Participant Initials			Date completed				
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year		

We would like to know how confident you are in doing certain activities. For each of the following questions, please choose the number that corresponds to your confidence that you can do the tasks regularly at the present time. (Please tick one box per line)

	Not at all confident								Totally confident	
	1	2	3	4	5	6	7	8	9	10
How confident are you that you can keep the fatigue caused by your disease from interfering with the things you want to do?										
How confident are you that you can keep the physical discomfort or pain of your disease from interfering with the things you want to do?										
How confident are you that you can keep the emotional distress caused by your disease from interfering with the things you want to do?										
How confident are you that you can keep any other symptoms or health problems from interfering with the things you want to do?										
How confident are you that you can do the different tasks and activities needed to manage your health condition so as to reduce your need to see a doctor?										
How confident are you that you can do things other than just taking medication to reduce how much your illness affects your everyday life?										

Version 2, 26.11.2004

A6.28 Self-help group membership at 52 weeks

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

1. Membership of a self-help group:

Are you currently a member of a local self-help group for CFS/ME? ☐ ☐
Yes No

2. Membership of a national CFS/ME patient organisation:

Are you currently a member of a national CFS/ME patient organisation? ☐ ☐
Yes No

If yes:

To which organisation(s) do you belong?

Version 1, 07.02.2005

A6.29 Self-paced step test of fitness

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Please refer to the SOP for the step test for further information.

Place a chair as close as possible to the step so that the patient can rest immediately afterwards.

1. BMI Height Weight

2. Record the resting heart rate

Record the participant's heart rate at rest using the heart rate monitor

Beats per minute

3. Step test – acclimatisation at baseline visit only

Ask the participants to do 2 or 3 step-up tests at a slow rate for acclimatisation, which will not be recorded

4. Step test – main test

After five minutes rest, ask the participant to do 20 step-ups at a normal pace.

If the participant is unable to complete 20 steps, please record the number of steps that they were able to complete:

5. Further results

Record the following information:

Time taken (in seconds) to do 20 complete step-ups

Heart rate in beats per minute immediately after the test taken from the heart rate monitor

6. Borg scale answer

Please record which number of the Borg scale for exertion that the participant indicated to be most representative:

A6.30 SF-36 physical function sub-scale

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

Please tick one box on each line

Activity	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports			
Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf			
Lifting or carrying groceries			
Climbing <u>several</u> flights of stairs			
Climbing <u>one</u> flight of stairs			
Bending, kneeling or stooping			
Walking <u>more than a mile</u>			
Walking <u>several hundred yards</u>			
Walking <u>one hundred yards</u>			
Bathing or dressing yourself			

Version 2, 26.11.2004

A6.31 Six minute walking test

PIN		Participant Initials			Date completed		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	

Year

1. Where to complete the test

Measure 10 metres of continuous walking space, which has a level and safe surface. Perform in a 10 metre space. If this is not possible an alternative level surface should be chosen.

2. Tell the participant:

"I am going to assess your walking. Please walk as far as you can. I will let you know when 3 and 5 minutes have passed. You should walk continuously if possible, but can slow down or stop if you need to. Please aim to walk as far as you can in 6 minutes. I am not going to give you any encouragement or talk to you during the test as I will be preoccupied counting, although I will say when 3 and 5 minutes have passed."

Do not give encouragement

Inform patient at 3 and 5 minutes.

Stop at 6 minutes

3. Count corridor (10 metre) lengths completed – you may wish to tally this below:

Number of times corridor length covered

4. Measure distance walked in the last incomplete corridor length (in metres)

Partial distance covered at the end to the nearest metre

The total distance covered will be calculated when the data is added to the database.

Comments on performance and any interruptions

A6.32 Symptom Interpretation Questionnaire

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Please indicate how much you agree or disagree with the following statements about your current symptoms by ticking the appropriate box. (Please tick only one box per line)

Views about your symptoms	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I am afraid that I will make my symptoms worse if I exercise	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My symptoms would be relieved if I were to exercise	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Avoiding unnecessary activities is the safest thing I can do to prevent my symptoms from worsening	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The severity of my symptoms must mean there is something serious going on in my body	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Even though I experience symptoms, I don't think they are actually harming me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
When I experience symptoms, my body is telling me that there is something seriously wrong.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physical activity makes my symptoms worse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SIQ continued

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Views about your symptoms	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Doing less helps symptoms					
Symptoms are a signal that I am damaging myself					
I am afraid I will have more symptoms if I am not careful					
I should avoid exercise when I have symptoms					
I worry that I may become permanently bedridden because of my symptoms					
I think that if my symptoms get too severe they may never decrease					
If I push myself too hard I will collapse					
My illness is awful and I feel that it overwhelms me					
If I overdo things it will cause a major relapse					
I will never feel right again					

SIQ continued

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Views about your symptoms	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
When I experience symptoms, I think about them constantly					
I worry when I am experiencing symptoms					
When I am experiencing symptoms it is difficult for me to think of anything else					
I think a great deal about my symptoms					
My symptoms are always at the back of my mind					
I spend a lot of time thinking about my illness					
I am embarrassed about my symptoms					
I worry that people will think badly of me because of my symptoms					
The embarrassing nature of my symptoms prevents me from doing things					
I avoid social situations because I am scared my symptoms will get out of control					

PIN		Participant Initials			Date completed				
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year		

Views about your symptoms	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I am ashamed of my symptoms					
My symptoms have the potential to make me look foolish in front of other people					
I stay in bed to control my symptoms					
When I experience symptoms, I rest					
I tend to avoid activities that make my symptoms worse					
I tend to nap during the day to control my symptoms					
I tend to overdo things when I feel energetic					
I find myself rushing to get things done before I crash					
I tend to overdo things and then rest up for a while					
I tend to do a lot on a good day and rest on a bad day					

PIN

--	--	--	--

Centre

Participant

Participant Initials

--	--	--

Fore. Midd. Sur.

Date completed

				2	0		
--	--	--	--	---	---	--	--

Day

Month

Year

Views about your symptoms	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I sleep when I'm tired in order to control my symptoms					
I avoid making social arrangements in case I'm not up to it					
I avoid exerting myself in order to control my symptoms					
I'm a bit all or nothing when it comes to doing things					
I avoid stressful situations					

Which of the following best describes the nature of your symptoms (please tick one):

My symptoms are physical	My symptoms are mainly physical	Both physical and psychological factors are involved in my symptoms	My symptoms are mainly psychological	My symptoms are psychological in nature

A6.33 Therapist Rating of Homework Compliance

PIN		Participant Initials			Date completed			
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year	

Session number: _____ Date of session: _____

Name of therapist: _____

In order to rate the homework compliance of the participant please indicate your answer on the scale below. This form should be completed after **every session**.

To what extent do you perceive this patient has completed their homework? This should include patient verbal report of homework completion as well as the written record.

0	10	20	30	40	50	60	70	80	90	100%
Not completed at all										Fully completed

Version 1, 23.09.2004

A6.34 Work and Social Adjustment Scale

PIN		Participant Initials			Date completed				
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Centre	Participant	Fore.	Midd.	Sur.	Day	Month	Year		

Please read each of the following questions and tick the appropriate box to indicate

	No impairment					Very severe impairment			
	0	1	2	3	4	5	6	7	8
Because of my CFS/ME, my ability to work is impaired.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Because of my CFS/ME, my home management (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Because of my CFS/ME, my social leisure activities (with other people, such as parties, bars, clubs, outings, visits, dating, home entertainment) are impaired.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Because of my CFS/ME, my private leisure activities (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Because of my CFS/ME, my ability to form and maintain close relationships with others, including those I live with, is impaired.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Version 2, 26.11.2004

A6.35 Non-serious Adverse Event report log

This log to be completed for all adverse events reported by the participant. Serious Adverse Events should be recorded using the appropriate form and log.

PIN Participant Initials

Start date of AE	Stop date of AE (if known)	Description of adverse event (Brief Description)	Was the event related to trial treatment? (Definitely related/Probably related/Possibly related/Definitely unrelated/Uncertain)	Has participant withdrawn from trial follow-up? (Yes/No)	Please rate the severity of the event if unsure or concerned, consult with Centre Leader (Mild/Moderate/Severe)	Any medication or therapy taken as a result? (Yes/No)	Staff Initials

A6.36 Adverse Event report form

For Office Use Only:
Event No _____

Serious Adverse Event Reporting Form

PIN	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	Participant Initials	<input type="text"/>	<input type="text"/>	<input type="text"/>	DoB	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
	Centre		Participant			Fore.	Midd.	Sur.		Day	Month	1	9			Year
Sex	<input type="checkbox"/>	<input type="checkbox"/>			Date of randomisation	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	2	0			Year
	Female	Male				Day	Month									
Centre	<input style="width: 100%;" type="text"/>															
Check against PIN: 01=Barts I, 02=Edinburgh, 03=Kings 04=Barts II, 05= Oxford, 06=Royal Free																

Please tick one: Initial report ☐ Follow-up report (one month) ☐

Description of adverse event (Continue on separate sheet if necessary)

Event Onset	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
	Day	Month	2	0						:						
Event Resolution	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
	Day	Month	2	0						:						
	Day	Month	Year	Year	Time (24 hours)	Time (24 hours)										

How severe was the event? (Required to be answered by a medically qualified co-investigator)

Mild ☐ Moderate ☐ Severe ☐

Was the event related to the study treatment?

Definitely related ☐

Probably related ☐

Possibly related ☐

Definitely unrelated ☐

Uncertain ☐

In the investigator's opinion, was the adverse event an unexpected or expected event?

Unexpected ☐ Expected ☐

Was intervention required? ☐ ☐

Yes No

If intervention required please give details (Continue on separate sheet if necessary)

PIN	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	Participant Initials	<input type="text"/>	<input type="text"/>	<input type="text"/>	DoB	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
												1	9			

Sex <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <input type="checkbox"/> Centre Female </div> <div style="text-align: center;"> <input type="checkbox"/> Participant Male </div> </div>	Centre <div style="border: 1px solid black; height: 20px; width: 100%;"></div> <small>Check against PIN: 01=Barts I, 02=Edinburgh, 03=Kings, 04=Barts II 05= Oxford, 06=Royal Free</small>	<div style="display: flex; justify-content: space-between;"> Fore. Midd. Sur. Day Month Year </div> <div style="border: 1px solid black; height: 20px; width: 100%;"></div>
---	--	---

Has the patient dropped out from the trial? <i>(If Yes please complete Drop-out Form)</i>	<input type="checkbox"/> Yes	<input type="checkbox"/> No
---	---------------------------------	--------------------------------

SERIOUSNESS Please tick if any of the following describe this event:	
Death	<input type="checkbox"/> 1
Life threatening	<input type="checkbox"/> 2
Results in, or prolongs patient hospitalisation	<input type="checkbox"/> 3
Increase in severe and persistent significant disability/incapacity	<input type="checkbox"/> 4
Any other important condition that may require medical or surgical intervention to prevent the above	<input type="checkbox"/> 5
Any episode of deliberate self harm	<input type="checkbox"/> 6
Please note: If any of the above has been ticked, this qualifies as an SAE and should be reported to your R&D and the Trial Manager immediately.	

IN THE CASE OF AN SAE: THIS SECTION TO BE COMPLETED WHEN FORWARDING TO YOUR R&D			
MREC/02/7/89	R&D No. (if applicable) _____		
Local Investigator _____			
Date study commenced	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Expected date of completion	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
No. of participants entered to date:	Trust _____	Whole Trial _____	
Expected total number to be recruited:	Trust _____	Whole Trial <u>600</u>	
Does the event raise any ethical issues not previously considered?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Will the Information Sheets/Consent Forms require amendment as a result of the Serious Adverse Event?	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	

Summarise any discussions held with the participant following the SAE
--

Investigator's Name _____	Date	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Investigator's Signature _____		Day	Month	Year

PIN	<input type="text"/>	<input type="text"/>	Participant Initials	<input type="text"/>	<input type="text"/>	<input type="text"/>	DoB	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
	Centre	Participant		Fore.	Midd.	Sur.		Day	Month	1	9			Year
Sex	<input type="checkbox"/>	<input type="checkbox"/>	Centre	<input type="text"/>										
	Female	Male		Check against PIN: 01=Barts I, 02=Edinburgh, 03=Kings, 04=Barts II 05= Oxford, 06=Royal Free										

Date of randomisation

				2	0	0	
--	--	--	--	---	---	---	--

Day Month Year

Date of release from PACE protocol

				2	0	0	
--	--	--	--	---	---	---	--

Day Month Year

Treatment patient randomised to:

APT + SSMC ☐ CBT + SSMC ☐ GET + SSMC ☐ SSMC Alone ☐

Please write a brief description explaining the reason for release from protocol

Who has taken the decision for this patient to drop-out of the trial?
Investigator ☐ Patient ☐ Therapist ☐ Other ☐
Please specify _____

Has the patient withdrawn from:
Treatment? ☐ Whole trial (including follow-up)? ☐

Please specify the primary reason(s) for release from protocol	
Eligibility criteria no longer met	
Patient no longer meets CFS/ME criteria (i.e. misdiagnosis, not recovery)	1
The patient has treatment needs that make participation in the PACE trial inappropriate	2
Patient is less than 18 years of age	3
The patient cannot speak and read English at a level adequate for participation in the trial	4
The patient has a psychiatric diagnosis that excludes them from the trial	5
The patient has withdrawn consent	6
The patient is not able to attend hospital regularly and reliably for the duration of the trial	7
There are contra-indications to the patient receiving the trial treatments	8

PTO

Investigator's Name _____
 Investigator's Signature _____
 Date

--	--

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2	0	0	
---	---	---	--

 Day Month Year

A6.38 Randomisation and Notification forms

1. Randomisation Request Form

To register a participant in the PACE trial, please first complete this form and then telephone or fax the Mental Health & Neuroscience Clinical Trials Unit (MH&N CTU) at the Institute of Psychiatry.

The office is open for randomisations 9am to 5pm, Monday to Friday, not Bank Holidays.

Telephone No.: 020 7848 0532

Fax No.: 020 7848 5229

NB: It is important to identify the PACE trial – this is the general telephone line for the CTU and all calls come through on this number. There may be a delay in response of up to 24 hours.

Centre		Fax number of caller	
Name of caller			
Date of randomisation request	20		

PARTICIPANT DETAILS

PIN	[2 digit centre no. followed by 3 digit participant no].		
Participant Name	<small>(NB: If this form is FAXED or SAVED ELECTRONICALLY, the participant's name MUST BE REMOVED first.)</small>	Participant Initials	
Date of Birth	19	Sex	

INCLUSION CRITERIA – All answers must be Yes for the participant to be eligible

1 Participant has given informed consent to be randomised, and to take part in full trial (2) including compliance with treatment and follow-up	Y <input type="checkbox"/>	N <input type="checkbox"/>
2 Participant age is 18 years or more	Y <input type="checkbox"/>	N <input type="checkbox"/>
3 Participant meets Oxford criteria for a clinical diagnosis of CFS	Y <input type="checkbox"/>	N <input type="checkbox"/>
4 Participant has a Chalder Fatigue Score of 6 or more	Y <input type="checkbox"/>	N <input type="checkbox"/>
5 Participant has a SF-36 physical function sub-scale score is less than 66	Y <input type="checkbox"/>	N <input type="checkbox"/>
6 Able to speak and read English at an acceptable level	Y <input type="checkbox"/>	N <input type="checkbox"/>
7 Able to attend hospital regularly, to complete all trial measures and to do any of the trial treatments	Y <input type="checkbox"/>	N <input type="checkbox"/>
8 Has not previously received any of the supplementary therapies to be trialled	Y <input type="checkbox"/>	N <input type="checkbox"/>

EXCLUSION CRITERIA – All answers must be No for participant to be eligible

1 Psychiatric diagnosis identified by SCID that excludes them from the trial	Y <input type="checkbox"/>	N <input type="checkbox"/>
2 Contra-indication to any of the treatments that might be provided in the trial	Y <input type="checkbox"/>	N <input type="checkbox"/>

OTHER INFORMATION NECESSARY FOR RANDOMISATION

London Criteria Met	Y <input type="checkbox"/>	N <input type="checkbox"/>
CDC Criteria Met	Y <input type="checkbox"/>	N <input type="checkbox"/>
Depressive Illness	Y <input type="checkbox"/>	N <input type="checkbox"/>
Chalder Fatigue Score		
SF-36 physical function sub-scale score		

I confirm that the above is complete and correct:

Name

Date

20

Signature

2. Randomisation Notification

Centre		Fax number of caller	
Name of person requesting randomisation			
Date of randomisation		20	

Participant Name	<i>[NB: If this form is FAXED or SAVED ELECTRONICALLY, the participant's name MUST BE REMOVED first].</i>
PIN	<i>[2 digit centre no. followed by 3 digit participant no].</i>
Participant Initials	
Date of Birth	19
Age	
Sex	

Participant Treatment Allocation

- ☐ SSMC
- ☐ SSMC+APT
- ☐ SSMC+CBT
- ☐ SSMC+GET

3. Randomisation Acknowledgement

***This page must be completed and faxed back to the MH&N CTU:
020 7848 5229
IMMEDIATELY after treatment allocation is received***

PACE centre staff name	Date	20
Signature		

Please send to MH&N CTU – Tel: 020 7848 0465 or Fax: 020 7848 5229

A7 Therapy Integrity Rating Scale

A) Alliance and facilitative conditions scale:

1. Supportive encouragement:

Was the therapist supportive of the client by acknowledging the client's gains during therapy, or by reassuring the client that gains will be forthcoming?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

2. Convey expertise:

Did the therapist convey that she/he understood the client's problems and is able to help the client?

1	2	3	4	5	6	7
not at all		some		considerably		very much

3. Therapist's communication style:

How interesting is the therapist's style of communication? (Consider (1) the vividness of her/his language; (2) the originality of her/his ideas; (3) the liveliness of her/his manner of speaking).

1	2	3	4	5	6	7
dull, uninteresting		less interesting than average		more interesting than average		very interesting

4. Involvement:

How involved was the therapist?

1	2	3	4	5	6	7
very detached		somewhat detached		mainly involved		very involved

5. Warmth:

Did the therapist convey warmth?

1	2	3	4	5	6	7
not at all or very little	some		a lot			very much

6. Rapport:

How much rapport was there between therapist and client (i.e. how well did the therapist and client get along?)

1	2	3	4	5	6	7
total absence		some		considerable		excellent
of rapport		rapport		rapport		rapport

7. Empathy:

Was the therapist empathic towards the client (i.e. did she/he convey an intimate understanding of and sensitivity to the client's experiences and feelings)?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

8. Patient self-discloses thoughts and feelings:

1	2	3	4	5	6	7
not at all		somewhat		quite a bit		very much so

9. Patient expresses strong emotions:

1	2	3	4	5	6	7
not at all		somewhat		quite a bit		very much so

10. Patient works actively with therapist's comments:

1	2	3	4	5	6	7
not at all		somewhat		quite a bit		very much so

11. Patient shows confidence in therapy and therapist:

1	2	3	4	5	6	7
not at all		somewhat		quite a bit		very much so

12. Patient and therapist agree on the kind of changes to make:

1	2	3	4	5	6	7
not at all		somewhat		quite a bit		very much so

13. Patient and therapist share same sense about how to proceed:

1	2	3	4	5	6	7
not at all		somewhat		quite a bit		very much so

14. Patient and therapist agree on salient themes:

1	2	3	4	5	6	7
not at all		somewhat		quite a bit		very much so

B) Therapy scales

CBT scale

1. Rationale for behavioural procedures:

Did the therapist provide a rationale which emphasised the importance for the client of undertaking specific activities in order to alleviate the client's symptoms?

1	2	3	4	5	6	7
not at all		some discussion		considerable discussion		extensive discussion

2. Practising/planning alternative behaviours:

Did the therapist work with the client to plan, or to practice alternative overt behaviours for the client to utilise outside of therapy?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

3. Rationale for cognitive procedures:

Did the therapist provide a rationale which emphasised the importance of evaluating the accuracy of the client's beliefs and changing inaccurate beliefs in order to alleviate the client's fatigue?

1	2	3	4	5	6	7
not at all		some discussion		considerable discussion		extensive discussion

4. Recognising cognitive errors:

Did the therapist help the client to identify specific types of cognitive distortions or errors (e.g. all-or-nothing thinking, over-generalisation) that were present in the client's thinking?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

5. Searching for alternative explanations:

Did the therapist help the client to consider alternative explanations for events besides the client's initial explanations for those events?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

6. Maintaining gains:

Did the therapist encourage the continued use after the end of therapy, of the skills the client had acquired during therapy?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

Adaptive Pacing Therapy Scale

1. Rationale for balancing activity:

Did the therapist provide a rationale which emphasised the importance for the client of balancing activity?

1	2	3	4	5	6	7
not at all		some		considerable		extensive
		discussion		discussion		discussion

2. Practising alternating physical and mental activities:

Did the therapist work with the client to plan and or practice alternating physical and mental activities outside of therapy?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

3. Rationale for energy conservation and expenditure:

Did the therapist provide a rationale which emphasised the importance of energy conservation and expenditure?

1	2	3	4	5	6	7
not at all		some		considerable		extensive
		discussion		discussion		discussion

4. Discussion about the importance of prioritising certain activity:

Did the therapist discuss with the client the importance of prioritising activity?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

5. Discussion about the importance of activity analysis and modification:

Did the therapist help the client to analyse and/or modify specific activities?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

6. Importance of rest and relaxation

Did the therapist teach and practice rest and relaxation techniques with the client?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

Graded Exercise Therapy Scale

1. Rationale for use of exercise or physical activity:

Did the therapist provide a rationale which emphasised the importance and benefits of exercise or physical activity?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

2. Discussion about the content of a physical exercise programme:

Did the therapist discuss the content of a physical activity or exercise programme with the participant?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

3. Monitoring the physiological effects of exercise:

Did the therapist discuss ways of monitoring the physiological effects of exertion (heart rate/Borg rating scale) with the participant?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

4. Incremental Changes

Did the therapist emphasis the importance of incremental, progressive changes in physical activity or exercise?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

5. Adapting programme

Did the therapist discuss how the participant could adapt their exercise or physical activity according to their changing circumstances or goals?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

1. Physical goals

Did the therapist discuss, review or refer to the patient's physical goals?

1	2	3	4	5	6	7
not at all		some		considerably		extensively

C) Finally

Homework assigned/reviewed: (same for all therapies)

Did the therapist or client develop one or more specific assignments for the client to engage in between sessions?

1	2	3	4	5	6	7
did no homework	some attempt to develop homework		considerable attempt to develop homework			extensive attempt to develop homework

Overall, how would you rate the therapeutic alliance?

1	2	3	4	5	6	7
very poor		fair		good		excellent

Was this therapy session:

Adaptive Pacing Therapy	1
CBT	2
Graded Exercise Therapy	3

A8 PACE Policy on Ancillary Studies

This is the policy to approve ancillary studies that involve PACE trial participants

Introduction

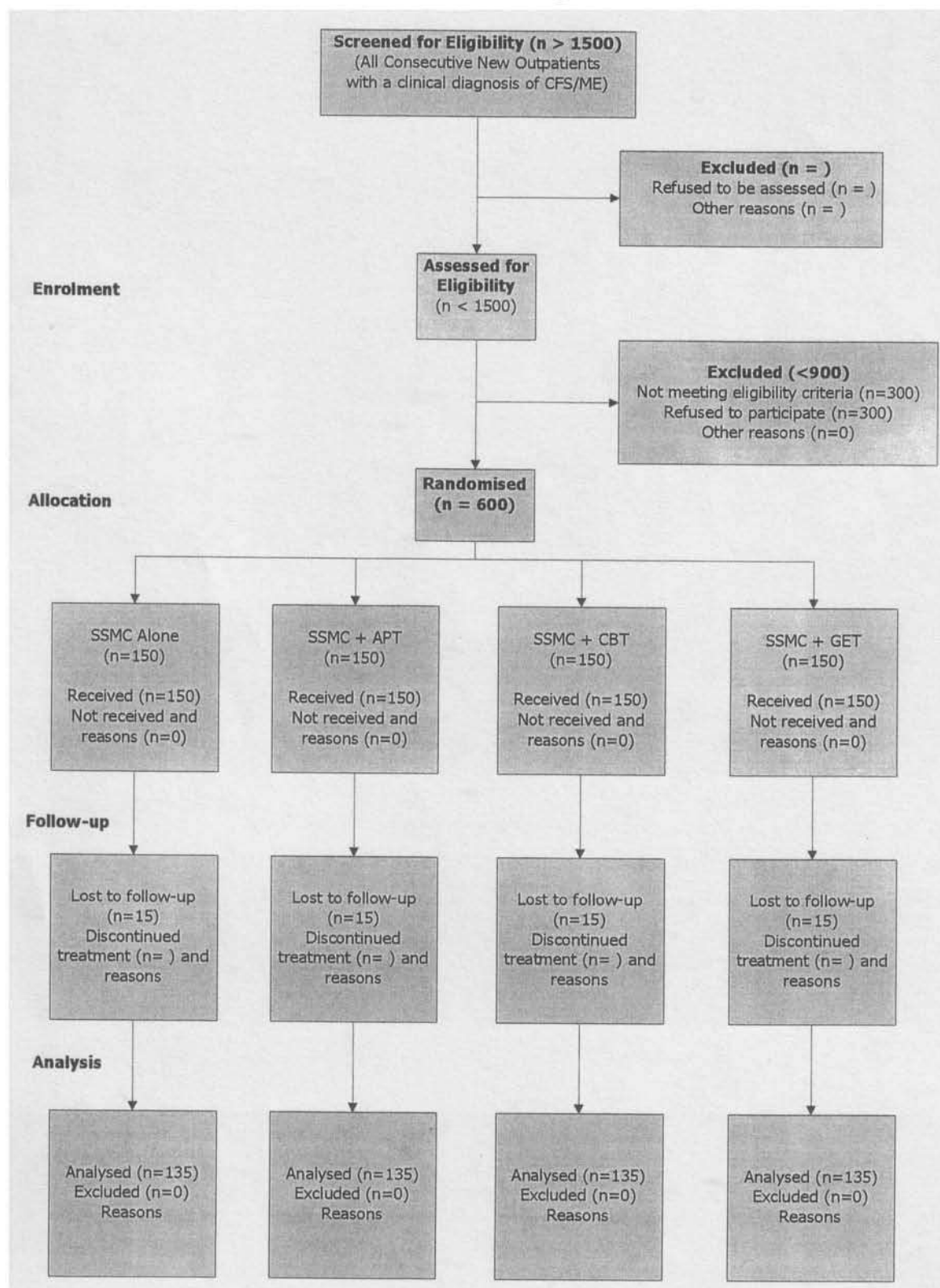
The PACE trial is an opportunity to answer related scientific questions about CFS/ME and its treatments. It is important that any ancillary studies do not affect the smooth running of the PACE trial in any way, do not affect recruitment or retention, and do not overburden the PACE participants or the PACE trial staff. The TMG have therefore agreed the following procedure that must be undertaken before any supplementary study is undertaken.

Procedure to approve ancillary studies

1. The principal investigator of the proposed ancillary study will submit a written protocol to one of the investigators (White, Sharpe or Chalder)
2. The receiving investigator will discuss the protocol with the other two investigators.
3. The investigators will decide whether to refuse the request, ask for further clarification, or submit the protocol for consideration at a meeting of the TMG. This will be communicated to the proposing PI.
4. The TMG will consider the request at one of its meetings and will bear in mind the following questions before making its decision:
 - a. Who are the investigators involved in the study, and are the three PIs named investigators?
 - b. Will the study use existing trial data or will new data be required?
 - c. What is the likely scientific value of the proposed study?
 - d. Does it have ethical approval, or is it likely to receive this?
 - e. How many patients and centres will it affect?
 - f. What effect will it have on participant recruitment, and retention?
 - g. What other studies are taking place at the centre/s involved?
 - h. Are the participants involved in any other research studies?
5. The TMG will consider the request at one of its meetings and will bear in mind the following principles before making its decision:
 - a. No ancillary study should be approved if there would be a significant risk that it would affect participant recruitment or retention.
 - b. Any ancillary study should receive the consensus of the TMG.
 - c. Any ancillary study should acknowledge the approval of the PACE TMG in any subsequent publication.
 - d. All publications will include the three PIs as co-authors.
6. If there is no consensus within the TMG, one of the PIs will discuss approval with the Chair of the TSC Professor Darbyshire.
7. The TMG will supply a cumulative list to the TSC of any approved ancillary studies which will include details of any extra burden to participants. The TSC will retain the power to veto any study previously approved by the TMG.

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A9 Consort Diagram



Version 1, 22.10.2004

Acknowledgment

This protocol was based on a template protocol supplied by the MRC Clinical Trials Unit of University College, London. We are grateful for being given permission to use this template.