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The research reported in this monograph was commissioned by the HTA Programme as project number 97/41/08. The contractual start date was in August 2000. The draft report began editorial review in October 2004 and was accepted for publication in February 2006. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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# Abstract

## Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme

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**Objectives:** To test the hypothesis that group cognitive behavioural therapy (CBT) will produce an effective and cost-effective management strategy for patients in primary care with chronic fatigue syndrome/myalgic encephalopathy (CFS/ME).

**Design:** A double-blind, randomised controlled trial was adopted with three arms. Outcomes were assessed at baseline and 6 and 12 months after first assessment and results were analysed on an intention-to-treat basis.

**Setting:** A health psychology department for the management of chronic illness in a general hospital in Bristol, UK.

**Participants:** Adults with a diagnosis of CFS/ME referred by their GP.

**Interventions:** The three interventions were group CBT incorporating graded activity scheduling, education and support group (EAS) and standard medical care (SMC).

**Outcome measures:** The primary outcome measure was the Short Form with 36 Items (SF-36) physical and mental health summary scales. Other outcome measures included the Chalder fatigue scale, Hospital Anxiety and Depression Scale, General Health Questionnaire, physical function (shuttles walked, walking speed and perceived fatigue), health utilities index and cognitive function (mood, recall and reaction times).

**Results:** A total of 153 patients were recruited to the trial and 52 were randomised to receive CBT, 50 to EAS and 51 to SMC. Twelve patients failed to attend for the 12-month follow-up and 19 patients attended one follow-up, but not both. The sample was found to be representative of the patient group and the characteristics of the three groups were similar at baseline. Three outcome measures, SF-36 mental health score, Chalder fatigue scale and walking speed, showed statistically significant differences between the groups. Patients in the CBT group had significantly higher mental health scores [difference +4.35, 95% confidence interval (CI) +0.72 to +7.97, $p = 0.019$], less fatigue (difference –2.61, 95% CI –4.92 to –0.30, $p = 0.027$) and were able to walk faster (difference +2.83 shuttles, 95% CI +1.12 to +5.53, $p = 0.0013$) than patients in the SMC group. CBT patients also walked faster and were less fatigued than those randomised to EAS (walking speed: difference +1.77, 95% CI +0.025 to +3.51, $p = 0.047$; fatigue: difference –3.16, 95% CI –5.59 to –0.74, $p = 0.011$). Overall, no other statistically significant difference across the groups was found, although for many measures a trend towards an improved outcome with CBT was seen. Except for walking speed, which, on average, increased by +0.87 shuttles (95% CI +0.09 to +1.65, $p = 0.029$) between the 6- and 12-month follow-ups, the scores were similar at 6 and 12 months. At baseline, 30% of patients had an SF-36 physical score within the normal range and 52% had an SF-36 mental health score in the normal range. At 12 months, the physical score was in the normal range for 46% of the CBT group, 26% of the EAS group and 44% of SMC patients. For mental health score the percentages were CBT 74%, EAS 67% and SMC 70%. Of the CBT group, 32% showed at least a 15% increase in physical function and 64% achieved a similar improvement in their mental health. For the EAS and SMC groups, this improvement in physical and mental health was achieved for 40 and 60% (EAS) and 49 and 53% (SMC), respectively. The cost-effectiveness of the intervention proved very difficult to assess and did not yield reliable conclusions.

**Conclusions:** Group CBT did not achieve the expected change in the primary outcome measure as a significant number did not achieve scores within the normal range post-intervention. The treatment did not return a significant number of subjects to within the

normal range on this domain; however, significant improvements were evident in some areas. Group CBT was effective in treating symptoms of fatigue, mood and physical fitness in CFS/ME. It was found to be as effective as trials using individual therapy in these domains. However, it did not bring about improvement in cognitive function or quality of life. There was also evidence of improvement in the EAS group, which indicates that there is limited value in the non-specific effects of therapy. Further research is needed to develop better outcome measures, assessments of the broader costs of the illness and a clearer picture of the characteristics best fitted to this type of intervention.

# Contents

# List of abbreviations

| | |
|---|---|
| AfME | Action for ME |
| AHA | Avon Health Authority |
| CBT | cognitive behavioural therapy |
| CEAC | cost-effectiveness acceptability curve |
| CFS | chronic fatigue syndrome |
| CI | confidence interval |
| CMO | Chief Medical Officer |
| CR10 | Category Ratio Scale |
| EAS | education and support |
| ECG | electrocardiogram |
| ECT | electroconvulsive therapy |
| EEG | electroencephalogram |
| GET | graded exercise therapy |
| GHQ | General Health Questionnaire |
| HADS | Hospital Anxiety and Depression Scale |
| HRT | hormone replacement therapy |
| HUI | health utilities index |
| IBS | irritable bowel syndrome |
| ICER | incremental cost-effectiveness ratio |
| IP | inpatient |
| IQR | interquartile range |
| ISWT | incremental shuttle walk test |
| LFT | liver function test |
| ME | myalgic encephalopathy |
| MOS | Medical Outcome Study |
| MRI | magnetic resonance imaging |
| NNT | number-needed-to-treat |
| NTF | National Task Force |
| OP | outpatient |
| QALY | quality-adjusted life-years |
| RCT | randomised control trial |
| RPF | rate of perceived fatigue |
| SATER | subanaerobic threshold exercise test |
| SD | standard deviation |
| SE | standard error |
| SF-36 | Short Form with 36 Items |
| SMC | standard medical care |
| SSRI | selective serotonin reuptake inhibitor |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

# Executive summary

## Background and objectives

This report describes the conduct and results of a double-blind randomised controlled trial to compare group cognitive behavioural therapy (CBT) with education and support (EAS) and with standard medical care (SMC) for the treatment of patients with chronic fatigue syndrome/myalgic encephalopathy (CFS/ME). The research hypothesis was that group CBT would provide an effective and cost-effective management strategy for patients in primary care with CFS/ME and that treatment gains in these areas would be found even when controlling for the non-specific effects of therapist exposure.

## Methods

### Design

A double-blind, randomised controlled trial was adopted with three arms. Outcomes were assessed at baseline and 6 and 12 months after first assessment and results were analysed on an intention-to-treat basis.

### Setting

The study was set in a health psychology department for the management of chronic illness in a general hospital in Bristol, UK.

### Participants

Adults with a diagnosis of CFS/ME were referred by their GP. Over a 2-year period (August 2000–July 2002), 153 eligible patients were recruited and consented to participate; 52 were randomised to receive CBT, 50 to EAS and 51 to SMC. The target sample size for the trial, set at 43 per condition, was met. Seven patients did not receive the treatment assigned for clinical or ethical reasons and fear of contamination but all analyses were carried out on an intention-to-treat basis. Twelve patients failed to attend for the 12-month follow-up and 19 patients attended one follow-up, but not both. The sample was found to be representative of the patient group and the characteristics of the three groups were similar at baseline.

### Interventions

The primary analyses compared the outcome scores between the three treatment interventions. Differences between the treatment cohorts are reported with 95% confidence intervals (CIs). For the primary outcome measures, the SF-36 physical and mental summary scales, the numbers of patients reporting a 15% increase over the baseline score (defined as a successful outcome) and the numbers returning to the normal range are also reported.

### Outcome measures

A range of generic outcome measures were used as validated disease-specific outcome measures were not available for this condition. The primary outcome measure was the Short Form with 36 Items (SF-36) physical and mental health summary scales. Other outcome measures included the Chalder fatigue scale, Hospital Anxiety and Depression Scale (HADS), General Health Questionnaire, measures of physical function (shuttles walked, walking speed and perceived fatigue), health utilities index, cognitive function (mood, recall and reaction times) and resource use. Outcomes were measured as baseline (before randomisation) and at 6 and 12 months after the initial assessment.

## Results

Three outcome measures, SF-36 mental health score, Chalder fatigue scale and walking speed, showed statistically significant differences between the groups. The CBT group had significantly higher SF-36 mental health scores (difference +4.35, 95% CI +0.72 to +7.97, $p = 0.019$), less fatigue (difference –2.61, 95% CI –4.92 to –0.30, $p = 0.027$) and was able to walk faster (difference +2.83 shuttles, 95% CI +1.12 to +5.53, $p = 0.0013$) than patients in the SMC group. CBT patients also walked faster and were less fatigued than those randomised to EAS (walking speed, difference +1.77, 95% CI +0.025 to +3.51, $p = 0.047$; fatigues, difference –3.16, 95% CI –5.59 to –0.74, $p = 0.011$). Overall, no other statistically significant difference across the groups was found, although for many measures a trend towards an improved outcome with CBT was seen. Excepting for walking speed, which, on average, increased by +0.87 shuttles (95% CI +0.09 to +1.65, $p = 0.029$) between the 6- and 12-month follow-ups, the scores were similar at 6 and 12 months.

At baseline, 30% of patients had an SF-36 physical score within the normal range and 52% had an SF-36 mental health score in the normal range. At 12 months, the physical score was in the normal range for 46% of the CBT group, 26% of the EAS group and 44% of SMC patients. For mental health score, the percentages were CBT 74%, EAS 67% and SMC 70%. Of the CBT group, 32% showed at least a 15% increase in physical function and 64% achieved a similar improvement in their mental health. For the EAS and SMC groups, this improvement in physical and mental health was achieved for 40 and 60% (EAS) and 49 and 53% (SMC), respectively, but these changes were not statistically significant.

There were multiple difficulties in completing the economic evaluation. A cost–utility (or cost-effectiveness) analysis was planned, but the quality of the data prevented this objective being realised. The intention was to use data from participating primary and secondary care centres and patient questionnaires. However, owing to the unexpected departure of the health economist early in the trial, the study was almost complete before it was realised that patient records would need to be scrutinised for resource use data. This meant that limited resources were available for this exercise, and minimal data were obtained. Also, the patient questionnaire was inadequate. It asked patients about treatments and medication use but failed to ascertain the cost involved. Data on direct patient costs and indirect societal costs was sought but the response was too poor for the data to be of much value, with a great deal of missing data. As a result, the quality of the health economic data was poor; the evaluation was limited to the perspective of the healthcare provider (NHS) and the reporting of results was descriptive only. The descriptive data tentatively suggest that most of the cost of CFS/ME is borne by family and friends. The economic impact appears substantial, with over 60% of patients citing the onset of CFS/ME as the main reason why they cannot work.

### Limitations

The trial had a number of limitations: patients were referred from the GP, without a specialist diagnosis, and the individuals' suitability for group treatment was not assessed prior to randomisation. One patient was withdrawn because an alternative diagnosis was made and several patients would not, in clinical practice, have been considered psychologically appropriate for group treatment. Also, some subjects were already using good management techniques and could not, therefore, be expected to show a significant improvement.

On average, the patients in the study population were more fatigued, had been ill for longer and were more distressed than samples used in previous research, although they were able to attend an outpatient programme, which implies a certain level of ability. It is not possible to assess from this trial whether the interventions investigated would be effective, ineffective or even hazardous for more severely disabled individuals.

## Conclusions

Group CBT did not significantly improve cognitive function, quality of life, employment status or healthcare utility measures, although such changes have been demonstrated in the literature for individual CBT. The increased measures of mood and fitness and decreased symptoms of fatigue seen with CBT are comparable to the changes seen in the individual research literature. The similarity of the Borg perceived fatigue scores across each condition, both initially and at follow-up, indicates that each cohort reported exercising to a similar level of fatigue. This indicates that the significant increase in shuttle walking found in the CBT group was not an artificial gain achieved by 'pushing through' fatigue. It appears to be more substantial. These subjects reported increases in their normal walking pace. It seems that the gain is for both speed and endurance. This is of great functional significance for CFS/ME sufferers. This study is unable to shed any light on the mechanism underlying this change, and it may be possible that patients are feeling more confident and able to manage the condition.

## Recommendations for future research

Further research is needed to develop better outcome measures, assessments of the broader costs of the illness and a clearer picture of the characteristics best fitted to this type of intervention.

# Chapter 1
# Introduction

## Overview

Chronic fatigue syndrome (CFS) or myalgic encephalopathy (ME) is a syndrome describing a range of symptoms and clinical characteristics that cause substantial suffering and disability. As with any chronic illness, the patient suffers across a range of domains: physical, psychological and social. There are financial implications as a result, in terms of the demand on the NHS, loss of time from work, social security and insurance claims.

Both patients and professionals struggle to understand the illness, and this often leads to unsatisfactory patient–professional relationships and ultimately to dissatisfied patients.[1] In the absence of any compelling evidence for either the cause or the cure, attention has turned to the question of how to manage the illness. The experience of rehabilitation and symptom management for other chronic conditions has informed the development of a treatment approach – cognitive behavioural therapy (CBT).

This report describes a trial that attempted to assess the efficacy of this treatment when delivered in a group format.

## Diagnosing CFS/ME

The aetiology of the illness remains unclear, although various hypotheses exist implicating immunological, virological, psychological and neuroendocrinological mechanisms. There is a lack of overwhelming evidence for any one of these hypotheses.

Komaroff (in 2000)[2] and Komaroff and Buchwald (in 1998)[3] have undertaken reviews of the research that has investigated biological markers. Several objective biological abnormalities have been found to be significantly more prevalent in patients with CFS than in comparison groups. The evidence indicates pathology of the central nervous system and immune system. However, the authors note that not all patients who met the international definition for CFS have these objective biological markers. Second, they note that the presence of these markers is correlational, not causative. They do not explain the pathogenesis of the illness, but indicate only that chronic immune activation is often present.

Several case definitions exist, but no one definition has been universally accepted. The first attempt to define the syndrome clinically was undertaken by Holmes and colleagues at the US Center for Disease Control in 1988.[4] Schluederberg and colleagues refined this definition in 1992.[5] Other definitions have been suggested by Sharpe and colleagues (1991) in England[6] and Lloyd and colleagues in Australia (1990).[7]

An internationally agreed definition was subsequently been proposed by Fukuda and colleagues[8] for the International Chronic Fatigue Syndrome Study Group, which includes US Center for Disease Control, Australian and British representatives. However, it has been criticised because of its restrictive criteria and it is therefore likely to produce an underestimate of the clinical and public health burden when used to draw epidemiological conclusions.[9]

An agreement on case definition is essential, since the interpretation of research findings is rendered almost impossible without this definition.

## Epidemiology

There is a paucity of studies looking at the epidemiology of CFS/ME, with a tendency to extrapolate from one population to another. Not surprisingly, different rates have been identified in different populations. There is no current consensus for an epidemiological case definition that would generally be acceptable and robust enough to yield consistent and comparable results in different locations. Thus, epidemiological data are variable but suggest a lifetime incidence rate in the range 3–7%.

Prevalence rates are estimated at 1–2 per 1000 population, or between 50,000 and 100,000 cases in the UK at any one time.[9] Peak incidence is in the 20–40 years age range, with a preponderance of females. There is considerable variation in epidemiological estimates as a result of varying

degrees of precision over case definition and the unspecific nature of the clinical features of the disease.

## Prognosis

With regard to the prognosis for patients with CFS/ME, once again there is no overall consensus. Variation is likely to be due to the heterogeneity of the condition, the problems with diagnosis and the uncertainty surrounding the aetiology. It is also likely that subgroups exist, with different clinical markers and pathways.

A number of authors have given mean values for the duration of the illness or for the proportions of patients still reporting symptoms after a specified time. However, the studies have been small and of dubious quality.[9]

A systematic review of 26 studies of prognosis[10] found that four studies of children indicated that 54–94% of children recovered. Five studies in adults found that fewer than 10% of subjects return to their previous level of function, the majority remaining significantly impaired. In studies using less stringent criteria, i.e. with fatigue lasting less than 6 months, at least 40% of patients improved.

Risk factors for poor prognosis are older age, more chronic illness, having a co-morbid psychiatric disorder and holding a belief that the illness is due to physical causes. Management strategies, which discourage avoidance of activity or enhance perceived control, could benefit the course of the illness.[9]

## Subgroup specification

An outbreak in New Zealand[11] was reported as 'an epidemic', with a rapid and distinct onset. The report makes it clear that this is not a single diagnostic entity, but rather a symptom complex in which dysfunction is multifactorial.

DeLuca and colleagues[12] compared a population with gradual onset of CFS with a rapid onset population for cognitive and psychiatric measures. The rate of concurrent co-morbid psychiatric disease was much higher in the gradual onset population. Cognitive deficits, especially functions of memory, were more noticeable in the rapid onset population. This has not been replicated but serves to emphasise the need for subgroup analyses.

Wilson and colleagues[13] compared the characteristics of patients presenting in eight international centres and attempted to subclassify them based on symptom profiles. Their findings were complicated and they conclude that "the basis for allocating subcategories is controversial and unclear". They felt that the broader the criteria became, for example increasing duration, distress and disability, the more likely the sample would be to include patients with psychiatric, somatoform-type disorders. They described patients presenting with these disorders as a statistically distinct group, independent of the usual clinical markers, and suggest that clinical criteria therefore do not distinguish subgroups in a robust fashion.

## Economic impact

The characteristics of this syndrome, chronic course, disabling consequences and lack of robust scientific information all indicate a condition with potentially high healthcare costs. The Chief Medical Officer (CMO) report[1] describes significant impact on work, finance and education. No detailed cost estimates have yet been made for the UK, but the National Task Force (NTF) report[14] reviewed studies in Australia and made a comparison with the UK, estimating the impact of CFS/ME to be £90 million per annum in terms of demand on health and social services, welfare costs and the economic impact.

There is a paucity of studies on the economic impact and those that exist have typically measured cost in terms of disability and functional impairment, rather than in resource consumption or lost productivity.

McCrone and colleagues[15] assessed the cost of both chronic fatigue and CFS in primary care in the UK. They found an average cost, for the 3-month period of their study, to be £1906, 9.3% of which was direct service cost. They concluded that over 90% of the costs were accounted for by the care provided by friends, family members and lost employment.

## Research into efficacious interventions

A working group was established recently to complement the findings of the NTF.[14] Part of its role was to provide an overview of current research and to answer the two questions put by the Chair,

Professor Allen Hutchinson, in 1999. The questions were:

1. How strong is the current evidence, where are the gaps and what do we need to fill them?
2. What are the important clinical and management questions which need to be addressed?

The discussion document produced in response to these questions concluded that much of the current evidence on causation was weak, that patients should be managed in primary care (with specialist back up where necessary), that multidisciplinary care was important and that trials of graded exercise and CBT had shown encouraging results when delivered on an individual basis.[9]

Pheby reviewed the growth in research publications in this area since the publication of the NTF report.[9] He concluded that the majority of research concentrated on elucidation and description of pathological and clinical features, with research on the management of the condition falling someway behind in terms of the number of publications.

There are only two systematic reviews of this area. Price and Couper[16] systematically reviewed all the existing controlled trials of CBT for adults with CFS. They searched electronic databases and trials registers, and also contacted lead researchers and departments. All randomised controlled trials (RCTs) in which adults with CFS received a CBT intervention were included. CBT could be either type 'A' – encouraging return to 'normal' levels of rest and activity – or type 'B' – encouraging rest and activity which were within levels imposed by the disorder. Functional outcome was used as the main measure of outcome.

The quality criteria for the review were as follows:

- Assignment of treatment was adequately controlled prior to allocation.
- The outcomes of patients who withdrew were described and included in the analysis.
- The outcome measures were clearly defined and valid, the assessor was blind and the duration of follow-up was appropriate.
- Appropriate baseline characteristics were reported and comparable.
- Care programmes were identical apart from the intervention.
- The inclusion/exclusion criteria were clearly defined.

Only three trials met their quality criteria. All three demonstrated that CBT, given on an individual basis, when compared with orthodox medical management or relaxation, significantly benefited physical functioning in adult outpatients.

They concluded that further research was needed to assess the effectiveness of CBT in people who are severely disabled by CFS, the impact of group CBT and the effect of CBT compared with graded activity only. They found that about two patients need to be treated with CBT for one adverse physical outcome to be prevented at about 6 months after the end of treatment [a number-needed to-treat (NNT) of two]. However, improvement continues beyond the end of treatment, hence the long-term NNT is much higher than two.

In addition, they found that the treatment effects were smaller where a placebo was used; the placebo had some effect itself, reducing the possible treatment benefit accruing from CBT. The effectiveness was also dependent on how much treatment was given/received and the average length of duration of symptoms. Participants with more longstanding symptoms may have been less likely to respond to treatment than those with symptoms of shorter duration.

The second systematic review[17] looked at 19 specialist databases from inception to July 2000. Of the 350 studies identified, 44 met the inclusion criteria for a controlled trial (randomised or non-randomised). Thirty-eight outcomes were evaluated using 130 different scales.

Studies were judged to show some effect in Whiting and colleagues' review if there was a significant difference between the intervention and control groups. Studies were classified as having an overall effect if they showed an effect for more than one clinical outcome.[17] Efforts were taken to negate the effects of publication bias by searching for unpublished work. Whiting and colleagues concluded that there were an insufficient number of trials with long-term follow-up, i.e. 6–12 months, which would allow for the fluctuation of the condition. Studies with a longer intervention period (longer than 3 months) were more likely to show a positive effect. Their review covered principally open trials and case series, with few RCTs.

Overall, the interventions demonstrated mixed results in terms of effectiveness. Interventions that

demonstrated some evidence of efficacy used rehabilitation interventions incorporating individual CBT and graded exercise therapy. The review did not describe any studies that had used a group therapy format. For individual therapy they found that a positive effect was more likely to be reported where the study was of better quality. There was a lack of agreement about the content of the treatment interventions, but considerable agreement about the basic elements and principles, even if the terminology may have suggested otherwise. There was no clarity regarding which elements of the treatment package were potent and differential responses were reported.

Five trials using CBT were identified by the review as being of adequate quality. All five used individual therapy. There was no overlap in the outcome measures used.

Follow-up varied from 7 months to 5 years (the latter demonstrating severely reduced efficacy[18]). The size of the sample varied from 60 to 278 subjects with an average drop-out rate of 15%. Only two of the trials defined a clinical success prior to the trial and both used different definitions.[18,19]

All five trials used a different diagnostic classification and only one controlled for the effects of therapist time and attention. None of the trials gave a detailed protocol of the treatment received. The level of experience of the therapist was variable.

## The rehabilitation and symptom management approach

There has been a steady increase in the number of services dedicated to the rehabilitation and management of the symptoms associated with CFS. This is, most likely, a result of the success of this approach with other chronic conditions, for example chronic pain.[20] The approach is based on CBT and addresses a range of areas implicated in the biopsychosocial model of disease and disability.

## The role of cognitions in health

It is increasingly recognised that individuals can make major contributions to their own health and well-being through the adoption of health-enhancing coping strategies. The identification of the underlying factors that lead to the adoption of helpful coping has been the focus of much research in psychology.[21] Effective rehabilitation should be based on the cognitive processes that influence an individual's health behaviour. There are many health behaviours relevant to CFS/ME that can improve self-management, delay progression of the illness or improve an individual's general sense of well-being. The underlying premise of using CBT in rehabilitation is that a change in an individual's cognitions or thoughts will have a direct effect on their behaviour. This can be used to promote the use of adaptive coping strategies, for example exercise. Given the heterogeneity of both the condition and the treatment, one would expect individuals to respond differentially.

Although CBT covers a wide variety of interventions provided in diverse clinical environments, all CBT interventions share a common set of theoretical assumptions regarding the interaction between environmental events, cognitions, behaviours and feelings that determine patients' actions and experiences.

CBT developed from an early form of the therapy used for behavioural and psychiatric disorders in the early 1970s. It has since been successfully applied to a range of other health problems, such as chronic pain and rheumatoid arthritis. The frequency of a behaviour can be linked to the consequential frequency of positive or aversive consequences.[22] The approach also posits that a change in the cognitive and affective factors within patients will lead to a change in behaviour. For patients with a chronic illness to manage, this means the adoption and enhancement of appropriate coping behaviours and adherence to rehabilitation regimes.

There are five underlying assumptions to CBT:

1. Individuals actively process information from the environment. Their beliefs and subsequent behaviours are shaped by their analysis of the consequence of these events. The analysis is influenced by both internal and external factors and especially previous experience. For example, if an individual experiences a severe increase in symptoms following increased activity, they may conclude that activity is unhelpful and avoid it.
2. Individuals' cognitions affect their behaviour and affective state. In this client group, beliefs about the causation of the illness and how best to manage rest and activity play a key role in determining the coping strategy selected.

3. The relationship between environmental events, cognitions and affective state is reciprocal.
4. Treatment strategies aim to bring about change. In order to do this, cognitive, affective and behavioural dimensions of the individual must be addressed.
5. Individuals must be active participants in the change process.

The CBT used in this trial was designed to do two things:

1. attempted modification of thoughts and beliefs about symptoms and illness
2. attempted modification of behavioural responses to symptoms and illness, such as rest, sleep and activity.

## Background to the use of exercise therapy in this study

Whiting and colleagues' review found three high-quality RCTs that investigated the value of graded exercise therapy (GET).[17] All of these trials demonstrated benefit, which led to the recommendation for people with CFS/ME to increase gradually their aerobic exercise levels, for example by walking or cycling. In contrast to this evidence are the findings of a survey conducted by the charity Action for ME (AfME) of patients who attend CFS/ME support groups.[23] These findings suggested that amongst this population, 38.8% percent had been made worse by the use of graded exercise, whereas 38.7% were helped. This disparity in findings is explored below in order to explain the rationale for the use of exercise within the current trial.

The history of previous attitudes and cognitions about the role of exercise in CFS/ME was summarised by McCully and colleagues.[24] It is important to recognise that the condition is partially defined by post-exertional malaise, so it would be natural to expect patients to report that exercise made their symptoms worse.

McCully and colleagues reported on early studies which tended to emphasise the ill-effects of maximal exercise tests, but by 1993 the evidence was becoming more complex, with only one out of 16 patients reporting a relapse following a maximal treadmill test.[25] Conversely, at the same time, Eaton was suggesting that repeated activity was "damaging".[26] By 1996, however, the Joint Working Group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners was recommending graded exercise.[27] It is interesting that this change in advice is paralleled by a change over a similar time frame in the management of low back pain, with advice to take bed rest for back pain being replaced with advice to remain active. The paradox for patients with either of these conditions is that activity or exercise can worsen their symptoms and, as a consequence, it can be difficult to perceive as beneficial a treatment approach that has the potential to make one feel worse. There is a clear link between what a person is thinking and how they behave. If an increase in symptoms is thought to signal a relapse of the illness, then the exercise programme will be stopped.

The controversy over the safety of exercise in CFS/ME is made more complex by three issues. The first is that by using the Medical Model as a paradigm for understanding treatment for the condition, the attention of some patients becomes focused upon finding a cause or impairment, then finding a treatment relevant to this impairment that will lead to a cure. However, there continues to be uncertainty about the causes of the condition. Of particular relevance to GET, controversy remains regarding the presence or absence of physical deconditioning in patients (comment from White and Fulcher[28] and response by Sargent and colleagues[29]). The application of graded exercise would make sense to strict adherents to the Medical Model if it were to address proven deconditioning, and if that deconditioning were the impairment that was central to CFS/ME. Often linked with this strict application of the Medical Model is the unhelpful application of a dualistic, mind-versus-body understanding of illness. This overlooks potential for a complex interaction of cognitions, behaviour, emotions, physiological factors, sleep patterns and social factors. The artificial separation of 'physical' and 'psychological' factors often associated with the Medical Model oversimplifies reality, and can lead to distracting debates about the nature of CFS/ME.

The second confounding issue is the heterogeneous nature of the condition.[1] It is probable that within the syndrome there is a range of different subgroups, some of which may differ in their response to exercise. People at different stages of the condition may also respond differently to GET, but this has not yet been researched in detail. The heterogeneity of CFS/ME is likely to be a confounding factor in all of the studies looking for deconditioning or post-

exertional relapse that have small numbers of patients, and may explain some of the conflicting results.

The third confounding issue is that the exercise tolerance of each individual patient is different, and therefore the prescription of graded exercise needs to be sensitive to the individual concerned. There are patients who feel that they are already working at the limits of their tolerance to physical activity, and who may indeed be experiencing regular setbacks which they attribute to overactivity. The simple application of a graded exercise programme without taking into account such a background of over- and underactivity cycling is likely to be unhelpful, in the clinical experience of the therapists involved in this trial.

It is notable that the AfME survey[23] recognised that it was not able to explain why GET had been so unhelpful in their population sample; it is possible that a significant proportion of the people answering the survey started at too high a level of exercise, or were at risk of a setback due to over- and underactivity cycling.

The evidence from the three RCTs found to be of high quality by the review[17] adds perspective to the debate. The first report was published in 1997 by Fulcher and White[30] and had a treatment group of 33 patients who exercised at 40% of their maximum aerobic capacity by walking between 5 and 15 minutes, 5 days per week. Increments were negotiated individually, from between 1 and 2 minutes per week up to a maximum of 30 minutes. Only one out of 29 completers reported feeling (a little) worse as a result. Four patients dropped out, and only one reported doing so because treatment made them feel worse. This group of patients made improvements in terms of fitness, fatigue and function. The comparison group were taught stretches and a relaxation programme and did not make as much progress as the aerobic exercise group. There was no control group receiving normal care. The stretch and relaxation group crossed over at 3 months to the aerobic programme and went on to achieve greater improvements following the aerobic exercise. Although controversy remains about whether deconditioning is part of the 'impairment' of CFS/ME, it was notable from this study that measurable improvements in fitness occurred, but that they were not correlated with self-report of improvement. Unfortunately, because of the design of the study, we cannot tell what improvements might have been attributable to the passage of time alone, and the ability to compare long-term outcomes was lost by the crossover design. The study supports the hypothesis that a supervised exercise programme is associated with improvements in self-reported status, fitness and fatigue levels in the majority of patients.

The second study was published by Wearden and colleagues in 1998[31] and compared the benefits of structured, graded exercise with a control group who received a review of activity diaries and advice to "do what they could when they felt capable" with regards to exercise. The exercise group were advised to spend 20 minutes three times per week, either walking, cycling or swimming at approximately 75% of their maximum aerobic capacity. This higher exercise prescription was associated with a higher drop-out rate (37% over 6 months) than in Fulcher and White's study[30] and drop-out was greater than in the control group (22%).

The third study, by Powell and colleagues in 2001,[32] was not primarily investigating the effects of GET but looking at the effects of an advice booklet upon compliance with GET. This trial used a cognitive tool, which was an information booklet that explained the symptoms of CFS/ME in terms of altered sleep patterns, circadian dysrhythmia and physical deconditioning. The graded exercise programme was worked out on an individual basis, from a very low level in some cases, such as three revolutions of the pedals of an exercise cycle, or two step-ups. Improvements in terms of fatigue and function were noted in the experimental groups. No control group was included in this trial. Of interest, a change in cognitions about the condition was noted, including the increased belief in the role of deconditioning in prolonging the condition.

## Use of structured exercise within the cognitive behavioural therapy treatment arm

The decision was taken to include structured exercise within the CBT groups, but not to include it within the education and support (EAS) groups. This was partly as a result of our interpretation of the research into GET (see above), but also because there are significant overlaps between GET and CBT.[33] In order to introduce exercise with a minimal risk of a setback, it is necessary, in the opinion of the therapists involved in this trial, to address the risk that patients with CFS/ME might significantly increase their exercise levels on

better days, when their symptoms are less severe. This risks a setback, which can lead to prolonged recovery and a loss of confidence in exercise. In order to address this risk, it is necessary to discuss it in some detail and to introduce the concept of a 'baseline' level of exercise, which is not likely to cause an unacceptable increase in symptoms. A correctly calculated 'baseline' will identify a much lower level of exercise than can be managed on better days, and may for some subjects mean starting with only one repetition of an exercise. In order to introduce the concept of a baseline, and to emphasise the value of small amounts of exercise with a plan to build up (pace up) slowly, a degree of cognitive work needs to take place. The careful introduction of a structured exercise programme can therefore be thought of as an element of CBT which involves the key aspects of pacing followed by 'step by step' increments, the value of movement (in particular, the value of regaining confidence in movement) and a behavioural experiment which can then be generalised to other, more directly functional activities once the exercise programme is under way.

It might be argued that any benefits of a CBT treatment that included GET could be ascribed to GET, if the research into GET gives a true indication of its value. There is certainly scope for a trial which compares GET with CBT including GET, and also trials that compare CBT without GET with GET. This was not the purpose of this trial, however, and it must be remembered that the value of contact with others with CFS/ME was the condition that was being compared with the CBT condition. It is common practice to include a structured, incremental exercise programme as an integral part of group CBT for other health conditions such as chronic pain, and we saw no reason to deprive the CBT cohort of this aspect of group CBT.

## Evaluating treatment outcomes

It has been acknowledged that change can occur in a range of domains. From the research in health psychology, it is now widely acknowledged that treatment may help the patient to feel more in control of the illness. This can lead to better management of the symptoms and an increase in mood and consequently reduce the impact of the illness on everyday life. Treatment may also impact directly on the experience of the symptoms in terms of both the quantity and the quality.

Since there are no biological markers for this illness, and a diagnosis is made on the basis of subjective symptoms and the history of the patient, most of the measures have to be self-report. There are a plethora of assessment scales available, but no international consensus on the principal outcomes for this population.

For this reason, we selected measures to cover three main areas: first, the symptoms frequently described (fatigue, cognitive problems and mood disorder), second, some measures of 'overall' functional ability and quality of life, and third, some aspects of physical performance/endurance. Hence we were attempting to assess the experience of the illness itself and its impact on general well-being and the activities of everyday life.

All of the measures employed in this study have previously been used with people with CFS (with the exception of the shuttle walk). The measures were chosen to reflect changes in functional and symptom status. The decision was made to use a number of generic measures of health status, because of the current limited knowledge of CFS. Given that the clinical markers for the condition could change, and considering that there are no specialised measures, it was reasoned that assessments standardised in the general population might also be useful for this client group. Furthermore when deciding on measures for the study, agreement was reached that they needed to be relatively brief since the participants were likely to fatigue easily.

We recommend that the standardisation of outcome measures in this population should be a priority for future research.

## The measures

### Physical and mental health summary scales [Short Form with 36 Items (SF-36)]

The primary outcome measure was the Medical Outcome Study (MOS) SF-36.[34] This is a 36-item questionnaire that produces an eight-scale profile of functional health and well-being, in addition to psychometrically based physical and mental health summary measures and a preference-based health utilities index (HUI). It is a generic measure, rather than one that targets a specific age, disease or treatment group, making it a good measure to use in a sample where the age and treatment group differs. As a measure it is used widely to compare the relative burden of diseases. The

questionnaire was constructed for self-administration by those aged 14 years and over.

The questions in the SF-36 are of a multiple-choice format, with some questions requiring either a 'yes' or 'no' answer whereas other questions provide up to five different choices. The scoring of the SF-36 was carried out according to the coding manual, and for the purpose of this study resulted in a physical health summary scale and a mental health summary scale. Higher scores represent increased functional levels.

A systematic review of RCTs of CBT for adults with CFS[16] found that the principal outcome measure used was one of physical functioning, and that this is usually measured by patient rated scales such as the physical function dimension of the SF-36, as in this study. The review also states that the SF-36 is additionally used to measure quality of life in CFS studies.

Reliability and validity studies for the SF-36[35,36] have shown adequate internal consistency, discriminant validity among subscales and substantial differences between patient and non-patient populations in the pattern of scores.

When used with populations of CFS sufferers, the SF-36 has shown adequate psychometric properties as a measure of functional status.[37] Furthermore, a study by Deale and colleagues[38] has shown that the SF-36 is sensitive to treatment change.

Friedberg and Jason[39] cite a possible limitation of the MOS scales for use with CFS participants. They claim that in moderate to severely disabled patients, there may be a floor effect (indicating severe disability), particularly on the physical disability scales, because there are few items that distinguish among very low levels of functioning. This floor effect is less likely to be present in this study because the participants needed to be sufficiently capable of attending a number of outpatient appointments, and therefore were very unlikely to be in the most severely disabled group (bed- or house-bound).

In 2003, Reeves and colleagues[40] published a paper which made recommendations for the resolution of the 1994 CFS research case definition. Amongst the recommendations was the use of internationally applicable instruments to measure symptoms, fatigue intensity and associated disability. The paper recommended the use of the SF-36, describing it as "a well validated instrument that measures the effects of the entire illness (i.e. fatigue and accompanying symptoms)". The paper also highlights the fact that there is considerable normative data available for many illnesses, including CFS.

In summary, the SF-36 provides a reliable, validated measure of functional status.

## Mood [Hospital Anxiety and Depression Scale (HADS)]

High levels of anxiety and depression have been frequently recorded in this population.[41,42] The contribution of these factors to the aetiology, symptom severity, prognosis and treatment outcome is unclear. Estimates suggest that approximately half of CFS patients experience anxiety and depressive disorders[43] at some point during the illness. The debate regarding their role in causality is controversial, but what is clear is that the treating professionals often minimise and invalidate the patient's experiences, which in itself may lead to low mood and poor self-esteem.[44] Any chronic illness has a range of psychosocial consequences, which include disruption to the patient's physical, social, recreational and vocational activities. Disturbances are observed in sleep, relationships, medication use and diet. All of these factors can reasonably be expected to affect mood, even if mood is not causal.

An improvement in mood will enhance the patient's level of function through the shift in thinking that allows the adoption of more positive and helpful coping strategies, and thus facilitate recovery.[43]

The HADS[45] was designed to provide a simple yet reliable tool that measures anxiety and depression in hospital outpatient clinics. The scale consists of two eight-item subscales, one relating to depression and the other to anxiety. It has been used in a number of chronic fatigue studies; for examples, see Deale and Wessely.[46] Excluded from the scale are all items that might relate to either somatisation of mood or to physical illness. It takes only 5–10 minutes to complete, making it ideal for a sample population of people who fatigue easily.[47]

Each item on the HADS is scored from 1 to 4. The anxiety items and the depression items are summed separately. The higher the score, the more severe are the anxiety and depression; 0–7 is in the normal range, 8–10 is considered borderline and 11+ caseness.

In 2002, Bjelland and colleagues[48] reviewed the validity of the HADS using 747 studies. They

concluded that the scale performed well in assessing the severity and caseness of anxiety disorders and depression in both somatic and psychiatric cases and in primary care patients and the general population. Deale and Wessely[46] highlighted how the similarity of symptoms between CFS and psychiatric disorders, such as depression, leads to difficulties in the routine clinical evaluation of psychiatric disorders in CFS patients. They recommended that doctors use the HADS along with other clinical features that discriminate between the disorders.

In their review of psychometric evaluation for CFS, Freidberg and Jason[39] point out that one of the depression items, "I feel as if I am slowed down", could be reflective of the person's physical condition rather than a sign of depression. Although one should tread with caution, the intervention used in the present trial included a graded exercise component which may have had an effect on this item for those in the CBT cohort. This would not be the case for the other cohorts, giving the CBT condition what would appear to be a greater improvement on the depression scale, but would in fact be due to a physical improvement and not a mood improvement.

A study by Bentall and colleagues[41] investigated the predictors of response to psychological treatments for CFS. The study found that dysphoria as measured by the HADS was a predictor of poor outcome. This demonstrates the importance of measuring this variable when looking at the effectiveness of interventions.

Furthermore, the HADS was tested as a screening instrument for psychiatric morbidity in CFS and was found to be a valid and efficient screening instrument for anxiety and depression by comparison with standard diagnostic criteria (DSM-III-R) and a threshold score for the number of psychiatric symptoms at a standardised psychiatric interview.[49]

However, more recently (in 2003, since the onset of this study) McCue and colleagues[50] published a study aimed at determining the psychometric properties of the HADS in individuals with CFS. In the study, 117 individuals with CFS completed the HADS online by accessing a dedicated website. McCue and colleagues found the HADS retained its internal reliability; however, factor analysis produced highly contradictory factor structures. An exploratory factor analysis found a three-factor underlying structure, which although it did not provide an optimal fit to the data, did prove to be a significantly better fit to the data when compared with the two-factor structure. A similar factor structure had been found in previous studies with different sample populations. The confirmatory factor analysis further supported these findings.

This result led the authors to conclude that "the HADS can not be recommended as a reliable and psychometrically robust index of anxiety and depression in individuals presenting with CFS".[50] The authors do, however, acknowledge the potential difficulty of having used a web-based sample, namely that there is evidence[51] that factor structures of psychological questionnaires may change subtly when they are converted from paper and pencil format to electronic equivalents.

## Detection of psychiatric disorder

### General Health Questionnaire (GHQ)

The GHQ[52] is a self-administered questionnaire and is used to detect psychiatric disorder. It focuses on the inability to carry out normal functions and the appearance of new and distressing phenomena. This study used the GHQ-12, a quick, reliable and sensitive short form, often used in research studies. The questions are answered in terms of how one's health has been over the past few weeks. The following is an example question from the GHQ-12: "have you recently been able to concentrate on whatever you are doing?" The participant chooses one of four responses, for example, "better than usual", "same as usual", "less than usual" and "much less than usual".

The questionnaire can be scored using one of two scoring systems. The first is bimodal or GHQ scoring, where responses score 0, 0, 1 and 1, respectively, and the second is Likert scoring, where responses score 0, 1, 2, and 3, respectively. This study uses the second method because it is more useful for comparing degree of disorder since it gives a less skewed distribution of scores, which range from 0 to 36. A higher GHQ score indicates a greater probability of a clinical disorder. Goldberg and Williams found the GHQ to be a valid and reliable measure in detecting cases of psychiatric disorder.[52]

A study by Pevalin[53] investigated whether multiple applications of the GHQ-12 led to long-term retest effects. The study analysed data from 4792 British respondents who had completed the GHQ-12 seven times from 1991 to 1997. The results showed no evidence of retest effects and concluded that GHQ-12 is a consistent and

reliable instrument when used in general population samples with relatively long intervals between applications. This present study administered the GHQ-12 three times within a period of 1 year; it is therefore worth noting that the GHQ may still be liable to retest effects.

Werneke and colleagues[54] tested the stability of the factor structure of the GHQ versions 12 and 28 in 15 different centres. Although there were substantial factor variations amongst the centres for the GHQ-12, the authors were able to conclude that two domains, depression and social dysfunction, appeared across the 15 centres.

The factor structure of the GHQ-12 was also investigated by Campbell and colleagues,[55] who reviewed research relating to the factor analysis of the GHQ-12, in addition to producing a confirmatory factor analysis on data from their own study in rural Tasmania. Campbell and colleagues found that the complete factor models were not replicated between studies, although isolated factors were replicated between some studies. These studies suggest that the GHQ-12 does not have a sound or an easy to replicate factor structure.

Nevertheless, the GHQ has been used by sizeable organisations to survey large parts of the country. For example, it was used by the South West Public Health Observatory as part of their health survey for England in 1999, and also for the health survey for England carried out on behalf of the Department of Health.[56,57] It therefore provides a generally robust, popular screen for psychiatric morbidity.

## Severity of fatigue (the fatigue scale)

The fatigue scale[58] is an 11-item self-rating scale developed to measure the severity of fatigue. It contains seven items on physical fatigue and four on mental fatigue. The mental fatigue items include difficulties with concentration and memory, whereas the physical fatigue scale includes items such as "Do you need more rest?" and "Do you have problems with tiredness?" The participant has a choice of four possible answers, for example, "less than usual", "no more than usual", "more than usual" and "much more than usual". A higher score indicates a more severe level of fatigue. Chalder and colleagues found the scale to be both reliable and valid, and with a high degree of internal consistency.[58]

Friedberg and Jason,[39] in their review of fatigue rating scales, highlighted the primary strength of the questionnaire as being its ability to be treatment sensitive. This is especially important considering the aim of the present study. In addition, they name two main limitations of the scale: the first is its inability to distinguish between CFS and primary depression patients and the second is that the items comprising the mental fatigue subscale describe cognitive difficulties rather than mental fatigue, which may not be the same thing.

A further limitation of the fatigue scale is the asking of respondents to compare him- or herself with how they were before (a method adopted by the GHQ). The proceedings of a workshop organised by the National Taskforce on CFS looked at research methodology in CFS. They concluded that a format of comparison with previous self could be perceived as insensitive in chronic conditions, since the 'usual' state here may be interpreted as one of illness.

Furthermore, an accurate comparison relies on the ability to remember pre-fatigue, which may be difficult for respondents who have been fatigued for a long period.

The workshop also concluded that the format could lead to confusion if, for example, the person feels better than usual compared with their recent level of symptoms, but worse than usual compared with their pre-morbid symptoms.[59]

Morriss and colleagues[60] explored the validity of the Chalder Fatigue Scale in Chronic Fatigue Syndrome. The study involved 136 CFS patients and examined the constructs of the 14-item fatigue scale. The study examined the scale using principal components analysis and correlations with subjective and objective measures of cognitive performance, physiological measures of strength and functional work capacity, depression, anxiety and subjective sleep difficulties. In contrast to the two constructs of fatigue obtained by Chalder and colleagues[58] using a general practice sample, Morriss and colleagues extracted four constructs of fatigue in CFS patients.

The findings of Morriss and colleagues[60] support the use of the 11-item version of the Chalder Fatigue Scale, which drops items such as 'loss of interest' because it doesn't correlate with any other measure of mental or physical functioning. The paper concludes that with the item 'loss in interest' removed there remains sufficient evidence to regard the fatigue scale as measuring two constructs, mental and physical fatigue.

In a paper identifying ambiguities in the 1994 Chronic Fatigue Syndrome research case definition, Reeves and colleagues[40] recommend the use of the Chalder Fatigue Scale where a short fatigue instrument is needed. They describe the scale as having been used in large community samples and having published receiver-operating characteristics.

## Health status (HUI)

The HUI measures health status, reports health-related quality of life and produces utility scores. The HUI has been shown to be very responsive to changes caused by treatment therapies or other influences. In addition, HUI measures of health-related quality of life can be used to calculate quality-adjusted life-years (QALYs) for cost–utility economic evaluations. The questionnaire format is multiple choice, with between four and six different answers. The questionnaire is scored as per the coding manual. The HUI is a widely used measure of health status and a number of studies have reported evidence of HUI validity, reliability and responsiveness. The present study used the 15-item version of HUI III designed for self-completion.

Macran and colleagues[61] compared EQ-5D, a modified version of HUI3 (mHUI3), and SF-12. The measures were assessed in terms of their practical viability, coverage and discrimination. The mHUI3 showed slightly better discrimination than the SF-12, and also identified more mild health states. The authors conclude, however, that despite the inherent differences, no one instrument performed better or worse than the others with respect to the criteria applied in the study.

In a paper 'Incorporating utility-based quality-of-life assessment measures in clinical trials. Two examples', Feeny and Torrance[62] cited the advantages of the utility approach as "generalizability, comprehensiveness, ability to integrate mortality and morbidity effects, ability to represent multiple viewpoints, and its incorporation of time and risk preferences in the scores". The paper also noted a number of the disadvantages, including some lack of precision and interviewer administration – although this is not a problem with the HUI since it is self-administered.

A paper by Suarez-Almazor and colleagues[63] used a sample of patients with low back pain to compare specific, generic and preference-based instruments. These included the HUI and the SF-36. Correlations between the instruments were generally low, suggesting that they measure different health domains.

The HUI was shown to be one of the scales that best discriminated between patients who improved and those who deteriorated at 3 months.

## Physical outcome measures [incremental shuttle walk test (ISWT)]

There is a lack of consensus regarding validated physical clinical outcome measures for CFS/ME. Previous studies into GET have used a physiological measure, $VO_2$ Max, which measures the efficiency of oxygen turnover in the body, measured in millilitres per kilogram of body weight per minute. This was measured at the subject's peak capacity on a treadmill test by Fulcher and White.[30] More recently, it was tested at 75% of the subjects' predicted maximum heart rate in a submaximal test by Wallman and colleagues.[64] These trials have usually involved exercise physiologists, who routinely use such measures. In clinical practice, the equipment used to measure oxygen consumption is not widely available, and the functional benefits of improved $VO_2$ Max have not been demonstrated. There is an ongoing debate about the relative contributions of capacity and performance to physical outcome measures in chronic disease. In reality, many measures are probably 'psychophysical' in that they measure the complex interaction of physical ability and willingness to perform. In the same way that the mind and the body can artificially be thought of as separate entities, so can capacity and performance. However, it is the combination of both that leads to improved function, hence the choice of a physical outcome measure that incorporates both aspects.

Sharpe and colleagues[19] used a 6-minute walk test, which measured the distance walked when the patient was asked to walk as quickly as possible within a 6-minute period. This test had previously been validated in populations with chronic airways obstruction. The shuttle walk test,[65] or the incremental shuttle walk test (ISWT), is thought to have advantages over the 6-minute walk test, including the achievement of a greater pulse rate during the test and a reduced influence of bias due to the reinforcement of the observer.[66] The ISWT is validated as an outcome measure for chronic obstructive airways disease, low back pain and rheumatoid arthritis. Following considerable discussion, the ISWT was chosen over the subanaerobic threshold exercise test (SATET) (which was our planned measure), since it offered a greater relevance to subjects' everyday function (i.e. increased validity).

One important consideration when choosing a physical outcome measure for CFS/ME is that the

patient may be capable of performing during the measure, but may suffer an unacceptable increase in symptoms later as a result. This information is not captured by any outcome measure known to the authors, either for this condition or for the somewhat related clinical area of chronic pain. In the present study, an attempt was made to capture this information by asking the subjects to state their rate of perceived fatigue (RPF) at the end of the ISWT using the modified (10-point) perceived exertion scale – the category ratio scale CR10[67] (see Appendix 13). Subjects were also asked to inform the tester when they had reached their normal walking speed, to gain further information about the functional ability of the subject.

It is possible to debate the relative contributions of capacity and performance when analysing many physical outcome measures in chronic disease. Although this is an interesting debate, the reality is that most measures are probably 'psychophysical' in that they measure the outcome of a complex interaction of physical ability and willingness to perform.

In the same way that the mind and the body are artificial categories, so are capacity and performance. In reality, it is a combination of both that leads to improved function.

### Cognitive function (short-form neurocognitive battery)

Problems with memory, attention and concentration are well-documented symptoms in CFS/ME and form part of the diagnostic criteria. Despite this, there is only limited research examining cognitive functioning in this area and, perhaps unsurprisingly, there is controversy over their primary or secondary symptom status: whether the cognitive problems are a result of co-morbid depressive disorders, or a result of the disturbance to the circadian rhythm, is unclear. One example (from the very limited research available in this area) is a study by Crowe and Casey, who found memory impairment which persisted once the effects of depression had been controlled for.[68] The study involved testing a relatively small sample of sufferers ($n$ = 26), with a matched control group, against a battery of standardised neuropsychological tests. Their findings supported a compromise of memory function, especially verbal learning.

The use of standard neuropsychological tests was ruled out because of the length of time needed to complete such a battery. For the present study, the decision was made to use the short-form neurocognitive battery developed by Smith and colleagues[69] as a way of taking this debate further. This battery provides a performance measure of reaction time, free recall and sustained attention, and has been standardised on a small CFS population.

### Measurement of cost (semi-structured questionnaire)

A semi-structured questionnaire was designed by the health economist at the beginning of the trial and was piloted on four CFS/ME sufferers prior to its use. A copy of the questionnaire is included (Appendix 7). The questions covered personal expenses, medication use, private treatments, informal help and employment details.

## Drop-out rates

Previously reported drop-out rates have varied. In Whiting and colleagues' review,[17] the overall drop-out rate was 15%. The highest drop-out was observed in the CBT trial and reached 19%. No reasons were given for this, but clearly if CBT is considered an effective treatment, the reasons for high drop-out in this area will be pertinent. Several authors have reported difficulties with patient drop-out,[17] but there have been no trials reporting drop-out rate from a treatment delivered in a group setting.

## Objectives

The objective of the trial was to test the hypothesis that group CBT will produce an effective and cost-effective management strategy for patients in primary care with CFS/ME. The treatment was compared with standard medical care and a placebo-response control.

The end-points of interest were:

1. physical functioning
2. symptom severity
3. quality of life
4. health service resource use.

It was hypothesised that treatment gains in these areas would be present even when the non-specific effects of therapist exposure are controlled for.

Given that CFS/ME is a heterogeneous syndrome, the treatment offered has several features and it is expected that subjects will respond differentially to the intervention.

The aim of the economic evaluation was to compare the cost-effectiveness of (i) group CBT, (ii) group EAS, and (iii) standard medical care (SMC) for primary care patients with chronic fatigue syndrome. The analysis was conducted from the perspective of the NHS and did not assess broader societal costs.

# Chapter 2
# Methods

## The setting

The group treatment was carried out in the Pain Management Centre at Frenchay Hospital, Bristol, UK. Subjects for the study were recruited from the catchment areas of North Bristol NHS Trust and the United Bristol Healthcare Trust.

## Research governance

The trial was approved by the North Bristol NHS Ethics Committee on 15 December 1999, the Southmead Local Research Committee on 6 January 2000 and the United Bristol Healthcare Trust Local Research Committee on 13 November 2000.

A Research Monitoring Committee was established at the start of the trial and first met on 29 August 2000. This group consisted of:

- Dr Hazel O'Dowd, Clinical Psychologist and Research Lead
- Dr Chris Rogers, Senior Statistician
- Assistant Psychologist (rotational post)
- Administrator
- Dr Andy Stainthorpe, Research and Development Coordinator, North Bristol NHS Trust.

  *Dr Stainthorpe left the post in 2002 and was replaced in 2004 by*

- Sandra Hollinghurst, Health Economist.

This group met bimonthly throughout the data collection period. Dr O'Dowd had two 8-month periods of maternity leave during the course of the trial and Nicholas Ambler, Consultant Clinical Psychologist, carried out her role during this period.

## Protocol deviation

There were several changes to the original protocol:

1. The subanaerobic threshold exercise test was not used for reasons detailed in the Introduction.
2. The 18-month follow-up was carried out by postal assessment rather than as an outpatient assessment owing to the shortfall in staffing resources.
3. An additional measure of economic impact was included in the HUI form following the advice of the Health Economist.
4. In order to generate more referrals, there was media exposure for the project, approximately half way through. It is possible, therefore, that subjects included in the trial may have heard of the project themselves and requested that they be referred. This represents a slightly different process to referrals that were purely GP generated in the first half of the trial.
5. There were several staff changes during the course of the trial. The Health Economist left post approximately half way through the trial and was not replaced until the very last stage. The physiotherapist changed after the first set of groups, but then remained constant. The psychologist left for maternity leave during the trial, and consequently one set of groups had a different psychologist.

## Consent

The consent of the patient was sought by the GP and included:

- consent to take part in the trial with respect to potential treatment
- consent to access their medical records
- consent to use their assessment data.

## Participants

The participants were NHS patients, currently managed in primary care, and included those treated under contract with private sector providers.

## Eligibility criteria

The eligibility criteria were as follows:

- presentation consistent with CFS/ME as described by Fukuda and colleagues,[8] from the Centre of Disease Control.

- subject had read and understood Patient Information Leaflet (copy included in Appendix 4)
- subject had given consent (copy included in Appendix 5).

The exclusion criteria were as follows:

- concurrent severe mental illness (i.e. psychosis and allied conditions)
- planned or concurrent rehabilitation
- inability to attend all treatment sessions
- ongoing physical investigations

## Delivery team

There were four therapists involved in treatment delivery over the course of the trial:

- Mr Nick Ambler: Consultant Clinical Psychologist with over 20 years' experience in the delivery of CBT, 15 years of which have been in chronic illness management.
- Dr Hazel O'Dowd: Clinical Psychologist with 12 years' experience of delivering CBT interventions, 7 years of which have been in a chronic illness management setting.
- Mr Peter Gladwell: Specialist Physiotherapist with 10 years' post-qualification experience. He has had an active interest in the management of chronic disease since qualification, and experience of working in a multidisciplinary team using CBT since 1999. He is involved in teaching physiotherapists to develop their skills in using a cognitive behavioural approach to rehabilitation.
- Mrs Meg Birch: Senior Occupational Therapist specialising in CFS and chronic pain. She has worked in pain management using CBT since 1994. She has considerable experience with this illness and has been working for AfME (a national charity) in a sessional capacity since November 2000.

## Interventions

A complete description of the course is given in Appendix 8. Both group treatments consisted of eight meetings, with each meeting lasting 2 hours. The meetings took place fortnightly and each group consisted of 8–12 individuals.

### Condition 1 – description of the CBT intervention

The CBT used in this trial was designed to do two things: first to attempt to modify thoughts and beliefs about symptoms and illness, and second to attempt to modify behavioural responses to symptoms and illness, such as rest, sleep and activity.

The ultimate goal of the treatment was to increase adaptive coping strategies and therefore reduce the distress and disability.

The content of the programme included:

- Elucidation of core beliefs regarding their illness and its management.
- Monitoring of activity levels and introduction of appropriate timetable.
- Introduction to exercises designed to increase general level of fitness, balance and confidence in exercise. A range of aerobic, strength, balance and stretching exercises were taught.
- Behavioural modification of sleep patterns.
- Mood management advice.
- Goal setting.

The CBT groups were introduced to a structured incremental exercise programme following a group discussion about the unhelpful nature of activity cycling, following CBT principles. The calculation of a deliberately low 'baseline' for exercise as a means of counteracting activity cycling was taught, and instructions were given about pacing up by small increments once the exercise level had been achieved successfully for several days (flexibility was allowed for patients to choose their own frequency of increments). Advice was given to patients to reduce the level of exercise considerably should a significant increase in symptoms be experienced at some stage in the future, and the balance between the risks and the benefits of prolonged rest during such a setback was explored. The management of setbacks was a specific subject included in the CBT group syllabus.

### Condition 2 – description of the EAS intervention

The same therapists met with these groups, in the same setting, at the same time and for the same duration and frequency as the CBT groups. The focus of these groups was on the sharing of experiences and the learning of basic relaxation skills. Each week, a different relaxation exercise was taught. A complete description of the course is given in Appendix 8. These groups served as a control for the non-specific effects of therapy and controlled for the effects of therapist time and attention.

In order to validate the role of the physiotherapist within the EAS condition, a stretch programme

was introduced. This included 16 stretches for major muscle groups in the body, and patients were advised to perform each stretch twice, in a relaxed manner. The purpose of the stretches was explained as loosening the muscles so that a state of relaxation in the muscles could be achieved. If further questions regarding exercise were asked in these groups, the group was informed that there was controversy regarding the value of aerobic exercise, and therefore we did not wish to introduce exercise if it were to be unhelpful for some patients. The physiotherapist also participated in the teaching of relaxation techniques, including in particular those that involved movement such as progressive muscle relaxation and slow diaphragmatic breathing.

### Condition 3 – description of SMC intervention

This group did not attend the hospital other than to complete the assessment material at baseline and 6 and 12 months. They continued to be managed in primary care and details of their use of resources were collected as part of the economic evaluation.

## Outcomes

The assessor was a graduate psychologist who was trained by the lead clinical psychologist and the physiotherapist in the administration of the measures.

These outcomes have been explained in detail above and included:

- symptoms, such as fatigue, pain, mood and cognitive deficits
- quality of life
- health service resource use, e.g. primary care consultation rate, secondary care referral rate, use of alternative practitioners, use of prescribed drugs
- compliance and acceptability of the interventions, such as drop-out rate
- employment status.

## Duration of follow-up

Subjects were assessed at three time points:

- immediately prior to randomisation
- 6 months later
- 12 months later.

Since the start of this trial, we have also sought ethical approval to send a postal assessment to all the subjects at 18 months after their baseline assessment. This is not yet complete and is not included in this report.

## Sample size

Our primary outcome measures were the SF-36 physical and mental health summary scales. The target sample size for the trial was set at 43 per condition, based on the hypothesis that 55, 19 and 10% of patients randomised to CBT, EAS and SMC, respectively, would have a successful outcome, defined as a 15% improvement over baseline.[37] The target success rates were based on work by Deale and colleagues[38] This sample size was sufficient to detect differences between CBT and SMC and between CBT and EAS at the 5% level of statistical significance (2.5% significance level for each comparison) with 90% power. This target sample size was achieved in all groups, although fewer than 43 patients in the CBT group completed the 12-month assessment.

The power calculation was based on the numbers of patients achieving a successful outcome, since data on the variability [standard deviation (SD)] of the standardised SF-36 summary scores in patients with CFS were not available. Data on the physical functioning subscale were reported in Deale and colleagues,[38] but these data were not used in the current study because (a) the scores were highly skewed and had been transformed to the logarithmic scale for analysis and (b) the SDs reported were for the untransformed scores; the SD of the transformed scores was not given. Replacing the scores with a binary response (achieved or not achieved a 15% improvement over baseline) reduces the sensitivity of the analysis to detect differences between the treatment groups and for this reason the actual scores were used in the analysis of the data.

## Randomisation

The randomisation scheme was prepared independently of those involved in the recruitment, treatment and assessment of study participants; a statistician not involved in the study prepared the scheme. Balance was achieved through block randomisation with varying block sizes. Allocation details were provided in sequentially numbered sealed opaque envelopes. The department administrator opened the

envelopes at the end of the first assessment and arranged the next appointment where necessary. The assessor was not involved in any aspect of this process. At the end of the trial, the randomisation scheme was released to the study statistician.

## Blinding/masking

Both the participants and those administering the assessments were unaware of which cohort the subject was in. It was not possible to mask participants in the SMC group for obvious reasons.

The assessors were instructed not to enquire about any treatment undertaken as part of the trial and to stop the subject from making any reference to the trial during the course of the reassessments. The assessor was not present during the intervention period.

The success of the blinding/masking was not formally assessed. However, it was observed that the EAS group spoke in terms of this being a valid and plausible treatment approach. The therapists involved in the delivery noted that many of the key concepts presented in the CBT group were spontaneously raised by EAS members.

## Statistical methods

Quality of life instruments were all scored according to the instructions accompanying the instrument. Data from the SF-36 questionnaire are expressed in terms of the physical and mental summary scales.[70] To maximise the sensitivity of the instrument, Likert scaling was used to score the Chalder scale and GHQ.

The data were analysed on the basis of intention-to-treat. Categorical data are summarised as number and percentage and continuous measurements as mean and SD or median and interquartile range (IQR) as appropriate. For all of the quality of life and cognitive scores, the median and IQR are reported. To allow comparison with results from other studies, mean responses are also given. The SD is reported for symmetrically distributed variables but is omitted for skewed data.

For the cognitive simple reaction time and repeated digits detection tests, the values recorded for each participant are the mean reaction time over the number of completed trials and hits, respectively. In analysing and reporting these outcomes, the data were weighted according to the number of values (completed trials or hits) contributing to the mean time. The word recall test involved patients recalling words from two lists. The total number of words recalled is analysed. For four patients (one at baseline, two at 6 months and one at 12 months), data for one of the two lists were missing. In these cases the missing values were imputed using the value from the other list.

Mixed random effects regression was used to compare the quality of life scores and cognitive test results across the three intervention cohorts (CBT, EAS and SMC). The normality assumption was assessed graphically and, if untenable, a natural logarithmic transformation was applied. The small number of zero values were replaced with a small positive number (less than any observed non-zero value) before the logarithmic transformation was applied. The goodness of fit of the regression model was assessed graphically. If outlying observations were identified, the analyses were repeated, the outliers excluded and the results compared. If the conclusion differed between the two analyses, both are described, otherwise the results are reported with outliers excluded. All analyses were adjusted for baseline scores and assessment set. The three intervention cohorts were compared at 6 and at 12 months. If the differences between the treatments were similar at the two time points, treatment effects pooled over the two time points are reported. If the effect of the three treatments differed between the two time points [i.e. a statistically significant interaction between intervention cohort and time was found ($F$-test using a 5% level of significance)], results are reported separately for the 6- and 12-month assessments. Results are presented as least-squares means with standard errors (SEs). Differences between the treatment cohorts are reported with 95% confidence intervals (CIs). No corrections for multiple comparisons were made, but our interpretation of the findings is based on the consistency of the findings and their magnitude in addition to their statistical significance.

A mixed model was chosen in preference to comparing the results at each time point because only 129 of the 153 participants recruited (84%) completed the 12-month assessment. A mixed-model approach allows **all** the data to be included in the analysis without the need to impute missing values. Hence study participants who completed both assessments and those who only attended one of the two follow-ups (either the 6- or the 12-month assessment) were included.

The primary analyses compare the patient scores across the three intervention groups, as this provides a more sensitive analysis of the data than simply comparing the proportion of patients who reach a certain level or achieve a pre-specified degree of improvement. It makes maximum use of the data available and hence has the greatest power to detect differences between groups. Similarly, adjusting for baseline scores is more efficient than comparing changes from baseline. However, when the study was conceived, data on which to base the power calculation were limited and effectiveness was defined in terms of the proportion of patients showing improvement from baseline. For this reason, for the primary outcome measures, the SF-36 physical and mental summary scales, the numbers of patients reporting a 15% increase over the baseline score (defined by Buchwald and colleagues[37] as a successful outcome) and the numbers returning to the normal range are also reported. A subject was assumed to have a score in the 'normal' range if the score was on or above the fifth centile for the distribution (estimated as the mean $-1.645 \times$ SD for the gender-specific age group). The age and gender-specific means and SDs for the general population were obtained from the SF-36 user manual. Population average logistic regression models were used to compare these outcomes across the three intervention groups. All analyses were adjusted for assessment set. The analysis of scores in the normal range was also adjusted for the status at baseline (i.e. whether the score was in the normal range at baseline). Differences between cohorts are reported as odds ratios with 95% CIs.

Mixed-model analyses were carried out using SAS version 8.2. All other analyses used Stata version 8.2.

## Economic evaluation

Data on health service resource use, for inclusion in the economic evaluation, were obtained by examination of patient GP records and through a patient questionnaire administered at baseline and 6 months and 12 months (*Table 1*).

## Healthcare contacts

Scrutiny of GP records was performed by the research assistant, who took note of all healthcare contacts over the 12 months following randomisation. We recorded all primary care consultations, any outpatient (OP) appointments and where these took place and any inpatient (IP) stays in hospital and the length and reason for the stay. Owing to the nature of chronic fatigue syndrome, we took as comprehensive an approach as possible for the cost analysis and included all healthcare contacts, irrespective of reason for encounter.

## Medication

Information on prescribed medication was obtained from a patient questionnaire administered at baseline and 6 and 12 months. Patients were asked about drugs they use, categorised into selective serotonin reuptake inhibitors (SSRIs), tricyclics, hypnotics, analgesics, anti-inflammatories, benzodiazapines and 'other'. Possible answers were 1, 'not taken'; 2, 'taking currently'; and 3, 'took previously but not now'. No information was sought regarding the number of prescriptions or the quantity.

The information obtained from the questionnaire is not sufficient to indicate the level of drug use over the 12-month period, which is necessary to complete a comprehensive economic evaluation. Nevertheless, in order to make the best possible use of the information available, and so as not to ignore the potential impact of drug costs, we devised a method of translating the questionnaire replies into an estimated quantity of medication. We developed an algorithm that would use the

***TABLE 1*** *Sources of resource use and valuation for economic evaluation*

| | Source | Valuation |
|---|---|---|
| GP appointments | GP records | Netten and Curtis, 2003[71] |
| OP appointments | GP records | NHS reference costs, 2003[72] |
| IP stays | GP records | NHS reference costs, 2003[72] |
| Medication | Patient questionnaire | Department of Health Prescription Cost Analysis: England, 2003[73] |

IP, inpatient; OP, outpatient.

***TABLE 2*** *Algorithm to convert questionnaire replies to an estimated number of prescriptions over the 12-month period*

| Questionnaire replies[a] | Estimated no. of prescriptions | Questionnaire replies[a] | Estimated no. of prescriptions | Questionnaire replies[a] | Estimated no. of prescriptions |
|---|---|---|---|---|---|
| 111 | 0.00 | 211 | 2.00 | 311 | 1.33 |
| 112 | 2.00 | 212 | 4.00 | 312 | 3.33 |
| 113 | 1.33 | 213 | 3.33 | 313 | 2.67 |
| 121 | 2.00 | 221 | 4.00 | 321 | 3.33 |
| 122 | 4.00 | 222 | 6.00 | 322 | 5.33 |
| 123 | 3.33 | 223 | 5.33 | 323 | 4.67 |
| 131 | 1.33 | 231 | 3.33 | 331 | 2.67 |
| 132 | 3.33 | 232 | 5.33 | 332 | 4.67 |
| 133 | 2.67 | 233 | 4.67 | 333 | 4.00 |

[a] 1, 'not taken'; 2, 'taking currently'; and 3, 'took previously but not now'.

three observations to estimate the likely number of prescriptions per drug type over the 12-month period. The minimum drug use was represented by three consecutive answers of 'not taken' (111) and given a score of 0, representing an estimate of no prescriptions over the 12-month period. The maximum use was represented by three consecutive answers of 'currently taking' (222) and given a score of 6, representing an estimate of six prescriptions for that drug type over the 12-month period. All other combinations of replies were assigned an estimated number of prescriptions (*Table 2*).

## The intervention

The active intervention (CBT) took the form of group sessions of CBT. Patients in the placebo-response group (EAS) received group sessions of EAS. All groups had between eight and 10 participants and the intervention consisted of eight sessions. In terms of resource use, only clinical and administration time is relevant as no equipment was used and the intervention took place on existing NHS premises; 48 hours of clinician time and 3 hours of administration time were involved in delivering each complete group intervention.

## Outcome data

The primary outcome measure for the economic evaluation is the HUI. This index was chosen with the aim of capturing all possible benefits from the intervention, and allowing for the possibility of forming QALYs.

## Missing data

Data on primary and secondary care contacts were all collected at the same time from the same source (practice records). Therefore, we were able to use complete case analysis for this part of the analysis. Data were available for 133 patients (CBT 45, EAS 45, SMC 43).

Data on medication use were obtained from patient questionnaires so missing data were randomly dispersed throughout the dataset. Complete case analysis would have yielded data for only 64 patients (CBT 21, EAS 23, SMC 20). Clearly this is a very small number from which to draw conclusions about differences in resource use, so we also used a method of imputation to provide estimates for as many patients as possible. This also allowed us to estimate a total mean cost per patient. We imputed missing data on resource use from the available data for the particular patient and mean values of comparable complete cases. Thus we were able to estimate the number of prescriptions issued to 152 patients (CBT 52, EAS 49, SMC 51).

## Valuation of resource use

Primary care appointments were valued according to Netten and Curtis.[71]

Secondary care contacts were valued using NHS reference costs.[72] OP appointments were costed as precisely as possible, depending on the level of information given in the notes. In some cases an average unit cost was used. Where possible, we costed first attendance and follow-up

appointments separately. IP stays were costed, where possible, on a cost per day basis, but in some cases we used average length of stay for the particular procedure.

Prescribed medication was valued using Prescription Cost Analysis: England 2003.[73] This source gives cost per prescription, by individual preparation. Our data were classified broadly, for example 'SSRI', so a weighted average cost per prescription was used. Drugs listed in the 'other' category of medication were costed as precisely as possible, given the level of information provided.

# Chapter 3
# Results

## Recruitment

Subjects were recruited from August 2000 to July 2002. Originally, the recruitment rate was estimated to be at 4–6 cases per week. These figures were based on national and local epidemiological data.[38,74]

Subjects were recruited via the GP. Every general practice in the catchment areas of North Bristol NHS Trust and the United Bristol Healthcare Trust was approached and asked to take part in the study. Each GP was sent an information pack and, where necessary, visits were arranged to the surgeries to explain the trial (see Appendix 3 for referral summary by GP practice).

## Participant flow

Subjects presented to their GP with a diagnosis of CFS/ME. Their GP described the trial and subjects expressed an interest (we have no information on how many dropped out at this stage). The GP wrote to the research team describing the subject, confirming their diagnosis and their consent to be involved.

Of this initial pool, 12 referrals were inappropriate since they did not meet the diagnostic criteria and a further 17 withdrew at this stage for unspecified reasons.

The remaining subjects were then invited to the hospital to complete the baseline assessment. From this point they took one of three paths:

1. attendance at treatment group (CBT)
2. attendance at treatment group (EAS)
3. SMC, no further attendance until 6-month assessment.

Each subject was then invited back for the 6- and then 12-month reassessments (Appendix 1).

## Numbers analysed

### Treatment assignment

A total of 153 patients met the criteria for the trial and gave consent to participate. Fifty-two were randomised to receive CBT, 50 to EAS and 51 to SMC. Seven patients did not receive the treatment assigned – three randomised to CBT received EAS and four randomised to EAS received CBT. The patient allocation was changed for clinical and ethical reasons. The transposed subjects were related to or closely associated with, other group members and it was felt that there would be contamination in the group process and leakage of the treatments. This was not ideal and highlighted the difficulty with the randomisation process, which does not allow clinical judgement to inform treatment decisions and is discussed in more detail later.

### Follow-up

Twelve of the 153 patients recruited failed to attend for follow-up. Nineteen patients attended one follow-up, but not both; 12 completed the 6-month follow-up only and seven attended for the 12-month follow-up only. The remaining 122 patients provided data at 6 and 12 months. *Figure 1* gives details of the data available by treatment condition. Reasons for drop-out are given in Appendix 9 and illustrated in *Figure 2*.

## Baseline data

### Demographics, symptoms and past history

The three groups were similar at baseline (Appendix 10). However, there were almost twice as many men in the CBT arm of the trial in comparison with the EAS and SMC cohorts (24, 12 and 15, respectively). The mean age for all patients in the study was 41.1 (SD 11.9) years. Two-thirds of the patients were female. The majority (61%) lived with a partner and almost half (48%) were without dependents.

Patients in all groups experienced multiple symptoms, the most common being poor concentration (96%), memory loss (88%) and weakness (88%). Almost half of the participants recruited (49%) had experienced symptoms for more than 5 years. Only two patients reported that they were free from pain.

All but three patients had undergone one or more tests for CFS, with blood tests being the most

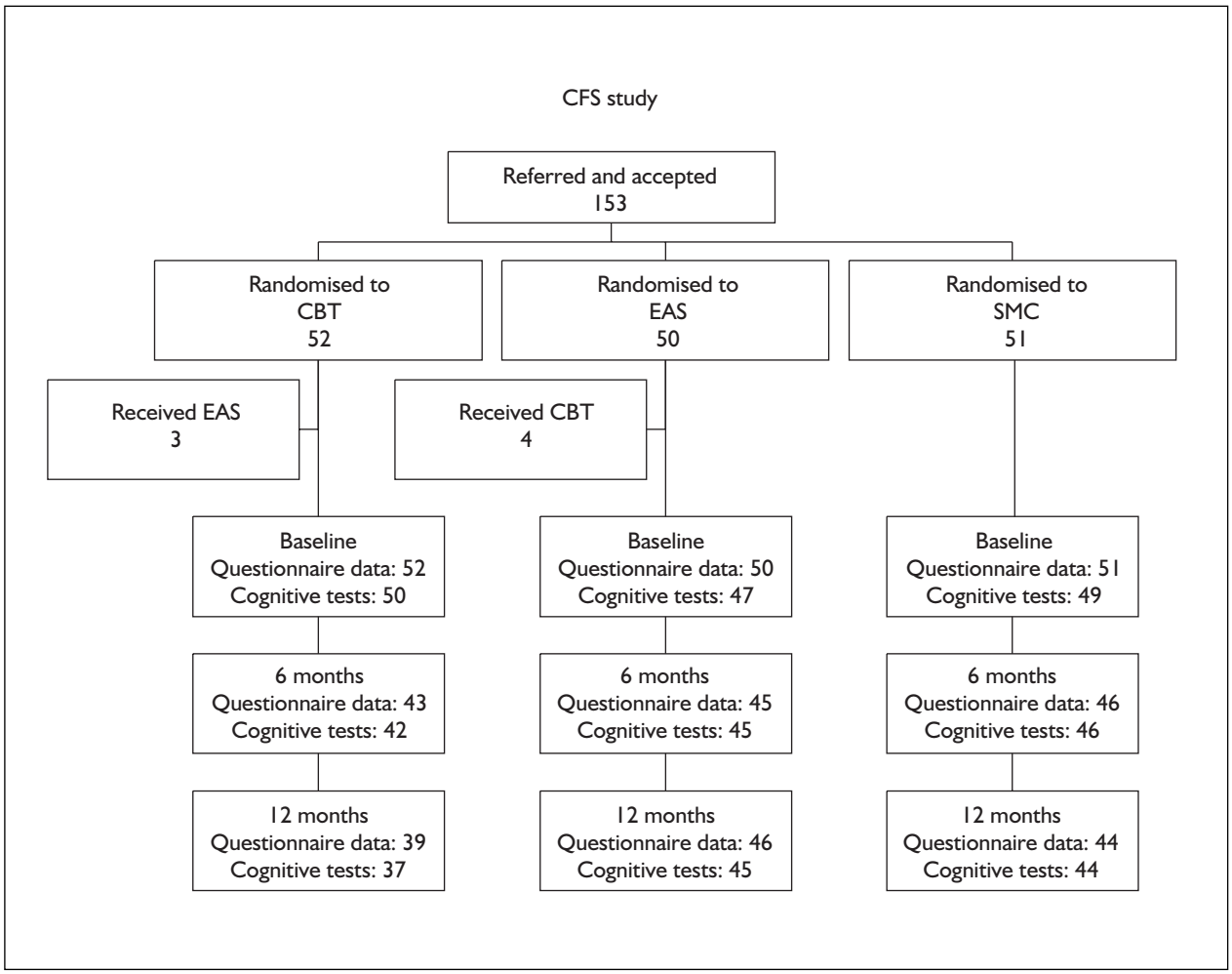


***FIGURE 1*** *Quantity of data available by treatment condition at each stage of the study*

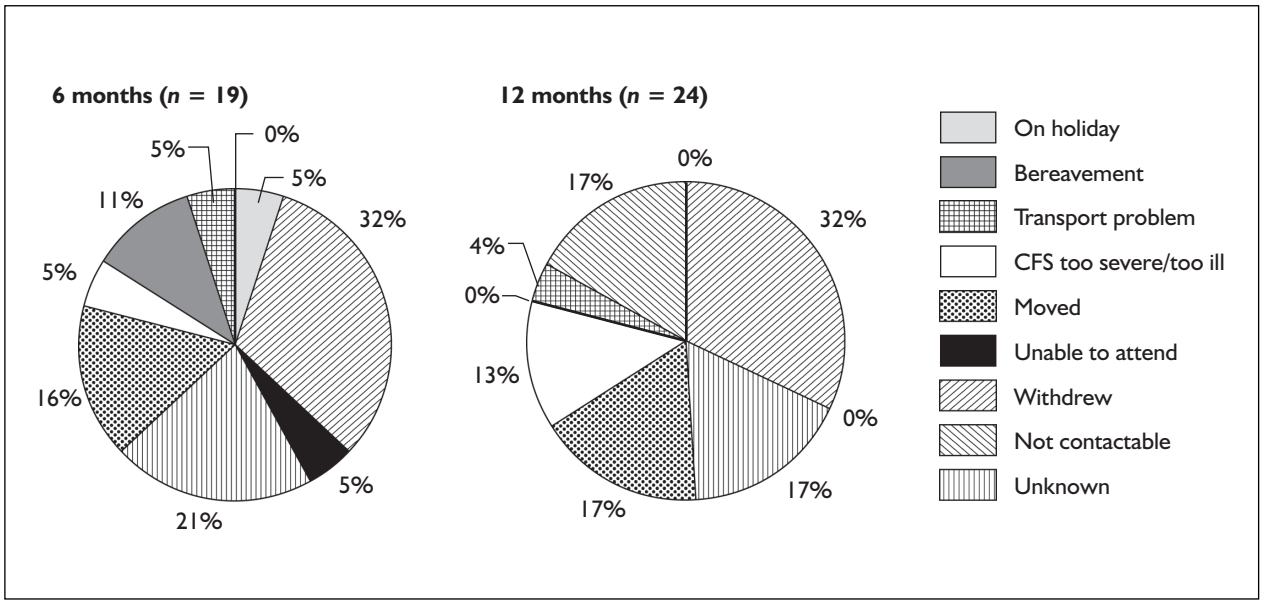


***FIGURE 2*** *Reasons for missing data at 6- and 12-month follow-ups*

common. Overall, 70% of blood tests were carried out more than 1 year before the start of the study. Few patients had received physiotherapy for CFS (6%). More than two-thirds of patients (69%) were either taking antidepressants or had taken them in the past and 58% were taking analgesics. Overall, 48.9% had undergone some form of psychological/psychiatric treatment prior to this trial. This included treatment for depression, anxiety or stress.

For the majority of patients (64%), the diagnosis of CFS was made by their GP. Almost all patients (89%) had been in full or part-time work prior to their illness and for 70% CFS had prevented them from continuing in that role.

## Quality of life and cognitive scores

Quality of life and cognitive scores were similar across the three groups (see *Table 3* for mean scores; median scores are given in Appendix 10).

SF-36 physical and mental health scores were of similar magnitude, and, as might be expected, the mental health scores showed greater variability (SD 11.2) than the physical scores (SD 7.9). Overall, 30% of patients had an SF-36 physical health score and 52% a mental health score **within** the normal range (i.e. at or above the estimated fifth centile for the age and gender specific sector of the population). While the mean scores were similar across the groups, for both the physical and mental health scores there were fewer patients in the EAS group with a baseline score within the normal range than in the other intervention cohorts [physical score within normal range, 16% vs 37% and 38% in the CBT and SMC groups, respectively; mental health score, 47% vs 54% and 56% in the CBT and SMC groups, respectively (see *Table 6*)].

In the cognitive test, the majority of words recalled were correct and the hit rate with the repeated digits detection test was approximately five times the false alarm rate.

***TABLE 3*** *Quality of life and cognitive scores at baseline*

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| *(a) Quality of life scores* | | | | | | |
| SF-36 | | | | | | |
| Physical health | 33.4 | 8.49 | 30.3 | 6.33 | 32.7 | 8.38 |
| Mental health | 35.5 | 11.4 | 35.1 | 11.5 | 35.7 | 11.1 |
| Physical performance | | | | | | |
| Perceived fatigue | 3.0 | | 3.5 | | 3.2 | |
| Shuttles walked | 24.3 | | 23.3 | | 26.2 | |
| Normal walking speed | 9.7 | | 8.9 | | 10.9 | |
| HADS | | | | | | |
| Anxiety | 9.94 | 3.83 | 11.2 | 4.44 | 9.74 | 4.27 |
| Depression | 8.46 | 3.99 | 9.28 | 3.51 | 8.39 | 3.05 |
| GHQ | 19.6 | 7.02 | 21.7 | 7.63 | 18.1 | 6.70 |
| Chalder | 25.0 | 6.64 | 24.9 | 5.87 | 23.9 | 6.76 |
| HUI3 overall utility score | 0.31 | 0.28 | 0.22 | 0.31 | 0.38 | 0.29 |
| *(b) Cognitive scores* | | | | | | |
| Mood | | | | | | |
| Alertness | 191.9 | 48.7 | 174.9 | 58.1 | 180.1 | 57.6 |
| Hedonic tone | 172.3 | 36.0 | 172.2 | 42.0 | 171.7 | 39.1 |
| Anxiety | 77.5 | 20.3 | 78.1 | 23.1 | 80.6 | 19.4 |
| Recall | | | | | | |
| Total words recalled | 11.02 | 3.72 | 11.46 | 3.69 | 10.82 | 3.99 |
| Correct words | 10.02 | 3.60 | 10.56 | 3.61 | 9.92 | 3.69 |
| Incorrect words | 1.00 | | 0.90 | | 0.90 | |
| Simple reaction time | | | | | | |
| Reaction time | 444.2 | | 414.3 | | 387.8 | |
| Trials completed | 26.1 | 1.89 | 26.2 | 1.81 | 26.3 | 1.92 |
| Repeated digits detection | | | | | | |
| Reaction time | 599.0 | 97.6 | 597.1 | 120.7 | 623.5 | 97.2 |
| Hit rate | 10.3 | | 9.04 | | 10.0 | |
| False alarms | 3.02 | | 1.78 | | 4.11 | |

# Outcomes at 6 and 12 months

## 6-month assessment

General 6-month outcome characteristics by treatment allocation are reported in Appendix 11. Mean quality of life and cognitive scores for those attending the 6-month follow-up are reported in *Table 4*; median scores are given in Appendix 11).

### *SF-36 physical and mental health summary scales*

The SF-36 physical summary scale means for all three groups showed little change from baseline; the mean change for the study cohort as a whole was +1.45 (SD 6.96) at 6 months. Overall, 36% of the study population had a physical health score **within** the normal range for the population as a whole, a 6% increase on the 30% reported at baseline. The percentages with a score within the normal range by intervention cohort are given in *Table 6*. The EAS group showed the greatest percentage increase from baseline (+8%, compared with +3% for the CBT group and +6% for the SMC group), but there were fewer patients with a score in the normal range at both time points. Some 28% of patients showed at least a 15% improvement over their baseline score. The percentages showing at least this level of improvement by intervention cohort were CBT 24%, EAS 33% and SMC 28% (see *Table 6*).

The average change in mental health score from baseline was greater than for the physical health score; the mean change for the study cohort as a whole was +5.67 (SD 11.4) at 6 months. Overall, 73% of the study population had a mental health score **within** the normal range for the population as a whole, a 21% increase on the 52% reported at baseline. The percentages with a score within the normal range by intervention cohort were CBT 86%, EAS 71% and SMC 62% (see *Table 6*). The CBT group showed the greatest percentage

***TABLE 4*** *Quality of life and cognitive scores at 6 months*

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| *(a) Quality of life scores* | | | | | | |
| SF-36 | | | | | | |
| Physical health | 33.4 | 9.04 | 32.3 | 9.30 | 34.5 | 9.95 |
| Mental health | 44.5 | 10.4 | 40.0 | 11.1 | 38.8 | 12.7 |
| Physical performance | | | | | | |
| Perceived fatigue | 2.79 | | 3.22 | | 3.17 | |
| Shuttles walked | 28.5 | | 25.6 | | 23.6 | |
| Normal walking speed | 12.1 | | 8.76 | | 9.39 | |
| HADS | | | | | | |
| Anxiety | 8.14 | 3.86 | 9.93 | 4.00 | 9.61 | 4.69 |
| Depression | 6.84 | 3.46 | 8.20 | 3.81 | 7.78 | 3.76 |
| GHQ | 13.7 | 7.05 | 17.4 | 7.68 | 16.6 | 7.57 |
| Chalder | 17.9 | 8.41 | 21.4 | 7.55 | 21.8 | 6.90 |
| HUI3 overall utility score | 0.43 | 0.28 | 0.34 | 0.32 | 0.41 | 0.25 |
| *(b) Cognitive scores* | | | | | | |
| Mood | | | | | | |
| Alertness | 211.4 | 43.0 | 186.2 | 60.3 | 181.6 | 60.4 |
| Hedonic tone | 177.3 | 35.5 | 176.7 | 40.6 | 168.9 | 43.2 |
| Anxiety | 81.0 | 17.4 | 83.8 | 23.3 | 83.4 | 24.5 |
| Recall | | | | | | |
| Total words recalled | 12.9 | 3.90 | 12.3 | 3.66 | 11.9 | 4.66 |
| Correct words | 12.0 | 3.80 | 11.8 | 3.77 | 10.9 | 4.49 |
| Incorrect words | 0.89 | | 0.54 | | 0.96 | |
| Simple reaction time | | | | | | |
| Reaction time | 470.9 | | 406.4 | | 383.2 | |
| Trials completed | 26.5 | 1.96 | 26.2 | 1.46 | 26.5 | 172 |
| Repeated digits detection | | | | | | |
| Reaction time | 594.8 | 95.2 | 599.1 | 108.8 | 631.4 | 93.7 |
| Hit rate | 11.1 | | 11.2 | | 11.3 | |
| False alarms | 2.16 | | 1.56 | | 2.43 | |

increase from baseline in the numbers of patients with a score in the normal range (+32%, compared with +24% for the EAS group and +6% for the SMC group). Overall, 47% of patients showed at least a 15% improvement over their baseline score. The percentages showing at least this level of improvement by intervention cohort were CBT 47%, EAS 52% and SMC 41% (see *Table 6*).

## 12-month assessment

General 12-month outcome characteristics by treatment allocation are reported in Appendix 12. Mean quality of life and cognitive scores are reported in *Table 5*; median scores are given in Appendix 12).

### *SF-36 physical and mental health summary scales*

The 12-month SF-36 physical summary scale means for all three groups showed little change from baseline and from 6 months; the mean change for the study cohort as a whole from baseline was +1.97 (SD 6.93) and, compared with the scores at 6 months, the mean change was +0.58 (SD 6.38). Overall, 38% of the study population had a physical health score **within** the normal range for the population as a whole at 12 months, an 8% increase on the 30% reported at baseline and 2% higher than the 36% observed at 6 months. Some 46% of patients in the CBT group had a score within the normal range at 12 months compared with 44% in the SMC group and 26% of the EAS cohort. The percentage increase from baseline was similar across the three groups (CBT +9%, EAS +10% and SMC +6%). Overall, 32% of patients showed at least a 15% improvement over their baseline score. The percentages showing this level of improvement by intervention cohort were CBT 26%, EAS 26% and SMC 43%. Taking the 6- and 12-month data together, 40% of patients reported a 15% improvement or better at one or both follow-ups. Within the CBT group, 32% showed this level of improvement, compared with 40% in the EAS group and 49% in the SMC group (*Table 6*).

***TABLE 5*** *Quality of life and cognitive scores at 12 months*

| | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| **Variable** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| *(a) Quality of life scores* | | | | | | |
| SF-36 | | | | | | |
| Physical health | 35.2 | 8.15 | 32.5 | 7.91 | 35.0 | 9.93 |
| Mental health | 43.1 | 11.0 | 39.6 | 11.5 | 40.5 | 11.5 |
| Physical performance | | | | | | |
| Perceived fatigue | 2.85 | | 3.39 | | 3.06 | 2.85 |
| Shuttles walked | 28.9 | | 24.1 | | 24.2 | 28.9 |
| Normal walking speed | 12.2 | | 10.0 | | 9.46 | 12.2 |
| HADS | | | | | | |
| Anxiety | 8.33 | 4.46 | 9.63 | 4.13 | 9.00 | 5.17 |
| Depression | 6.82 | 3.80 | 7.74 | 4.02 | 7.44 | 4.42 |
| GHQ | 14.5 | 7.83 | 18.1 | 8.75 | 15.3 | 7.42 |
| Chalder | 17.4 | 7.32 | 21.4 | 7.79 | 18.8 | 7.19 |
| HUI3 overall utility score | 0.45 | 0.34 | 0.34 | 0.35 | 0.46 | 0.30 |
| *(b) Cognitive scores* | | | | | | |
| Mood | | | | | | |
| Alertness | 194.1 | 49.5 | 178.5 | 56.9 | 184.8 | 62.5 |
| Hedonic tone | 178.2 | 37.4 | 172.8 | 43.6 | 173.2 | 38.0 |
| Anxiety | 79.8 | 18.5 | 77.7 | 22.3 | 81.8 | 16.4 |
| Recall | | | | | | |
| Total words recalled | 13.2 | 4.84 | 12.5 | 4.34 | 12.8 | 5.41 |
| Correct words | 12.5 | 4.85 | 11.8 | 4.12 | 12.1 | 5.15 |
| Incorrect words | 0.69 | | 0.63 | | 0.66 | |
| Simple reaction time | | | | | | |
| Reaction time | 384.9 | | 401.7 | | 392.9 | |
| Trials completed | 25.9 | 1.87 | 26.2 | 1.82 | 26.5 | 2.12 |
| Repeated digits detection | | | | | | |
| Reaction time | 588.3 | 104.0 | 587.0 | 115.4 | 620.7 | 97.6 |
| Hit rate | 12.0 | | 10.8 | | 10.9 | |
| False alarms | 1.77 | | 1.15 | | 1.64 | |

***TABLE 6*** *Numbers of patients reporting an SF-36 health score (a) in the normal range and (b) at least 15% higher than at baseline and (c) the odds ratios for these outcomes with 95% CIs*

| | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** |
| *(a) SF-36 health summary scores within the normal range for the population* | | | | | | |
| *Physical health* | | | | | | |
| Baseline | 19 | 37 | 8 | 16 | 19 | 38 |
| 6 months | 17 | 40 | 11 | 24 | 20 | 44 |
| 12 months | 18 | 46 | 12 | 26 | 19 | 44 |
| *Mental health* | | | | | | |
| Baseline | 28 | 54 | 23 | 47 | 28 | 56 |
| 6 months | 37 | 86 | 32 | 71 | 28 | 62 |
| 12 months | 29 | 74 | 31 | 67 | 30 | 70 |
| | **CBT** | | **EAS** | | **SMC** | |
| | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** |
| *(b) SF-36 health summary scores at least 15% higher than at baseline* | | | | | | |
| *Physical health* | | | | | | |
| 6 months | 11 | 24 | 15 | 33 | 13 | 28 |
| 12 months | 10 | 26 | 12 | 26 | 19 | 43 |
| 6 and/or 12 months | 15 | 32 | 19 | 40 | 23 | 49 |
| *Mental health* | | | | | | |
| 6 months | 21 | 47 | 24 | 52 | 19 | 41 |
| 12 months | 25 | 64 | 19 | 41 | 16 | 36 |
| 6 and/or 12 months | 30 | 64 | 29 | 60 | 25 | 53 |
| | **EAS vs CBT** | | **SMC vs CBT** | | **SMC vs EAS** | |
| | **Odds ratio** | **95% CI** | **Odds ratio** | **95% CI** | **Odds ratio** | **95% CI** |
| *(c) Odds ratios for SF-36 health summary scores* | | | | | | |
| *Score within normal range* | | | | | | |
| Physical health | 1.03 | 0.38 to 2.73 | 1.51 | 0.58 to 3.91 | 1.47 | 0.56 to 3.81 |
| Mental health | 0.61 | 0.25 to 1.45 | 0.41 | 0.17 to 0.97 | 0.66 | 0.29 to 1.48 |
| *15%+ rise on baseline* | | | | | | |
| Physical health | 1.29 | 0.58 to 2.86 | 1.68 | 0.76 to 3.69 | 1.30 | 0.61 to 2.76 |
| *Mental health* | | | | | | |
| 6 months | 1.32 | 0.57 to 3.01 | 0.78 | 0.34 to 1.80 | 0.59 | 0.25 to 1.36 |
| 12 months | 0.43 | 0.18 to 1.03 | 0.35 | 0.14 to 0.86 | 0.82 | 0.35 to 1.92 |

The mean change in mental health score from baseline to 12 months for the cohort as a whole was +5.62 (SD 11.2) and was unchanged from 6 months [the mean change from 6 to 12 months was –0.01 (SD 10.4)]. Overall, 70% of the study population had a mental health score **within** the normal range for the population as a whole, an 18% increase on the 52% reported at baseline (*Table 6*). Some 20% more patients in the CBT and EAS groups had a mental health score in the normal range at 12 months than at baseline, compared with a 14% increase in the SMC group. Overall, 47% of patients showed at least a 15% improvement over their baseline scores (*Table 6*). Taking the 6- and 12-month data together, 59% of patients reported a 15% improvement or better at one or both follow-ups. Within the CBT group, 64% showed this level of improvement, compared with 60% in the EAS group and 53% in the SMC group.

## Comparison of outcomes by intention-to-treat

### Quality of life instruments

#### *SF-36 physical health summary scale*

Comparing the physical health summary scores at 6 and 12 months across the three interventions,

there was no evidence to suggest that mean scores changed between 6 and 12 months ($p = 0.38$), that they differed between the three treatment conditions ($p = 0.36$) or that the trend across the groups changed between the 6- and 12-month assessments ($p = 0.88$). The means scores pooled over the two follow-up points, after adjusting for baseline score and assessment set, are shown in *Table 7* and the differences in mean score between the groups are given in *Table 8*. On average, the score for patients in the CBT group was 0.40 lower (95% CI –2.86 to 2.06) than in the EAS group and 1.63 lower (95% CI –4.05 to 0.78) than in the SMC group.

Comparing the proportion of patients with a physical health score within the normal range led to the same conclusion. After adjusting for assessment set and whether the score was in the normal range at baseline, there was no evidence to suggest that the probability of achieving a score in the normal range changed between 6 and 12 months ($p = 0.67$), that the probability differed between the three treatment conditions ($p = 0.63$) or that the trend across the groups changed between the 6- and 12-month assessments ($p = 0.87$). The odds ratios for achieving a score in the normal range, pooled over the two follow-up points, were EAS versus CBT 1.03 (95% CI 0.38 to 2.73), SMC versus CBT 1.51 (95% CI 0.58 to 3.91) and SMC versus EAS 1.47 (95% CI 0.56 to 3.81) (*Table 6*). Although the odds ratios suggest that patients in the SMC group were at approximately 50% greater 'risk' of achieving a score in the normal range than patients in the CBT and EAS groups, the increase was not statistically significant and the CIs for both comparisons are wide and encompass 1.

The analysis comparing the proportion achieving a 15% increase or better above the baseline physical health score also indicated that there was no statistically significant difference between the three interventions. There was no evidence to suggest that the probability of achieving a 15%+ increase changed between 6 and 12 months ($p = 0.95$), that the probability differed between the three treatment conditions ($p = 0.43$) or that the trend across the groups changed between the 6- and 12-month assessments ($p = 0.17$). The odds ratios for achieving a 15%+ increase above baseline pooled over the two follow-up points, after adjusting for assessment set, are given in *Table 6*.

The secondary analysis examining the impact of number and duration of symptoms and taking of antidepressants on the physical summary scores suggested that duration of symptoms and taking of antidepressants were not significantly associated with the outcome ($p \geq 0.33$ for both factors) but that the number of symptoms did impact on the score ($p < 0.0001$). As the number of symptoms increased, the score, on average, reduced by 0.84 (SE 0.24). A patient with three symptoms had, on average, a score $3 \times 0.84 = 2.52$ lower than a patient without symptoms and $2 \times 0.84 = 1.68$ lower than a patient with one symptom reported at baseline.

***TABLE 7*** *Mean scores, pooled over the 6- and 12-month follow-ups, adjusted for baseline score and assessment set*

| Variable | CBT | | EAS | | SMC | | Overall *p*-value |
|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | |
| SF-36 | | | | | | | |
| Physical health | 32.06 | 0.90 | 33.46 | 0.86 | 34.70 | 0.81 | 0.36 |
| Mental health | 43.42 | 1.22 | 40.26 | 1.06 | 39.07 | 1.38 | 0.044 |
| Physical performance | | | | | | | |
| Perceived fatigue[a] | 1.33 | 0.049 | 1.33 | 0.056 | 1.34 | 0.037 | 0.97 |
| Shuttles walked[a] | 22.0 | 1.078 | 19.0 | 1.077 | 18.3 | 1.064 | 0.16 |
| Normal walking speed | 11.58 | 0.71 | 9.82 | 0.53 | 8.76 | 0.47 | 0.006 |
| HADS | | | | | | | |
| Anxiety | 8.55 | 0.44 | 9.06 | 0.40 | 9.83 | 0.46 | 0.13 |
| Depression | 7.36 | 0.36 | 7.49 | 0.34 | 7.92 | 0.44 | 0.61 |
| GHQ | 14.61 | 0.82 | 16.40 | 0.81 | 16.82 | 0.88 | 0.14 |
| Chalder | 18.03 | 0.92 | 21.19 | 0.79 | 20.64 | 0.72 | 0.027 |
| HUI3 overall utility score | 0.42 | 0.029 | 0.39 | 0.033 | 0.39 | 0.029 | 0.76 |

LS mean, least-squares mean.

[a] Data for perceived fatigue and shuttles walked were transformed to the logarithmic scale prior to analysis, in order to reduce skewness and induce approximately normal random variation. Data are geometric means and SE after transformation back to the original measurement scale.

### *SF-36 mental health summary scale*

In contrast to the physical scores, some statistically significant differences with respect to mental health were indicated. There was no evidence to suggest that mean scores changed between 6 and 12 months ($p = 0.99$) or that the trend across the groups changed between the 6- and 12-month assessments ($p = 0.63$), but a difference between the three treatment conditions was found ($p = 0.044$). The means scores pooled over the two follow-up points, after adjusting for baseline score and assessment set, are given in *Table 7* and the differences in mean score between the groups are reported in *Table 8*. The mean score, after adjusting for baseline score and assessment set and pooling over the two follow-up points, was highest for the CBT cohort, followed by the EAS cohort, and was lowest for the SMC group (*Table 7*). No significant difference was found between the EAS and SMC cohorts (difference 1.19, 95% CI –2.26 to 4.63, $p = 0.50$) and the difference between CBT and EAS groups was of borderline statistical significance (difference 3.16, 95% CI –0.05 to 6.38, $p = 0.054$), but a clear difference was found between the CBT and SMC cohorts. On average, the mental health score for patients given CBT was 4.35 points higher than for patients receiving SMC (95% CI 0.72 to 7.97, $p = 0.019$).

The second analysis comparing the proportion of patients with a mental health score within the normal range also suggested that the probability of achieving a score in the normal range did not change significantly between 6 and 12 months ($p = 0.16$) and that the trend across the groups was similar at the 6- and 12-month assessments ($p = 0.25$). In contrast to the analysis of the scores, the global test for a difference across the three treatment conditions also suggested that overall the odds of achieving a 'normal' score did not vary significantly between the groups ($p = 0.13$). Nevertheless, the odds ratios for achieving a score in the normal range suggested the odds were less for patients in the SMC group than the CBT group (odds ratio 0.41, 95% CI 0.17 to 0.97, $p = 0.042$). No other group differences were indicated (*Table 6*).

The analysis comparing the proportion achieving a 15% increase or better above the baseline mental health score revealed a different trend in the data, namely that the pattern across the groups in the percentage of patients achieving this threshold changed between 6 and 12 months ($p = 0.059$). At 6 months, the number achieving the 15% threshold was similar across the groups ($p = 0.47$), whereas at 12 months, a clear difference between the groups was indicated ($p = 0.038$). The odds ratios for achieving a 15% increase in mental health score at 6 and 12 months, reported in *Table 6*, indicate that patients in the CBT were almost three times more likely to achieve a 15% increase in score than patients receiving SMC (odds ratio SMC versus CBT 0.3, 95% CI 0.14 to 0.86, $p = 0.021$) and more than twice as likely to achieve this threshold at 12 months than patients in the EAS group (odds

***TABLE 8*** *Differences in mean scores with 95% CIs, pooled over the 6- and 12-month follow-ups, adjusted for baseline score and assessment set*

| Variable | CBT – EAS | | CBT – SMC | | EAS – SMC | |
|---|---|---|---|---|---|---|
| | Difference | 95% CI | Difference | 95% CI | Difference | 95% CI |
| SF-36 | | | | | | |
| Physical health | –0.40 | –2.86 to 2.06 | –1.63 | –4.05 to 0.78 | –1.23 | –3.52 to 1.05 |
| Mental health | 3.16 | –0.05 to 6.38 | 4.35 | 0.72 to 7.97 | 1.19 | -2.26 to 4.63 |
| Physical performance | | | | | | |
| Perceived fatigue[a] | 1.00 | 0.86 to 1.16 | 0.98 | 0.87 to 1.12 | 0.99 | 0.87 to 1.13 |
| Shuttles walked[a] | 1.16 | 0.94 to 1.43 | 1.20 | 0.99 to 1.45 | 1.04 | 0.86 to 1.24 |
| Normal walking speed | 1.77 | 0.025 to 3.51 | 2.83 | 1.12 to 5.53 | 1.06 | –0.37 to 2.49 |
| HADS | | | | | | |
| Anxiety | –0.51 | –1.70 to 0.68 | –1.27 | –2.52 to –0.02 | –0.76 | –2.00 to 0.47 |
| Depression | –0.13 | –1.13 to 0.87 | –0.56 | –1.69 to 0.58 | –0.43 | –1.56 to 0.70 |
| GHQ | –1.80 | –4.17 to 0.57 | –2.21 | –4.52 to 0.10 | –0.41 | –2.81 to 1.98 |
| Chalder | –3.16 | –5.59 to –0.74 | –2.61 | –4.92 to –0.30 | 0.55 | –1.56 to 2.66 |
| HUI3 overall utility score | 0.023 | –0.065 to 0.11 | 0.029 | –0.052 to 0.11 | 0.006 | –0.082 to 0.095 |

[a] Data for perceived fatigue and shuttles walked were transformed to the logarithmic scale prior to analysis. The differences observed have been back-transformed to give a ratio. A ratio of 1.2 would indicate a 20% increase and a ratio of 0.8 a 20% decrease.

ratio EAS versus CBT 0.43, 95% CI 0.18 to 1.03, $p = 0.057$). Similar numbers in the EAS and SMC cohorts achieved this threshold at 12 months ($p = 0.65$).

The secondary analysis examining the impact of number and duration of symptoms and taking of antidepressants on the mental summary scores suggested that duration of symptoms and taking of antidepressants were not significantly associated with the outcome ($p \geq 0.42$ for both factors) but, as was found for the physical scale, the number of symptoms did impact on the score ($p = 0.014$). As the number of symptoms increased, the score, on average, reduced by 0.85 (SE 0.34).

### *Chalder fatigue scale*

The Chalder fatigue scale also showed some statistically significant differences. Initial analysis of the data suggested that mean scores were similar at 6 and 12 months ($p = 0.19$) and that the trend across the groups did not change significantly between the 6- and 12-month assessments ($p = 0.13$), but did indicate a difference between the three treatment conditions ($p = 0.039$). However, three influential outlying observations were identified and, after removing these values from the analysis, there was a suggestion of a change in trend across the groups between 6 and 12 months ($p = 0.087$), in addition to an overall significant difference between the groups ($p = 0.027$). For the CBT and EAS groups, there was no significant change in mean score with time ($p = 0.90$ and 0.45, respectively), but for the SMC cohort, the mean score was lower at 12 than at 6 months (mean score at 6 months 21.87 versus 19.41 at 12 months, difference 2.46, 95% CI 0.32 to 4.61, $p = 0.024$).

As both analyses (with and without the outliers removed) indicated an overall statistically significant difference between treatments, overall mean scores, pooled over the two time points, are reported in *Table 7*. The means given are adjusted for assessment set and baseline score and exclude the three outlying observations. The mean score was significantly lower for the CBT cohort than for the other two groups. No significant difference was found between the EAS and SMC cohorts (difference 0.55, 95% CI –1.56 to 2.66, $p = 0.61$), but a difference between CBT and EAS groups and between the CBT and SMC cohorts was found. On average, the mean Chalder fatigue score for the CBT group was 3.16 lower than for the EAS group (95% CI –5.59 to –0.74, $p = 0.011$) and 2.16 lower than for the SMC cohort (95% CI –4.92 to –0.30, $p = 0.027$).

### *HADS anxiety and depression*

Mean HADS anxiety and depression scores, adjusted for baseline score and assessment set, are presented in *Table 7* and a comparison of these mean scores between the groups is given in *Table 8*. Comparing the scores, there was no evidence to suggest that mean scores changed between 6 and 12 months (anxiety $p = 0.29$, depression $p = 0.52$), that they differed between the three treatment conditions (anxiety $p = 0.13$, depression $p = 0.61$) or that the trend across the groups changed between the 6- and 12-month assessments (anxiety $p = 0.65$, depression $p = 0.77$).

On average, both the anxiety and depression scores for patients in the CBT group were lower (reduced anxiety and depression) than in the EAS and SMC groups. The SMC group reported the highest mean scores for both HADS components (*Table 7*). Of the six comparisons between groups (three for anxiety and three for depression), one, the difference in mean score between the CBT and SMC groups for anxiety, was of borderline statistical significance (1.27 lower, 95% CI –2.52 to –0.02, $p = 0.045$). This may be the result of the number of statistical tests carried out, as we have made no adjustment for the multiple tests done and would expect one in 20 to reach statistical significance by chance.

Comparison of the numbers of patients with scores between 8 and 11 indicates borderline clinically significant anxiety and depression. Scores of 11+ indicate 'caseness'. These are reported in *Table 9* and further illustrate the trends seen in the mean scores.

### *HUI utility score*

Mean utility scores are presented in *Table 7* and compared between the groups in *Table 8*. The mean scores reported at 6 months were similar to those reported at 12 months ($p = 0.50$), no difference between the three treatment conditions was indicated ($p = 0.76$) and the trend across the groups was unchanged between the 6- and 12-month assessments ($p = 0.29$).

### *General Health Questionnaire*

The mean GHQ scores reported at 6 months were similar to those reported at 12 months ($p = 0.66$) and the trend across the groups was unchanged between the 6- and 12-month assessments ($p = 0.47$). Overall, across the groups the

***TABLE 9*** *HADS anxiety and depression scores*

| | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| *HADS anxiety* | | | | | | |
| Baseline | | | | | | |
| Score <8 | 13 | 25 | 11 | 22 | 20 | 40 |
| Score 8–11 | 22 | 42 | 15 | 30 | 13 | 26 |
| Score >11 | 17 | 33 | 24 | 48 | 17 | 34 |
| 6 months | | | | | | |
| Score <8 | 21 | 49 | 13 | 29 | 18 | 39 |
| Score 8–11 | 14 | 32 | 15 | 33 | 14 | 30 |
| Score >11 | 8 | 19 | 17 | 38 | 14 | 30 |
| 12 months | | | | | | |
| Score <8 | 18 | 46 | 17 | 37 | 23 | 52 |
| Score 8–11 | 11 | 28 | 13 | 28 | 9 | 20 |
| Score >11 | 10 | 26 | 16 | 35 | 12 | 27 |
| *HADS depression* | | | | | | |
| Baseline | | | | | | |
| Score <8 | 26 | 50 | 11 | 22 | 18 | 35 |
| Score 8–11 | 22 | 23 | 15 | 54 | 13 | 53 |
| Score >11 | 14 | 27 | 12 | 24 | 6 | 12 |
| 6 months | | | | | | |
| Score <8 | 25 | 58 | 22 | 49 | 24 | 52 |
| Score 8–11 | 12 | 28 | 13 | 29 | 14 | 30 |
| Score >11 | 6 | 14 | 10 | 22 | 8 | 17 |
| 12 months | | | | | | |
| Score <8 | 25 | 64 | 25 | 54 | 22 | 51 |
| Score 8–11 | 9 | 23 | 13 | 28 | 15 | 35 |
| Score >11 | 5 | 13 | 8 | 17 | 6 | 14 |

differences were not statistically significant ($p = 0.14$), although the difference between CBT and SMC was nearing statistical significance ($p = 0.061$). On average, the score was 2.21 lower in the CBT group than in the SMC group (95% CI –4.52 to 0.10). The scores for the CBT and EAS treatment cohorts were similar (*Tables 7* and *8*).

### *Physical performance – shuttles walked*

Similar trends were seen with the number of shuttles walked, as was seen for the GHQ scores, with more shuttles walked in the CBT treatment cohort and fewer in the SMC treatment cohort, with the EAS cohort showing results similar to the SMC group. Patients in the CBT cohort completed an average of 22 shuttles (200 m) compared with an average of 19 shuttles in the EAS treatment cohort and 18.3 in the SMC group (*Table 7*).

Again, overall across the three groups the differences were not statistically significant ($p = 0.16$), but the difference between CBT and SMC was nearing statistical significance ($p = 0.060$). On average, patients in the CBT group completed 20% more shuttles than those randomised to SMC (odds ratio 1.20, 95% CI 0.99 to 1.45). As was seen for the other quality of life measures, the mean scores reported at 6 months were similar to those reported at 12 months ($p = 0.80$) and the trend across the groups was unchanged between the 6- and 12-month assessments ($p = 0.99$).

Five clear outlying observations were omitted from the analysis of shuttles walked. Three were very low values (0 or 2) and two were amongst the highest values (60 and 75), but were from a patient with a low baseline score (9). If these outliers were retained, the SEs increased and difference between CBT and SMC was no longer statistically significant ($p = 0.17$).

The number of shuttles walked is illustrated in *Figure 3*. The distribution was positively skewed in each group, hence median scores are presented. The increase in the median number of shuttles walked in the CBT treatment condition from 20.5 (205 m) at baseline to 30 (300 m) at 12 months suggests an improvement, which did not reach statistical significance. The change from a median of 20.5 shuttles at baseline to 30 shuttles at

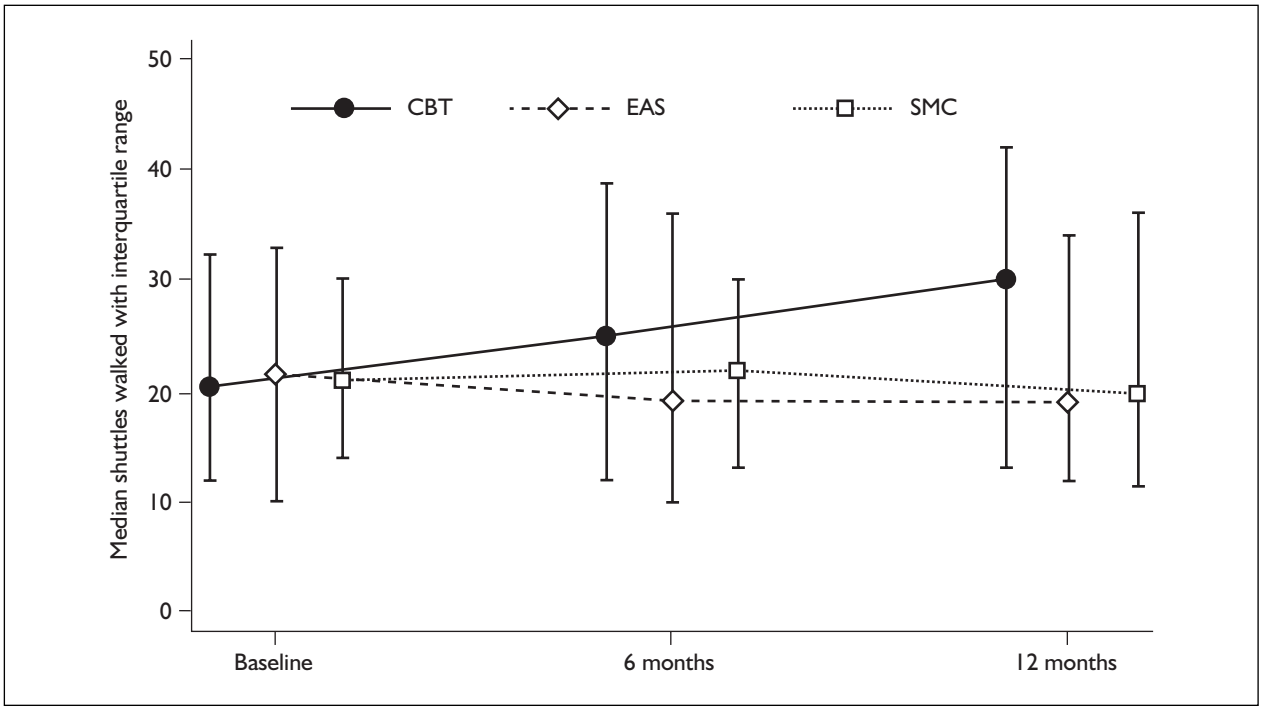


***FIGURE 3*** *Median numbers of shuttles walked by subjects under each condition*

12 months in the CBT cohort represents an increase in walking speed at the end of the test from 2.64 to 3.02 miles per hour. The median increase is composed of an additional 4.5 shuttles at 2.64 miles per hour (level 5) and five shuttles at 3.02 miles per hour (level 6).

### *Physical performance – walking speed*

The outcome showing the greatest difference across the treatment groups was walking speed ($p = 0.0055$), with the CBT cohort displaying significantly greater walking speeds than the other two groups, where the speed was similar ($p = 0.15$). A time effect was also seen, with increased speeds at 12 months compared with 6 months ($p = 0.029$) in all groups (difference +0.87, 95% CI +0.09 to +1.65). No interaction between intervention and time was found ($p = 0.94$), indicating that the pattern across the groups (i.e. higher walking speeds in the CBT group and similar average speeds in the other groups) was seen at both 6 and 12 months. On average, the walking speed for subjects randomised to CBT increased by 1.77 shuttles (95% CI 0.025 to 3.51) compared with those allocated to EAS and by 2.83 shuttles compared with those in the SMC group.

For this outcome, differences across the assessment sets were also apparent ($p = 0.017$). The walking speeds were higher for patients in sets 1 and 2 [average scores of 10.97 (SE 0.68) and 11.45 (SE 0.77), respectively] than in the other sets [means (SE) for sets 3, 4 and 5: 8.76 (0.57), 9.17 (0.72) and 9.62 (0.84), respectively].

Under the CBT condition, the subjects' reported normal walking speed increased from a median of 8 shuttles at baseline to 13 shuttles at 12 months. In the EAS group, the median at 12 months was 10 shuttles and in the SMC group 8 shuttles. At baseline these groups had medians of 8 and 8.5 respectively.

### *Physical performance – perceived fatigue*

The perceived fatigue, which was administered after the ISWT, was similar across the three groups ($p = 0.98$) and did not vary significantly between the two follow-up points ($p = 0.84$). The trend across the groups was also unchanged between 6 and 12 months ($p = 0.29$). The mean scores for the groups were 2.79 for CBT, 2.73 for EAS and 2.75 for SMC (*Table 7*), which equates to moderate fatigue (see Appendix 13).

In common with walking speed, perceived fatigue showed differences across the assessment sets ($p = 0.0019$). The fatigue scores were higher for patients in sets 3 and 4 [geometric mean scores of 3.11 (SE 1.06) and 3.38 (SE 1.07), respectively] than in the other sets [means (SE) for sets 1, 2 and 5: 2.44 (1.11), 2.33 (1.08) and 2.66 (1.11), respectively].

## Cognitive tests

Results of the analyses of the cognitive tests are given in *Tables 10* and *11*. The means scores pooled over the two follow-up points, after adjusting for baseline score and assessment set, are shown in *Table 10* and the differences in mean score between the groups are reported in *Table 11*.

For all the cognitive tests, the pattern of mean responses across the three intervention groups was similar at 6 and 12 months; no significant interactions between intervention and time were indicated ($p \geq 0.092$ for all outcomes). With the exception of the recall measures (total words and correct words recalled), there was no evidence to suggest a difference between the patient responses at 6 and 12 months ($p \geq 0.12$ for all outcomes). The mood scores, simple reaction time and repeated digits detection data were similar at 6 and 12 months. For the two recall measures, a

***TABLE 10*** *Mean scores, pooled over the 6- and 12-month follow-ups, adjusted for baseline score and assessment set*

| Variable | CBT | | EAS | | SMC | | Overall *p*-value |
|---|---|---|---|---|---|---|---|
| | LS mean | SE | LS mean | SE | LS mean | SE | |
| Mood | | | | | | | |
| Alertness | 196.11 | 5.99 | 190.18 | 5.66 | 182.40 | 6.80 | 0.32 |
| Hedonic tone | 178.07 | 4.74 | 175.38 | 4.38 | 168.87 | 3.85 | 0.29 |
| Anxiety | 78.22 | 1.87 | 80.50 | 2.24 | 82.27 | 2.03 | 0.32 |
| Recall | | | | | | | |
| Total words recalled | 13.13 | 0.42 | 12.36 | 0.37 | 12.43 | 0.42 | 0.33 |
| Correct words | 12.56 | 0.40 | 11.72 | 0.38 | 11.76 | 0.38 | 0.24 |
| Simple reaction time | | | | | | | |
| Reaction time[a] | 361.5 | 1.03 | 365.8 | 1.03 | 386.8 | 1.03 | 0.21 |
| Trials completed | 26.16 | 0.22 | 26.29 | 0.18 | 26.57 | 0.21 | 0.36 |
| Repeated digits detection | | | | | | | |
| Reaction time[a] | 590.1 | 1.02 | 590.6 | 1.02 | 618.7 | 1.01 | 0.059 |
| Hit rate | 11.13 | 0.67 | 11.30 | 0.44 | 10.66 | 0.45 | 0.58 |

LS mean = least-squares mean.
[a] Data for perceived reaction time were transformed to the logarithmic scale prior to analysis, in order to reduce skewness and induce approximately normal random variation. Data are geometric means and SE after transformation back to the original measurement scale.

***TABLE 11*** *Differences in mean scores with 95% CIs, pooled over the 6- and 12-month follow-ups, adjusted for baseline score and assessment set*

| Variable | CBT – EAS | | CBT – SMC | | EAS – SMC | |
|---|---|---|---|---|---|---|
| | Difference | 95% CI | Difference | 95% CI | Difference | 95% CI |
| Mood | | | | | | |
| Alertness | 5.92 | –10.50 to 22.35 | 13.71 | –4.08 to 31.51 | 7.79 | –9.52 to 25.09 |
| Hedonic tone | 2.69 | –10.00 to 15.39 | 9.20 | –2.91 to 21.31 | 6.51 | –5.26 to 18.28 |
| Anxiety | –2.28 | –8.05 to 3.50 | –4.06 | –9.40 to 1.29 | –1.78 | –7.67 to 4.11 |
| Recall | | | | | | |
| Total words recalled | 0.77 | –0.32 to 1.86 | 0.69 | –0.47 to 1.86 | –0.076 | –1.20 to 1.05 |
| Correct words | 0.84 | –0.26 to 1.94 | 0.80 | –0.30 to 1.89 | –0.044 | –1.14 to 1.05 |
| Simple reaction time | | | | | | |
| Reaction time[a] | 0.99 | 0.90 to 1.08 | 0.93 | 0.86 to 1.02 | 0.95 | 0.87 to 1.03 |
| Trials completed | –0.13 | –0.68 to 0.43 | –0.41 | –1.00 to 0.18 | –0.29 | –0.83 to 0.25 |
| Repeated digits detection | | | | | | |
| Reaction time[a] | 1.00 | 0.95 to 1.05 | 0.95 | 0.91 to 1.00 | 0.95 | 0.91 to 1.00 |
| Hit rate | –0.17 | –1.75 to 1.41 | 0.47 | –1.13 to 2.06 | 0.64 | –0.60 to 1.88 |

[a] Data for perceived reaction time were transformed to the logarithmic scale prior to analysis, in order to reduce skewness and induce approximately normal random variation. Data are geometric means and SE after transformation back to the original measurement scale.

change over time was indicated; for all three cohorts, the number of words recalled increased between 6 and 12 months (total recall, 0.75 words, 95% CI 0.13 to 1.36, $p = 0.017$; correct recall, 0.85 words, 95% CI 0.31 to 1.40, $p = 0.0022$). A small number of outlying observations were omitted from these analyses. If these outliers were retained, the SEs increased and differences over time were not so apparent (total recall, $p = 0.16$; correct recall, $p = 0.056$).

Comparing the scores between the intervention cohorts, with the possible exception of the repeated digits detection test, no significant differences in response to the cognitive tests were found ($p \geq 0.21$ for all tests, *Table 10*). For the repeated digits detection test, a difference was suggested ($p = 0.059$). On average, patients assigned to the CBT and EAS cohorts displayed 5% shorter reaction times for this test than patients in the SMC cohort [ratio 0.95, 95% CI 0.91 to 1.00, $p = 0.041$ (CBT), $p = 0.049$ (EAS)].

However, despite the lack of statistical significance for the other tests, a trend towards improved cognitive responses in the CBT cohort was observed (*Table 10*). The cognitive responses obtained at each time point are illustrated in Appendix 14.

## Economic analysis

*Table 12* gives the number of primary care consultations, OP appointments and IP hospital stays by randomisation group. On average, patients consulted their GP 6.1 times over the 12 months. This rate was highest in the SMC group and lowest in the CBT group, although differences between groups were not significant at the 95% level. On average, there were 1.5 OP appointments per patient. The CBT group had the fewest appointments on average and the EAS group had the highest, but again, these differences were not significant at the 95% level. There was a total of eight hospital stays over the 12 months, with half of these occurring in patients receiving SMC. All resource use data are highly skewed, with a high number of zero observations. This is particularly true of secondary care contacts, where over half of all patients had no contact with the secondary care sector. The CBT group had the highest percentage of these patients (60%).

*Table 13* reports medication use. It shows the percentage of patients in each group who used each type of medicine during the 12 months and the mean number of prescriptions likely to have been issued. Overall, the most commonly used drug group was analgesics in terms of the number

***TABLE 12*** *Primary and secondary care consultations by randomisation group*

| | CBT ($n = 45$) | EAS ($n = 45$) | SMC ($n = 43$) |
|---|---|---|---|
| *GP visits* | | | |
| Mean | 5.8 | 6.0 | 6.5 |
| SD | 4.0 | 5.0 | 6.4 |
| CI lower | 4.6 | 4.5 | 4.5 |
| CI upper | 7.0 | 7.5 | 8.4 |
| Median | 5 | 5 | 5 |
| Minimum | 0 | 0 | 0 |
| Maximum | 13 | 20 | 26 |
| *OP appointments* | | | |
| Mean | 1.3 | 1.7 | 1.5 |
| SD | 2.1 | 2.5 | 2.3 |
| CI lower | 0.6 | 1.0 | 0.8 |
| CI upper | 1.9 | 2.4 | 2.2 |
| Median | 0 | 1 | 0 |
| Minimum | 0 | 0 | 0 |
| Maximum | 10 | 12 | 10 |
| *IP stays* | | | |
| Total | 1 | 3 | 4 |
| Mean | 0.02 | 0.07 | 0.09 |
| Minimum | 0 | 0 | 0 |
| Maximum | 1 | 1 | 1 |

***TABLE 13*** *Medication use by randomisation group*

| Drug type | CBT ($n$ = 21) | | EAS ($n$ = 23) | | SMC ($n$ = 20) | |
|---|---|---|---|---|---|---|
| | Proportion of patients (%) | Mean no. of prescriptions | Proportion of patients (%) | Mean no. of prescriptions | Proportion of patients (%) | Mean no. of prescriptions |
| SSRIs | 43 | 1.2 | 46 | 1.9 | 57 | 1.5 |
| Tricyclics | 33 | 1.5 | 54 | 2.2 | 48 | 1.1 |
| Hypnotics | 14 | 0.3 | 21 | 0.7 | 19 | 0.3 |
| Analgesics | 71 | 2.2 | 79 | 3.0 | 52 | 2.2 |
| Anti-inflammatories | 29 | 0.8 | 63 | 2.0 | 57 | 1.3 |
| Benzodiazapines | 5 | 0.3 | 17 | 0.3 | 10 | 0.1 |
| Other | 19 | 0.4 | 29 | 0.5 | 19 | 0.3 |

of patients and the number of prescriptions. This is also true for the CBT and EAS groups, although there was a higher percentage of patients using both anti-inflammatories and SSRIs in the SMC group. Benzodiazapines were the least commonly used drug type.

## Healthcare facilities

*Table 14* gives the mean cost per patient of the use of healthcare facilities. The cost of caring for patients in the SMC group was greater than those in either of the other groups. However, the high values of the SDs in all cases indicate considerable variability. Thus the comparison of groups indicates no statistically difference at the 95% level of significance.

## Medication

*Tables 15* and *16* give estimated costs per patient of prescribed medication. Results using complete case analysis and those using imputed values for number of prescriptions are shown separately. By imputing, we are able to estimate total mean cost per patient, which would not otherwise be possible because the results in *Table 15* relate to a different set of patients for each category. The estimated mean cost of prescriptions was greatest for patients receiving the EAS intervention and lowest for those in the SMC group. There is no significant difference between the cost of drugs used by patients receiving CBT and those in either the placebo-response group or those receiving standard medical care.

Over one-third of the total cost of prescriptions is accounted for by SSRIs.

## The intervention

The total cost of providing both the CBT and the EAS intervention was estimated as £3100. For a group of nine, on average, the cost per patient is thus £344.

## Total cost

The total cost per patient is given in *Table 17*. Including the cost of the intervention, the annual cost of caring for patients in the intervention arm was £700. This compares with £810 for those receiving the group placebo and £452 for those receiving SMC.

***TABLE 14*** *Mean cost per patient of the use of healthcare facilities*

| Facility | Mean (SD) cost per patient (£) | | | Difference in mean cost (£) ($p$-value) | |
|---|---|---|---|---|---|
| | CBT | EAS | SMC | CBT vs EAS | CBT vs SMC |
| GP appointments | 86.3 (59.8) | 89.3 (74.9) | 97.0 (96.0) | | |
| OP appointments | 171.0 (326.2) | 180.8 (266.1) | 163.7 (240.0) | | |
| IP stays | 27.2 (182.5) | 106.3 (463.4) | 130.2 (512.0) | | |
| All healthcare facility contacts | 284.5 (467.7) | 376.4 (635.5) | 390.8 (571.5) | –91.86 (0.44) | –106.3 (0.34) |

***TABLE 15*** *Cost of prescribed medication using complete case analysis*

| Drug type | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | *n* | Mean (SD) cost (£) | *n* | Mean (SD) cost (£) | *n* | Mean (SD) cost (£) |
| SSRIs | 27 | 22.02 (31.1) | 27 | 34.30 (41.2) | 25 | 27.44 (29.9) |
| Tricyclics | 28 | 6.21 (9.3) | 30 | 9.35 (9.9) | 25 | 5.16 (7.3) |
| Hypnotics | 26 | 0.93 (3.2) | 27 | 1.98 (3.6) | 24 | 0.86 (2.2) |
| Analgesics | 28 | 13.25 (10.3) | 27 | 18.17 (11.5) | 27 | 13.59 (14.1) |
| Anti-inflammatories | 26 | 8.48 (13.1) | 27 | 20.91 (20.2) | 26 | 13.77 (15.8) |
| Benzodiazapines | 26 | 0.48 (1.4) | 27 | 0.58 (1.5) | 24 | 0.22 (0.8) |
| Other | 52 | 14.37 (25.3) | 49 | 13.3 (21.0) | 51 | 6.51 (13.1) |

***TABLE 16*** *Cost of prescribed medication using imputed values*

| Drug type | Mean (SD) cost per patient (£) | | | Difference in mean cost (£) (*p*-value) | |
|---|---|---|---|---|---|
| | CBT (*n* = 51) | EAS (*n* = 49) | SMC (*n* = 51) | CBT vs EAS | CBT vs SMC |
| SSRIs | 22.78 (31.3) | 34.82 (39.3) | 27.04 (31.0) | | |
| Tricyclics | 6.71 (8.8) | 7.15 (9.2) | 5.3 (7.5) | | |
| Hypnotics | 0.89 (2.6) | 1.41 (2.9) | 1.21 (2.6) | | |
| Analgesics | 14.95 (11.5) | 16.13 (11.6) | 12.96 (12.6) | | |
| Anti-inflammatories | 12.43 (14.1) | 16.45 (18.4) | 12.21 (14.8) | | |
| Benzodiazapines | 0.36 (1.1) | 0.53 (1.4) | 0.19 (0.6) | | |
| Other | 14.37 (25.3) | 13.3 (21.0) | 6.51 (13.1) | | |
| All prescribed medication | 71.36 (52.6) | 89.80 (58.8) | 64.26 (41.3) | –18.44 (0.10) | 7.10 (0.45) |

***TABLE 17*** *Total mean cost per patient*

| Item | CBT | EAS | SMC | CBT vs EAS | CBT vs SMC |
|---|---|---|---|---|---|
| Healthcare facilities | 284.5 (467.7) | 376.4 (635.5) | 390.4 (571.5) | | |
| Medication | 71.36 (52.6) | 89.80 (58.8) | 64.26 (41.3) | | |
| Intervention | 344.44 (0.0) | 344.44 (0.0) | | | |
| Total | 699.49 (480.59) | 809.77 (656.87) | 451.57 (585.73) | –110.28 (0.366) | 247.93 (0.032) |

## Health utilities index

The results for the outcome measure are given in *Table 18*. This shows the mean score for each group at baseline and at the 12-month follow-up. Complete data were available for 127 patients at the 12-month follow-up stage (CBT 38, EAS 46, SMC 43). All groups improved their average score but the difference in improvement was not significant between the groups.

## Self-report questionnaire on costs

A review of the data collected by the self-assessment form (Appendix 7) yielded some interesting descriptive data (Appendices 10–12).

In terms of societal costs, partners and immediate family provided the most support to subjects across all three groups. None of the participants allocated to CBT reported receiving help from

***TABLE 18*** *HUI[2] scores at baseline and at 12-month follow-up*

| Time point | CBT | | EAS | | SMC | | CBT vs EAS | CBT vs SMC |
|---|---|---|---|---|---|---|---|---|
| | *n* | Mean (SD) | *n* | Mean (SD) | *n* | Mean (SD) | | |
| Baseline | 52 | 0.592 (0.205) | 50 | 0.525 (0.215) | 51 | 0.631 (0.207) | | |
| 12 months | 38 | 0.683 (0.210) | 46 | 0.616 (0.215) | 43 | 0.659 (0.211) | | |
| Difference | 38 | 0.047 (0.120) | 46 | 0.075 (0.157) | 43 | 0.021 (0.214) | –0.028 (0.363) | 0.026 (0.511) |

social services and only 0–2% of the rest of the sample were in regular receipt of this type of help. Private therapies were used frequently, but their use declined in the CBT arm post-intervention. At baseline, 42% of those allocated to CBT were using some form of alternative therapy. This dropped to 32% at 12 months. In contrast, the percentage of subjects using alternative therapies in the other two groups increased, from 30 to 65% in EAS and from 47 to 53% in SMC.

# Chapter 4
# Discussion

## Summary

The complex nature of this illness, the paucity of current high-quality research and the pragmatic and clinical difficulties of running a trial in this area all contribute to a highly complex analysis and interpretation. We have presented all of our data, with explanations of our reasoning, so that the work is as transparent as possible.

The principal outcome measure, the SF-36, did not demonstrate any difference in the number of subjects whose physical function scores returned to within the normal range at the end of the trial. However, there were significant improvements in the CBT group in the measures used for fatigue, mental health and walking speed. The treatment did not, therefore, restore 'normal' levels of physical function on the SF-36, but did produce improvements in three other key areas.

The group CBT significantly increased measures of mood and fitness and it significantly decreased symptoms of fatigue. This was comparable to the changes seen in the individual research literature. In Whiting and colleagues' review, studies were classified as having an overall effect if they showed an effect for more than one clinical outcome.[17]

Group CBT did not significantly improve cognitive function, quality of life (as measured by the physical subscale of the SF-36), employment status or healthcare utility measures. However, the quality of the data obtained for the last item was too poor to be used in any analysis. Such changes have been demonstrated in the literature for individual CBTs.

The outcome measures showed a consistent trend towards improved health status for the research population randomised to CBT. The group did not, however, return a significantly higher proportion of subjects back to the 'normal' range of physical function on the SF-36 than the other treatment interventions. It proved too difficult to provide an adequate assessment of the cost-effectiveness of the intervention and the reasons for this are discussed below.

## Limitations

In the interpretation of the data, the limitations of the trial should be understood. First, there is little accepted literature on what constitutes a useful clinical improvement. When designing the study, we used a 15% change over baseline as an index of clinical significance as this has been described previously. However, that study sample was different, the diagnostic criteria were not the same and the study patients received a different type of intervention. In our sample, the diagnosis was left primarily to the GP, since this was both inexpensive and time efficient. Each patient's details were cross-checked against the referral criteria (Appendix 2) by the research psychologist and any queries were double-checked by the lead clinician. However, it is possible, in the absence of a specialist diagnosis, that some of the patients may have been misdiagnosed. One subject was withdrawn during the trial because an alternative diagnosis had been made. However, the general rate of misdiagnosis is low, quoted at only 1%.[1]

In addition, the absence of a clinical interview prior to randomisation meant that the individuals' suitability for group treatment could not be assessed. The nature of the design meant that several patients were admitted to the trial who would not, in clinical practice, have been considered psychologically appropriate for group treatment. There are no standardised methods for assessing suitability currently available, so it was decided to adopt the outlined method; matching individual characteristics to particular treatment types is a difficult procedure, not well developed in other conditions and seriously neglected in CFS/ME. The fact remains that there was a small proportion of the sample who were not clinically appropriate to this treatment approach. The subjects' current coping mechanisms were not assessed, nor was their readiness to change existing methods. That is to say, some subjects were already using good management techniques when we first met them and could not, therefore, be expected to show a significant improvement. We were unable to assess the subjects' willingness to take part in a group process and their capacity to engage in a therapy such as CBT. This created an artificial treatment group who were not

'matched' to the intervention and this will have diluted the effects of the treatment.

A significant omission in this trial was not attempting to map the mechanism by which change may have occurred. Given that the treatment is based on the illness belief system of the individual in other conditions, illness specific measures are taken as a measure of change. The changes observed in functional outcome are likely to have occurred as a result of a long chain of internal events, which include cognitive, emotional and behavioural shifts. It is a change in these domains that brings about significant reductions in distress and disability.

Changes in cognitions, illness beliefs, coping and attributional style were not recorded, and the difficulty of attempting to do so were considerable at this stage. There are no measures relating specifically to this patient group for illness beliefs, cognitions, coping styles or attributional style. In the future, such measures may prove very useful when selecting matching treatments to patients and the development of such a scale is an important next step in the research.

It was not within the scope of this trial to attempt a differential subgroup analysis; a subgroup analysis of the potential moderating and mediating factors may be undertaken at a later stage, but did not form part of the research question. For example, it may be that gender, age, level of psychological distress and duration of symptoms are all relevant in a differential response to this type of treatment.

This study is unable to exclude definitively the impact of possible sources of confounding on the findings, for example due to differences in drugs taken, such as SSRIs, or in the use of alternative therapies or in attendance for outpatient appointments. However, the data collected for the cost analyses suggest that the use of SSRIs and alternative therapies were similar across the groups. Also, as patients were randomised to treatment and the data analysed on an intention-to-treat basis, we believe the differences observed represent unbiased estimates of the treatment effects.

Taken as a whole, it would appear that the patients in our sample were more fatigued, had higher levels of unemployment, had been ill for longer, and were more distressed than those in samples used in previous research into CBT for CFS/ME (see Appendix 15 for a detailed comparison of this study sample with those studied previously).

However, although the patients in our sample may have been presenting with a higher degree of disability, they were all still able to attend an OP programme. Participants were only eligible if they could physically get to the clinic, which implies a certain level of ability. Those people who were severely affected were automatically excluded. It is therefore not possible to assess whether the interventions investigated would be effective, ineffective or even hazardous for a more severely disabled group of people.

We also had a higher number of men in the CBT arm of the trial (46%), but the influence of gender on the primary outcome measures was examined and revealed no significant differences across the two measures (SF-36 physical function, $p = 0.58$; SF-36 mental health, $p = 0.41$). Of course, it is possible that men respond differentially to this type of treatment, although there is no precedent for such an assumption, and other factors, such as attributional style (mentioned above), may prove more pertinent.

Some patients failed to attend at least one of the two follow-up assessments, for a variety of reasons. The analysis method used ensured that patients with partial data were not excluded, and recognised the correlation between repeated measures from the same patient, but where data were missing, it was assumed to be missing at random; the probability of drop-out (i.e. possible informative censoring) was not considered. Methods for modelling drop-out explicitly as part of the analysis of longitudinal data are available but, with just two follow-ups and only three patients reporting explicitly that they were too ill to attend, it was felt that the additional complexity was not justified.

Whereas randomisation was at the patient level, the interventions were administered in groups. For some patients the allocation was changed because the subject was related to, or closely associated with, other group members and it was thought there would be contamination in the group process and leakage of the treatments. Any intervention administered in groups raises the possibility of clustering in the data. There are a number of ways in which potential clustering can be handled in the analysis. In this study, the group administration of the intervention was accounted for by including a covariate indicating the assessment set.

There were multiple difficulties in completing the economic evaluation. In terms of design, the

protocol described the economic evaluation as a 'cost–benefit analysis'. This would have entailed valuing the health gain of patients in terms of money, which was never intended. What was intended was a comparison of costs with change in the HUI, implying a cost–utility (or cost-effectiveness) analysis.

This is a complex intervention, aimed to improve the health of patients with a multifaceted condition. It would have been better to conduct a cost–consequences analysis, which would have presented results in a disaggregated way. Thus costs to the NHS, patients and carers and society could separately have been compared with a range of outcomes as measured in the RCT. The EQ-5D instrument could have been included as an outcome (rather than the HUI, which is less widely used), so that any utility could be captured from a UK 'Societal perspective'. This would have allowed for a cost–utility analysis to be carried out if meaningful differences had been detected.

Two main sources of data collection were identified in the protocol: participating primary and secondary care centres and patient questionnaire. The trial was almost over before researchers realised that patient records would need to be scrutinised for resource use data. This meant that limited resources were available for this exercise, and minimal data were obtained: this was restricted to number of GP visits and information on secondary care recorded in GP records. Ideally, patients' GP records would have been used to obtain details of all primary care contacts: who was seen (e.g. doctor, nurse, therapist); treatment and investigations; medication prescribed; and referrals to secondary care. The patient questionnaire could have been used to gather more information about secondary care contacts, as the information in the GP records was unclear in places.

The questionnaire used in the trial asked patients about the use of physiotherapy, psychological treatments and alternative therapies, but failed to ascertain whether these services were provided by the NHS and, if not, how much patients paid for them. Ideally, these questions would have been asked and this information added to the appropriate cost total. As it was, the information was of no use.

The questionnaire asked patients about medication use, categorising these into six groups (plus 'other') and asking if each had been 'not taken', 'taking currently' or 'took previously but not now'. As it stands, this information tells us nothing about total cost of medication for the duration of the trial, and many patients were clearly not familiar with the labels used, e.g. 'hypnotics', 'benzodiazapines', and were unable to complete the table accurately. Information on the use of medication could have been extracted from GP records if it had been planned, or patients could have been asked about prescribed medication received over the year, by name, strength, dose and quantity.

The protocol stated that 'costs borne to patients will be collected through questionnaires'. The greatest cost burden to patients is likely to have been travel costs to and from healthcare facilities and payment for private treatment. Neither of these was addressed in the questionnaire. Patients could have been asked about mode of travel, fares paid, distance, if by car, and car parking charges when attending intervention sessions and other healthcare facilities.

Given these significant limitations, the analysis was conducted on poor-quality data. Cost-effectiveness is normally estimated by constructing an incremental cost-effectiveness ratio (ICER), which compares the extra cost of an intervention, per patient, with the extra benefit in terms of health or health–related utility. In this study, we found no significant difference in the outcomes of the three groups with respect to health utility. The traditional approach to dealing with this is to report costs only, and the study becomes a cost-minimisation analysis. However, recent advances in statistical techniques have suggested this is not an appropriate method, as the study would not have been powered to detect significant differences in costs. An alternative approach is to use bootstrapping to generate an artificial dataset of ICERs and construct a cost-effectiveness acceptability curve (CEAC).

In the case of this study, however, we felt that this approach would be unsuitable, since the data quality does not justify the application of sophisticated statistical techniques. We therefore limited the reporting to a description of the results only.

## Interpretation

Overall, there was an improvement in the CBT treatment cohort, which was maintained 6 months after the end of treatment; there were statistically significant changes in the levels of fatigue, mental

health function and physical performance scores in the direction of the research hypothesis. There was, however, no evidence that the treatment restored normal levels of function for the majority of patients. The EAS cohort also showed significantly less fatigue than the SMC group. Additionally, the data show a consistent and clear trend between the EAS and the SMC cohorts on other measures.

It is difficult to compare this treatment with individual CBTs for this condition. There are several reasons for this: differences in the treatment protocol in terms of both content and time, differences in the outcome measures used, differences in the patient samples (in terms of severity) and differences in methodology. Finally, only one trial adequately defined 'success' prior to the trial. If the definition from this trial were used, it would appear that the current trial has demonstrated a successful clinical outcome when compared with individual CBTs.

As mentioned in Chapter 1, a decision was taken to incorporate GET within the CBT approach. Patients within the CBT condition were encouraged to set a manageable, low level of exercise (see Appendix 8 for more details) and to consider making gradual increases in their exercise levels once a period of stability at each level of exercise had been reached. This is the approach to CBT commonly used for chronic pain management within the NHS. It does differ from the models used for individual CBTs in previous research. We can therefore only infer that the combined treatment approach used in this trial was responsible for the changes in outcomes, and we cannot specifically attribute the changes (or lack of change) to either the CBT or the GET *per se*.

The principal measure used in the original proposal was the SF-36.[34] Although the majority of patients continued to have score(s) below the normal range, there was evidence of significant improvement. There are two subscales, the physical health and the mental health scales. For the former, there was no difference between the groups. For the latter, the scores for the CBT group were significantly higher than those for the SMC cohort. This means the mental health status was improved 6 months after the end of treatment. Although not statistically significant, the EAS cohort had also improved over the SMC group, which suggests potential for benefits of being in a group environment. The SF-36 had not been used in other studies to assess psychological health. The HADS and GHQ scales, which are also measures of psychological health, both showed a similar trend across the groups, although neither showed statistically significant differences. Both scales have a suggested cut-off score that is clinically significant. Six months after treatment had finished, fewer patients in both the CBT and EAS groups were at or above the threshold (i.e. experiencing psychological/psychiatric problems) on both scales. Once again, the trend was consistent but not different statistically, with the CBT arm having the lowest number above the threshold, followed by the EAS treatment cohort, which performed better than the SMC cohort.

The battery of neurocognitive tests did not demonstrate any statistically significant differences across the treatment interventions, but did show the same trend relevant in this outcome domain.

Two measures of fatigue were used in this study, the Chalder fatigue scale and the Borg perceived fatigue. The Chalder scale is a measure of persistent fatigue and its consequences, whereas the Borg scale measures the experience of fatigue at a specific moment, associated with physical exertion. The Chalder scale showed a statistically significant difference between groups after treatment, with the CBT group showing the least and the SMC group the greatest fatigue, but the Borg perceived fatigue scores were similar across each condition both initially and at follow-up. The similarity of the Borg scores indicates that each cohort reported exercising to a similar level of fatigue, which suggests that the significant increase in shuttle walking speed found in the CBT group was not an artificial gain achieved by 'pushing through' fatigue: it appears to be more substantial. These subjects reported increases in their normal walking pace. This is consistent with the results for the Chalder scale, which also point to an increase in activity and a decrease in the experience of general fatigue for the CBT group. This study is unable to shed any light on the mechanism underlying this change, and it may be possible that patients are feeling more confident and able to manage the condition. Whatever the mechanism, any improvement is likely to be of significance for CFS/ME sufferers.

The ISWT, used as a physical performance measure, has normative reference data described by Taylor and colleagues.[75] Their sample of 122 healthy subjects (mixed gender and age) walked a mean of 67 × 10-m shuttles. By comparison, the baseline mean in the current study was 24.6 × 10-m shuttles, reflecting a level of incapacity similar to that found in a group of back pain

sufferers also sampled by Taylor and colleagues. Although the CBT group showed a statistically significant improvement in walking speed compared with the EAS and SMC groups, it is not clear whether the improvement observed is clinically significant. The 46% increase over baseline in median shuttles walked in the CBT condition suggests that a useful change might have taken place for some individuals, which did not reach statistical significance at a group level. Walking performance remains an important variable for the evaluation of CFS/ME interventions. The authors are not aware of any research which has attempted to estimate the level of clinically significant change for the ISWT in any population. Further validation work is needed with the ISWT for this population, including estimation of what constitutes a clinically meaningful change.

The results of the economic evaluation were limited to the 6-month period following delivery of the intervention. Owing to missing data and inadequate assessment measures, the economic evaluation was limited to the perspective of the healthcare provider (NHS). A more rigorous approach would have been to include patient and societal costs.

This study was unable to investigate the economic impact of either CFS/ME on the individual or the cost–benefit of treatment. The fact that 63–77% of the whole sample cited the onset of CFS/ME as the main reason why they cannot work is consistent with other studies.

However, collecting reliable data with which to make such estimates is notoriously difficult, particularly with vulnerable patient groups, and that proved to be the case here. The original questionnaire attempted to collect data relating to direct patient costs and indirect societal costs, but the response was too poor for the data to be of much value, with a great deal of missing data.

## Relevance to the NHS

The provision of group-based treatment during the research was generally well received by the research participants, who appreciated the associated opportunities to share information with their peers and gain mutual support. This was particularly important for those who had not had contact with other people with CFS/ME, and for those who had unfortunately not had their illness validated in prior contacts with the health service. Although group-based treatments are not appropriate for everyone, and an individual assessment regarding the needs of the patient is required, the authors believe that group treatment remains a positive option for an NHS service and for its patients. It may be a particularly positive service option because of the potential for greater efficiency than offering a series of individual appointments. The very low drop-out rate from the research indicates the acceptability of group-based treatment to people with CFS/ME.

The results of this study suggest that all three interventions failed to return the majority of participants to normal functional levels. One implication of this finding for NHS services relates to informed consent. If a patient were considering attending a CBT-based group, for example, it would be reasonable to inform them that, on the basis of the current evidence, they could not expect the treatment to be curative. However, it would also be reasonable to inform them that those attending group-based CBT are more likely to show an improvement in fatigue, fitness and mood compared with those receiving SMC. This should allow the patient to make an informed decision about whether to participate in this form of treatment.

The provision of CBT-based treatment for people with CFS/ME has been contentious in the past, partly because CBT originated as a treatment for mental health disorders, and an implication was drawn from this that CFS/ME was being treated as a psychological condition. In this study, the CBT was delivered in a general hospital department by clinicians experienced in CBT-based treatments for chronic health problems such as arthritis, chronic pain and chronic respiratory disease. The delivery of group CBT within this setting did not appear to have been problematic for the research participants.

This research was based in a hospital OP department, which immediately selects those people with CFS/ME who are able to attend. The results of this trial therefore do not directly inform the management of people with severe CFS/ME, whose care is likely to be based on domiciliary assessment and management, or occasionally on IP care.

## Research recommendations

The researchers generated a range of recommendations for further research as the study progressed. These include validation of outcome

measures, investigation of the mechanism of action of CBT and investigation of prognostic factors for patients participating in CBT-based self-management groups. All of the above factors could be investigated alongside normal clinical practice. Another vital area of research is in early management: can appropriate rehabilitation input following the early diagnosis of CFS/ME improve outcomes? All of the above needs to be set in a context, which is that research into the aetiology and treatment of CFS/ME is somewhat limited while uncertainty exists about the existence of and identification of subgroups within CFS/ME.

There is potential to validate appropriate outcome measures further for people with CFS/ME. Ideally, this should be a collaborative project between the research community and people with CFS/ME. Although a generic measure such as the SF-36 has a considerable history as an outcome measure, there is no evidence regarding the magnitude of change that someone with CFS/ME might consider to be clinically significant. The ISWT has been validated for other health conditions, but has not been validated within this patient population and again does not have an evidence base to indicate what might be a clinically significant improvement for a patient. Qualitative methods linked with clinical interventions should allow researchers a greater insight into the relevance of CBT to the individuals who take part in the treatment, in order to highlight the outcome domains which are relevant to the individuals themselves.

The authors recommend further research into the mechanism of action of the CBT. Clinically, it was apparent to the researchers that a number of the participants in the CBT arm already possessed a range of chronic illness management skills. Some participants would not normally have been put forward for CBT because their current coping strategies were successful, indicating that they did not require this form of treatment. This fact will have diluted the size of the effect of CBT in this study. For other participants, it was clear to the clinicians and to the participants that there were management skills that it would be beneficial to improve upon, using CBT as a means to develop these skills. This would suggest that the experience of the CBT groups was different for these two subgroups. It would be helpful to investigate qualitatively the experience of group participants who have clearly benefited from CBT, to identify the key domains in which change has taken place. For example, a patient who benefits significantly from CBT might report improved pacing, increased ability to relax, increased confidence in exercise and physical activity, an increased ability to set appropriate goals for themselves or an increase in acceptance of the condition. These are 'softer' outcome measures than those used in the trial, but they are outcome measures that may be highly relevant to an individual living with a chronic illness. It would be helpful if such research led to improved clinical decision-making about who to offer CBT to, in addition to directing the attention of clinicians to the elements of CBT which patients report are of most benefit.

Ongoing audit of CBT-based self-management groups will provide important supplementary information. These groups will be composed of people with CFS/ME who have opted to attend, and have been selected by clinicians as being appropriate for CBT. This population will therefore be different from the population of this trial, who otherwise may not have chosen to attend or may not have been selected by clinicians to attend the group. This trial will provide a reference point for future therapy, in that groups with a patient population with similar baseline measurements as in the research can expect to make equivalent progress, or potentially greater progress.

Chapter 1 made reference to the decision to combine a GET and CBT approach and to the potential value of further research into these two potentially overlapping treatment approaches. This research question has already been taken further by the Medical Research Council (MRC)-funded PACE trial, and further recommendations regarding this line of research should await the results of this trial.

A vital focus for future research will be the management of this illness in the subacute phase. We know that early diagnosis is helpful to promote recovery. What might the best management strategies be to promote earlier recovery? Unstructured evidence from people with CFS/ME suggests that pacing of activity is important, along with the ability to judge appropriately the increments in activity required to make progress without risking a relapse through overexertion. Appropriate intervention in the subacute phase might provide the skills to manage these difficult issues. Again, it should be noted that some people who have post-viral fatigue syndrome rapidly apply a successful management strategy and would not be likely to benefit from such an intervention. Others might realise the need for support with self-management, or a healthcare professional

might be concerned that the individual's management strategy might not be conducive to recovery. A structured approach to learning pacing, accepting the need for appropriate rest, and to planning appropriate increases in activity levels would be a valuable intervention to investigate, especially if it were to lead to a higher recovery rate. Anecdotal evidence for people with CFS/ME suggests that it can take time to learn to accept that they are ill, and that a different approach to the illness is required: often, a sense of regret is expressed that a more appropriate management strategy was not applied from the outset. This might be a valuable insight to inspire future research.

Recommendations for future research can be summarised as follows:

1. illness-specific validation of physical outcome measures
2. estimation of the minimal clinically important difference for research outcome measures in CFS/ME
3. qualitative research investigating relevant outcome domains for CBT in CFS/ME
4. investigation of the mechanism of action of CBT, with an aim of improving patient selection
5. research into early management and secondary prevention strategies.

# Acknowledgements


## Contribution of authors

H O'Dowd (Consultant Clinical Psychologist) contributed to the conception, design, analysis, interpretation, drafting and revision of the report. P Gladwell (Specialist Physiotherapist) contributed to the drafting, revision, discussion and appendices. CA Rogers (Statistician) contributed to the drafting, revision, discussion and appendices. S Hollinghurst (Lecturer in Health Economics) carried out the economic evaluation. A Gregory (Assistant Psychologist) contributed to the drafting, revision and appendices.

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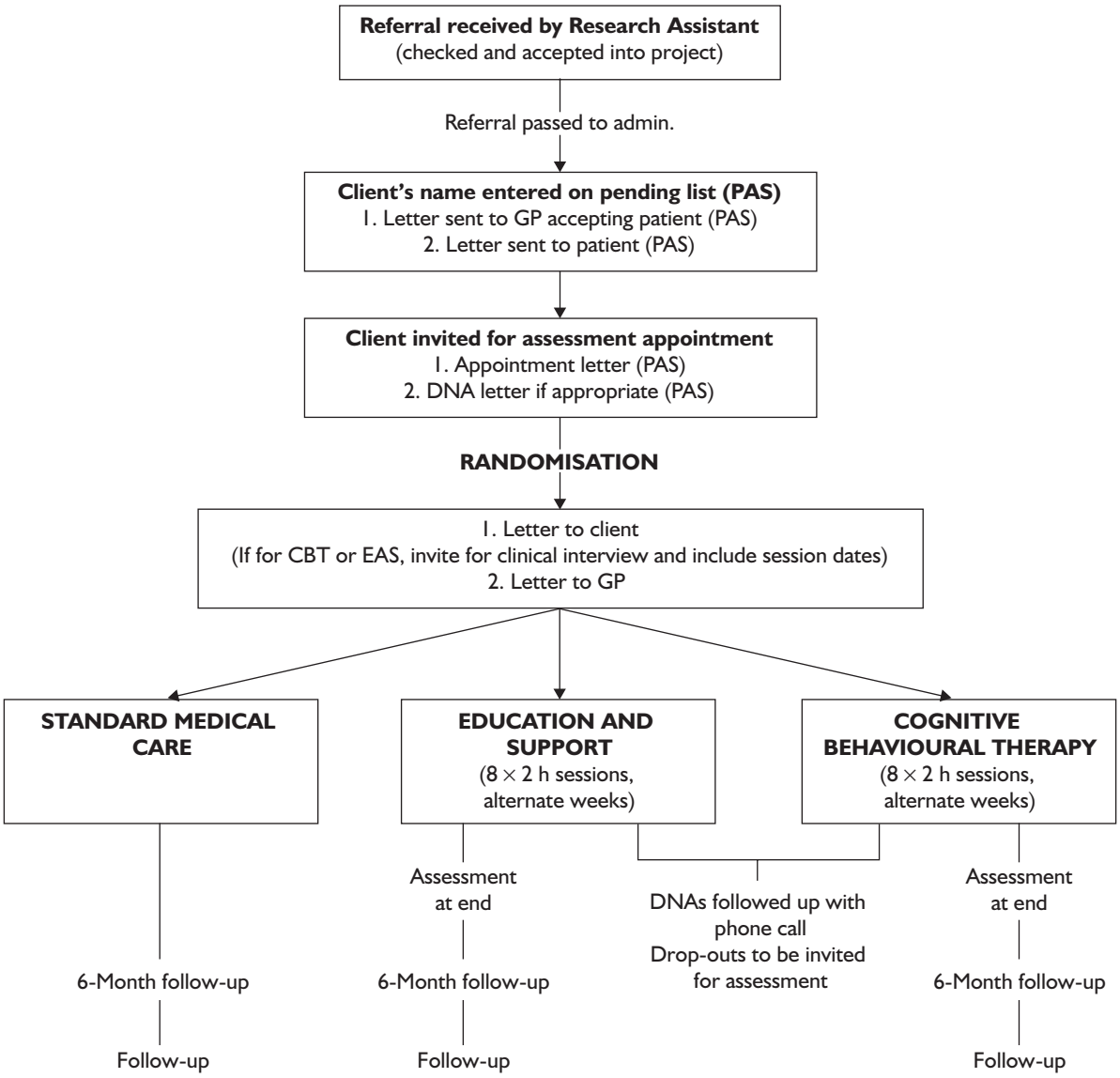
# Appendix 1

## CFS research project administration flowchart




DNA, did not attend; PAS, patient administration system.

# Appendix 2

## Referral criteria

### Chronic Fatigue Syndrome Research Project

**Standard Referral Criteria (Centre for Disease Control):**

1. Fatigue, with definite onset, as the principal symptom.
2. Four or more of the following symptoms concurrently present for six months or longer: impaired memory and concentration, sore throat, muscle pain, multi-joint pain, new headaches, unrefreshing sleep, post-exertion malaise, tender cervical or auxiliary lymph nodes.
3. Fatigue is medically unexplained, i.e. by abnormalities on examination and investigation, by diagnosed physical disorder or by a major psychiatric disorder (psychosis, bipolar affective disorder, severe depressive illness).
4. Fatigue is of sufficient severity to disable or distress the patient.

**Further Referral Criteria:**

5. There must be no ongoing physical investigations.
6. There must be no concurrent treatments planned.
7. Patient must be able to travel to Frenchay Hospital for all group intervention sessions.

**Contact details for any further information:**

**Dr. Hazel O'Dowd** (Clinical Psychologist), or **Caroline Haigh** (Research Psychologist) at:

The Pain Management Centre
Ward 22
Frenchay Hospital
Bristol
BS16 1LE

Telephone: (0117) 975 3890
Fax Number: (0117) 975 3891

# Appendix 3

## Referral summary

### Bristol East PCT

| Practice | Referrals made | Referrals accepted | Intervention under way | Intervention pending | Relevant information |
|---|---|---|---|---|---|
| Fishponds Health Centre | 8 | 8 | 4 | 0 | 2 patients withdrew pre-assessment<br>2 patients inappropriate |
| St George Health Centre | 8 | 4 | 4 | 0 | |
| Air Balloon | 10 | 6 | 4 | 0 | 2 patients withdrew pre-assessment<br>2 patients inappropriate |
| Eastville Health Centre | 4 | 4 | 4 | 0 | |
| Lodgeside | 2 | 2 | 2 | | |

### North West Bristol PCT

| Practice | Referrals made | Referrals accepted | Intervention under way | Intervention pending | Relevant information |
|---|---|---|---|---|---|
| Bradgate Surgery | 8 | 8 | 4 | 0 | 4 patients withdrew pre-assessment.<br>1 patient inappropriate |
| Fallodon Way | 10 | 10 | 1 | 0 | 2 patients withdrew pre-assessment |
| Gloucester Road | 6 | 6 | 6 | 0 | 2 patient withdrew pre-assessment.<br>1 patient inappropriate |
| Stokes Medical Centre | 6 | 6 | 4 | 0 | |
| Helios Medical Centre | 2 | 2 | 2 | 0 | |
| Horfield Health Centre | 2 | 2 | 0 | 0 | 1 patient on hold |

### Woodspring PCT

| Practice | Referrals made | Referrals accepted | Intervention under way | Intervention pending | Relevant information |
|---|---|---|---|---|---|
| Sunnyside, Clevedon | 1 | 1 | 0 | 0 | 4 patients withdrew pre-assessment |
| Haywood, Pill | 1 | 1 | 1 | 0 | 2 patients withdrew pre-assessment |

### Pre-assessment attrition figures (as at 12 September 2001)

- Inappropriate referrals 12
- Withdrawn pre-assessment 17
- Total pre-assessment attrition 29
- Total pre-assessment attrition rate, excluding those on hold 15.9%
- Referrals currently on hold, pending either patient readiness for inclusion, duration of symptoms or transient failure to meet some other criteria 14
- Total referral to study to date 153

# Appendix 4

## Patient information leaflet

The Pain Management Centre
Frenchay Hospital
Frenchay Park Road
BRISTOL BS16 1LE

Telephone: 0117 975 3890
Fax no: 0117 975 3891

### CHRONIC FATIGUE SYNDROME (CFS) PATIENT INFORMATION LEAFLET

**Introduction:**

We are evaluating treatments for Chronic Fatigue Syndrome (or M.E.). In the long term, we hope our study will help people like you to overcome this problem and help establish the most appropriate approach to treatment. There is currently no NHS treatment proven to aid recovery from CFS, although there are approaches that are used in current practice to aid recovery.

The aim of this investigation is to observe how effective approaches for the treatment of CFS are to the short-term progress of the disease.

**What will I have to do if I decide to take part?**

The aim of this study is to find out how CFS affects quality of life, mood and the ability to undertake mild physical activity. The study has a three-month *study phase* with follow-up over 12 months to monitor progress. To evaluate which of the three current approaches is most effective we will involve 130 participants.

If you agree to take part in the study you will receive an interview appointment at Frenchay Hospital and you will be allocated by chance to one of the current approaches to treating CFS. The research team will not be aware of which of the three approaches you are receiving, although your G.P. will know. The group to which you are allocated might or might not involve additional visits to Frenchay. You will be eligible to claim your travelling costs if required (please see note below).

The treatments under investigation include approaches based on minimal intervention. In this group your care might differ little from the care you are presently receiving. This might be the most appropriate way to aid recovery from CFS, at present we do not know. Once randomised, we will provide more information about the group you are in. The study, which is funded by the NHS, cannot accommodate movement between groups, and will only answer the study question if participants follow their allocated regime.

On your first visit (before the start of the trial), we will check your general health and ask you to complete three short questionnaires about your current health and quality of life and do a simple exercise test. Once you have completed the study course we would like you to attend on two further occasions (six monthly intervals), to repeat the assessments and questionnaires. This will provide longer-term follow-up on the approaches in question.

You will be able to continue your current medication and therapy whilst in the trial. The research team or your G.P. will be able to advise you with respect to any questions you might have in relation to the study.

You may be asked to attend a group at the hospital with other people, like yourself who have CFS. The group will be run by a physiotherapist, occupational therapist and psychologist. This group will meet eight times over sixteen weeks. You will not be asked to do anything which will worsen your condition.

**What are the possible risks of taking part?**

All the treatments used in the study are in current use in the NHS for the management of chronic conditions. There have been no reported problems or detrimental side-effects associated with the approaches to be used in the investigation. However, we will monitor your progress at every visit. Regular checks and monitoring are for your safety and are a means of observing progress.

**Are there any possible benefits?**

It is anticipated that the approaches for supporting CFS sufferers to be evaluated in this study will be of benefit to participants. However, this has yet to be proven. The information that we obtain from the study will help us gain knowledge as to the most beneficial way to manage Chronic Fatigue Syndrome/M.E. As such it may influence the provision of treatment both locally and nationally.

**Do I have to take part?**

No, you do not have to take part, this is entirely voluntary. If you would prefer not to take part you do not have to give a reason.

This study will not alter in any way the normal care you receive from your doctor, the hospital or social services. You are of course free to refuse and/or you can withdraw at any time without giving a reason and you will still be cared for in the normal way.

**What happens now?**

If you decide that you would like to take part in the study you will be briefed further about the study by the researcher whom you meet on your first visit to Frenchay Hospital when there will be an opportunity to ask further questions. You will then complete the first data collection step.

For further information, please contact:

Caroline Haigh (Research Psychologist)
The Pain Management Centre
Frenchay Hospital
Tel no: 0117 9753890

**Travel costs:**
These will be reimbursed at the rate of 17p per mile, or a full reimbursement of public transport costs (except taxi fares).

# Appendix 5

## Patient consent form

The Pain Management Centre
Frenchay Hospital
Frenchay Park Road
Bristol BS16 1LE

Telephone: 0117 975 3890
Fax No: 0117 975 3891

Study Number:

**CONSENT FORM**
**CHRONIC FATIGUE SYNDROME RESEARCH PROJECT**

Name of Researcher:

I have read the patient information and agree to participate in the research project into chronic fatigue syndrome. I understand that this will involve being allocated to one of three particular treatments, purely by chance. I am aware that I can withdraw from the study at any time without having to give my reasons, and that this would in no way alter the regular care I receive.

Please initial box.

1. I confirm that I have read and understand the information sheet for the above study. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. ☐
3. I am willing to allow access to my medical records but understand that strict confidentiality will be maintained. The purpose of this is to check that the study is being carried out correctly. ☐
4. I agree to take part in the above study. ☐

| _____ | _____ | |
|---|---|---|
| Name of patient | Date | Signature |
| _____ | _____ | |
| Name of person taking consent (if different from researcher) | Date | Signature |
| _____ | _____ | |
| Researcher | Date | Signature |

1 for patient; 1 for researcher; 1 to be kept with hospital notes

# Appendix 6

## CFS assessment pack

DATE: _____ RESEARCH No: _____

The following questions ask for your views about your health, how you feel and how well you are able to do your usual activities. If you are unsure about how to answer any question, please give the best answer you can.

**It is important for you to answer every question.**

1. In general, would you say your health is:

Please tick (✓) one

| | |
|---|---|
| Excellent | |
| Very good | |
| Good | |
| Fair | |
| Poor | |

2. Compared to one year ago, how would you rate your health in general now:

Please tick (✓) one

| | |
|---|---|
| Much better now than one year ago | |
| Somewhat better now than one year ago | |
| About the same as one year ago | |
| Somewhat worse now than one year ago | |
| Much worse now than one year ago | |

## Health and Daily Activities

**RESEARCH No:**_____

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

Please tick (✓) one box on each line

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports | | | |
| b) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf | | | |
| c) Lifting or carrying groceries | | | |
| d) Climbing several flights of stairs | | | |
| e) Climbing one flight of stairs | | | |
| f) Bending, kneeling, or stooping | | | |
| g) Walking more than a mile | | | |
| h) Walking half a mile | | | |
| i) Walking 100 yards | | | |
| j) Bathing and dressing yourself | | | |

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Please tick (✓) Yes or No for each question

| | Yes | No |
|---|---|---|
| a) Cut down on the amount of time you spent on work and other activities | | |
| b) Accomplished less than you would like | | |
| c) Were limited in the kind of work or other activities | | |
| d Had difficulty performing the work or other activities (for example, it took extra effort) | | |

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Please tick (✓) Yes or No for each question

| | Yes | No |
|---|---|---|
| a) Cut down on the amount of time you spent on work and other activities | | |
| b) Accomplished less than you would like | | |
| c) Didn't do work or other activities as carefully as usual | | |

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Please tick (✓) one

| | |
|---|---|
| Not at all | |
| Slightly | |
| Moderately | |
| Quite a bit | |
| Extremely | |

7. How much bodily pain have you had during the past 4 weeks?

Please tick (✓) one

| | |
|---|---|
| None | |
| Very mild | |
| Mild | |
| Moderate | |
| Severe | |
| Very severe | |

8. During the past 4 weeks, how much did pain interfere with your normal work (including work both outside the home and housework)?

Please tick (✓) one

| | |
|---|---|
| Not at all | |
| A little bit | |
| Moderately | |
| Quite a bit | |
| Extremely | |

## Your Feelings

**RESEARCH No:**_____

9. These questions are about how you feel and how things have been with you during the past 4 weeks. *(For each question, please give the one answer that comes closest to the way you have been feeling).*

Please tick (✓) one box on each line

| How much time during the past 4 weeks: | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| a) Did you feel full of life? | | | | | | |
| b) Have you been a very nervous person? | | | | | | |
| c) Have you felt so down in the dumps that nothing could cheer you up? | | | | | | |
| d) Have you felt calm and peaceful? | | | | | | |
| e) Did you have a lot of energy? | | | | | | |
| f) Have you felt down-hearted and low? | | | | | | |
| g) Did you feel worn out? | | | | | | |
| h) Have you been a happy person? | | | | | | |
| i) Did you feel tired? | | | | | | |

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?

Please tick (✓) one

| | |
|---|---|
| All of the time | |
| Most of the time | |
| Some of the time | |
| A little of the time | |
| None of the time | |

## Health in General

**RESEARCH No:**_____

11. Please choose the answer that best describes how true or false each of the following statements is for you?

Please tick (✓) one box on each line

| | Definitely true | Mostly true | Not sure | Mostly false | Definitely false |
|---|---|---|---|---|---|
| a) I seem to get ill a little more easily than other people | | | | | |
| b) I am as healthy as anybody I know | | | | | |
| c) I expect my health to get worse | | | | | |
| My health is excellent | | | | | |

**RESEARCH No:**_____

**This questionnaire is designed to help describe how you feel. Read each item and then place a tick in the box next to the reply which comes closest to how you have been feeling in the past week. Try to give your first reaction. This will probably be more accurate than spending a long time thinking about an answer.**

**I feel tense or wound up**
- Most of the time ☐
- A lot of the time ☐
- Time to time, occasionally ☐
- Not at all ☐

**I still enjoy the things I used to enjoy**
- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

**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 ☐

**I can laugh and see the funny side of things**
- As much as I always could ☐
- Not quite so much now ☐
- Definitely not so much now ☐
- Not at all ☐

**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 ☐

**I feel cheerful**
- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

**I can sit at ease and feel relaxed**
- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

**I feel as if I am slowed down**
- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

**I get a sort of frightened feeling like butterflies in the stomach**
- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

**I have lost interest in my appearance**
- Definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

**I feel restless as if I have to be on the move**
- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

**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 ☐

**I get sudden feelings of panic**
- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

**I can enjoy a good book or radio or TV programme**
- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

**RESEARCH No:_____**

We would like to know whether or not you have been having any problems with feeling tired, weak or lacking energy in the last month. Please answer ALL questions simply by underlining or ticking the answer which you think most nearly applies to you. We would like you to answer the questions whether or not you have these symptoms. We also would like to know how you feel either at the moment or recently, rather than a long time ago. If you have been feeling tired for a long time, we want you to compare yourself to how you felt when last well.

| | | | | |
|---|---|---|---|---|
| **Do you have problems with tiredness?** | Less than usual | No more than usual | More than usual | Much more than usual |
| **Do you need to rest more?** | Less than usual | No more than usual | More than usual | Much more than usual |
| **Do you feel sleepy or drowsy?** | Less than usual | No more than usual | More than usual | Much more than usual |
| **Do you have problems starting things?** | Less than usual | No more than usual | More than usual | Much more than usual |
| **Do you lack energy?** | Better than usual | No more than usual | More than usual | Much more than usual |
| **Do you have less strength in your muscles?** | Better than usual | No more than usual | More than usual | Much more than usual |
| **Do you feel weak?** | Less than usual | Same as usual | More than usual | Much more than usual |
| **Do you have difficulty concentrating?** | Less than usual | Same as usual | Worse than usual | Much worse than usual |
| **Do you make slips of the tongue when speaking?** | Less than usual | No more than usual | Worse than usual | Much worse than usual |
| **Do you find it more difficult to find the correct word?** | Less than usual | No more than usual | Worse than usual | Much worse than usual |
| **How is your memory?** | Better than usual | No worse than usual | Worse than usual | Much worse than usual |

The next questions ask about muscle pain.

| | | | | |
|---|---|---|---|---|
| **Do your muscles hurt at rest?** | Less than usual | No more than usual | Worse than usual | Much worse than usual |
| **Do your muscles hurt after exercise?** | Less than usual | No more than usual | Worse than usual | Much worse than usual |

***If you are tired at the moment please indicate approximately how long this has lasted. (Please circle the answer which applies to you.)***

| | | | |
|---|---|---|---|
| Less than 1 week | Less than 3 months | Between 3 and 6 months | 6 months or more |

**RESEARCH No:_____**

***Overall what percentage of the time do you feel tired?***
***(Please circle the answer which applies to you.)***

| | | | |
|---|---|---|---|
| 25% of the time | 50% of the time | 75% of the time | All the time |

***Why do you think you are feeling tired? Please try to give one reason below.***

*We should like to know if you have had any medical complaints and how your health has been in general over the past few weeks. Please answer ALL the questions on the following page simply by underlining the answer you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past. It is important that you answer ALL the questions.*

## HAVE YOU RECENTLY:

| | | | | |
|---|---|---|---|---|
| **Been able to concentrate on whatever you're doing** | Better than usual | Same as usual | Less than usual | Much less than usual |
| **Lost much sleep over worry?** | Not at all | No more than usual | Rather more than usual | Much more than usual |
| **Felt that you are playing a useful part in things?** | More so than usual | Same as usual | Less useful than usual | Much less useful |
| **Felt capable of making decisions about things?** | More so than usual | Same as usual | Less so than usual | Much less capable |
| **Felt constantly under strain?** | Not at all | No more than usual | Rather more than usual | Much more than usual |
| **Felt you couldn't overcome your difficulties?** | Not at all | No more than usual | Rather more than usual | Much more than usual |
| **Been able to enjoy your normal day-to-day activities?** | More so than usual | Same as usual | Less so than usual | Much less than usual |
| **Been able to face up to your problems?** | More so than usual | Same as usual | Less able than usual | Much less able |
| **Been feeling unhappy and depressed?** | Not at all | No more than usual | Rather more than usual | Much more than usual |
| **Been losing confidence in yourself?** | Not at all | No more than usual | Rather more than usual | Much more than usual |
| **Been thinking of yourself as a worthless person?** | Not at all | No more than usual | Rather more than usual | Much more than usual |
| **Been feeling reasonably happy, all things considered?** | More so than usual | About same as usual | Less so than usual | Much less than usual |

**RESEARCH No:_____**

This questionnaire contains a set of questions which ask about various aspects of your health. When answering these questions please think about your health and your ability to do things on a day to day basis, during the past 4 weeks. To define the four week period, please think about what the date was 4 weeks ago and recall the major events you have experienced during this period. Please focus your answers on your overall abilities, disabilities and how you felt during the past four weeks.

You may feel that some of the questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

Please read each question and consider your answers carefully. For each question, please select one answer that best describes your level of ability or disability during the past 4 weeks. Please indicate the selected answer by circling the letter (a,b,c,…) beside the answer.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about your abilities and feelings.

1 Which one of the following best describes your ability, during the past 4 weeks, to see well enough to read ordinary newsprint?
   a. Able to see well enough without glasses or contact lenses.
   b. Able to see well enough with glasses or contact lenses.
   c. Unable to see well enough even with glasses or contact lenses.
   d. Unable to see at all.

2 Which one of the following best describes your ability, during the past 4 weeks, to see well enough to recognise a friend on the other side of the street?
   a. Able to see well enough without glasses or contact lenses.
   b. Able to see well enough with glasses or contact lenses.
   c. Unable to see well enough even with glasses or contact lenses.
   d. Unable to see at all.

3 Which one of the following best describes your ability, during the past 4 weeks, to hear what was said in a group conversation with at least three other people?
   a. Able to hear what was said without a hearing aid.
   b. Able to hear what was said with a hearing aid.
   c. Unable to hear what was said even with a hearing aid.
   d. Unable to hear what was said but did not wear a hearing aid.
   e. Unable to hear at all.

4 Which one of the following best describes your ability, during the past 4 weeks, to hear what was said in a conversation with one other person in a quiet room?
   a. Able to hear what was said without a hearing aid.
   b. Able to hear what was said with a hearing aid.
   c. Unable to hear what was said even with a hearing aid.
   d. Unable to hear what was said but did not wear a hearing aid.
   e. Unable to hear at all.

5 Which one of the following best describes your ability, during the past 4 weeks, to be understood when speaking your own language with people who do not know you?
   a. Able to be understood completely.
   b. Able to be understood partially.
   c. Unable to be understood.
   d. Unable to speak at all.

6 Which one of the following best describes your ability, during the past 4 weeks, to be understood when speaking with people who know you well?
   a. Able to be understood completely.
   b. Able to be understood partially.
   c. Unable to be understood.
   d. Unable to speak at all.

7 Which one of the following best describes how you have been feeling during the past 4 weeks?
   a. Happy and interested in life.
   b. Somewhat happy.
   c. Somewhat unhappy.
   d. Very unhappy.
   e. So unhappy that life was not worthwhile.

8 Which one of the following best describes the pain and discomfort you have experienced during the past 4 weeks?
   a. Free of pain and discomfort.
   b. Mild to moderate pain or discomfort that prevented no activities.
   c. Moderate pain or discomfort that prevented a few activities.
   d. Moderate to severe pain or discomfort that prevented some activities.
   e. Severe pain or discomfort that prevented most activities.

9 Which one of the following best describes your ability, during the past 4 weeks, to walk? Note: walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.
   a. Able to walk around the neighbourhood without difficulty, and without walking equipment.
   b. Able to walk around the neighbourhood with difficulty, but did not require walking equipment or the help of another person.
   c. Able to walk around the neighbourhood with walking equipment, but without the help of another person.
   d. Able to walk only short distances with walking equipment, and required a wheelchair to get around the neighbourhood.
   e. Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and required a wheelchair to get around the neighbourhood.
   f. Unable to walk at all.

10 Which one of the following best describes your ability, during the past 4 weeks, to use your hands and fingers?
   a. Full use of two hands and ten fingers.
   b. Limitations in the use of hands or fingers, but did not require special tools or the help of another person.
   c. Limitations in the use of hands or fingers, independent with use of special tools (did not require the help of another person).
   d. Limitations in the use of hands or fingers, required the help of another person for some tasks (not independent even with the use of special tools).
   e. Limitations in the use of hands or fingers, required the help of another person for most tasks (not independent even with the use of special tools).
   f. Limitations in the use of hands or fingers, required the help of another person for all tasks (not independent even with the use of special tools).

11 Which one of the following best describes your ability, during the past 4 weeks, to remember things?
   a. Able to remember most things.
   b. Somewhat forgetful.
   c. Very forgetful.
   d. Unable to remember anything at all.

12 Which one of the following best describes your ability, during the past 4 weeks, to think and solve day to day problems?
   a. Able to think clearly and solve day to day problems.
   b. Had a little difficulty when trying to think and solve day to day problems.
   c. Had some difficulty when trying to think and solve day to day problems.
   d. Had great difficulty when trying to think and solve day to day problems.
   e. Unable to think or solve day to day problems.

13 Which one of the following best describes your ability, during the past 4 weeks, to perform basic activities?
   a. Eat, bathe, dress and use the toilet normally.
   b. Eat, bathe, dress and use the toilet independently with difficulty.
   c. Required mechanical support to eat, bathe, dress or use the toilet independently.
   d. Required the help of another person to eat, bathe, dress or use the toilet.

14 Which one of the following best describes how you have been feeling during the past 4 weeks?
   a. Generally happy and free from worry.
   b. Occasionally fretful, angry, irritable, anxious or depressed.
   c. Often fretful, angry, irritable, anxious or depressed.
   d. Almost always fretful, angry, irritable, anxious or depressed.
   e. Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help.

15 Which one of the following best describes the pain or discomfort you have experienced during the past 4 weeks?
   a. Free of pain and discomfort.
   b. Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.
   c. Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities.
   d. Frequent pain or discomfort; frequent disruption of normal activities. Discomfort required prescription narcotics for relief.
   e. Severe pain or discomfort. Pain not relieved by drugs and constantly disrupted normal activities.

16 Overall, how would you rate your health over the past 4 weeks?
   a. Excellent.
   b. Very good.
   c. Good.
   d. Fair.
   e. Poor.

17 How did you complete the questionnaire? Please select the one answer that best describes your situation.
   a. By myself, without any help from anyone else.
   b. By myself, except someone else circled the answers on the questionnaire form for me.
   c. With the help of someone else.
   d. This questionnaire was completed by a family member, without help from the subject or patient.
   e. This questionnaire was completed by a nurse or other health professional, without help from the subject or patient. Please specify type of health professional.

      _____

   f. This questionnaire was completed by another person, without help from the subject or patient. Please specify relationship to subject or patient.

      _____

# Appendix 7

# Self-report questionnaire on costs

## Sheet 1

Assessment 3

**CHRONIC FATIGUE SYNDROME PROJECT**

ID ☐☐☐

1. Name: _____

2. Assessment date (day, month, year) ☐☐ ☐☐ ☐☐☐☐

3. Home situation Lives alone ☐ Lives with Partner ☐ 2 Other ☐ 3

If other, please specify _____

4. Number of dependants (if there are no dependants please enter 0) ☐☐

5. Do you currently experience pain in any of the following areas?

| | Yes | No | If YES describe the nature of the pain | Constant Yes | Intermittent Yes | On exertion Yes | Comes and goes with exertion Yes |
|---|---|---|---|---|---|---|---|
| a) Head and neck | ☐ 1 | ☐ 2 | | ☐ 1 | ☐ 1 | ☐ 1 | ☐ 1 |
| b) Shoulders | ☐ 1 | ☐ 2 | | ☐ 1 | ☐ 1 | ☐ 1 | ☐ 1 |
| c) Chest | ☐ 1 | ☐ 2 | | ☐ 1 | ☐ 1 | ☐ 1 | ☐ 1 |
| d) Upper limbs | ☐ 1 | ☐ 2 | | ☐ 1 | ☐ 1 | ☐ 1 | ☐ 1 |
| e) Abdomen | ☐ 1 | ☐ 2 | | ☐ 1 | ☐ 1 | ☐ 1 | ☐ 1 |
| f) Back | ☐ 1 | ☐ 2 | | ☐ 1 | ☐ 1 | ☐ 1 | ☐ 1 |
| g) Lower limbs | ☐ 1 | ☐ 2 | | ☐ 1 | ☐ 1 | ☐ 1 | ☐ 1 |

6. Do you suffer from any of the following symptoms?

| | Yes | No | | Yes | No |
|---|---|---|---|---|---|
| a) Numbness | ☐ 1 | ☐ 2 | g) Breathlessness | ☐ 1 | ☐ 2 |
| b) Sensory disturbance | ☐ 1 | ☐ 2 | h) Palpitations | ☐ 1 | ☐ 2 |
| c) Weakness | ☐ 1 | ☐ 2 | i) Nausea | ☐ 1 | ☐ 2 |
| d) Dizziness | ☐ 1 | ☐ 2 | j) Sleep difficulties | ☐ 1 | ☐ 2 |
| e) Poor concentration | ☐ 1 | ☐ 2 | k) Other | ☐ 1 | ☐ 2 |
| f) Memory loss | ☐ 1 | ☐ 2 | If other, please specify _____ | | |

# Sheet 2

ID ☐☐☐

**Investigations**

8. Have you had any of the following investigations since your last assessment for the trial?

| | Yes | No |
|---|---|---|
| a) Blood Tests | ☐ 1 | ☐ 2 |
| b) Brain Scan | ☐ 1 | ☐ 2 |
| c) X-rays | ☐ 1 | ☐ 2 |
| d) Other | ☐ 1 | ☐ 2 |

If other please specify _____

---

**Physiotherapy for CFS**

9. Have you had, or are you having, physiotherapy since your last assessment for the trial? Yes ☐ 1 No ☐ 2

If YES

10. a) How many sessions did you or have you had? 1–2 ☐ 1 3–4 ☐ 2 5–6 ☐ 3 6> ☐ 4 Unknown ☐ 5

b) Did you or have you found it helpful? Yes ☐ 1 No ☐ 2

---

**Psychiatric/Psychological treatment for CFS**

11. Have you had, or are you having, psychiatric/psychiatric/psychological treatment since your last assessment for the trial? Yes ☐ 1 No ☐ 2

If YES

12. a) How many sessions did you or have you had? 1–2 ☐ 1 3–4 ☐ 2 5–6 ☐ 3 6> ☐ 4 Unknown ☐ 5

b) Did you or have you found it helpful? Yes ☐ 1 No ☐ 2

---

**Medication**

13. Have you taken or are you taking any of the following since your last assessment for the trial?

| | Not taken | Taking currently | Took previously, but not now |
|---|---|---|---|
| SSRIs | ☐ 1 | ☐ 2 | ☐ 3 |
| Tricyclics | ☐ 1 | ☐ 2 | ☐ 3 |
| Hypnotics | ☐ 1 | ☐ 2 | ☐ 3 |
| Analgesics | ☐ 1 | ☐ 2 | ☐ 3 |
| Anti-inflammatories | ☐ 1 | ☐ 2 | ☐ 3 |
| Benzodiazapines | ☐ 1 | ☐ 2 | ☐ 3 |
| Other | ☐ 1 | ☐ 2 | ☐ 3 |

If other please specify _____

# Sheet 3

ID ☐☐☐

**Alternative Therapies**

14. Have you tried any of the following treatments since your last assessment for the trial?

| | Currently | | | | Helpful? | |
|---|---|---|---|---|---|---|
| | Yes | No | If NO, have you taken them previously | Yes | No | Yes | No |
| a) Homeopathy | ☐ 1 | ☐ 2 | | ☐ 1 | ☐ 2 | ☐ 1 | ☐ 2 |
| b) Acupuncture | ☐ 1 | ☐ 2 | If NO, have you taken them previously | ☐ 1 | ☐ 2 | ☐ 1 | ☐ 2 |
| c) Reflexology | ☐ 1 | ☐ 2 | If NO, have you taken them previously | ☐ 1 | ☐ 2 | ☐ 1 | ☐ 2 |
| d) Chinese medicine | ☐ 1 | ☐ 2 | If NO, have you taken them previously | ☐ 1 | ☐ 2 | ☐ 1 | ☐ 2 |
| e) Massage | ☐ 1 | ☐ 2 | If NO, have you taken them previously | ☐ 1 | ☐ 2 | ☐ 1 | ☐ 2 |
| f) Aromatherapy | ☐ 1 | ☐ 2 | If NO, have you taken them previously | ☐ 1 | ☐ 2 | ☐ 1 | ☐ 2 |
| g) Other | ☐ 1 | ☐ 2 | If NO, have you taken them previously | ☐ 1 | ☐ 2 | ☐ 1 | ☐ 2 |

If other please specify _____

Please estimate how much money you have spent on alternative therapies since your last assessment for the trial
£ _____ (nearest £5)

**Equipment**

15. Do you have any of the following equipment at home to help with the management of your symptoms?

| | Yes | No |
|---|---|---|
| a) Handrail | ☐ 1 | ☐ 2 |
| b) Stool | ☐ 1 | ☐ 2 |
| c) Walking stick/crutch | ☐ 1 | ☐ 2 |
| d) Stair-lift | ☐ 1 | ☐ 2 |
| e) Hoist | ☐ 1 | ☐ 2 |
| f) Special cooking utensils | ☐ 1 | ☐ 2 |
| g) Other | ☐ | ☐ |

If other please specify _____

**Physical Performance**

16. Perceived fatigue ☐☐•☐

17. Number of shuttles walked ☐☐☐

18. Normal walking speed ☐☐☐

**Impact on daily routine**

| | Yes | No |
|---|---|---|
| 19. Has CFS prevented you from continuing in the main occupation you previously had? | ☐ 1 | ☐ 2 |

# Sheet 4

ID ☐☐☐

20. Please tick the boxes which most closely summarise the main occupation that you have currently (If none tick the box in the last row)

| Type of role | Current | Type of role | Current |
|---|---|---|---|
| Director | ☐ 1 | Skilled Manual | ☐ 5 |
| Senior Manager | ☐ 2 | Unskilled Manual | ☐ 6 |
| Manager | ☐ 3 | Student | ☐ 7 |
| Administration | ☐ 4 | None | ☐ 8 |

21. Since your last assessment for the trial have you had to obtain any assistance (professional or from family members) with caring or domestic commitments (e.g. caring for a relative or children) that you undertook previously

Yes ☐ 1 No ☐ 2

22. If YES indicate who this assistance was provided by (enter 0 if not provided)

| | Estimated input hours/week |
|---|---|
| a) Partner | ☐☐☐ |
| b) Immediate family (parent, in law, sister etc) | ☐☐☐ |
| c) Friends | ☐☐☐ |
| d) Social Services | ☐☐☐ |
| e) Health Services | ☐☐☐ |
| f) Other | ☐☐☐ |

If other please specify _____

23. Please indicate your current use of transport and mobility for a typical week (enter 0 if not used)

| | Percentage used |
|---|---|
| a) Private car (driving) | ☐☐☐ |
| b) Private car (driven by others) | ☐☐☐ |
| c) Public Transport | ☐☐☐ |
| d) Taxi | ☐☐☐ |
| e) Bicycle | ☐☐☐ |
| f) Walking | ☐☐☐ |

24. Please estimate how many miles you currently travel in a typical week

| | 0–10 | 11–50 | 51–100 | 101–250 | 250+ |
|---|---|---|---|---|---|
| a) Work | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b) Personal | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

## Sheet 5

ID ☐☐☐

25. Since your last assessment for the trial has suffering from CFS caused you to require additional assistance with your personal and domestic care?

| Yes | No |
|---|---|
| ☐ 1 | ☐ 2 |

26. If YES, please detail the assistance you currently receive

| **Help provided by** | **Care provided** | **No. of hours/ week** |
|---|---|---|
| a) Partner | _____ | ☐☐☐ |
| b) Immediate family (parent, in law, sister etc) | _____ | ☐☐☐ |
| c) Friends | _____ | ☐☐☐ |
| d) Social Services | _____ | ☐☐☐ |
| e) Health Services | _____ | ☐☐☐ |
| f) Other | _____ | ☐☐☐ |

If other please specify _____

# Appendix 8

# CBT and education and support sessions

## CBT sessions

This appendix summarises the content of the CBT sessions. Each session lasted from 12 am until 2 pm, with a short comfort break at 1 pm. Exercise sessions were normally before the break to allow a period of recovery after the journey to hospital and prior to the journey home. Meetings were held on alternate weeks, that is, the eight sessions were delivered over a 16-week period.

Slight variations in the content and the order of presentation occurred owing to staff annual leave. The majority of the talks lasted between 20 and 30 minutes. The following is a typical outline:

### Session one

- Introduction to staff and other participants and housekeeping rules.
- Outline of CFS/ME as a syndrome with clear symptoms and psychosocial consequences but with unknown organic pathology. As a result, the course was being directed at best management of the symptoms, and their consequences.
- Group exercise following the impact of the condition upon a typical sufferer, along a timeline from onset to 2 years post-onset. The wide range of symptoms was explored, in addition to the impact of symptoms upon psychological and social functioning.
- Impact of symptom-contingent over- and underactivity cycling explored.
- Introduction to setting baselines for activity and exercise to avoid activity cycling.
- Introduction to graded exercise as a means of regaining fitness and confidence in movement.

### Session two

- Introduction to using an activity diary to analyse pacing skills.
- Review of baselines set for first exercises.
- Further exercises taught.
- Introduction to goalsetting.
- Small group work focusing upon individual goalsetting.

### Session three

- Review of activity diary use and pacing skills.
- Obstacles to progress; session focusing upon behaviours that may prevent benefit being gained from the programme.
- Disease model analysis; analysis of usual expectation that identification of an illness leads to treatment and then to recovery. Redirection of participant's attention away from seeking a cure towards a 'best management strategy' that involves enhanced coping, and may lead to increased chances of recovery.
- Exercise review and 'troubleshooting' session.
- Small group work focusing upon individual goalsetting.

### Session four

- Introduction to stress management.
- Slow diaphragmatic breathing taught.
- Relaxation practice, recordings of relaxation protocol lent for home practice.
- Small group work focusing upon individual goalsetting.

### Session five

- Assertiveness and communication with others, particularly with regard to the importance of paced activity.
- Dealing with setbacks; setting up a recovery plan.
- Feedback regarding relaxation practice and 'troubleshooting'.
- Exercise programme progressed.
- Small group work focusing upon individual goalsetting.

### Session six

- Dealing with depression.
- Exercise programme progressed.
- Relaxation practice (imagery).
- Feedback regarding the books lent to patients (*Coping with chronic fatigue* by Trudie Chalder).[76]
- Small group work focusing upon individual goalsetting.

### Session seven
- The influences of positive and negative thinking upon coping, and how to deal with negative automatic thoughts.
- Exercise review; focus upon exercise habits for the future.
- Moving from illness identity into 'well' thinking.
- Small group work focusing upon individual goalsetting.

### Session eight
- Strategies for keeping going with self-management.
- Risks for a setback in the future: how to avoid the risks and review of recovery planning.
- Summary of the benefits and disappointments of the programme.
- Information about the research programme and the importance of the reassessments.

## Education and support sessions

This appendix summarises the content of the EAS group sessions. Each session lasted from 12 am until 2 pm, with a short comfort break with hot drinks available at 1 pm. Meetings were held on alternate weeks, that is, the eight sessions were delivered over a 16-week period.

Slight variations in the content and the order of presentation occurred due to staff annual leave. The majority of the talks lasted between 20 and 30 minutes. The therapists allowed free discussion on the topics introduced and responded to direct questions in a non-directive style. The following is a typical outline:

### Session one
- Introduction to staff and other participants and housekeeping rules.
- Rules for group work, for example confidentiality, respect for others in the group.
- Outline of CFS/ME as a syndrome with clear symptoms but with unknown organic pathology.
- Exploring the variety and nature of the symptoms.
- Time spent allowing each participant to explain their situation and the history of their illness, including past treatments and their effects.

### Session two
- First part of session allowed for feedback from participants about how they had been since the previous session. Support of the other participants towards each other was fostered and staff used a reflective style in responding.
- Exploration of the differences between the fatigue of CFS/ME and 'normal' fatigue.
- Exploration of the differences between rest and relaxation and between active and passive rest.
- Introduction to the concept of recuperative rest and the importance of allowing adequate time for this to occur.

### Session three
- Feedback from participants about how they had been since the previous session.
- Discussion about the nature of stress and relaxation, the benefits of relaxation and the consequences of lack of relaxation.
- Group exercise with the use of a pulse oximeter to read pulse rates.
- Group exercise analysing their own respiratory rate and the role of the rib cage and the diaphragm in breathing.
- Slow, diaphragmatic breathing taught and regular practice encouraged.

### Session four
- First part of session allowed for feedback from participants about how they had been since the previous session.
- Slow diaphragmatic breathing reviewed.
- Relaxation practice developed with progressive muscle relaxation taught.
- Group exercise – group split into two and asked to consider what their GP management had been and what they would in retrospect have found useful.

### Session five
- First part of session allowed for feedback from participants about how they had been since the previous session.
- Feedback regarding relaxation practice and 'troubleshooting'.
- Relaxation training progressed, with introduction of imagery. Recordings of relaxation protocols were lent to patients.
- Group discussion on their experience of stigma regarding their condition.

### Session six
- First part of session allowed for feedback from participants about how they had been since the previous session.
- Discussion about the uncertain role of aerobic exercise in managing CFS/ME; evidence suggests that whereas some people find benefit, others feel worse afterwards. Discussion about what forms of exercise group

members have found that they can and cannot manage.
- Stretching programme introduced with a focus on the role of stretches to reduce muscle tension. Sixteen stretches covering most muscle groups were taught and two repetitions of each were prescribed.
- Relaxation practice (imagery).

### Session seven

- First part of session allowed for feedback from participants about how they had been since the previous session.
- Review of stretches.
- Discussion about work and how CFS/ME has affected work.
- Dealing with stigma and the reaction of others to their illness.

### Session eight

- First part of session allowed for feedback from participants about how they had been since the previous session.
- Summary of the benefits and disappointments of the programme.
- What might help in the future?
- Information about the research programme and the importance of the reassessments.

# Appendix 9

## Reasons for drop-out

| Intervention | 6 months | 12 months |
|---|---|---|
| SMC | 3 withdrew from study (84, 123, 143)<br>1 on holiday (66)<br>1 unable to attend (99) | 3 withdrew from study (84, 123, 143)<br>2 were not contactable (99, 152)<br>1 transport problems (98)<br>1 unknown (7) |
| EAS | 1 moved away (153)<br>1 CFS too severe (140)<br>1 wrote and said did not find approach helpful (17)<br>2 unknown (56, 73) | 1 CFS too severe (140)<br>1 too ill to attend (138)<br>1 not contactable (96)<br>1 unknown (56) |
| CBT | 2 moved away (20, 76)<br>1 dropped out following an argument (31)<br>1 dropped out owing to work pressures (154)<br>1 transport problems (137)<br>2 unable to attend owing to a bereavement (132, 142)<br>2 unknown (23, 119) | 4 moved away (14, 20, 28, 76)<br>1 dropped out following an argument (31)<br>1 dropped out owing to work pressures (65)<br>1 dropped out (137)<br>1 said she could not see the point (132)<br>1 too ill to attend (150)<br>1 could not be contacted (145)<br>1 declined to make further appointment (154)<br>2 unknown (34, 37) |

# Appendix 10

# Baseline characteristics

## General baseline characteristics[a]

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Male gender | 24 | 46 | 12 | 24 | 15 | 29 |
| Age at initial assessment[b] | 41.6 | 12.0 | 38.8 | 11.8 | 42.9 | 11.6 |
| Home situation | | | | | | |
| Lives alone | 7 | 14 | 6 | 12 | 11 | 22 |
| Lives with partner | 34 | 65 | 30 | 60 | 29 | 57 |
| Other | 11 | 21 | 14 | 28 | 11 | 22 |
| Dependents | | | | | | |
| 0 | 24 | 46 | 27 | 54 | 23 | 46 |
| 1 | 10 | 19 | 8 | 16 | 8 | 16 |
| 2 | 14 | 27 | 13 | 26 | 14 | 28 |
| 3+ | 4 | 8 | 2 | 4 | 5 | 10 |
| Pain | | | | | | |
| Head and neck | 35 | 73 | 37 | 77 | 34 | 74 |
| Shoulders | 27 | 54 | 25 | 54 | 24 | 53 |
| Chest | 17 | 35 | 10 | 22 | 11 | 24 |
| Upper limbs | 38 | 78 | 36 | 73 | 32 | 68 |
| Abdomen | 19 | 39 | 18 | 39 | 11 | 23 |
| Back | 27 | 56 | 34 | 71 | 29 | 60 |
| Lower limbs | 44 | 88 | 45 | 90 | 43 | 84 |
| Symptoms | | | | | | |
| Numbness | 24 | 46 | 29 | 58 | 29 | 57 |
| Sensory disturbance | 37 | 73 | 38 | 76 | 39 | 76 |
| Weakness | 45 | 86 | 45 | 90 | 45 | 88 |
| Dizziness | 36 | 69 | 46 | 92 | 41 | 80 |
| Poor concentration | 49 | 94 | 49 | 98 | 49 | 96 |
| Memory loss | 44 | 85 | 45 | 90 | 47 | 92 |
| Breathlessness | 25 | 48 | 29 | 58 | 27 | 53 |
| Palpitations | 33 | 63 | 31 | 62 | 32 | 63 |
| Nausea | 24 | 46 | 34 | 68 | 33 | 65 |
| Sleep difficulties | 39 | 75 | 43 | 86 | 40 | 82 |
| Other | 44 | 90 | 43 | 90 | 44 | 90 |
| Total number of symptoms[c] | 7 | 6.5–9 | 9 | 8–10 | 9 | 7–10 |
| Time since symptoms started | | | | | | |
| No symptoms | 0 | 0 | 0 | 0 | 1 | 2 |
| <6 months | 0 | 0 | 0 | 0 | 1 | 2 |
| 6–12 months | 6 | 12 | 4 | 8 | 5 | 10 |
| 13–24 months | 8 | 16 | 6 | 12 | 3 | 6 |
| 25–36 months | 5 | 10 | 8 | 16 | 5 | 10 |
| 37–48 months | 4 | 8 | 4 | 8 | 4 | 8 |
| 49–60 months | 6 | 12 | 3 | 6 | 4 | 8 |
| > 60 months | 21 | 42 | 25 | 50 | 27 | 54 |
| Investigations | | | | | | |
| Blood tests | 51 | 98 | 49 | 98 | 49 | 98 |
| Brain scan | 15 | 30 | 9 | 19 | 12 | 26 |
| X-rays | 14 | 29 | 12 | 26 | 17 | 37 |
| Other | 23 | 48 | 27 | 56 | 17 | 38 |

*continued*

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Physiotherapy | | | | | | |
| For CFS | 3 | 6 | 2 | 4 | 4 | 8 |
| For other injury | 28 | 54 | 18 | 36 | 33 | 66 |
| Psychiatric or psychological treatment | | | | | | |
| For CFS | 8 | 17 | 6 | 13 | 9 | 18 |
| For depression | 9 | 21 | 9 | 20 | 7 | 16 |
| For anxiety | 5 | 13 | 2 | 5 | 4 | 10 |
| Stress | 4 | 11 | 5 | 13 | 0 | 0 |
| For pain management | 1 | 3 | 1 | 3 | 0 | 0 |
| Other | 6 | 16 | 4 | 11 | 8 | 19 |
| Medication | | | | | | |
| Antidepressants | | | | | | |
| Current | 20 | 44 | 22 | 46 | 13 | 30 |
| In the past | 9 | 20 | 12 | 25 | 18 | 42 |
| Tranquillisers | | | | | | |
| Current | 4 | 9 | 2 | 4 | 4 | 10 |
| In the past | 3 | 7 | 3 | 7 | 4 | 10 |
| Analgesics | | | | | | |
| Current | 28 | 61 | 28 | 60 | 24 | 53 |
| In the past | 0 | 0 | 4 | 9 | 4 | 9 |
| Other | | | | | | |
| Current | 16 | 36 | 12 | 25 | 9 | 21 |
| In the past | 1 | 2 | 4 | 8 | 0 | 0 |
| Time since diagnosis | | | | | | |
| < 6months | 9 | 18 | 11 | 25 | 8 | 17 |
| 6–12 months | 12 | 24 | 13 | 30 | 10 | 21 |
| 13–24 months | 10 | 20 | 1 | 2 | 7 | 15 |
| 25–36 months | 7 | 14 | 4 | 9 | 3 | 6 |
| > 36 months | 11 | 22 | 15 | 34 | 19 | 40 |
| Diagnosed by | | | | | | |
| GP | 31 | 63 | 25 | 58 | 32 | 70 |
| Consultant | 15 | 31 | 18 | 42 | 14 | 30 |
| Other | 3 | 6 | 0 | 0 | 0 | 0 |
| Advice | | | | | | |
| Rest | 18 | 39 | 21 | 48 | 13 | 27 |
| Pace | 23 | 49 | 23 | 50 | 17 | 35 |
| Do what you can | 17 | 38 | 13 | 30 | 7 | 15 |
| Carry on | 5 | 12 | 6 | 14 | 3 | 7 |
| Push | 3 | 7 | 1 | 2 | 1 | 2 |
| Eat healthily | 11 | 25 | 10 | 23 | 8 | 17 |
| Other | 19 | 40 | 20 | 43 | 21 | 44 |
| Alternative therapies | | | | | | |
| Homeopathy | 10 | 20 | 5 | 10 | 5 | 11 |
| Acupuncture | 2 | 4 | 4 | 8 | 5 | 11 |
| Reflexology | 2 | 4 | 3 | 6 | 3 | 7 |
| Chinese meditation | 1 | 2 | 1 | 2 | 2 | 4 |
| Massage | 3 | 6 | 0 | 0 | 3 | 7 |
| Aromatherapy | 3 | 6 | 2 | 4 | 3 | 7 |
| Equipment at home to help with CFS | | | | | | |
| Handrail | 2 | 4 | 2 | 4 | 1 | 2 |
| Stool | 5 | 6 | 5 | 10 | 3 | 6 |
| Walking stick | 3 | 6 | 6 | 12 | 2 | 4 |
| Stair lift | 0 | 0 | 0 | 0 | 0 | 0 |
| Hoist | 0 | 0 | 0 | 0 | 0 | 0 |
| Special utensils | 0 | 0 | 0 | 0 | 2 | 4 |
| Other | 7 | 14 | 6 | 12 | 8 | 16 |

*continued*

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Employment status prior to CFS | | | | | | |
| Full/part time work | 45 | 94 | 42 | 86 | 44 | 88 |
| Looking for work | 0 | 0 | 0 | 0 | 0 | 0 |
| Retired | 0 | 0 | 0 | 0 | 1 | 2 |
| Unable to work | 0 | 0 | 0 | 0 | 0 | 0 |
| Caring for family | 0 | 0 | 0 | 0 | 1 | 2 |
| Other | 3 | 6 | 7 | 14 | 4 | 8 |
| CFS prevented continuation of main occupation | 36 | 77 | 29 | 63 | 35 | 70 |
| Main occupation | | | | | | |
| Director | | | | | | |
| Before CFS | 1 | 2 | 0 | 0 | 1 | 2 |
| After CFS | 1 | 2 | 0 | 0 | 1 | 2 |
| Senior manager | | | | | | |
| Before CFS | 1 | 2 | 0 | 0 | 0 | 0 |
| After CFS | 1 | 2 | 0 | 0 | 0 | 0 |
| Manager | | | | | | |
| Before CFS | 11 | 21 | 11 | 22 | 8 | 16 |
| After CFS | 1 | 2 | 3 | 6 | 3 | 6 |
| Administrative | | | | | | |
| Before CFS | 13 | 25 | 13 | 26 | 8 | 16 |
| After CFS | 1 | 2 | 2 | 4 | 3 | 6 |
| Skilled manual | | | | | | |
| Before CFS | 10 | 19 | 13 | 26 | 14 | 27 |
| After CFS | 2 | 4 | 4 | 8 | 6 | 12 |
| Unskilled manual | | | | | | |
| Before CFS | 4 | 8 | 1 | 2 | 1 | 2 |
| After CFS | 0 | 0 | 0 | 0 | 1 | 2 |
| Student | | | | | | |
| Before CFS | 3 | 6 | 6 | 12 | 4 | 8 |
| After CFS | 4 | 8 | 2 | 4 | 1 | 2 |
| None | | | | | | |
| Before CFS | 0 | 0 | 1 | 2 | 2 | 4 |
| After CFS | 20 | 38 | 22 | 44 | 16 | 31 |
| Not specified | | | | | | |
| Before CFS | 9 | 17 | 5 | 10 | 13 | 25 |
| After CFS | 22 | 42 | 17 | 34 | 20 | 39 |
| Time spent in main occupation | | | | | | |
| Full time | 41 | 87 | 36 | 77 | 41 | 85 |
| 4 days/week | 1 | 2 | 7 | 15 | 4 | 8 |
| 3 days/week | 5 | 11 | 3 | 6 | 0 | 0 |
| 2 days/week | 0 | 0 | 0 | 0 | 1 | 2 |
| Not applicable | 0 | 0 | 1 | 2 | 2 | 4 |
| Required help because of CFS | 25 | 68 | 30 | 73 | 29 | 66 |
| Help provided by[d] | | | | | | |
| Partner | 21 | 57 | 21 | 54 | 17 | 44 |
| Immediate family | 11 | 31 | 16 | 44 | 14 | 39 |
| Friends | 3 | 10 | 4 | 12 | 4 | 11 |
| Social services | 0 | 0 | 0 | 0 | 0 | 0 |
| Health services | 1 | 3 | 0 | 0 | 0 | 0 |
| Other | 3 | 10 | 0 | 0 | 3 | 8 |
| Transport usage before CFS (% usage)[c] | | | | | | |
| Driving car | 70 | 0–95 | 57.5 | 20–80 | 70 | 30–90 |
| Passenger in car | 0 | 0–15 | 0 | 0–15 | 0 | 0–0 |
| Public transport | 0 | 0–10 | 0 | 0–10 | 0 | 0–10 |
| Taxi | 0 | 0–0 | 0 | 0–0 | 0–0 | |
| Bicycle | 0 | 0–0 | 0 | 0–0 | 0 | 0–0 |
| Walking | 15 | 2–45 | 16.5 | 5–30 | 10 | 0–20 |

*continued*

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Miles travelled/week before CFS | | | | | | |
| Work | | | | | | |
| 0–10 | 6 | 14 | 6 | 14 | 5 | 11 |
| 11–50 | 14 | 33 | 15 | 34 | 16 | 36 |
| 51–100 | 12 | 29 | 12 | 27 | 15 | 33 |
| 101–250 | 7 | 17 | 4 | 9 | 2 | 4 |
| >250 | 3 | 7 | 7 | 16 | 7 | 16 |
| Personal | | | | | | |
| 0–10 | 5 | 12 | 5 | 11 | 7 | 16 |
| 11–50 | 16 | 38 | 14 | 32 | 15 | 33 |
| 51–100 | 15 | 36 | 16 | 36 | 11 | 24 |
| 101–250 | 5 | 12 | 6 | 14 | 9 | 20 |
| >250 | 1 | 2 | 3 | 7 | 3 | 7 |
| CFS has changed mobility | 37 | 95 | 39 | 98 | 36 | 92 |
| Transport usage since CFS (% usage)[c,e] | | | | | | |
| Driving car | 50 | 0–80 | 45 | 1–75 | 60 | 2–90 |
| Passenger in car | 22.5 | 0–60 | 40 | 10–70 | 15 | 0–50 |
| Public transport | 0 | 0–10 | 0 | 0–5 | 0 | 0–5 |
| Taxi | 0 | 0–0 | 0 | 0–0 | 0 | 0–0 |
| Bicycle | 0 | 0–0 | 0 | 0–0 | 0 | 0–0 |
| Walking | 5 | 0–10 | 2 | 0–10 | 5 | 0–15 |
| Miles travelled/week since CFS[e] | | | | | | |
| Work | | | | | | |
| 0–10 | 31 | 78 | 32 | 74 | 30 | 73 |
| 11–50 | 5 | 12 | 7 | 16 | 8 | 20 |
| 51–100 | 2 | 5 | 2 | 5 | 1 | 2 |
| 101–250 | 0 | 0 | 1 | 2 | 1 | 2 |
| >250 | 2 | 5 | 1 | 2 | 1 | 2 |
| Personal | | | | | | |
| 0–10 | 21 | 50 | 15 | 34 | 21 | 47 |
| 11–50 | 16 | 38 | 23 | 52 | 19 | 42 |
| 51–100 | 5 | 12 | 3 | 7 | 4 | 9 |
| 101–250 | 0 | 0 | 3 | 7 | 1 | 2 |
| Able to care for personal and domestic needs before CFS | 37 | 88 | 35 | 81 | 39 | 91 |
| CFS caused the need for further assistance with personal and domestic care | 22 | 52 | 16 | 37 | 18 | 40 |
| Help provided by[d] | | | | | | |
| Partner | 12 | 33 | 11 | 28 | 5 | 14 |
| Immediate family | 8 | 24 | 8 | 23 | 6 | 17 |
| Friends | 1 | 3 | 0 | 0 | 3 | 9 |
| Social Services | 0 | 0 | 0 | 0 | 1 | 3 |
| Health Services | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 4 | 13 | 0 | 0 | 2 | 6 |

[a] Data are reported as numbers and percentages except where indicated. Percentages are calculated after excluding missing data.
[b] Mean and SD.
[c] Median and IQR.
[d] Percentages are for the total number who responded, not the subset who required assistance.
[e] Data are given for all who responded, whether or not they reported a change.

## Baseline quality of life scores (median, IQR)

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | Median | IQR |
| Physical performance | | | | | | |
| Perceived fatigue | 3 | 2–4 | 3 | 3–4 | 3 | 3–4 |
| Shuttles walked | 20.5 | 12–32.5 | 21 | 10–32 | 21 | 14–30 |
| Normal walking speed | 8 | 5–13 | 8 | 5–10 | 8.5 | 6–14 |
| SF-36 | | | | | | |
| Physical health | 33.2 | 26.1–39.7 | 30.7 | 26.2–33.3 | 32.5 | 26.9–39.0 |
| Mental health | 34.1 | 26.2–45.1 | 32.7 | 27.4–44.0 | 34.7 | 28.0–42.3 |
| HADS | | | | | | |
| Anxiety | 10 | 7.5–12 | 11 | 8–15 | 9.5 | 7–12 |
| Depression | 7.5 | 5.5–12 | 9 | 8–11 | 8 | 7–10 |
| GHQ | 18.5 | 15–23 | 23.5 | 15–27 | 16.5 | 14–22 |
| Chalder | 27 | 22–30 | 26.5 | 22–29 | 26 | 20–29 |
| HUI3 overall utility score | 0.33 | 0.09–0.52 | 0.15 | –0.002–0.43 | 0.36 | 0.16–0.65 |

## Baseline cognitive scores (median, IQR)

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | Median | IQR |
| Mood | | | | | | |
| Alertness | 186 | 162–220 | 169 | 138–215 | 179 | 149–213 |
| Hedonic tone | 167 | 148–196 | 167 | 145–195 | 167 | 147–196 |
| Anxiety | 76 | 67–87 | 76 | 63–93 | 76 | 67–90 |
| Recall | | | | | | |
| Total words recalled | 11.5 | 9–13.5 | 12 | 10–14 | 10 | 8–13 |
| Correct words | 10 | 8–12 | 10 | 9–13 | 10 | 7–12 |
| Incorrect words | 1 | 0–1 | 1 | 0–1 | 1 | 0–1 |
| Simple reaction time | | | | | | |
| Mean reaction time | 358.5 | 300.4–454.4 | 356.2 | 299.4–478.7 | 353.4 | 290.7–421.0 |
| Trials completed | 26 | 25–27 | 26 | 25–27 | 26 | 25–28 |
| Repeated digits detection | | | | | | |
| Mean reaction time | 625.8 | 541.5–670.4 | 594.3 | 528.7–733.3 | 608.3 | 552.2–692.1 |
| Hit rate | 10 | 6.5–13.5 | 9.5 | 5–13 | 11 | 8–12 |
| False alarms | 2 | 1–3.5 | 1 | 0–3 | 2 | 1–5 |

## Other symptoms reported at initial assessment

| Specify symptom | Frequency | Percent | Cumulative frequency |
|---|---|---|---|
| Aching bones | 1 | 0.75 | 0.75 |
| Aching muscles, 'flu-like symptoms | 1 | 0.75 | 1.50 |
| Alcohol intolerance | 1 | 0.75 | 2.26 |
| Always feel unwell | 1 | 0.75 | 3.01 |
| Anxiety and depression as a consequence of CFS/ME | 1 | 0.75 | 3.76 |
| Anxiety, digestive problems | 1 | 0.75 | 4.51 |
| Bad coordination | 1 | 0.75 | 5.26 |
| Bad headaches, feel desperately unwell | 1 | 0.75 | 6.02 |
| Balance problems, digestion problems | 1 | 0.75 | 6.77 |
| Bloated, minor illnesses, brain fog, bladder problems | 1 | 0.75 | 7.52 |
| Bowel problems, kidney pain, migraines | 1 | 0.75 | 8.27 |
| Brain fog, pins and needles, feeling off colour | 1 | 0.75 | 9.02 |
| Brain fog in morning for 1.5 hours | 1 | 0.75 | 9.77 |
| Brain slowing down | 1 | 0.75 | 10.53 |
| Cold legs, poor circulation, bladder problems | 1 | 0.75 | 11.28 |
| Constant headaches, moodiness | 1 | 0.75 | 12.03 |
| Continual headaches, IBS | 1 | 0.75 | 12.78 |
| Difficulty in speech, sore throat | 1 | 0.75 | 13.53 |
| Digestion, irritable bowel, burning feeling | 1 | 0.75 | 14.29 |
| Digestive problems, muscle spasm, lightheadedness | 1 | 0.75 | 15.04 |
| Digestive problems | 1 | 0.75 | 15.79 |
| Ear/eye pain, tender gum, tinnitus, pins and needles | 1 | 0.75 | 16.54 |
| Excessive sweating, hot flushes | 1 | 0.75 | 17.29 |
| Exhaustion, difficult digestion, tingling | 1 | 0.75 | 18.05 |
| Extreme tiredness, lack of energy | 1 | 0.75 | 18.80 |
| Extremities swelling, can't walk straight | 1 | 0.75 | 19.55 |
| Eye ache, pins and needles, shaky on exertion | 1 | 0.75 | 20.30 |
| Eye ache, pins and needles, cold fingers, light headed | 1 | 0.75 | 21.05 |
| Faint a lot, goes funny colour, sore throat | 1 | 0.75 | 21.80 |
| Fear of people | 1 | 0.75 | 22.56 |
| Feel drunk, tinnitus, stiffness | 1 | 0.75 | 23.31 |
| Feeling frantic | 1 | 0.75 | 24.06 |
| Feeling low | 1 | 0.75 | 24.81 |
| Feels very hot/really cold for no external reason | 1 | 0.75 | 25.56 |
| Foggy brain | 1 | 0.75 | 26.32 |
| Food allergies | 1 | 0.75 | 27.07 |
| Fungal infections, digestive problems | 1 | 0.75 | 27.82 |
| Has difficulty finding words | 1 | 0.75 | 28.57 |
| Headache, dyspraxia – mild, constantly cold, dry mouth | 1 | 0.75 | 29.32 |
| Headaches | 11 | 8.27 | 37.59 |
| Headaches and temperature fluctuations | 1 | 0.75 | 38.35 |
| Headaches, agitation | 1 | 0.75 | 39.10 |
| Headaches, sore throat, muscles twitching | 1 | 0.75 | 39.85 |
| Headaches, stomach aches | 1 | 0.75 | 40.60 |
| Headaches, temperature regulation | 2 | 1.50 | 42.11 |
| Heavy arms, light hands, pins and needles | 1 | 0.75 | 42.86 |
| Heightened sense of smell – things become stronger | 1 | 0.75 | 43.61 |
| IBS, bad skin, weight gain | 1 | 0.75 | 44.36 |
| IBS, chemical sensitivity, mouth ulcers | 1 | 0.75 | 45.11 |
| IBS, pins and needles | 1 | 0.75 | 45.86 |
| Irritability | 2 | 1.50 | 47.37 |
| Irritability, mental and physical exhaustion | 1 | 0.75 | 48.12 |
| Irritable bowel | 1 | 0.75 | 48.87 |
| Irritable bowel, numbness/pressure feeling | 1 | 0.75 | 49.62 |
| Itchy | 1 | 0.75 | 50.38 |
| Jumpy digestive problems, bad dreams, can't sleep | 1 | 0.75 | 51.13 |
| Lack of energy | 1 | 0.75 | 51.88 |
| Lack of energy, frustration | 1 | 0.75 | 52.63 |
| Legs leaden, cold hands/feet, head feels | 1 | 0.75 | 53.38 |
| Lightheadedness | 1 | 0.75 | 54.14 |

| Specify symptom | Frequency | Percent | Cumulative frequency |
|---|---|---|---|
| Loose voice | 1 | 0.75 | 54.89 |
| Loss of voice when tired, loss of balance | 1 | 0.75 | 55.64 |
| Low mood, depression | 1 | 0.75 | 56.39 |
| Mood swings, tired and irritable, wobbly legs | 1 | 0.75 | 57.14 |
| Mood – ups and downs | 1 | 0.75 | 57.89 |
| Muscle aches, like 'flu, chest pain, hot/cold | 1 | 0.75 | 58.65 |
| Muscle spasms | 1 | 0.75 | 59.40 |
| Muscle spasms, stabbing pains (joints) | 1 | 0.75 | 60.15 |
| Muscles ache, headache, pins and needles in extremities | 1 | 0.75 | 60.90 |
| Occasional lack of speech comprehension | 1 | 0.75 | 61.65 |
| Pain behind eyes, tinnitus, confusion | 1 | 0.75 | 62.41 |
| Pins and needles | 1 | 0.75 | 63.16 |
| Pins and needles, feeling low and frustrated | 1 | 0.75 | 63.91 |
| Pins and needles all over, odd sense of time | 1 | 0.75 | 64.66 |
| Pins and needles | 2 | 1.50 | 66.17 |
| Pins and needles in limbs | 1 | 0.75 | 66.92 |
| Pins and needles, photophobia | 1 | 0.75 | 67.67 |
| Pins and needles, slowed speech | 1 | 0.75 | 68.42 |
| Pins and needles, very vivid dreams | 1 | 0.75 | 69.17 |
| Pins and needles | 1 | 0.75 | 69.92 |
| Pins and needles in hands | 1 | 0.75 | 70.68 |
| Pins and needles, dry eyes, swollen glands, pain | 1 | 0.75 | 71.43 |
| Pins and needles, shaky hands, IBS, panic and anxiety | 1 | 0.75 | 72.18 |
| Pins and needles, twitching muscles, hot/cold | 1 | 0.75 | 72.93 |
| Pins and needles, difficult making sense of things | 1 | 0.75 | 73.68 |
| Pins and needles, oversensitive to noise and light | 1 | 0.75 | 74.44 |
| Pinching muscles, swollen hands/throat | 1 | 0.75 | 75.19 |
| Racing thoughts, lots of strange dreams | 1 | 0.75 | 75.94 |
| Sensation in the middle of head | 1 | 0.75 | 76.69 |
| Sensitive to loud noises | 1 | 0.75 | 77.44 |
| Shakes | 1 | 0.75 | 78.20 |
| Shakes | 1 | 0.75 | 78.95 |
| Shaking hands, feeling faint, cold sweats | 1 | 0.75 | 79.70 |
| Sinus problem, facial pain, loss of limb | 1 | 0.75 | 80.45 |
| Sometimes feel tired and agitated | 1 | 0.75 | 81.20 |
| Sore throat, temperature regulation | 1 | 0.75 | 81.95 |
| Sore throats, headaches | 2 | 1.50 | 83.46 |
| Sore throat and mouth, very itchy skin | 1 | 0.75 | 84.21 |
| Stammer, shaky, hot/cold spells, disoriented | 1 | 0.75 | 84.96 |
| Sudden disorientation | 1 | 0.75 | 85.71 |
| Susceptibility to secondary depression | 1 | 0.75 | 86.47 |
| Sweating – temperature control, depression | 1 | 0.75 | 87.22 |
| Swollen glands (neck) | 1 | 0.75 | 87.97 |
| Temperature regulation | 1 | 0.75 | 88.72 |
| Tender lumps on head, sweats, hot/cold sensations | 1 | 0.75 | 89.47 |
| Tension, pins and needles | 1 | 0.75 | 90.23 |
| Thumping sensation in head | 1 | 0.75 | 90.98 |
| Tingling | 1 | 0.75 | 91.73 |
| Tingling cold feelings | 1 | 0.75 | 92.48 |
| Tingling in arms, IBS/diarrhoea, brain fog | 1 | 0.75 | 93.23 |
| Tinnitus | 1 | 0.75 | 93.98 |
| Tinnitus, misinterpreting people, depressed | 1 | 0.75 | 94.74 |
| Tinnitus, tight muscles, loss of balance | 1 | 0.75 | 95.49 |
| Tiredness, feels like he has a hangover | 1 | 0.75 | 96.24 |
| Tremor, balance problems | 1 | 0.75 | 96.99 |
| Very bad headaches, mood swings | 1 | 0.75 | 97.74 |
| Very sore throat, enlarged glands | 1 | 0.75 | 98.50 |
| Viral like symptoms, e.g. swollen glands | 1 | 0.75 | 99.25 |
| Weepiness, frustration | 1 | 0.75 | 100.00 |
| Total | 133 | 100.00 | |

## Other investigations reported at initial assessment

| Specify symptom | Frequency | Percent | Cumulative frequency |
|---|---|---|---|
| Allergy tests | 1 | 1.47 | 1.47 |
| Autoimmune tests | 1 | 1.47 | 2.94 |
| Blood sugar, endoscopy | 1 | 1.47 | 4.41 |
| BP monitor | 1 | 1.47 | 5.88 |
| CNT/stomach specialist | 1 | 1.47 | 7.35 |
| Cognitive evoked potential test | 1 | 1.47 | 8.82 |
| Cognitive function, sensory tests | 1 | 1.47 | 10.29 |
| Cognitive tests electrodes | 1 | 1.47 | 11.76 |
| Connective tissue disorder, arthritis screen | 1 | 1.47 | 13.24 |
| CT scan, ultrasound | 1 | 1.47 | 14.71 |
| ECG – slight murmur of the heart | 1 | 1.47 | 16.18 |
| ECG | 1 | 1.47 | 17.65 |
| ECG | 1 | 1.47 | 19.12 |
| ECGs | 1 | 1.47 | 20.59 |
| ECG, EEG | 1 | 1.47 | 22.06 |
| ECG, exercise test | 1 | 1.47 | 23.53 |
| Echocardiogram, ECGs, upper body scan | 1 | 1.47 | 25.00 |
| Endoscopy (food intolerance?) | 1 | 1.47 | 26.47 |
| Endoscopy × 2 | 1 | 1.47 | 27.94 |
| Endoscopy (for IBS) | 1 | 1.47 | 29.41 |
| Endocrinologist/ECG 24-hour tape | 1 | 1.47 | 30.88 |
| Endoscopies | 1 | 1.47 | 32.35 |
| Endoscopy | 1 | 1.47 | 33.82 |
| Endoscopy (for digestion problems) | 1 | 1.47 | 35.29 |
| Endoscopy – bowel, womb and stomach | 1 | 1.47 | 36.76 |
| Evoked potentials, *** scan | 1 | 1.47 | 38.24 |
| Full body scan | 1 | 1.47 | 39.71 |
| Glandular fever, anaemia, liver count | 1 | 1.47 | 41.18 |
| Head scan of sinuses | 1 | 1.47 | 42.65 |
| Heart and lung function tests | 1 | 1.47 | 44.12 |
| Kidney function test | 1 | 1.47 | 45.59 |
| Liver function, hydroid function, MS screen | 1 | 1.47 | 47.06 |
| Liver function, thyroid | 1 | 1.47 | 48.53 |
| Aching calf muscles (?DVT) | 1 | 1.47 | 50.00 |
| Lumbar puncture | 2 | 2.94 | 52.94 |
| Lumbar, nerve-ending tests | 1 | 1.47 | 54.41 |
| MRI | 1 | 1.47 | 55.88 |
| MRI 2 years ago | 1 | 1.47 | 57.35 |
| MRI body scan, brain response test | 1 | 1.47 | 58.82 |
| MRI scan | 3 | 4.41 | 63.24 |
| MRI scan, tests for diabetes | 1 | 1.47 | 64.71 |
| MRI, CAT scan, eface potentials | 1 | 1.47 | 66.18 |
| Muscle fibre test | 1 | 1.47 | 67.65 |
| Neuro tests | 1 | 1.47 | 69.12 |
| Neurological tests | 2 | 2.94 | 72.06 |
| Neurologists, kidney and bladder scan | 1 | 1.47 | 73.53 |
| Psychological test only | 1 | 1.47 | 75.00 |
| Smell/taste tests | 1 | 1.47 | 76.47 |
| Endoscopy/biopsy, EEG | 1 | 1.47 | 77.94 |
| Stool samples, urine tests | 1 | 1.47 | 79.41 |
| Stool tests, urine, etc. | 1 | 1.47 | 80.88 |
| Synaxthin | 1 | 1.47 | 82.35 |
| Tests for diet intolerance/thyroid problem | 1 | 1.47 | 83.82 |

| Specify symptom | Frequency | Percent | Cumulative frequency |
|---|---|---|---|
| Thyroid function test | 1 | 1.47 | 85.29 |
| Throat swab | 1 | 1.47 | 86.76 |
| Thyroid, liver | 1 | 1.47 | 88.24 |
| Timed heart monitor | 1 | 1.47 | 89.71 |
| Ultrasound | 1 | 1.47 | 91.18 |
| Ultrasound scans | 1 | 1.47 | 92.65 |
| Ultrasound, urine tests | 1 | 1.47 | 94.12 |
| Urine and stool, ECG and ultrasound | 1 | 1.47 | 95.59 |
| Urine test | 2 | 2.94 | 98.53 |
| Vision, neck muscles (for headache complaint) | 1 | 1.47 | 100.00 |
| Total | 68 | 100.00 | |

## Other treatment specified at initial assessment

| Specify symptom | Frequency | Percent | Cumulative frequency |
|---|---|---|---|
| Assessed mood, suicidal idealism | 1 | 6.67 | 6.67 |
| Assessment for the symptoms | 1 | 6.67 | 13.33 |
| Bad temper/just medication | 1 | 6.67 | 20.00 |
| Being physically attacked | 1 | 6.67 | 26.67 |
| Bereavement and family issues | 1 | 6.67 | 33.33 |
| Childhood difficulties and counselling | 1 | 6.67 | 40.00 |
| Coming off valium after 12 years, induced | 1 | 6.67 | 46.67 |
| Counselling due to impact of CFS | 1 | 6.67 | 53.33 |
| Counselling – advice in coping with CFS | 1 | 6.67 | 60.00 |
| Counselling | 1 | 6.67 | 66.67 |
| Family relationships | 1 | 6.67 | 73.33 |
| General counselling – felt at end of tether | 1 | 6.67 | 80.00 |
| Personal development | 1 | 6.67 | 86.67 |
| Self-esteem/relationship issues | 1 | 6.67 | 93.33 |
| Trauma councillor re: events in Uganda | 1 | 6.67 | 100.00 |
| Total | 15 | 100.00 | |

## Other medication reported at initial assessment

| Medication | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Anti-histamine (for sleep) | 1 | 2.08 | 2.08 |
| Antibiotic – doxycycline | 1 | 2.08 | 4.17 |
| Antibiotics | 2 | 4.17 | 8.33 |
| Antihistamine | 1 | 2.08 | 10.42 |
| Bendrofluazide for blood pressure | 1 | 2.08 | 12.50 |
| Beta blockers | 2 | 4.17 | 16.67 |
| Chinese herbs | 1 | 2.08 | 18.75 |
| Cimetidine, epilim, fludrocortisone, carbamazopine | 1 | 2.08 | 20.83 |
| Cod liver oil, evening primrose, novelle | 1 | 2.08 | 22.92 |
| Efamast, propranolol, noresthisterone | 1 | 2.08 | 25.00 |
| Ginseng, magnesium citrate | 1 | 2.08 | 27.08 |
| HRT, tear replacements | 1 | 2.08 | 29.17 |
| IBS | 1 | 2.08 | 31.25 |
| Insulin, tegratol (2152) | 1 | 2.08 | 33.33 |
| Iron tablets | 2 | 4.17 | 37.50 |
| Iron tablets, zoton (for bowels) | 1 | 2.08 | 39.58 |
| Kliofem (HRT) | 1 | 2.08 | 41.67 |
| Lamotrigine (anti-epileptic) | 1 | 2.08 | 43.75 |
| Many vitamins and mineral supplements | 1 | 2.08 | 45.83 |
| Mebeverin | 1 | 2.08 | 47.92 |
| Mebeverine, epamast, ventilators | 1 | 2.08 | 50.00 |
| Multi-vitamins, gentle iron | 1 | 2.08 | 52.08 |
| Non-sedative antihistamine (zirtek), propranolol | 1 | 2.08 | 54.17 |
| Oestrodeum | 1 | 2.08 | 56.25 |
| Peppermint oil | 1 | 2.08 | 58.33 |
| Peppermint oil for IBS | 1 | 2.08 | 60.42 |
| Phenothiazine (stemetil), colofac, clarily | 1 | 2.08 | 62.50 |
| Prochlorperazine (dizziness) | 1 | 2.08 | 64.58 |
| Salbutamol inhaler, beclomethasone | 1 | 2.08 | 66.67 |
| Simvastatin | 1 | 2.08 | 68.75 |
| Sonata – prn for sleep. Previously temazepam | 1 | 2.08 | 70.83 |
| St John's Wort, vitamins C and E | 1 | 2.08 | 72.92 |
| Steroids | 1 | 2.08 | 75.00 |
| Stomach tablets for IBS | 1 | 2.08 | 77.08 |
| Supplements | 1 | 2.08 | 79.17 |
| Thioriadizine | 1 | 2.08 | 81.25 |
| Thyroxine | 1 | 2.08 | 83.33 |
| Thyroxine, hydrocortisone | 1 | 2.08 | 85.42 |
| Thyroxine, reboxetine | 1 | 2.08 | 87.50 |
| Ventolin inhaler | 1 | 2.08 | 89.58 |
| Vitamin supplement | 1 | 2.08 | 91.67 |
| Vitamins | 1 | 2.08 | 93.75 |
| Vitamins, antibiotics | 1 | 2.08 | 95.83 |
| Zautac, Sudafed | 1 | 2.08 | 97.92 |
| Zinc, vitamin C, echinachea, co-enzyme | 1 | 2.08 | 100.00 |
| Total | 48 | 100.00 | |

## Other responsible for diagnosis

| Specify other | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Clinical psychologist | 1 | 25.00 | 25.00 |
| Company doctor | 1 | 25.00 | 50.00 |
| Consultant | 1 | 25.00 | 75.00 |
| Partner diagnosed themselves | 1 | 25.00 | 100.00 |
| Total | 4 | 100.00 | |

## Other equipment (total; not split by group)

| Specify equipment | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| 'Helping hand' – to pick up objects | 1 | 4.76 | 4.76 |
| ***** chairs | 1 | 4.76 | 9.52 |
| Aluminium foil under mat protect from electric fire | 1 | 4.76 | 14.29 |
| Furniture positioned to help getting up | 1 | 4.76 | 19.05 |
| Got rid of computer | 1 | 4.76 | 23.81 |
| Hired a four-wheel drive shopping scooter | 1 | 4.76 | 28.57 |
| Moved to a bungalow to get away from stairs | 1 | 4.76 | 33.33 |
| Needs to support neck with a high back | 1 | 4.76 | 38.10 |
| New taps | 1 | 4.76 | 42.86 |
| SAD light | 1 | 4.76 | 47.62 |
| Seat in shower cubicle | 1 | 4.76 | 52.38 |
| Shower seat, mobility scooter | 1 | 4.76 | 57.14 |
| Special chair outside | 1 | 4.76 | 61.90 |
| Stair rail | 1 | 4.76 | 66.67 |
| TENS machine for headaches | 1 | 4.76 | 71.43 |
| TENS and massage | 1 | 4.76 | 76.19 |
| Wheelchair | 3 | 14.29 | 90.48 |
| Wheelchair, bed downstairs | 1 | 4.76 | 95.24 |
| Wheelchair, electric scooter, bath chair | 1 | 4.76 | 100.00 |
| Total | 21 | 100.00 | |

## Text if answered 'other' to employment status before CFS

| Specify occupation | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| 1 | 1 | 6.67 | 6.67 |
| At school | 1 | 6.67 | 13.33 |
| College full time | 1 | 6.67 | 20.00 |
| Full-time student | 1 | 6.67 | 26.67 |
| Full-time university student | 1 | 6.67 | 33.33 |
| Full-time student | 3 | 20.00 | 53.33 |
| Full-time study and part-time work | 1 | 6.67 | 60.00 |
| Just graduated | 1 | 6.67 | 66.67 |
| Not working, not looking | 1 | 6.67 | 73.33 |
| Part-time college course and full-time mum | 1 | 6.67 | 80.00 |
| School | 1 | 6.67 | 86.67 |
| Studying | 1 | 6.67 | 93.33 |
| Too young – since age 10 | 1 | 6.67 | 100.00 |
| Total | 15 | 100.00 | |

## If answered 'other' to 'who provides assistance (any help)?'

| Specify assistance | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| At worst 28 hours week | 1 | 14.29 | 14.29 |
| Cleaner | 2 | 28.57 | 42.86 |
| Employed members of community | 1 | 14.29 | 57.14 |
| Live-in housekeeper | 1 | 14.29 | 71.43 |
| Private carers | 1 | 14.29 | 85.71 |
| Uses Internet and delivery services | 1 | 14.29 | 100.00 |
| Total | 7 | 100.00 | |

## If answered 'other' to 'who provides assistance with personal/domestic care?'

| Specify assistance | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Cleaner | 2 | 66.67 | 66.67 |
| Housekeeper | 1 | 33.33 | 100.00 |
| Total | 3 | 100.00 | |

# Appendix 11

# 6-Month outcome characteristics

## General 6-month outcome characteristics[a]

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Months since initial assessment[b] | 7.9 | 6.9–9.2 | 7.6 | 6.9–8.7 | 7.7 | 7.0–9.0 |
| Home situation | | | | | | |
| Lives alone | 3 | 7 | 7 | 16 | 10 | 22 |
| Lives with partner | 29 | 69 | 28 | 62 | 26 | 58 |
| Other | 10 | 24 | 10 | 22 | 9 | 20 |
| Dependents | | | | | | |
| 0 | 21 | 50 | 25 | 56 | 25 | 56 |
| 1 | 7 | 17 | 7 | 16 | 6 | 13 |
| 2 | 12 | 29 | 12 | 27 | 10 | 22 |
| 3+ | 2 | 5 | 1 | 2 | 4 | 9 |
| Pain | | | | | | |
| Head and neck | 22 | 51 | 30 | 70 | 29 | 64 |
| Shoulders | 12 | 29 | 19 | 46 | 20 | 44 |
| Chest | 12 | 28 | 9 | 21 | 7 | 16 |
| Upper limbs | 24 | 56 | 29 | 66 | 28 | 61 |
| Abdomen | 11 | 26 | 16 | 39 | 6 | 13 |
| Back | 19 | 46 | 26 | 60 | 21 | 46 |
| Lower limbs | 32 | 74 | 35 | 80 | 34 | 74 |
| Symptoms | | | | | | |
| Numbness | 19 | 44 | 22 | 49 | 29 | 63 |
| Sensory disturbance | 27 | 63 | 34 | 77 | 27 | 59 |
| Weakness | 30 | 70 | 38 | 84 | 40 | 87 |
| Dizziness | 23 | 53 | 36 | 80 | 32 | 68 |
| Poor concentration | 41 | 95 | 40 | 89 | 38 | 83 |
| Memory loss | 34 | 79 | 36 | 80 | 37 | 80 |
| Breathlessness | 19 | 44 | 26 | 58 | 24 | 52 |
| Palpitations | 24 | 56 | 25 | 56 | 24 | 52 |
| Nausea | 17 | 40 | 28 | 62 | 26 | 57 |
| Sleep difficulties | 27 | 63 | 40 | 89 | 34 | 74 |
| Other | 29 | 67 | 32 | 73 | 28 | 61 |
| Total number of symptoms[c] | 7 | 5–8 | 9 | 7–10 | 8 | 6–9 |
| Investigations | | | | | | |
| Blood tests | 8 | 19 | 11 | 26 | 14 | 33 |
| Brain scan | 1 | 2 | 2 | 5 | 1 | 2 |
| X-rays | 4 | 9 | 1 | 2 | 6 | 14 |
| Other | 4 | 9 | 6 | 14 | 10 | 24 |
| Physiotherapy for CFS | 3 | 7 | 3 | 7 | 3 | 7 |
| Psychiatric or psychological treatment for CFS | 4 | 10 | 3 | 7 | 3 | 7 |
| Medication | | | | | | |
| Antidepressants | | | | | | |
| Current | 14 | 34 | 16 | 41 | 12 | 29 |
| In the past | 8 | 20 | 9 | 23 | 5 | 12 |
| Tranquillisers | | | | | | |
| Current | 1 | 2 | 4 | 11 | 1 | 3 |
| In the past | 3 | 7 | 3 | 8 | 1 | 3 |
| Analgesics | | | | | | |
| Current | 18 | 42 | 18 | 49 | 13 | 32 |
| In the past | 3 | 7 | 3 | 8 | 4 | 8 |

*continued*

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Other | | | | | | |
| Current | 9 | 22 | 15 | 39 | 12 | 30 |
| In the past | 4 | 10 | 2 | 5 | 2 | 5 |
| Alternative therapies | | | | | | |
| Homeopathy | 5 | 12 | 6 | 14 | 3 | 7 |
| Acupuncture | 1 | 2 | 2 | 5 | 3 | 7 |
| Reflexology | 2 | 5 | 4 | 9 | 2 | 4 |
| Chinese meditation | 0 | 0 | 1 | 2 | 0 | 0 |
| Massage | 3 | 7 | 6 | 14 | 3 | 7 |
| Aromatherapy | 1 | 2 | 5 | 11 | 2 | 4 |
| Equipment at home to help with CFS | | | | | | |
| Handrail | 0 | 0 | 4 | 9 | 2 | 4 |
| Stool | 4 | 9 | 6 | 13 | 5 | 11 |
| Walking stick | 2 | 5 | 4 | 9 | 2 | 4 |
| Stair lift | 0 | 0 | 0 | 0 | 1 | 2 |
| Hoist | 0 | 0 | 0 | 0 | 1 | 2 |
| Special utensils | 1 | 1 | 1 | 1 | 1 | 1 |
| Other | 5 | 12 | 7 | 16 | 3 | 7 |
| CFS prevented continuation of main occupation | 29 | 67 | 28 | 65 | 31 | 70 |
| Current occupation | | | | | | |
| Director | 1 | 2 | 0 | 0 | 0 | 0 |
| Senior manager | 1 | 2 | 0 | 0 | 0 | 0 |
| Manager | 1 | 2 | 2 | 4 | 5 | 11 |
| Administrative | 4 | 9 | 5 | 11 | 6 | 13 |
| Skilled manual | 9 | 20 | 7 | 15 | 2 | 4 |
| Unskilled manual | 0 | 0 | 2 | 4 | 1 | 2 |
| Student | 1 | 2 | 2 | 4 | 4 | 9 |
| None | 20 | 44 | 23 | 50 | 21 | 46 |
| Not specified | 8 | 18 | 5 | 11 | 7 | 15 |
| Required help because of CFS | 16 | 37 | 19 | 44 | 19 | 42 |
| Help provided by[d] | | | | | | |
| Partner | 14 | 32 | 15 | 35 | 8 | 19 |
| Immediate family | 4 | 10 | 6 | 16 | 8 | 20 |
| Friends | 0 | 0 | 2 | 5 | 2 | 5 |
| Social services | 0 | 0 | 0 | 0 | 2 | 5 |
| Health services | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 2 | 5 | 1 | 3 | 4 | 10 |
| Current transport usage (% usage)[c] | | | | | | |
| Driving car | 70 | 48–90 | 40 | 10–75 | 70 | 30–90 |
| Passenger in car | 0 | 0–30 | 40 | 10–70 | 10 | 0–30 |
| Public transport | 0 | 0–0 | 0 | 0–0 | 0 | 0–0 |
| Taxi | 0 | 0–0 | 0 | 0–0 | 0 | 0–0 |
| Bicycle | 0 | 0–0 | 0 | 0–0 | 0 | 0–0 |
| Walking | 10 | 0–20 | 5 | 0–20 | 10 | 0–20 |
| Miles travelled/week | | | | | | |
| Work | | | | | | |
| 0–10 | 31 | 74 | 34 | 77 | 31 | 69 |
| 11–50 | 5 | 12 | 5 | 11 | 6 | 13 |
| 51–100 | 2 | 5 | 4 | 9 | 5 | 11 |
| 101–250 | 3 | 7 | 1 | 2 | 1 | 2 |
| >250 | 1 | 2 | 0 | 0 | 2 | 4 |
| Personal | | | | | | |
| 0–10 | 10 | 23 | 14 | 32 | 14 | 30 |
| 11–50 | 23 | 53 | 21 | 48 | 24 | 52 |
| 51–100 | 8 | 19 | 7 | 16 | 7 | 15 |
| 101–250 | 2 | 5 | 2 | 5 | 0 | 0 |
| >250 | 0 | 0 | 0 | 0 | 1 | 2 |

continued

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Further assistance with personal and domestic care needed since first assessment | 6 | 14 | 10 | 23 | 9 | 20 |
| Help provided by[d] | | | | | | |
| Partner | 6 | 14 | 4 | 18 | 4 | 9 |
| Immediate family | 0 | 0 | 1 | 3 | 3 | 7 |
| Friends | 0 | 0 | 1 | 3 | 1 | 3 |
| Social Services | 0 | 0 | 0 | 0 | 1 | 3 |
| Health Services | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 2 | 5 |

[a] Data are reported as numbers and percentages except where indicated. Percentages are calculated after excluding missing data. Data are given for all who responded, whether or not they reported a change.
[b] Mean and SD.
[c] Median and IQR.
[d] Percentages are for the total number who responded, not the subset who required assistance.

## 6-Month quality of life scores (median, IQR)

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | Median | IQR |
| Physical performance | | | | | | |
| Perceived fatigue | 3 | 2–3 | 3 | 2–4 | 3 | 2.75–4 |
| Shuttles walked | 25 | 12–39 | 19 | 10–36 | 21.5 | 13–29.5 |
| Normal walking speed | 10 | 6–18 | 8 | 5–11 | 8 | 6–11 |
| SF-36 | | | | | | |
| Physical health | 34.0 | 25.7–39.9 | 31.7 | 25.0–36.8 | 33.1 | 27.5–41.3 |
| Mental health | 47.0 | 37.2–53.1 | 40.8 | 30.2–48.1 | 39.3 | 28.3–50.7 |
| HADS | | | | | | |
| Anxiety | 8 | 5–11 | 10 | 7–13 | 9 | 6–12 |
| Depression | 7 | 4–9 | 9 | 6–11 | 7 | 5–10 |
| GHQ | 13 | 7–18 | 17 | 11.5–21.5 | 15.5 | 11–22 |
| Chalder | 19 | 11–25 | 22 | 16–27 | 22 | 17–27 |
| HUI3 overall utility score | 0.39 | 0.20–0.64 | 0.32 | 0.09–0.61 | 0.44 | 0.19–0.58 |

## 6-Month cognitive scores (median, IQR)

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | Median | IQR |
| Mood | | | | | | |
| Alertness | 209 | 183–240 | 184 | 141–226 | 180.5 | 148–200 |
| Hedonic tone | 174.5 | 150–202 | 172 | 148–193 | 164.5 | 144–194 |
| Anxiety | 77.5 | 70–84 | 78 | 68–100 | 84 | 71–95 |
| Recall | | | | | | |
| Total words recalled | 13 | 11–15 | 12 | 9–15 | 11.5 | 9–14 |
| Correct words | 12 | 10–15 | 12 | 9–15 | 10.5 | 8–13 |
| Incorrect words | 1 | 0–1 | 0 | 0–1 | 1 | 0–1 |
| Simple reaction time | | | | | | |
| Reaction time | 343.3 | 290.8–456.9 | 354.0 | 295.7–436.3 | 353.5 | 291.2–436.6 |
| Trials completed | 26 | 25–28 | 26 | 25–27 | 26 | 26–28 |
| Repeated digits detection | | | | | | |
| Reaction time | 610.7 | 535.2–660.5 | 599.3 | 517.7–684.7 | 617.5 | 559.0–689.3 |
| Hit rate | 11 | 7–14 | 11 | 9–15 | 11 | 9–14 |
| False alarms | 2 | 0–3 | 1 | 0–2 | 2 | 1–3 |

## Other symptoms reported at 6-month assessment

| Specify symptom | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Ache all over | 1 | 1.12 | 1.12 |
| Aches everywhere, fatigue | 1 | 1.12 | 2.25 |
| Anxiety/panic, shakes, continually getting tired | 1 | 1.12 | 3.37 |
| Balance differs, feeling bloated, pins and needles | 1 | 1.12 | 4.49 |
| Body temperature rapidly changes, slow memory function | 1 | 1.12 | 5.62 |
| Body temperature variation | 1 | 1.12 | 6.74 |
| Brain fog, disorientation | 1 | 1.12 | 7.87 |
| Chemical sensitivity to smell and taste | 1 | 1.12 | 8.99 |
| Co-ordination difficulties, clumsiness | 1 | 1.12 | 10.11 |
| Cold extremities, feeling of weepiness | 1 | 1.12 | 11.24 |
| Cold extremities, indigestion, headaches | 1 | 1.12 | 12.36 |
| Diarrhoea | 1 | 1.12 | 13.48 |
| Digestive problems | 1 | 1.12 | 14.61 |
| Disorientation very occasionally | 1 | 1.12 | 15.73 |
| Fatigue | 1 | 1.12 | 16.85 |
| Fatigue, recurrent bouts of thrush | 1 | 1.12 | 17.98 |
| Feeling faint | 1 | 1.12 | 19.10 |
| Feeling of 'vacantness', depression, lethargy | 1 | 1.12 | 20.22 |
| Feels joints/back lock up, body parts | 1 | 1.12 | 21.35 |
| Feels like something is in head that shouldn't be | 1 | 1.12 | 22.47 |
| 'Flu-like symptoms | 1 | 1.12 | 23.60 |
| Forget words, mispronounce words, panic | 1 | 1.12 | 24.72 |
| Foul taste in mouth | 1 | 1.12 | 25.84 |
| Frustration | 1 | 1.12 | 26.97 |
| Headaches | 6 | 6.74 | 33.71 |
| Heavy sweating, gets cold and shivery | 1 | 1.12 | 34.83 |
| IBS | 1 | 1.12 | 35.96 |
| IBS, pins and needles | 1 | 1.12 | 37.08 |
| IBS, migraine, bad period, swollen neck glands | 1 | 1.12 | 38.20 |
| IBS – 2 years | 1 | 1.12 | 39.33 |
| Indecisiveness, depression | 1 | 1.12 | 40.45 |
| Intolerance to certain food/alcohol, fuzzy head | 1 | 1.12 | 41.57 |
| Intolerance to certain foods | 1 | 1.12 | 42.70 |
| Irregular bowel movements, difficulty with temperature control | 1 | 1.12 | 43.82 |
| Irritability | 1 | 1.12 | 44.94 |
| Irritable bowel | 2 | 2.25 | 47.19 |
| Irritable bowel syndrome, fatigue | 1 | 1.12 | 48.31 |
| Ligaments all sensitive, dry eyes | 1 | 1.12 | 49.44 |
| Muscle stiffness | 1 | 1.12 | 50.56 |
| No co-ordination, pins and needles (arms/hands) | 1 | 1.12 | 51.69 |
| Occasional loss of co-ordination | 1 | 1.12 | 52.81 |
| Painful hips – leg longer than other, irritable bowel syndrome | 1 | 1.12 | 53.93 |
| Partial paralysis of arms and legs, exhaustion | 1 | 1.12 | 55.06 |
| Pins and needles | 1 | 1.12 | 56.18 |
| Pins and needles | 1 | 1.12 | 57.30 |
| Pins and needles in hands | 1 | 1.12 | 58.43 |
| Pins and needles, food intolerance, loss of appetite | 1 | 1.12 | 59.55 |
| Pins and needles, sinus problems | 1 | 1.12 | 60.67 |
| Pins and needles, muscle spasm (far better) | 1 | 1.12 | 61.80 |
| Pins and needles | 3 | 3.37 | 65.17 |
| Pins and needles, catarrh | 1 | 1.12 | 66.29 |
| Pins and needles, gets slower and slower as day goes on | 1 | 1.12 | 67.42 |
| Pins and needles, deep muscle ache | 1 | 1.12 | 68.54 |
| Pins and needles, anxiety and panicky | 1 | 1.12 | 69.66 |
| Pins and needles, oversensitive to sound, epigastric disturbance | 1 | 1.12 | 70.79 |
| Pins and needles, general, overall lethargy | 1 | 1.12 | 71.91 |
| Poor co-ordination | 1 | 1.12 | 73.03 |
| Poor co-ordination, forgetfulness | 1 | 1.12 | 74.16 |
| Poor temperature regulation, digestive problems | 1 | 1.12 | 75.28 |
| Sexual difficulties | 1 | 1.12 | 76.40 |

| Specify symptom | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Shaking | 1 | 1.12 | 77.53 |
| Shivering, extreme thirst, gastric disturbance | 1 | 1.12 | 78.65 |
| Shooting 'split-second' head pains | 1 | 1.12 | 79.78 |
| Sight for motion improved | 1 | 1.12 | 80.90 |
| Skin irritations, spatial awareness | 1 | 1.12 | 82.02 |
| Slow | 1 | 1.12 | 83.15 |
| Slow digestion, constipation, tingling sensation | 1 | 1.12 | 84.27 |
| Sore eyes, pins and needles, altered sensations | 1 | 1.12 | 85.39 |
| Swelling glands, pins and needles, anxiety | 1 | 1.12 | 86.52 |
| Swelling of glands in neck, sore throat | 1 | 1.12 | 87.64 |
| Swollen glands in neck | 1 | 1.12 | 88.76 |
| Temperature regulation, gets even when cold | 1 | 1.12 | 89.89 |
| Tiredness | 1 | 1.12 | 91.01 |
| Tremors | 1 | 1.12 | 92.13 |
| Twitching muscles, sore throat, p[swollen nodules | 1 | 1.12 | 93.26 |
| Unrefreshing sleep, relate to bowel, depression | 1 | 1.12 | 94.38 |
| Unsteadiness | 1 | 1.12 | 95.51 |
| Unsteady on feet | 1 | 1.12 | 96.63 |
| Variety of sleep disorders, mood/emotions | 1 | 1.12 | 97.75 |
| Warts and verrucas, IBS, frequent cold and tingling | 1 | 1.12 | 98.88 |
| Woozy head | 1 | 1.12 | 100.00 |
| Total | 89 | 100.00 | |

## Other tests reported at 6-month assessment

| When was other test | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Barium enema and counselling | 1 | 5.00 | 5.00 |
| Bladder/bowel/kidney ultrasound | 1 | 5.00 | 10.00 |
| Bone scan – oncology and follow-up breast cancer | 1 | 5.00 | 15.00 |
| Coeliac disease | 1 | 5.00 | 20.00 |
| Cervical smear | 1 | 5.00 | 25.00 |
| Cognitive tests for memory loss at BRACE Centre | 1 | 5.00 | 30.00 |
| Colon cancer treatment colonoscopy | 1 | 5.00 | 35.00 |
| CT scan of left leg and spine | 1 | 5.00 | 40.00 |
| ECT | 1 | 5.00 | 45.00 |
| Heart investigations | 1 | 5.00 | 50.00 |
| Lung function test for breathlessness | 1 | 5.00 | 55.00 |
| Lung specialist | 1 | 5.00 | 60.00 |
| MRI | 1 | 5.00 | 65.00 |
| Pregnant | 1 | 5.00 | 70.00 |
| Rectal examination | 1 | 5.00 | 75.00 |
| Tested adrenaline levels | 1 | 5.00 | 80.00 |
| Thyroid tests | 1 | 5.00 | 85.00 |
| To see if anything was missed previously | 1 | 5.00 | 90.00 |
| Urine test | 2 | 10.00 | 100.00 |
| Total | 20 | 100.00 | |

## Other medication reported at 6-month assessment

| Specify medication | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Adrenoceptor stimulant, corticosteroid | 1 | 2.33 | 2.33 |
| Antibiotic | 1 | 2.33 | 4.65 |
| Antibiotics | 1 | 2.33 | 6.98 |
| Anti-cholesterol | 1 | 2.33 | 9.30 |
| Anti-fungal | 1 | 2.33 | 11.63 |
| Anti-hypertension, diuretic | 1 | 2.33 | 13.95 |
| Anti-spasmodic, nasal decongestant | 1 | 2.33 | 16.28 |
| Antibiotics | 1 | 2.33 | 18.60 |
| Antibiotics, steroids, Nasonex, Lixonase | 1 | 2.33 | 20.93 |
| Asthma medication | 2 | 4.65 | 25.58 |
| Beta-blockers, sinus medication, pseudoephedrine | 1 | 2.33 | 27.91 |
| Beta-blockers, corticosteroid, and propranolol | 1 | 2.33 | 30.23 |
| Bronchodilator, corticosteroid and propranolol | 1 | 2.33 | 32.56 |
| Cyclopyrrolone, antihistamine, thyroid | 1 | 2.33 | 34.88 |
| Cyclopyrrolone | 1 | 2.33 | 37.21 |
| Diuretics | 1 | 2.33 | 39.53 |
| Efamast, Mebevine (for IBS), inhalers | 1 | 2.33 | 41.86 |
| Heart medication, acid sta | 1 | 2.33 | 44.19 |
| Hormone replace therapy, cyclopyrrolone | 1 | 2.33 | 46.51 |
| Hormone replacement oestrogen | 1 | 2.33 | 48.84 |
| HRT | 3 | 6.98 | 55.81 |
| HRT Prempack | 1 | 2.33 | 58.14 |
| Inhaler – not asthma | 1 | 2.33 | 60.47 |
| Inhalers for asthma | 1 | 2.33 | 62.79 |
| Laxative | 1 | 2.33 | 65.12 |
| Lipid lowering and anti-diabetic | 1 | 2.33 | 67.44 |
| Lofepromine – took previously | 1 | 2.33 | 69.77 |
| Propranolol – bet. | 1 | 2.33 | 72.09 |
| Proton pump inhibitor | 1 | 2.33 | 74.42 |
| Steroid nasal spray, antibacterial before onset | 1 | 2.33 | 76.74 |
| Steroids | 1 | 2.33 | 79.07 |
| Thyroid hormone | 1 | 2.33 | 81.40 |
| Thyroid medication, thyroxine | 1 | 2.33 | 83.72 |
| Tamazepan, sleeping tablets and fluoxetine | 1 | 2.33 | 86.05 |
| Ventolin and Becotide for asthma | 2 | 4.65 | 90.70 |
| Vitamin supplements | 1 | 2.33 | 93.02 |
| Vitamins | 1 | 2.33 | 95.35 |
| Vitamins and minerals | 1 | 2.33 | 97.67 |
| Zinc, magnesium, aloe vera juice | 1 | 2.33 | 100.00 |
| Total | 43 | 100.00 | |

## Other equipment (total, not split by group)

| Specify equipment | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Camera – for taking pictures to remember | 1 | 6.67 | 6.67 |
| Helping hand | 1 | 6.67 | 13.33 |
| Mobility scooter | 1 | 6.67 | 20.00 |
| Reclining chair | 1 | 6.67 | 26.67 |
| Relaxation tapes | 1 | 6.67 | 33.33 |
| SAD light | 1 | 6.67 | 40.00 |
| Sofa bed to lie on downstairs | 1 | 6.67 | 46.67 |
| Sometimes uses wheelchair | 1 | 6.67 | 53.33 |
| Special bath stool | 1 | 6.67 | 60.00 |
| Table by settee, wheelchair, cordless phone | 1 | 6.67 | 66.67 |
| Use power tools rather than manual tool | 1 | 6.67 | 73.33 |
| Walking stick, hire of scooter at mall | 1 | 6.67 | 80.00 |
| Wheelchair | 1 | 6.67 | 86.67 |
| Wheelchair for 'days out', shopping | 1 | 6.67 | 93.33 |
| Wheelchair for daytrips | 1 | 6.67 | 100.00 |
| Total | 15 | 100.00 | |

## If answered 'OTHER' to 'Who provides assistance (any help)?'

| Specify assistance | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Cleaner | 3 | 42.86 | 42.86 |
| Housekeeper | 1 | 14.29 | 57.14 |
| Paid cleaner | 1 | 14.29 | 71.43 |
| Personal assistant | 1 | 14.29 | 85.71 |
| Private home help | 1 | 14.29 | 100.00 |
| Total | 7 | 100.00 | |

## If Answered 'OTHER' to 'Who provides assistance with personal/domestic care?'

| Specify assistance – now | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Cleaner | 2 | 100.00 | 100.00 |
| Total | 2 | 100.00 | |

# Appendix 12

# 12-Month outcome characteristics

## General 12-month outcome characteristics[a]

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Months since initial assessment[b] | 13.9 | 13.2–14.6 | 14.0 | 13.1–14.6 | 13.9 | 13.2–15.0 |
| Home situation | | | | | | |
| Lives alone | 3 | 8 | 4 | 9 | 11 | 25 |
| Lives with partner | 25 | 69 | 27 | 60 | 23 | 52 |
| Other | 8 | 22 | 14 | 31 | 10 | 23 |
| Dependents | | | | | | |
| 0 | 20 | 54 | 25 | 56 | 27 | 61 |
| 1 | 7 | 19 | 7 | 16 | 5 | 11 |
| 2 | 9 | 24 | 11 | 24 | 8 | 18 |
| 3+ | 1 | 3 | 2 | 4 | 4 | 9 |
| Pain | | | | | | |
| Head and neck | 24 | 65 | 33 | 73 | 32 | 73 |
| Shoulders | 13 | 35 | 17 | 38 | 20 | 48 |
| Chest | 10 | 27 | 9 | 20 | 11 | 26 |
| Upper limbs | 19 | 51 | 25 | 56 | 26 | 59 |
| Abdomen | 10 | 27 | 14 | 31 | 9 | 21 |
| Back | 20 | 54 | 27 | 60 | 22 | 50 |
| Lower limbs | 29 | 78 | 31 | 69 | 35 | 81 |
| Symptoms | | | | | | |
| Numbness | 18 | 49 | 21 | 47 | 23 | 52 |
| Sensory disturbance | 22 | 59 | 33 | 73 | 29 | 66 |
| Weakness | 29 | 78 | 37 | 82 | 41 | 93 |
| Dizziness | 18 | 49 | 30 | 67 | 30 | 68 |
| Poor concentration | 30 | 81 | 35 | 80 | 37 | 84 |
| Memory loss | 28 | 76 | 29 | 66 | 34 | 77 |
| Breathlessness | 16 | 43 | 16 | 36 | 24 | 55 |
| Palpitations | 18 | 49 | 18 | 40 | 21 | 48 |
| Nausea | 11 | 30 | 26 | 58 | 22 | 50 |
| Sleep difficulties | 24 | 65 | 34 | 76 | 32 | 73 |
| Other | 22 | 61 | 32 | 73 | 28 | 67 |
| Total number of symptoms[c] | 7 | 4.5–8.5 | 7 | 5–9 | 7 | 6–10 |
| Investigations | | | | | | |
| Blood tests | 16 | 43 | 13 | 30 | 13 | 30 |
| Brain scan | 1 | 3 | 1 | 3 | 2 | 5 |
| X-rays | 5 | 14 | 3 | 7 | 1 | 3 |
| Other | 10 | 27 | 10 | 22 | 4 | 9 |
| Physiotherapy for CFS | 1 | 3 | 2 | 4 | 2 | 5 |
| Psychiatric or psychological treatment for CFS | 6 | 16 | 3 | 7 | 4 | 9 |
| Medication | | | | | | |
| Antidepressants | | | | | | |
| Current | 9 | 26 | 14 | 36 | 12 | 32 |
| In the past | 4 | 11 | 2 | 5 | 3 | 8 |
| Tranquillisers | | | | | | |
| Current | 2 | 6 | 2 | 5 | 1 | 3 |
| In the past | 0 | 0 | 1 | 3 | 0 | 0 |
| Analgesics | | | | | | |
| Current | 11 | 33 | 15 | 38 | 13 | 34 |
| In the past | 2 | 6 | 2 | 5 | 0 | 0 |

*continued*

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Other | | | | | | |
| Current | 10 | 29 | 13 | 32 | 14 | 36 |
| In the past | 3 | 9 | 4 | 10 | 1 | 3 |
| Alternative therapies | | | | | | |
| Homeopathy | 4 | 11 | 9 | 20 | 6 | 14 |
| Acupuncture | 1 | 3 | 6 | 14 | 3 | 7 |
| Reflexology | 2 | 5 | 4 | 9 | 3 | 7 |
| Chinese meditation | 0 | 0 | 1 | 2 | 0 | 0 |
| Massage | 2 | 5 | 3 | 7 | 5 | 11 |
| Aromatherapy | 3 | 8 | 6 | 13 | 6 | 14 |
| Equipment at home to help with CFS | | | | | | |
| Handrail | 2 | 5 | 6 | 13 | 1 | 2 |
| Stool | 4 | 11 | 6 | 13 | 6 | 14 |
| Walking stick | 4 | 11 | 6 | 13 | 2 | 5 |
| Stair lift | 0 | 0 | 1 | 2 | 1 | 2 |
| Hoist | 0 | 0 | 0 | 0 | 1 | 2 |
| Special utensils | 1 | 0 | 1 | 2 | 5 | 11 |
| Other | 3 | 8 | 7 | 16 | 4 | 9 |
| CFS prevented continuation of main occupation | 26 | 70 | 25 | 57 | 34 | 77 |
| Current occupation | | | | | | |
| Director | 1 | 3 | 0 | 0 | 0 | 0 |
| Senior manager | 0 | 0 | 0 | 0 | 1 | 2 |
| Manager | 1 | 3 | 5 | 11 | 6 | 14 |
| Administrative | 6 | 15 | 6 | 13 | 5 | 11 |
| Skilled manual | 4 | 10 | 8 | 17 | 7 | 16 |
| Unskilled manual | 0 | 0 | 2 | 4 | 1 | 2 |
| Student | 4 | 10 | 3 | 7 | 2 | 5 |
| None | 19 | 49 | 19 | 41 | 19 | 43 |
| Not specified | 4 | 10 | 3 | 7 | 3 | 7 |
| Required help because of CFS | 11 | 30 | 13 | 29 | 15 | 34 |
| Help provided by[d] | | | | | | |
| Partner | 9 | 25 | 8 | 18 | 8 | 19 |
| Immediate family | 4 | 11 | 7 | 16 | 9 | 21 |
| Friends | 2 | 6 | 3 | 7 | 1 | 2 |
| Social services | 0 | 0 | 2 | 5 | 1 | 2 |
| Health services | 0 | 0 | 1 | 2 | 0 | 0 |
| Other | 2 | 6 | 1 | 2 | 0 | 0 |
| Current transport usage (% usage)[c] | | | | | | |
| Driving car | 75 | 49–85 | 50 | 25–85 | 55 | 22–80 |
| Passenger in car | 10 | 0–50 | 25 | 1–60 | 15 | 0–50 |
| Public transport | 0 | 0–1 | 0 | 0–0 | 0 | 0–3 |
| Taxi | 0 | 0–0 | 0 | 0–0 | 0 | 0–0 |
| Bicycle | 0 | 0–0 | 0 | 0–0 | 0 | 0–0 |
| Walking | 4 | 0–10 | 5 | 0–20 | 10 | 0–28 |
| Miles travelled/week | | | | | | |
| Work | | | | | | |
| 0–10 | 24 | 69 | 29 | 67 | 29 | 71 |
| 11–50 | 7 | 20 | 5 | 12 | 7 | 17 |
| 51–100 | 1 | 3 | 5 | 12 | 3 | 7 |
| 101–250 | 2 | 6 | 2 | 5 | 0 | 0 |
| >250 | 1 | 3 | 2 | 5 | 2 | 5 |
| Personal | | | | | | |
| 0–10 | 8 | 22 | 11 | 25 | 12 | 27 |
| 11–50 | 23 | 62 | 21 | 48 | 25 | 57 |
| 51–100 | 4 | 11 | 12 | 27 | 6 | 14 |
| 101–250 | 2 | 5 | 0 | 0 | 1 | 2 |
| >250 | 0 | 0 | 0 | 0 | 0 | 0 |

continued

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Further assistance with personal and domestic care needed since first assessment | 4 | 11 | 5 | 11 | 7 | 16 |
| Help provided by[d] | | | | | | |
| Partner | 3 | 8 | 3 | 7 | 3 | 7 |
| Immediate family | 1 | 3 | 2 | 4 | 1 | 2 |
| Friends | 1 | 3 | 0 | 0 | 1 | 2 |
| Social services | 0 | 0 | 0 | 0 | 1 | 2 |
| Health services | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 1 | 2 |

[a] Data are reported as numbers and percentages except where indicated. Percentages are calculated after excluding missing data.
[b] Mean and SD.
[c] Median and IQR.
[d] Percentages are for the total number who responded, not the subset who required assistance.
[e] Data are given for all who responded, whether or not they reported a change.

## 12-Month quality of life scores (median, IQR)

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | Median | IQR |
| Physical performance | | | | | | |
| Perceived fatigue | 3 | 2–3.5 | 3 | 2–4 | 3 | 2–3.5 |
| Shuttles walked | 30 | 13–42 | 18 | 11–32 | 20 | 11–36 |
| Normal walking speed | 13 | 6–17 | 10 | 6–13 | 8 | 6–13 |
| SF-36 | | | | | | |
| Physical health | 34.4 | 29.7–40.6 | 31.3 | 27.0–37.9 | 33.6 | 28.6–40.6 |
| Mental health | 45.3 | 33.0–52.9 | 38.6 | 29.5–49.5 | 41.7 | 32.6–49.0 |
| HADS | | | | | | |
| Anxiety | 8 | 5–12 | 9 | 7–13 | 7 | 5.5–12 |
| Depression | 7 | 4–10 | 7 | 5–10 | 7 | 4–10 |
| GHQ | 13 | 9–19 | 16.5 | 11–24 | 15 | 10–21 |
| Chalder | 17.5 | 11–24 | 21.5 | 16–28 | 17.5 | 14–24.5 |
| HUI3 overall utility score | 0.48 | 0.14–0.72 | 0.34 | –0.01–0.65 | 0.52 | 0.21–0.64 |

## 12-Month cognitive scores (median, IQR)

| Variable | CBT | | EAS | | SMC | |
|---|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | Median | IQR |
| Mood | | | | | | |
| Alertness | 188 | 170–217 | 171 | 145–202 | 178.5 | 150–211 |
| Hedonic tone | 175 | 156–203 | 167 | 147–195 | 168 | 148–200 |
| Anxiety | 81 | 67–89 | 77 | 61–92 | 79.5 | 67–92 |
| Recall | | | | | | |
| Total words recalled | 13 | 11–16 | 12 | 10–14 | 13 | 10–15 |
| Correct words | 12 | 10–15 | 11 | 9–14 | 12 | 9–14 |
| Incorrect words | 0 | 0–1 | 0 | 0–1 | 0 | 0–1 |
| Simple reaction time | | | | | | |
| Reaction time | 347.8 | 305.2–412.7 | 344.2 | 294.8–499.9 | 354.8 | 291.9–422.4 |
| Trials completed | 26 | 25–27 | 27 | 25–27 | 27 | 25–28 |
| Repeated digits detection | | | | | | |
| Reaction time | 582.7 | 524.8–679.7 | 583.1 | 513.0–711.7 | 602.4 | 571.7–676.8 |
| Hit rate | 12 | 8–17 | 11 | 6–16 | 9 | 8–13 |
| False alarms | 1 | 0–3 | 0.5 | 0–2 | 1 | 1–2.5 |

## Other symptoms reported at 12-month assessment

| Specify symptom | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Allergies, joint pain and noise | 1 | 1.19 | 1.19 |
| Anxiety attacks | 1 | 1.19 | 2.38 |
| Aversion to strong smells and bright light | 1 | 1.19 | 3.57 |
| Bad digestion, pins and needles, hot and cold | 1 | 1.19 | 4.76 |
| Bad temper/mood irritability/lack of pattern | 1 | 1.19 | 5.95 |
| Body throb | 1 | 1.19 | 7.14 |
| Brain fog | 1 | 1.19 | 8.33 |
| Clumsiness, unsettled bowels | 1 | 1.19 | 9.52 |
| Cold extremities, IBS, chemical sensitivity | 1 | 1.19 | 10.71 |
| Constantly thirsting, overproduction of sweat | 1 | 1.19 | 11.90 |
| Depression alleviated in good weather, dispirited | 1 | 1.19 | 13.10 |
| Depression, shaking | 1 | 1.19 | 14.29 |
| Digestion problems | 1 | 1.19 | 15.48 |
| Digestive problems, anxiety | 1 | 1.19 | 16.67 |
| Digestive problems, intolerance of some foods | 1 | 1.19 | 17.86 |
| Dryness of eyes, 'overacting brain' | 1 | 1.19 | 19.05 |
| Electrical sensation in head and brain | 1 | 1.19 | 20.24 |
| Eye muscle twitching | 1 | 1.19 | 21.43 |
| Falling feeling | 1 | 1.19 | 22.62 |
| Feel 'drunk', tension in head, low mood, giddiness | 1 | 1.19 | 23.81 |
| Feeling very faint, 'seizes up' | 1 | 1.19 | 25.00 |
| Feels heavy, pins and needles, leg muscle spasms | 1 | 1.19 | 26.19 |
| Finding the right words | 1 | 1.19 | 27.38 |
| 'Flu-like symptoms, (glands up/fever/aching) | 1 | 1.19 | 28.57 |
| Fuzzy head, swollen glands if tired and fatigue | 1 | 1.19 | 29.76 |
| Glands in neck swell up and become tender | 1 | 1.19 | 30.95 |
| Hand trembles | 1 | 1.19 | 32.14 |
| Headache | 1 | 1.19 | 33.33 |
| Headaches | 1 | 1.19 | 34.52 |
| Heat in head, brain fog | 1 | 1.19 | 35.71 |
| Hot flushes, cold spells | 1 | 1.19 | 36.90 |
| IBS and HPV wart infections | 1 | 1.19 | 38.10 |
| IBS, depression, panic attacks | 1 | 1.19 | 39.29 |
| Intolerance of noise, poor temperature regulation, excessive sweating | 1 | 1.19 | 40.48 |
| Irritable bowel syndrome | 2 | 2.38 | 42.86 |
| Itchy sore eyes, irritable bowel | 1 | 1.19 | 44.05 |
| Leg gives away suddenly | 1 | 1.19 | 45.24 |
| Light headedness, foggy, spaced IBS and low mood | 1 | 1.19 | 46.43 |
| Limb, chest feel heavy, feels like cannot move | 1 | 1.19 | 47.62 |
| Loss of appetite | 1 | 1.19 | 48.81 |
| Low mood | 1 | 1.19 | 50.00 |
| Mental fatigue | 1 | 1.19 | 51.19 |
| Moodiness, lack of stamina, poor mobility | 1 | 1.19 | 52.38 |
| Muscle twitching, IBS, vivid dreams, loss control | 1 | 1.19 | 53.57 |
| Nervousness with people | 1 | 1.19 | 54.76 |
| Night sweats, intermittent rash | 1 | 1.19 | 55.95 |
| Over-irritable, clumsy, light sensitivity | 1 | 1.19 | 57.14 |
| Panic attacks, depression, irritable | 1 | 1.19 | 58.33 |
| Perceives temperature acutely | 1 | 1.19 | 59.52 |
| Pins and needles | 1 | 1.19 | 60.71 |
| Pins and needles, confusion, frustration, low mood | 1 | 1.19 | 61.90 |
| Pins and needles in extremities | 1 | 1.19 | 63.10 |
| Pins and needles, IBS, cramp, cold extremities | 1 | 1.19 | 64.29 |
| Pins and needles, mood changes (sudden swings) | 1 | 1.19 | 65.48 |
| Pins and needles, panic attacks, bruising easily | 1 | 1.19 | 66.67 |
| Pins and needles | 3 | 3.57 | 70.24 |
| Pins and needles, giddy | 1 | 1.19 | 71.43 |
| Pins and needles, itchy scalp | 1 | 1.19 | 72.62 |
| Pins and needles, tingling in extremities | 1 | 1.19 | 73.81 |
| Pins and needles, clumsiness, irritable bowels | 1 | 1.19 | 75.00 |

| Specify symptom | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Pins and needles, tearful, depression | 1 | 1.19 | 76.19 |
| Pins and needles in fingers, twitchy eyes | 1 | 1.19 | 77.38 |
| Pins and needles, IBS, dry mouth, alcohol binging | 1 | 1.19 | 78.57 |
| Poor co-ordination, bad spatial awareness | 1 | 1.19 | 79.76 |
| Pressure on forehead, IBS, tinnitus | 1 | 1.19 | 80.95 |
| Severe pins and needles, bad dreams, agitation | 1 | 1.19 | 82.14 |
| Shakes | 1 | 1.19 | 83.33 |
| Sinus pain | 1 | 1.19 | 84.52 |
| Sinus pressure | 1 | 1.19 | 85.71 |
| Skin irritation, swollen glands, headaches | 1 | 1.19 | 86.90 |
| Slow reactions in hand, movements, pins and needles | 1 | 1.19 | 88.10 |
| Speech difficulty, reading difficulty | 1 | 1.19 | 89.29 |
| Stomach – irritable bowel syndrome | 1 | 1.19 | 90.48 |
| Strange feeling in head, diarrhoea | 1 | 1.19 | 91.67 |
| Temperature control | 1 | 1.19 | 92.86 |
| Tingling in arms | 1 | 1.19 | 94.05 |
| Tingling sensations | 1 | 1.19 | 95.24 |
| Tiredness | 1 | 1.19 | 96.43 |
| Vertigo | 1 | 1.19 | 97.62 |
| Vomit pass out | 1 | 1.19 | 98.81 |
| Weight loss, blocked sinuses, poor temp r | 1 | 1.19 | 100.00 |
| Total | 84 | 100.00 | |

## Other tests reported at 12-month assessment

| When was other test | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Abdomen scan | 1 | 4.00 | 4.00 |
| ECG | 1 | 4.00 | 8.00 |
| Eye examination | 1 | 4.00 | 12.00 |
| Eye investigations | 1 | 4.00 | 16.00 |
| Gastroenterologist, haematologist | 1 | 4.00 | 20.00 |
| Gastroscopy, barium enema | 1 | 4.00 | 24.00 |
| Hearing test | 1 | 4.00 | 28.00 |
| Hysterectomy 8/2001 | 1 | 4.00 | 32.00 |
| Investigations for bladder/kidney problems | 1 | 4.00 | 36.00 |
| LFT | 1 | 4.00 | 40.00 |
| Liver function test | 1 | 4.00 | 44.00 |
| Liver scan | 1 | 4.00 | 48.00 |
| Mammograph | 1 | 4.00 | 52.00 |
| Now uses a hearing aid | 1 | 4.00 | 56.00 |
| Smear test | 1 | 4.00 | 60.00 |
| Stool test, saliva tests | 1 | 4.00 | 64.00 |
| Stool test, urinary test | 1 | 4.00 | 68.00 |
| Thyroid tests | 1 | 4.00 | 72.00 |
| Ultrasound scans, urine test | 1 | 4.00 | 76.00 |
| Ultrasound, mammogram, biopsy | 1 | 4.00 | 80.00 |
| Urine test | 1 | 4.00 | 84.00 |
| Urine test, head scan and sinus surgery | 1 | 4.00 | 88.00 |
| Urine test, MRI scan on leg, knee surgery | 1 | 4.00 | 92.00 |
| Urologist, cystoscopy | 1 | 4.00 | 96.00 |
| Visual EEG | 1 | 4.00 | 100.00 |
| Total | 25 | 100.00 | |

## Other medication reported at 12-month assessment

| Specify medication | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| 2 | 3 | 6.38 | 6.38 |
| Amoxicillin for ear infection | 1 | 2.13 | 8.51 |
| Amitriptyline, pain killers, Nurofen | 1 | 2.13 | 10.64 |
| Antacid, lipid regulator, nasal and antihistamine | 1 | 2.13 | 12.77 |
| Antispasmodic | 1 | 2.13 | 14.89 |
| Antibiotic | 1 | 2.13 | 17.02 |
| Antihistamine, adrenoceptor agonist and antibiotic | 1 | 2.13 | 19.15 |
| Anti-nausea medication | 1 | 2.13 | 21.28 |
| Anti-viral, diuretic, anti-hypertensive and antibiotic | 1 | 2.13 | 23.40 |
| Antibiotic, cyclopyrrolone and proton pump | 1 | 2.13 | 25.53 |
| Antispasmodic | 1 | 2.13 | 27.66 |
| Anutuphytine sleep disturbance | 1 | 2.13 | 29.79 |
| Aumatlyroid | 1 | 2.13 | 31.91 |
| $B_{12}$ injections | 1 | 2.13 | 34.04 |
| Becotide and Seravent (asthma) | 1 | 2.13 | 36.17 |
| Beta blocker | 1 | 2.13 | 38.30 |
| Beta-blocker and diuretic | 1 | 2.13 | 40.43 |
| Corticosteroid | 1 | 2.13 | 42.55 |
| Corticosteroid nasal spray | 1 | 2.13 | 44.68 |
| Diuretic | 1 | 2.13 | 46.81 |
| Doxyectine 100 mg | 1 | 2.13 | 48.94 |
| Eye drops, uses cannabis | 1 | 2.13 | 51.06 |
| Eye ointment and gel, cyclopyrrolone, HRT | 1 | 2.13 | 53.19 |
| Fexofenadine, flixonase, colpennin | 1 | 2.13 | 55.32 |
| For sleep | 1 | 2.13 | 57.45 |
| Gynaecological | 1 | 2.13 | 59.57 |
| HRT and cyclopyrrolone | 1 | 2.13 | 61.70 |
| HRT, anti-malarial | 1 | 2.13 | 63.83 |
| Hydrocortisone cream, cetirizine 10 mg | 1 | 2.13 | 65.96 |
| Laxative and steroid currently, folic acid | 1 | 2.13 | 68.09 |
| Magnesium vitamin supplements | 1 | 2.13 | 70.21 |
| Melatonin, contraceptive pill, antibiotics | 1 | 2.13 | 72.34 |
| Occasional paracetamol | 1 | 2.13 | 74.47 |
| Pancreatic lipase inhibitor, anti-diabetic | 1 | 2.13 | 76.60 |
| Propranolol, citaloprom, colpennin | 1 | 2.13 | 78.72 |
| Proteriam, antispasmodic, compound algina | 1 | 2.13 | 80.85 |
| Salbutamol, Serevent, Becotide | 1 | 2.13 | 82.98 |
| St John's Wort and antispasmodic for IBS | 1 | 2.13 | 85.11 |
| Statin | 1 | 2.13 | 87.23 |
| Steroid inhaler, proton pump inhibitor | 1 | 2.13 | 89.36 |
| Thyroid hormone | 1 | 2.13 | 91.49 |
| Thyroid hormone, antispasmodic and thyroxine | 1 | 2.13 | 93.62 |
| Thyroxine | 1 | 2.13 | 95.74 |
| Tramadol, amitryptaline, venlaflaxine and thyroxine | 1 | 2.13 | 97.87 |
| Ventolin and S (for asthma) | 1 | 2.13 | 100.00 |
| Total | 47 | 100.00 | |

## Other equipment (total; not split by group)

| Specify equipment | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| Bathboard | 1 | 7.14 | 7.14 |
| Downstairs toilet specifically since chronic fatigue | 1 | 7.14 | 14.29 |
| Electric masseur | 1 | 7.14 | 21.43 |
| Electric toothbrush, wheelchair | 1 | 7.14 | 28.57 |
| Electrical bed, TENS machine, wheelchair | 1 | 7.14 | 35.71 |
| Exercise bike, sit up frame | 1 | 7.14 | 42.86 |
| Massaging cushion, electric scooter | 1 | 7.14 | 50.00 |
| Moved to bungalow to avoid stairs | 1 | 7.14 | 57.14 |
| Portable stool when going out | 1 | 7.14 | 64.29 |
| Seat in shower, electric scooter | 1 | 7.14 | 71.43 |
| Use wheelchair occasionally | 1 | 7.14 | 78.57 |
| Wheelchair | 1 | 7.14 | 85.71 |
| Wheelchair | 1 | 7.14 | 92.86 |
| Wheelchair for long periods out of house | 1 | 7.14 | 100.00 |
| Total | 14 | 100.00 | |

## If answered 'OTHER' to 'Who provides assistance (any help)?'

| Specify assistance | Frequency | Percentage | Cumulative frequency |
|---|---|---|---|
| 0 | 1 | 33.33 | 33.33 |
| Cleaner | 1 | 33.33 | 66.67 |
| Paid help | 1 | 33.33 | 100.00 |
| Total | 3 | 100.00 | |

# Appendix 13

# Incremental Shuttle Walk Test Protocol and the Borg Perceived Fatigue Scale

## Incremental shuttle walk test protocol

The incremental shuttle walk test (ISWT) is carried out on a flat, non-slippery surface. A 10-m course is measured and marker cones are placed 0.5 m in from the end, so that the subject does not need to change direction abruptly.

The procedure for the test was read to the subject from a script:

> "I would like you to walk around the shuttles – up one way and down the other. I will play the cassette, which will contain a series of beeps. The aim is to turn around a cone as you hear a beep on the cassette. When you begin, you will have 15 seconds to reach the next cone. This will give you a starting walking speed of … [tester demonstrates the pace at this stage.] When you hear three beeps together, this means that the pace is increasing and you will need to walk more quickly. However, the aim will still be to turn around the cone on a single beep. If you fail to meet two cones consecutively, I will ask you to stop. However, if at any point during this test you feel that you would like to stop, please do so. I do not want you to feel ill tomorrow, so I want you to be aware of your own limits. When you reach your normal walking speed please let me know."

The tester then checked that the subject knew what was required before starting the test. The number of completed 10-m shuttles was recorded, together with the shuttle that was the speed the subject feels most closely relates to their normal walking speed. If the subject appeared to be struggling to keep up, they were reminded that they could stop whenever they wanted to. On completion of the ISWT, they were shown a Modified Borg Perceived Fatigue Scale and asked to select the number which best described their level of fatigue on completing the ISWT.

The ISWT test tape and instructions are available from the Department of Respiratory Medicine, Glenfield General Hospital, Leicester LE3 9QP, UK.

## The Borg Perceived Fatigue Scale[67]

| | |
|---|---|
| 0 | Nothing at all |
| 0.5 | Very, very slight (just noticeable) |
| 1 | Very slight |
| 2 | Slight |
| 3 | Moderate |
| 4 | Somewhat severe |
| 5 | Severe (heavy) |
| 6 | ↓ |
| 7 | Very severe |
| 8 | ↓ |
| 9 | ↓ |
| 10 | Very, very severe (almost maximal) |

| Level | Speed | | No. of shuttles per level (per minute) |
|---|---|---|---|
| | m/s | mph | |
| 1 | 0.50 | 1.12 | 3 |
| 2 | 0.67 | 1.50 | 4 |
| 3 | 0.84 | 1.88 | 5 |
| 4 | 1.01 | 2.26 | 6 |
| 5 | 1.18 | 2.64 | 7 |
| 6 | 1.35 | 3.02 | 8 |
| 7 | 1.52 | 3.40 | 9 |
| 8 | 1.69 | 3.78 | 10 |
| 9 | 1.86 | 4.16 | 11 |
| 10 | 2.03 | 4.54 | 12 |
| 11 | 2.20 | 4.92 | 13 |
| 12 | 2.37 | 5.30 | 14 |

# Appendix 14

## Graphical representation of cognitive scores

Graphical representations are shown in *Figures 4–12*.

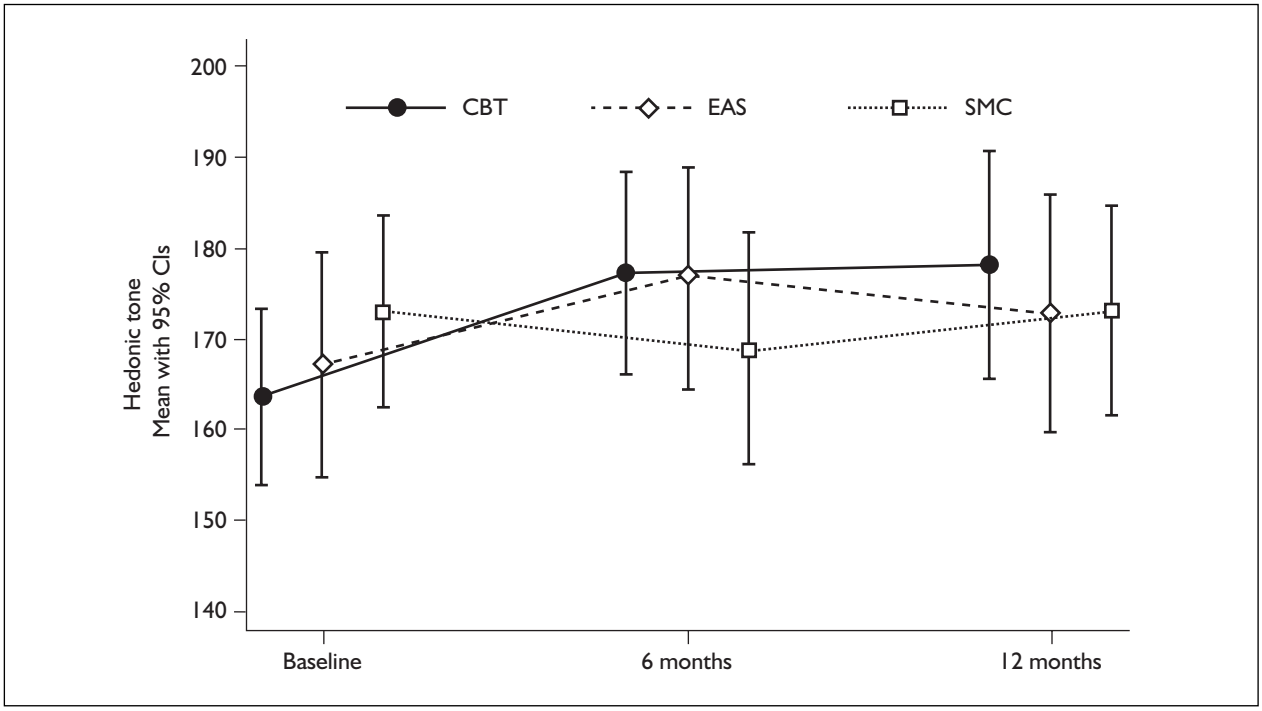



***FIGURE 4*** *Hedonic tone under each of the three conditions*

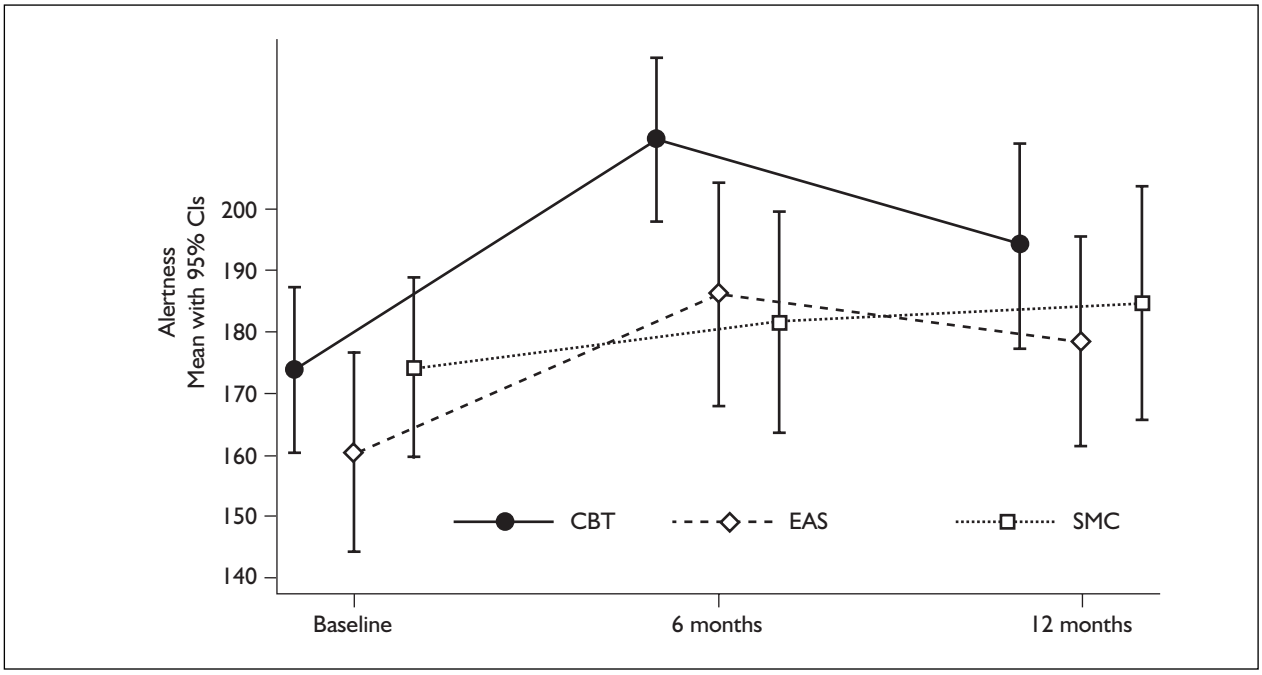



***FIGURE 5*** *Alertness under each of the three conditions*

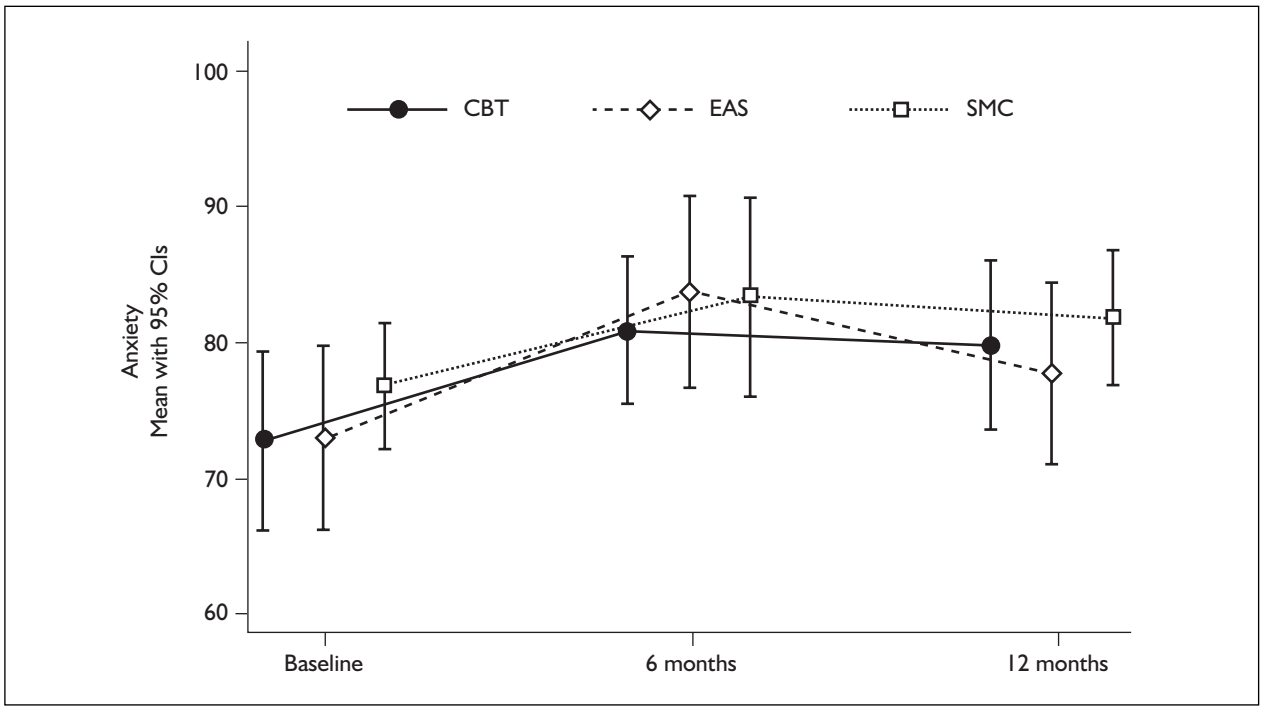



***FIGURE 6*** *Anxiety under each of the three conditions*

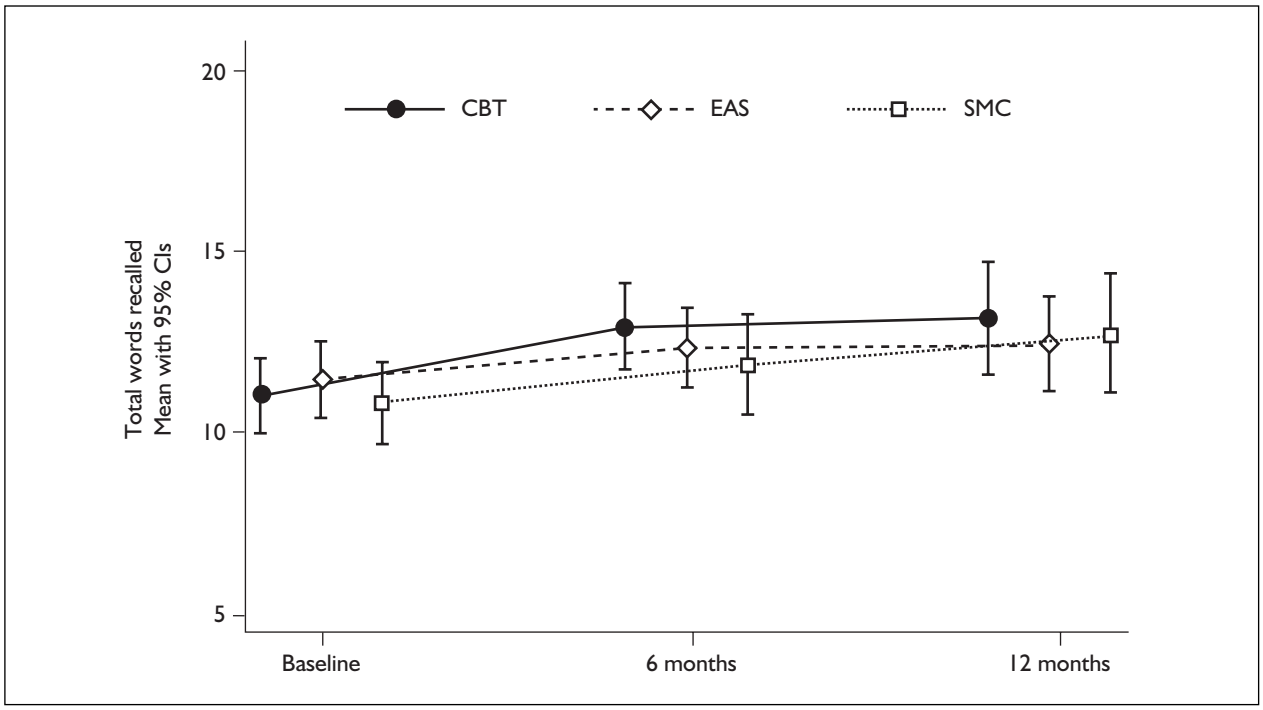



***FIGURE 7*** *Total words recalled under each of the three conditions*

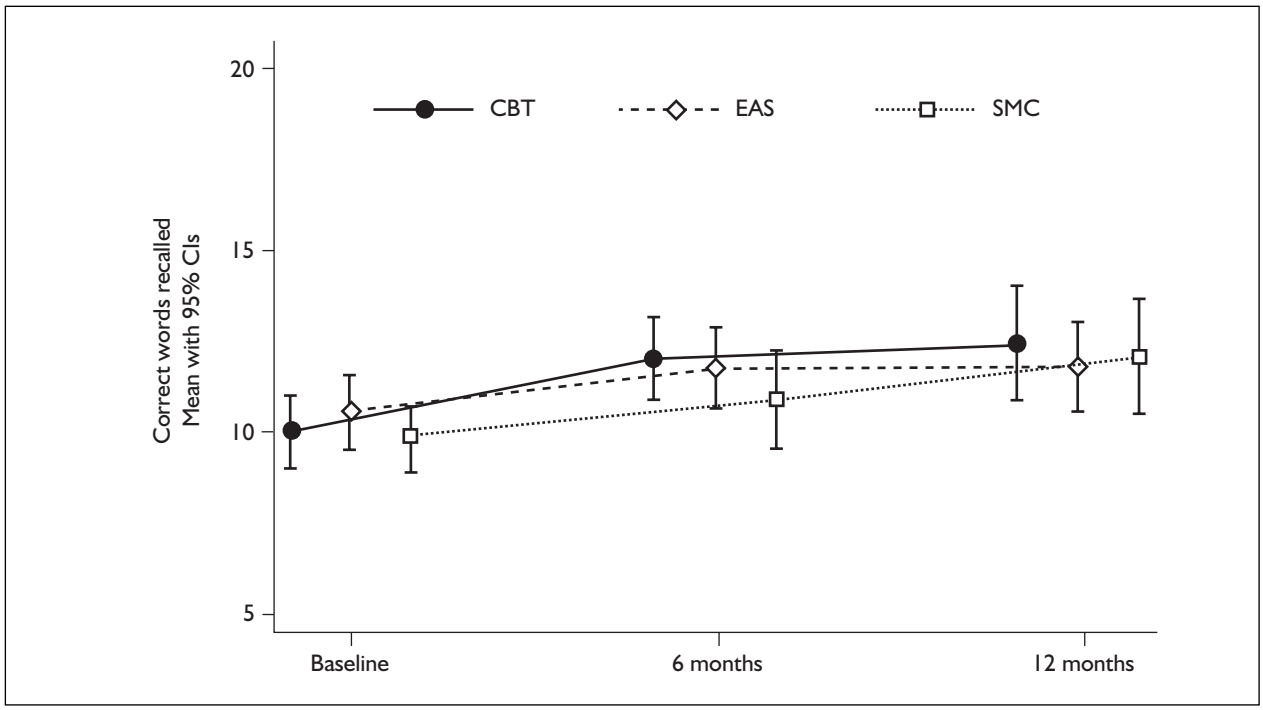



***FIGURE 8*** *Correct words recalled under each of the three conditions*

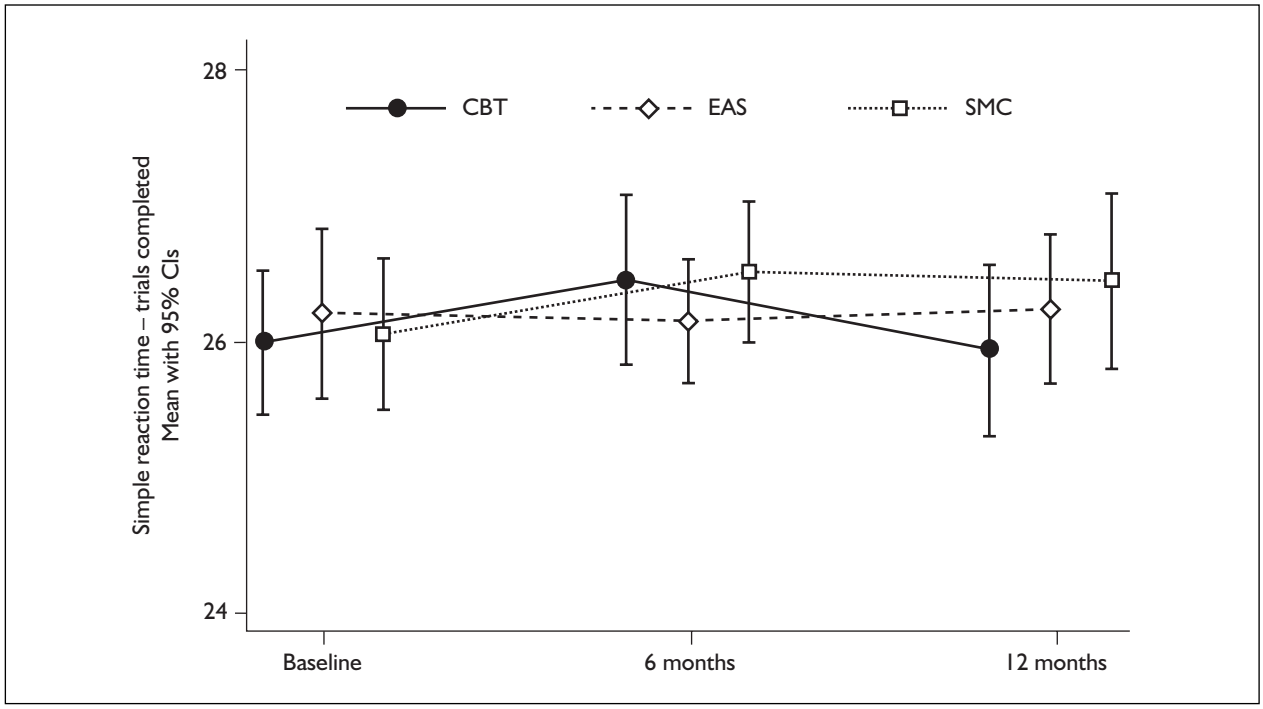



***FIGURE 9*** *Simple reaction time under each of the three conditions*

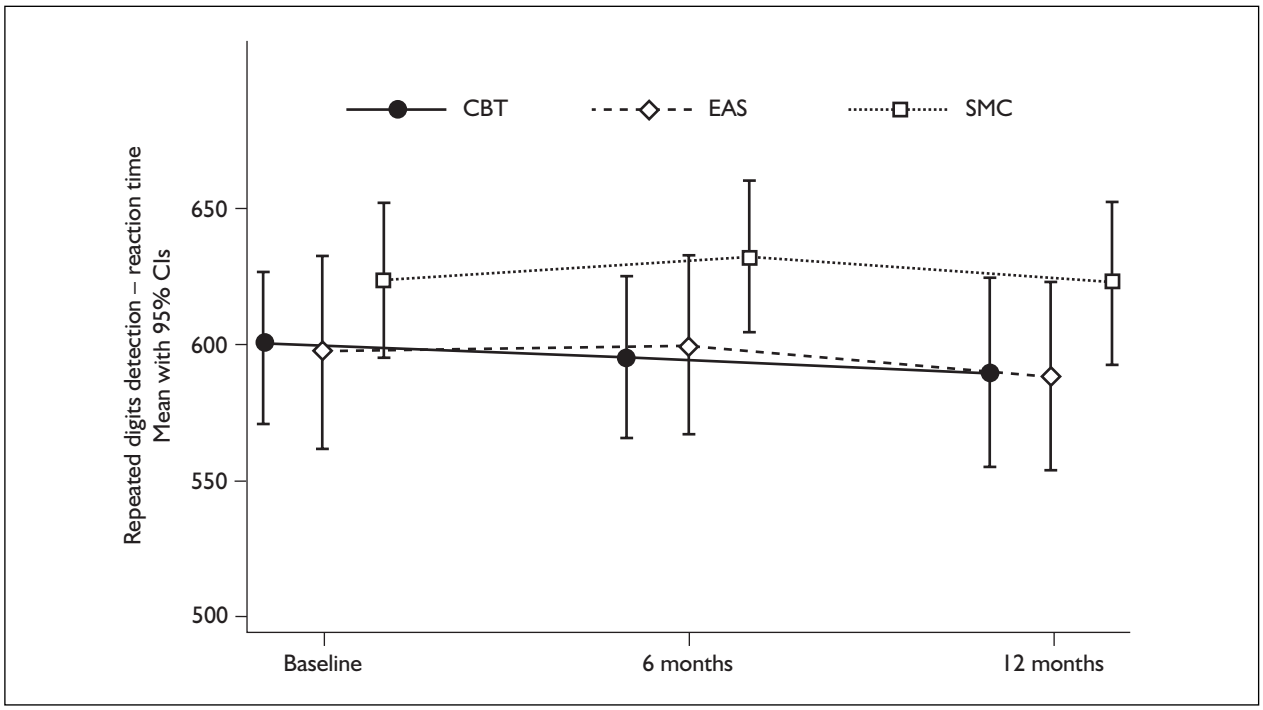



***FIGURE 10*** *Repeated digits detection (reaction time) under each of the three conditions*

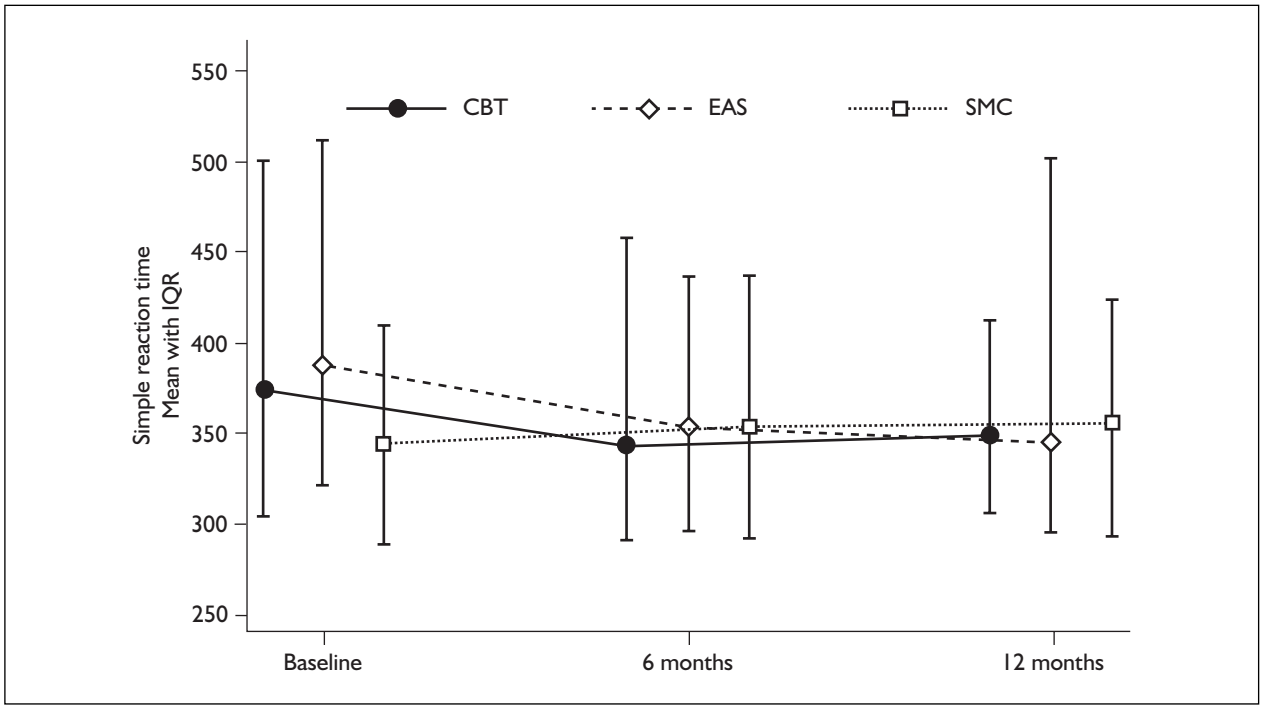



***FIGURE 11*** *Simple reaction time under each of the three conditions*

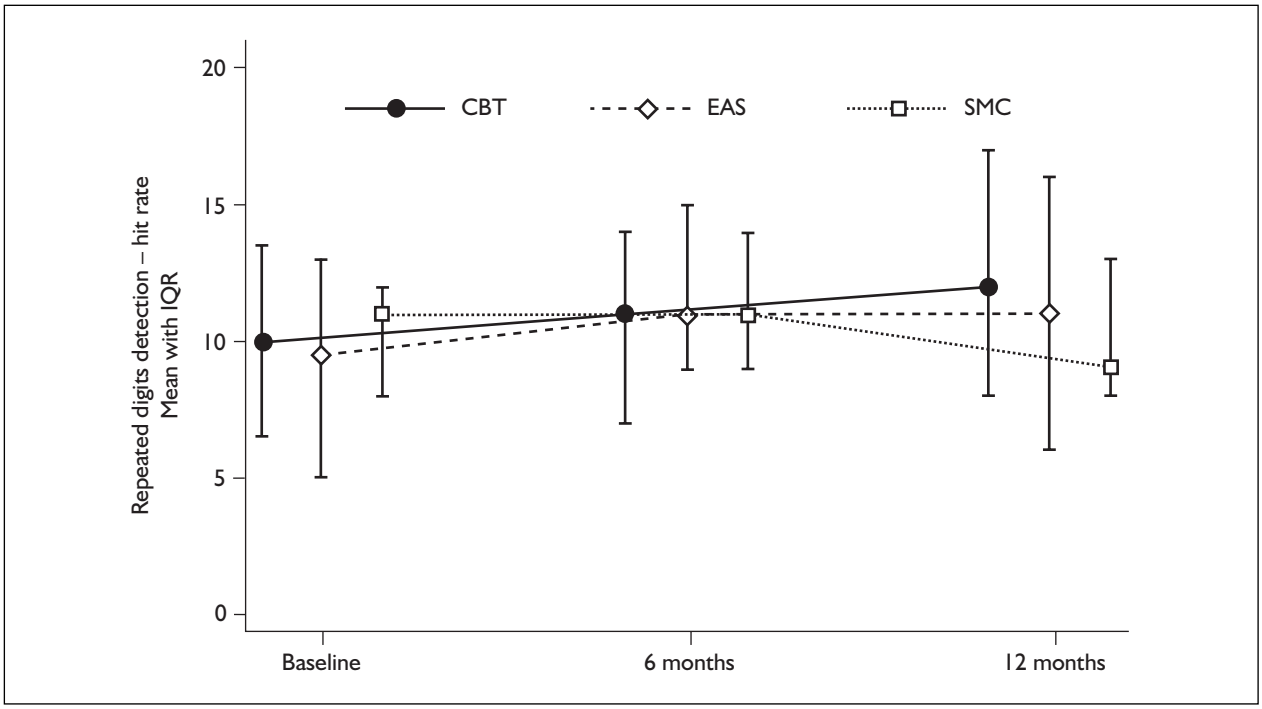



***FIGURE 12*** *Repeated digits detection (hit rate) under each of the three conditions*

# Appendix 15

## Comparison of study sample with other study cohorts

Owing to the huge variation in outcome measures used (estimated at 130 in Whiting and colleagues' review[17]), it was difficult to make comparisons with other trials at baseline. Using the trials described previously as meeting the quality criterion,[16,17] the following comparisons can be made.

- In our trial, 70% of the subjects were not working compared with 87% (a figure reported in only one of the key trials[19]).

Three of the outcome measures used in the current study were used in these key trials – the HADS, the Chalder scale and the GHQ.

- The mean HADS scores were much lower in the previous trial[19] at only 6.7 (anxiety) and 6.3 (depression) compared with overall means of 10.3 and 8.7 for anxiety and depression, respectively, in this trial. This suggests that our sample were more psychologically distressed.
- For the Chalder scale, the subjects in the present study showed a higher level of fatigue (overall mean score at baseline of 24.6) in comparison with those in a previous trial carried out by Deale and colleagues (10).[18,38] This suggests that our subjects were more fatigued.
- For the GHQ, a similar pattern was noted; an average score of 6 has been quoted[18,38] compared with an overall mean of 19.8 in the present study. This suggests a higher level of physical ill health for our subjects.

Other comparisons show a shorter treatment time – 16 hours of group therapy in this trial compared with 15/16 hours of individual therapy in the previous trials.[18,19,38] The average duration of symptoms was higher in the present trial, with over 50% of the sample reporting symptoms for 5 years or more, compared with the average duration of 48 months[19] and 32 months.[19,38] Once again, this indicates a more severely affected sample. See Appendix 10 for a detailed breakdown of duration of symptoms.

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## Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

***We look forward to hearing from you.***

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