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THE PACE TRIAL IDENTIFIER – THE MEDICAL RESEARCH COUNCIL

1. Trial identifier

1.1 Full title of trial

RCT of CBT, graded exercise, and pacing versus usual medical care for the chronic fatigue syndrome

1.2 Acronym

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

2. The need for a trial

2.1 What is the problem to be addressed?

The chronic fatigue syndrome (CFS) is a condition characterised by chronic disabling fatigue and other symptoms, which is not associated with either an identifiable disease process or a major psychiatric illness.[1-3] Myalgic encephalomyelitis (ME) is thought by most to be synonymous with CFS.[1-5] The prevalence of CFS in primary care is between 1 and 2%.[3] An independent working party, reporting to the English Chief Medical Officer, 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 are unemployed,[6] and they have 10 times the amount of sick-leave of other general medical outpatients.[7] 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 premorbid functioning.[3,8] The management of patients with CFS consumes significant resources in both primary and secondary cafe.[2,3] CFS patients use an annual average of 13 visits to their general practitioner and 5 visits to secondary care.[6] However there is now evidence that specific treatments can improve patient outcome. The CMO's working party concluded;

"Therapeutic strategies that can enable improvement include graded exercise/activity programmes, cognitive behaviour therapy, and pacing."[4] This positive statement was balanced in the report by, first the concern of patient organisations that graded exercise therapy (GET) and cognitive behaviour therapy (CBT) may worsen symptoms and disability, and second that pacing, although widely advocated by patients' organisations, is as yet unsupported by scientific evidence.

2.2 What are the principal research questions to be addressed?

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

2.3 Why is a trial needed now?

Efficacy: Two independent systematic reviews have found that rehabilitative CBT and GET were the most promising treatments for CFS in secondary care.[5,9,10,11] Yet the authors criticised the methodology of the published trials for being too small, too selective, and using different outcome measures. No other treatments for CFS have been shown to be helpful in more than one RCT.[5,11] CBT is a more complex therapy than GET, requiring highly trained therapists, and is therefore less available through the NHS. In contrast to this evidence, 2,338 members of the patient charity *Action for ME* (*AfME*) reported that CBT and GET were more likely to make them worse rather than better.[12] Pacing and rest were reported to be more helpful.[12] 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.[4,13] It has been advocated by exponents of

the "envelope theory" of CFS, which states that a patient has a fixed and finite amount, or envelope, of energy that they must adapt to by managing activity.[13] 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.[14] A recent systematic review concluded that there was insufficient evidence to recommend adaptive pacing at present[5,9,11] There is therefore an urgent need to: (a) compare CBT and GET with both APT and usual medical care alone (UMC), seeking evidence of both benefit and harm (b) compare APT against UMC, and (c) compare CBT and GET to each other to clarify differential predictors and mechanisms of change.

Differential outcomes: Because CBT and GET are based on graded exposure to activity or exercise, they may preferentially improve disability, whilst APT, being based on the theory of staying within the limits of a finite amount of "energy", may improve symptoms, but at the expense of disability. By measuring both symptoms and disability as our primary outcomes, we will be able to address this issue.

Process of treatment: We do not know the essential mechanism of successful rehabilitation from CFS. Do illness beliefs or focussing of attention on symptoms (symptom focusing) need to be changed by CBT? Or does CBT work solely by graded exposure to avoided activity, which also occurs with GET? Is increased physical fitness following increased physical activity, essential to recovery or not? How important is the alliance between therapist and patient? Is it important to adapt to the illness to allow symptomatic relief? A greater understanding of these processes will shed light on the nature of recovery from CFS and allow the development of more efficient treatments.

Predictors of outcome: We also need to know which patients require the more complex CBT rather than the simpler and more readily available GET. Previously found predictors of a negative outcome with treatment include mood disorder, membership of a self-help group, being in receipt of a disability pension, focusing on physical symptoms, and pervasive inactivity.[3,15] No predictive factor has been found in more than one published study, probably due to a type II error.

Cost-effectiveness: There are no published data on the cost-effectiveness of treatments for CFS. CBT is relatively expensive and uses scarce therapeutic resources: we need to know relative cost-effectiveness and cost-utility.

2.4 Systematic reviews

Two recent systematic reviews of treatments for CFS were published together, because their conclusions were the same.[11] Whiting and colleagues concluded that RCTs had shown that CBT and GET were "promising treatments", with criticisms outlined in section 2.3. They found insufficient evidence to recommend adaptive pacing. The York University guidance, stemming from their review, recommended that a comparison of CBT, GET and pacing was particularly needed.[5]

2.5 How will the results of this trial be used?

The results of this trial will: (a) allow health planners, clinicians and patients to choose treatment on the basis of both efficacy and cost; (b) provide evidence to either reassure or confirm patients' doubts about the efficacy and negative effects of the more active rehabilitation therapies (CBT and GET) in contrast to adaptive pacing; (c) provide the first test of pacing against usual medical care; (d) indicate which patient characteristics predict response to which treatment; and (e) define the essential aspects of effective treatment as a step toward the development of more efficient therapies.

The trial will recruit from secondary care clinics run by three different disciplines (immunology, infectious disease and psychiatry) in six different centres in both England and Scotland to 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 problematic in previous studies. Two recent trials of treatment for prolonged fatigue using large and well established primary care research networks

recruited only 46 patients with CFS in three years in one study[16] and 44 patients in 2.5 years in the other (personal communication, Lucy Darbishire).

2.6 Risks to safety of the patients in the trial

There is a discrepancy between patient organisation reports of the safety of CBT and GET and the published evidence of minimal risk from RCTs. A survey of AfME members suggested that GET can sometimes cause a set-back in symptoms or disability, rather than improvement.[12] AfME suggests that such set-backs probably results from rigidly applied GET that is not tailored to the patient's disabi|ity. Our treatment manual by being based on mutually agreed and flexible programme that varies according to patient response. We will also carefully monitor for any adverse effects of the treatments, and will undertake a detailed assessment, at home if necessary, for any subject who drops out of treatment for this reason, following which they will be offered appropriate help.

3. The proposed trial

3.1 The proposed trial

This trial will compare the efficacy and adverse effects of four different treatments for CFS. All subjects will receive usual medical care (UMC), and in three arms this will be supplemented by a specific therapy. Hence the four groups will be CBT and UMC, GET and UMC, APT and UMC, and UMC alone while on a waiting list for treatment. We will also (a) study the process and predictors of effective therapy and (b) compare the cost-effectiveness of each treatment condition.

3.2 What is the proposed trial design?

A four arm, single blind, randomised controlled trial in consecutive referrals of patients who meet operationalised criteria for CFS, with follow-up for 12 months.

3.4 What are the planned trial interventions?

All patients will receive UMC. Those allocated to specific treatments will all also receive 14 sessions of that treatment (CBT, GET or APT) with equal therapist time (90 minutes in the first session, and 50 minutes thereafter) for each therapy. We have chosen 14 sessions on the basis of the positive trials of CBT and GET,[15,17,20] as well as extensive clinical experience. RCTs of the least effective CBT and GET used 6 and 8 sessions.[20,21] Although one study of a pragmatic rehabilitation found that only 4t sessions were helpful,[22] we believe 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. All interventions will be based on manuals apart from UMC, where guidance will be given to treat patients as usual (see appendices).

CBT will be based on the illness model of fear avoidance, used in the three positive trials of CBT.[15,17,18] 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) Challenging of unhelpful beliefs about symptoms and activity (see appendices 2 & 6).

GET will be based on the illness model of both deconditioning and exercise avoidance, used in the previous trials.[19,20,22] Therapy involves an assessment of physical capacity, negotiation of an individually designed home aerobic exercise programme with set target heart rates and times, and sessional feedback with mutual planning of the next fortnight's home exercise programme (see appendices 3 & 6).

APT will be based on the illness model that CFS is an undetermined organic disease, but that APT can improve quality of life without affecting the core disease. APT 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.[13] A/ME have helped to design 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 4,6 & 11).

UMC (the control treatment) will include symptomatic pharmacotherapy (see appendix 5), with no specific advice regarding activity and rest management beyond that normally given by the clinician; there will be no specific therapist involvement. In particular there will be no diary monitoring with consequent advice. Subjects randomised to UMC will be placed on a waiting list for the therapy of their choice, to start after their last follow-up interview, in order to improve recruitment and ensure adequate care. The nature of UMC actually given by individual clinicians will be recorded (see appendix 5).

3.4 What are the proposed practical arrangements for allocating participants to trial groups?

The Clinical Trial Unit (CTU) trial statistician will prepare subject numbers for each centre by permuted block randomisation, using a computerised randomisation system, so that equal allocation is achieved every N subjects recruited in each centre. N will be unknown to trial centres and will vary throughout the trial to prevent allocation predictions. Local centre doctors (including centre leaders) will assess consecutive clinic new patients, as usual, and pass on details of willing potentially eligible patients to the centre research nurse (RN) for trial screening. Reasons for non-participation at this stage, and demographic details, will be recorded. Once an eligible subject has given informed consent, and completed the baseline assessment by the centre RN, the RN will contact the centre leader, who will contact the CTU web-site for an automatically given trial identification number and treatment allocation, with the trial co-ordinator (TC) being automatically informed at the same time. The centre leader will immediately inform the subject of his/her treatment group in person or by phone, and also inform the appropriate therapist or clinician (for UMC). We will not stratify our sample by anything beyond centres since there is no replicated evidence that any factor influences treatment response (section 2.3; predictors of outcome) and stratification by all possible factors would be elaborate and reduce recruitment. Potential predictors are common enough to be well distributed by chance alone in the 600 subjects to be studied.

3.5 What are the proposed methods for protecting against other biases?

Assessment bias at outcome will be minimised by use of self-rated primary outcomes. The secondary measures include an exercise test and we will therefore endeavour to keep the outcome assessor conducting these (Research nurse: RN) blind to treatment group.

Bias by non-participation will be measured by recording measures from potential subjects who did not meet criteria for the trial and from those who refuse consent. Therapists will receive training and some supervision together in order to minimise inter-centre differences.

Therapist compliance with treatments will be monitored in two ways. (1) All therapists will receive weekly local supervision and monthly central group supervision. All therapy sessions will be audiotaped. Some tapes will be used by trainers/supervisors to provide feedback to therapists on competence and treatment fidelity. Any significant deviations from the manual will be noted. (2) One taped session per subject will be randomly chosen and assessed blindly and independently by two assessors to assess adherence to manual defined therapy.

Subject non-compliance with treatment will be measured both by recording attendance and by therapist ratings of adherence to therapy using a visual analogue scale.

Generalisability will be measured by comparing between different centres and disciplines.

3.6 What are the planned inclusion/exclusion criteria?

Inclusion criteria: Subjects will be required to meet operationalised Oxford criteria for CFS.2 This means 6 months or more of medically unexplained, severe, disabling fatigue affecting physical and mental functions.[2] We will operationalise CFS in terms of fatigue severity and disability as follows: a Chalder fatigue score[23] of four or more and an SF36 physical function score[24] of less than 75 (see section 3.9). We chose these broad criteria in order to enhance generalisability and recruitment. The more narrowly defined CDC criteria are about to be revised and then superseded by an empirically derived definition (PDW is a member of this CDC led group). Those subjects who also meet the criteria for "fibromyalgia" (chronic widespread pain) will be identified but included,[25] because CFS and "fibromyalgia" commonly coexist.26 Subjects will be of either gender. There will be no upper age limit, but all subjects will be aged at least 18 years old, since younger

patients usually require a different family oriented approach.[27] Subjects will be discouraged from starting over the counter medicines or alternative treatments, but if they do, they will be encouraged to report their use to the centre research nurse, so that their use can be compared between centres and treatment groups.

Exclusion criteria: The RN will use a standardised psychiatric interview,[28] under supervision by the centre psychiatrist, to exclude those who are at significant risk of self-harm and those with a chronic somatisation disorder, as well as determine the psychiatric exclusions listed in the Oxford diagnostic criteria for CFS.[2] All potential subjects will be screened for important medical exclusions, by history and physical examination.[1,2,4] Appropriate investigations4 will be undertaken by either the referring doctor or the centre consultants (checked by the RN). Other exclusions will be: subjects who do not speak or read English adequately (because of the self-report questionnaires); subjects unable to either attend hospital reliably or to do therapies; those less than 18 years old (see inclusions); those who have previously been treated within a fatigue clinic with CBT, GET or APT.

3.7 What is the proposed duration of treatment period?

All subjects will have their first 4 sessions once weekly, and will then be seen fortnightly for 10 further sessions, making 14 sessions in total over 23 weeks. Clinical experience suggests that this initially intense therapy works best. The same amount of time spent with the therapist will control for non-specific therapeutic effects.

3.8 What is the proposed frequency and duration of follow up?

Subjects will be seen at 10 weeks (between the 7th and 8th treatment sessions), 24 and 52 weeks after treatment starts.

3.9 What are the proposed outcome measures?

Primary efficacy measures:

Since we are interested in changes in both symptoms and disability we have chosen to make both fatigue and physical function 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,[23] and has been the most frequently used measure of fatigue in most previous trials of these interventions. We will use the 0,0,1,1 item scores to allow a categorical threshold measure of "abnormal" fatigue with a score of 4 having been previously shown to indicate abnormal fatigue.[23] A Likert scoring (0,1,2,3) will also be used, as a secondary outcome measure, to better measure response to treatment. The SF-36 physical function sub-seal[24] measures physical function, and has often been used as an important outcome measure in trials of CBT and GET. We will count a score of 75 (out of a maximum of 100) or more as indicating normal function, this score being one standard deviation below the mean score (90) for the UK working age population.[29]

Secondary measures:

Efficacy: 1. 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.[30] 2. Daytime physical movement (an objective measure of activity) will be measured over 48 hours with an Actiwatch attached to the ankle. 3. The Hospital Anxiety and Depression scale will measure change in anxiety and depression.[31] 4. The 36 item short-form health survey (SF-36) measures not only physical but also social and role functioning.[24] 5. The EuroQOL (EQ-5D) visual analogue scale provides a simple global measure of quality of life.[32] 6. The Client Service Receipt Inventory (CSRI), adapted for use in CFS,[33] will measure hours of employment/study, wages and benefits received, allowing another more objective measure of function. 7. An operationalised Likert scale (from much better to much worse) of the nine CDC symptoms of CFS.[1]

Adverse effects: Apart from finding out why subjects who prematurely stop their therapy did so (see section 2.6), we will also administer the CGI, the SF-36 physical functional scale and the operationalised nine CDC symptoms of CFS1 at all interviews, in order to monitor for significant set-backs.

Possibly predictive variables (*measured at baseline*): 1. The Queen's College three minute step test (which measures heart rate response to exercise and estimates VO2max).[34] 2. Body mass index, which has been

shown to predict poor functional response to GET.[35] 3. Pervasive inactivity (measured by actigraphy) has predicted poor response to CBT.[15] 4. Hospital Anxiety and Depression sub-scale scores for depression and anxiety have been shown to predict poor outcome with treatment.[36] 5. Current membership of a self-help group, shown to predict poor outcome with CBT.[36] 5. The CSRI will measure disability benefits received,[33] again shown to predict poor outcome with CBT.[15,36] 6. We will ask subjects their preferential treatment. 7. We will also examine whether CDC or "ME" criteria define response, because of many patients and some clinicians belief that pacing is better than CBT and GET in these patients.[1,4]

Process variables (*measured during therapy and at follow-up*): Changes in fitness,[34] physical activity (by actigraphy), the belief that exercise/activity is harmful, the belief that symptoms indicate harm, the belief that control of activity is beneficial, and an enhanced sense of control of the illness will all be measured. We will also measure the strength of the therapeutic alliance.[37]

Economic: The number of hours per week of voluntary and paid work or study will be calculated. Service utilisation and costs of treatment will be calculated. The CSRI will collect service utilisation data, wages and benefits received.

3.10 How will the outcomes be measured at follow-up?

All subjects will be re-assessed in clinic. Self-rated measures will be posted to the subject prior to the visit and checked for completion by the RN. Although all our primary and secondary outcomes are either self-rated or objective, we will endeavour to keep the RNs blind to treatment group in order to minimise interview bias. Subjects 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 (or failing this assessment by telephone or by post). Those subjects who have dropped out of the study will be telephoned to offer an opportunity to learn why, and will be sent questionnaires by post for the two primary outcomes, if willing to receive them.

3.11 Will health service research issues be measured at follow-up?

We will be measuring health and other service utilisation for all subjects, and the associated costs (best national estimates of long-run marginal opportunity costs). Lost productivity and caregiver costs will also be measured.

3.12 What is the proposed sample size and what is the justification for the assumptions underlying the power calculations?

Assumptions: At one year we assume that 60% will improve with CBT, 50% with GET, 25% with APT and 10% with UMC. The existing evidence suggests that at one year follow up, 50 to 63% of subjects with CFS had a positive outcome, by intention to treat, in the three RCTs of rehabilitative CBT,[15,17,18] with 69% improved after an educational rehabilitation that closely resembled CBT.[22] This compares to 18 to 63% improved in the two RCTs of GET,[19,20] and 47% improvement in a clinical audit of GET.[38] For usual medical care 6% to 17% improved by one year in two RCTs.[15,22] There are no previous RCTs of APT to guide us," 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.[18,19] We propose that a clinically important difference would be between 2 and 3 times the improvement rate of UMC.

Power analyses: Our planned intention to treat analyses will compare APT against UMC, and both CBT and GET against APT. Assuming $\alpha = 5$ % and a power of 90 %, we require a minimum of 135 subjects in the UMC and APT groups, 80 subjects in the GET group and 40 in the CBT group.[39] 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 subject per group; numbers beyond a realistic two-arm trial. Therefore, we will study equal numbers of 135 subjects 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 and 3,10, and 40% in the three studies of rehabilitative CBT.[12,14] On the basis

of our own previous trials, we estimate a dropout rate of 10%. We therefore require approximately 150 subjects in each treatment group, or 600 subjects 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. Since costs are not expected to vary significantly between or within groups, the treatment determined number of 150 per arm is likely to find significant differences in cost-effectiveness.

3.13 What is the planned recruitment rate?

All centres will recruit at a rate of a minimum of 33 subjects per year. All centres see a minimum of 100 new patients with undiagnosed chronic fatigue per year. We estimate that 50 patients will meet eligibility criteria, and a conservative estimate is that two thirds will agree to enter the trial. Only seven and 15% of eligible subjects refused to participate in the previous GET trials[15,16] and three, 10 and 26% of those eligible refused CBT.[12,14] We are therefore confidant that recruitment, at an overall rate of 200 subjects per year is feasible and will achieve 600 participants over three years. We will however closely monitor recruitment, especially in the first six months, and the trial management committee, after advice from the TSC, will consider replacing those centres that either do not recruit sufficient subjects, or fail to provide quality data.

3.14 Are there likely to be any problems with compliance?

Non-compliance was less than 10% in our own 3 RCTs, although higher in others trials. Since our estimates of efficacy were based on all these studies, which incorporated non-compliance, our numbers of subjects should be adequate, especially as non-compliance will not differentially affect predictors and process.

Compliance with both the treatments and the study will be maximized by the collaboration and support of *AfME*, and by the inclusion of APT, which is recommended by most patient charities, in the trial. The acceptability of and compliance with the UMC will be maximized by being placed on a waiting list for the therapy of their choice.

3.15 What is the likely rate of loss to follow-up?

We estimate 10% on the basis of data summarized in section 3.12. We will contact lost subjects to gather as much outcome data as possible, particularly the two primary outcome measures, which could be recovered by phone, fax, or post.

3.16 How many centres will be involved? Six

3.17 Are there any planned subgroup analyses?

Not beyond the inter-centre comparisons of the two primary outcomes.

3.18 What are the proposed type of analyses

Efficacy: We will analyse all outcomes by intention to treat. We will perform pair-wise comparisons of the proportions with a positive primary outcome in the APT and UMC groups, and in the APT and combined GET and CBT groups, using chi-squared tests. We will perform chi-squared tests for trend across the UMC, APT and GET groups, and across the UMC, APT and CBT groups. Any inter-centre or baseline significant inter-group differences will be controlled for using logistic regression. Secondary end-points for efficacy will compare changes from baseline to 12 months on both the 33-point Chalder fatigue scale and 100-point SF36 physical function scores using analysis of covariance. Other secondary outcome measures will be compared by t tests or Kruskall Wallis tests, depending on the distribution.

Adverse effects: The drop-out rates and the prevalence of both specific and any adverse effects will be compared by Chi square test.

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 first order interactions. 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 patients outside the trial. Economic evaluations: The incremental cost-effectiveness/utility ratios will be derived and confidence intervals reported. Considering the difficulties of a ratio measure and the common finding of non-normality in the distribution of the criterion variable, we will employ bootstrapping methods. Cost-effectiveness acceptability curves will be fitted and net benefits calculated. Sensitivity analyses will also be carried out.

3.19 What is the proposed frequency of analyses?

We will do one post-trial analysis, because we are interested in process, predictors and cost-effectiveness, which will require the fall number of subjects. The Data Monitoring and Ethics committee may wish to collate blind adverse outcome data during the trial to ensure that no specific therapy is causing undue adverse effects.

3.20 Has any pilot study been carried out using this design?

We ourselves completed three out of seven of the RCTs of CBT and GET. The therapies and measures to be used are essentially the same as used in these successful trials. Because APT is less well tested, we will pilot this treatment in the first six months of the trial.

3.21 Will there be NHS cost implications for this trial?

Yes; the costs of the extra therapists and the service support costs.

3.21 Over what period is funding requested? Five years

4. Trial management

4.1 What are the arrangements for day to day management of the trial?

The trial will be run by the trial co-ordinator who will be based at Barts and the London , with the principal investigator (PI), and alongside two of the six clinical centres. He/she will liaise regularly with staff at the Clinical Trials Unit (CTU) who themselves will be primarily responsible for randomisation and database design and management (overseen by the centre statistician Dr Tony Johnson), directed by Professor Simon Wessely, in collaboration with Professor Janet Darbyshire at the MRC CTU.

The six centre leaders, and co-leaders where appropriate, will oversee recruitment, inform subjects and therapist of their randomisation, and will help screen subjects. They will also be responsible for recruitment, training, and day-to-day supervision of the local therapists, centre RN and database/clerical officer. The PI (PW) will chair the trial management committee (TMC, composed of applicants, collaborators, and TC), which will initially meet every 2 months for the first year and then as necessary.

4.2 What will be the responsibilities of the applicants?

Drs. Peter White (PW), Michael Sharpe (MS) and Trudie Chalder (TC) will be centre leaders. PW will be the co-trainer and co-supervisor of GET (with Ms Lucy Darbishire) and will supervise the trial coordinator. MS and TC will oversee training and supervision of CBT (with Mr Vincent Deary). TC will oversee training and co-supervise APT (with Dr Diane Cox). PW, MS, and TC will oversee treatment adherence.

4.4 What will be the responsibilities of the staff employed on the grant?

The *Trial co-ordinator* (TrCo) will be responsible for checking the quality of the central trial database, and will send local research nurses (RNs) query forms as necessary. The TrCo will monitor trial recruitment against targets and regularly communicate these data to centre leaders and the PL Along with the applicants, he/she will train and help to supervise the local centre RNs and database/clerical officers. The TrCo will write a regular trial newsletter for subjects and trial staff. The TrCo will service the meetings of the TMC, TSC and DMEC. He/she will be primarily responsible for analysis and writing up, with appropriate support.

The local centre 0.6 WTE *Research Nurses* (RNs) will screen all potential and participating subjects, consenting the eligible subjects, and execute baseline and outcome assessments, endeavouring to remain

blind to trial arm, providing preliminary summary analyses of actigraphy data analysed locally. They will send birthday and Christmas (or New Year) cards to all their centre subjects for the duration of the project

The local centre 0.5 WTE *database entry clerical officer* will enter the hard copy data on the CTU designed database at a local level, sending the data regularly and electronically to the CTU. They will also be responsible for communication by phone and letter with potential and actual trial subjects, with an ansaphone available out of hours.

The three 0.5 WTE *therapists* at each centre, funded by the NHS, will receive training in both London and their centres in the first 6 months, then treat the subjects locally, monitor their subjects' treatment adherence and attendance, audiotaping every session, and attend the appropriate London centres monthly for supervision. In order to encourage manual adherence and treatment enthusiasm, the therapies will be provided by separate staff (CBT by a CB therapist, GET by a physiotherapist, and APT by an occupational therapist). Ms Lucy Darbishire (GKT), Dr Diane Cox (St Martin's College, Lancaster) and Mr Vincent Deary (South London and the Maudsley Trust) will help to train and supervise GET, APT and CBT respectively, on a part-time basis. Dr Paul McCrone (GKT) will analyse the health economic data.

4.4 What will be the responsibilities of the named collaborators?

Prof. Anthony Pinching will lead the Baits immunology centre. Dr David Wilks will co-lead the Edinburgh centre. Prof. Tim Peto and Dr Eleanor Feldman will co-lead the Oxford centre. Dr Gabrielle Murphy will lead the Royal Free centre. Professors Peto and Pinching and Dr Wilks will advise regarding any uncertain medical exclusions. Prof. Simon Wessely will oversee the CTU, with the support of Dr Tony Johnson and Prof. Janet Darbyshire. Prof. Martin Knapp will oversee the analysis of the health economic data. Prof. Tom Meade (London School of Hygiene and Tropical Medicine) is a senior consultant. Mr. Chris Clark, CEO of A/ME, will be a member of the TMC and help with external relations.

4.5 Who will be the trial statistician?

TBA (CTU post about to be appointed) will be supervised by Dr Tony Johnson.

4.6 Trial Steering committee

Chairman: Professor Tom Craig, (GKT). *Independent members*: Professor Anne Farmer (Institute of Psychiatry); Dr Meirion Llewelyn (University of Wales); Mrs. Frankie Campling (ex-sufferer and CFS counsellor). *Applicants*: PW, MS and TC, and the trial co-ordinator.

5 Financial details of the trial

5.1 Financial summary

The total cost to the MRC is: ***£1,921.883***

Research staff costs: One London based trial co-ordinator (grade AR4) for 5 years: £234,258. Two non-London (Oxford & Edinburgh) based 0.6 WTE RNs (grade G) for 4.25 years: £164,440. Two non-London based 0.5 WTE database entry/clerical officers (CG5) 4.25 years: £102,186. Two London (RFH & GKT) based 0.6 WTE RNs (grade G) for 4.25 years: £183,302. Two London based 0.5 WTE database entry/clerical officers (CG5) for 4.25 years: £114,568. One London (two Barts/London centres) based WTE RN (grade G) for 4.25 years: £152,753. One London based WTE database entry/clerical officer (CG5) for 4.25 years: £120,729. One London based economist: 165 days over 5 years: £21,869. ***Total: £1,097,266***

Overheads: 46 per cent of research salaries: Total: ***£504,742***

Equipment: 12 "Actiwatch Plus" activity sensors (Cambridge Neurotechnology), 6 "Sleepwatch" analysis packages, 6 reader/interface base stations, 11 computers, printers and software, 36 Polar heart rate monitors and transmitter belts, 6 digital metronomes, twelve-inch steps and stop-watches for fitness testing, 18 audio machines, 3,150 audiotapes. ***Total: £36,360***

Staff Travel: Inter alia: Travel and/or accommodation (5 nights maximum) expenses of therapists and research staff for training and/or supervision, centre leaders for TMC meetings. ***Total: £64,880***

Consumables: Inter alia: CTU randomisation and database design and maintenance (78 days @ £385): £30,030. Therapist training/supervision consultancy: £45,240. Travel expenses for treatment of subjects: £10 per session for 450 subjects (14 visits): £63,000. Research travel expenses for subjects (£20 x 4 x 600): £48,000. A/ME consultancy costs: £4,312 (14 days). ***Total: £218,635***

Costs to the NHS: ***£1.179.909***

Costs of therapists: We have approached our NHS providers for these costs. We need 7 WTE therapists in the 6 centres: 2.5 WTE of CBT, 2 WTE physiotherapists, and 2.5 WTE OTs. Considering different costs in and out of London, this amounts to £241,424 p.a. over 4.5 years (including 6 months training), a total of £1,086,359. Service costs amount to £93,550. ***Total: £1,179,909***.

Year	2003/4	2004/5	2005/6	2006/7	2007/8	Total
Research	398,205	415,622	423,268	429,429	255,359	1,921,883
Treatment	241,424	241,424	241,424	241,424	120,663	1,086,359
Service	24,600	19,700	19,700	19,700	9,850	93,550
TOTAL	664,229	676,746	684,392	690,553	385,872	3,101,792

5.2 Justification for support requested

The trial coordinator will be an experienced post-doctorate science graduate with research, administrative, statistical and computer experience. This experience is necessary for the multiple tasks required.

The six 0.6 WTE local research nurses (RNs) need to be trained in the use of the assessments and trial research methodology, and be able to use a computer in order to summarise actigraphy data. We have chosen nurses in order to be able to adopt a consistent and caring approach to subjects through the trial, helping to reduce dropouts, especially in the UMC arm. Each RN will complete 400 assessments in total, 100 a year, on top of screening other potential subjects. The initial assessment and consenting will take 3 hours, the later ones taking 1.5 hours. Face-to-face interviews are necessary for the SCDD and fitness/activity measures. Some assessments will be done at a subject's home.

The six 0.5 WTE local data entry/clerical officers will code and enter the trial data onto the CTU designed database at a local level, sending the data to the CTU by email. They will be responsible for keeping hard copies of data and consent forms, as well as being a contact point for staff and subjects.

NHS funded therapists need to be appropriately trained and experienced in treating patients independently as well as under supervision. When not treating trial patients they may be treating non-participants and will be required after the trial to provide treatments for the UMC group. Because of the relatively small number of subjects, they will be employed half time on the trial.

Equipment & Consumables: All research staff need computers for analysis and communication. We have previously found that travel expenses for subjects significantly enhances recruitment. Double expenses for research interviews allow subjects to return the Actiwatches. Co-training with specific therapists will enhance the quality of therapy. CTU expenses will enhance the quality of the data.

Travel: Centre leaders will attend the TMC every 2 months and then less often for 5 years. Therapists and their supervisors will attend London for 10 days initial training and then monthly supervision; to ensure optimal manual based therapy.

Economics: 165 days will be required over 5 years for training RNs and analysis.

6 Application History

6.1 A similar application of a much smaller two arm trial (FATIMA; Grant number G9825745) was submitted in full to the MRC in 1999, rated Alpha B, but not funded. The outline proposal of this study (G010039) was approved for a full proposal in October 2001. The major innovations in this application include close collaboration with *Action for ME*, two new arms (APT and UMC), a much larger number of subjects and centres, and the involvement of a clinical trial unit.

6.2 We submitted a similar trial to the Department of Social Security (now Work and Pensions) in 2000, and agreement in principle to fund was given, although final funding was not forth-coming.

Appendices

1. Participating centres. 2. CBT manual. 3. GET manual. 4. APT manual. 5. UMC guidance. 6. Manual explaining the essential elements of the therapies and how they are differentiated. 7. Knowledge of other current CFS trials. 8. Names and addresses of proposed members of the TSC. 9. Names and addresses of proposed members of the DMEC. 10. Proposed patient information sheet. 11. Letter of support from *AfME*. 12. Letters of agreement to be applicants or collaborators (lodged with MRC). 13. Letters confirming NHS provider support for the project (lodged with MRC).

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