No.	Question	Answer
PATIENTS and their diagnoses		
1.	What is CFS?	Chronic Fatigue Syndrome (CFS) is an illness in which a person is disabled by severe fatigue and other symptoms, which have lasted at least six months, and for which there is no other disease to explain it.
2.	How is CFS defined?	There are several published definitions or criteria that can be applied to decide if a person has CFS. We used the Oxford definition to define CFS in the PACE trial. We also assessed participants to see if they met the International (Centers for Disease Control) definition (see question 4), to see whether the effects of treatments were different in those who met this alternative definition.
3.	What are the “Oxford” criteria for CFS?	These require that a person has had at least six months of severe fatigue, with fatigue being their main symptom, which is disabling and is usually accompanied by other symptoms. No other medical or psychiatric explanation for the symptoms has been found. All patients in the PACE trial met these criteria.
4.	Why did you choose the Oxford criteria for defining CFS?	We chose the Oxford criteria for several reasons: (a) we wanted to find out which treatments were best in those who had fatigue as their principal symptom. Some patients, clinically diagnosed as having CFS, may have another symptom, such as pain, as their primary symptom. (b) The Oxford criteria include a greater number of patients with CFS, by not requiring a specific number of additional symptoms, as other definitions of CFS do. (We wanted to make sure our findings applied to the greatest number of patients.) (c) The Oxford definition of CFS is the most straightforward to use in clinical practice.
5.	Do the Oxford criteria exclude patients with neurological symptoms?	Having “neurological symptoms”, like memory difficulties or muscle weakness, did not exclude anyone from taking part in the trial, since these symptoms were medically recognised symptoms of CFS. Neurological conditions, such as Parkinson’s disease which might be an alternative cause for the symptoms, did exclude patients from participation, since the diagnosis would have been Parkinson’s disease, not CFS.
6.	What are the International (Center for Disease Control) criteria for CFS?	These require that a person is suffering from fatigue, and also has at least four of eight other symptoms, these being: (1) post-exertional fatigue, (2) muscle pain, (3) joint pain, (4) headaches, (5) sore throat, (6) tender lymph nodes, (7) poor concentration and memory, and (8) sleep disturbance, with no other medical or psychiatric explanation for these symptoms. 67% of PACE trial patients met the CDC criteria.
7.	What is ME?	ME or myalgic encephalomyelitis/encephalopathy refers to an illness in which severe fatigue is a symptom, which is characteristically exacerbated by minimal activity, along with other symptoms that fluctuate over time. We assessed whether patients in the PACE trial met the London criteria for ME, which are based on the original description of the illness. We did this to see whether the effects of treatment differed in those who met criteria for ME. 51% of PACE trial patients met the London criteria for ME.
8.	What is the difference between CFS and ME?	ME is a similar or related condition to CFS. Some regard it as the same condition; others believe it to be a distinct illness. It may be a sub-group of CFS.
9.	Did the trial include patients with ME?	All patients met the Oxford criteria for CFS. 67% also met the international (CDC) criteria for CFS, and 51% also met the London criteria for ME. We analysed our data separately for all these groups and found that the pattern of the effects of treatments were similar in all three groups.
10.	Why were the Canadian consensus criteria for defining ME not used?	These criteria were designed for use in clinical practice, rather than research, and have therefore been very little used in research. One of the important reasons for this is that they include many symptoms, some of which may not be related to ME or CFS. The criteria are

		similar in some respects to the London ME criteria, which we did use in PACE; for instance both require post-exertional malaise or fatigue. We used the London criteria for ME since they included this characteristic symptom, were based on Ramsay's original description of ME, and were simpler to apply.
11.	Would it have made a difference if the Canadian definition for ME had been chosen?	We cannot know for sure, but when we analysed data from those participants who met the London criteria for ME, the pattern of results was the same; both CBT and GET, combined with SMC, were the most effective treatments. This was also the case when we analysed only data from participants who met the International (CDC) criteria for CFS, another way of defining the illness (see question 6).
12.	Were the participants of the PACE trial representative of all patients with CFS?	We included only participants who were able to attend hospital for the trial treatments and assessments. However, some of the PACE trial participants were quite severely disabled and had to use mobility aids. Participants were representative of patients who attend clinics with a diagnosis of CFS in the UK.
13.	Are the results applicable to those worst affected?	We do not know as we did not study housebound participants. Results cannot be therefore be extrapolated to those who are severely affected.
14.	Why did you change entry criteria while the trial was recruiting participants?	We made two changes. First, we increased the threshold for physical functioning by one incremental point as we decided the original level of functioning we required for entry was too low, and also to reduce the number of otherwise eligible patients who were excluded from the trial for this reason. The overall mean score for the physical function scale of participants was similar to those in previous trials conducted in hospital clinics. Second, we decided to exclude only those who had already received a trial treatment in a PACE trial centre, because we found it difficult to be certain whether patients treated elsewhere (not at a PACE centre) with something like CBT or GET had received a proper course of treatment consistent with that provided in the trial. Both these changes were approved by the independent Trial Steering Committee.
TREATMENTS		
15.	What treatments did you test?	All participants received specialist medical care (SMC). One group received this alone. The other three groups also received either adaptive pacing therapy (APT), cognitive behaviour therapy (CBT) or graded exercise therapy (GET). All treatments were provided on an individual patient basis.
16.	What was SMC?	Specialist Medical Care (SMC) consisted of seeing a doctor in a clinic that specialised in the management of CFS. This included providing general advice about managing the illness and prescribing medicines for symptoms such sleep problems and pain, as well as encouraging self-help when SMC was provided by itself without an additional therapy.
17.	What was APT?	Adaptive Pacing Therapy (APT), delivered by occupational therapists, assumed that the illness cannot be changed by changing behaviour, and aimed to help the patient to use their energy wisely and to allow natural recovery, by both stabilising and balancing activities with rest, while staying within the limits imposed by the illness. All participants also received Specialist Medical Care (SMC).
18.	What was CBT?	Cognitive behaviour therapy (CBT) was provided by a clinical psychologist or nurse therapist. After stabilising the level of activity CBT aimed to help the patient to do more and feel better by testing out the best ways to cope with the illness. This included a gradual return to activities and challenging what both patients and therapists had identified as potentially unhelpful ways of coping and thinking about the illness. All participants also received SMC.
19.	What was GET?	Graded exercise therapy (GET), delivered by physiotherapists, consisted of an individually tailored exercise programme. This began

		with stabilisation of levels of activity and then incremental increases in physical activity, agreed between participant and physiotherapist. The planned increments took into account symptoms, fitness, and current level of activity levels. The treatment aimed to help patients do more and feel better by gradually increasing their physical activity. All participants also received SMC.
20.	Why did you select these treatments for study?	CBT and GET had been shown in previous small studies to be moderately effective treatments for patients with CFS. However some patient organisations had expressed concern about their safety and efficacy, and had reported that patients preferred pacing or specialist medical care. We thought it was essential to know whether the treatments were safe and which treatments were more effective.
MEASURING THE OUTCOMES OF THE TRIAL		
21.	Why did you select what patients reported as the primary outcomes?	CFS and ME are defined by the symptoms and problems reported by patients. We believe that useful treatment should improve those symptoms and reduce disability.
22.	Why did you choose a fatigue questionnaire and a scale measuring physical function as the primary outcome measures?	After discussion with patients and a national patient charity, we believed that these measures best reflected improvement in symptoms and ability to lead a more normal life, while not being too long or complicated for participants to score.
23.	What is the Chalder fatigue questionnaire?	This 11 item scale measures different aspects of fatigue, and was scored by the trial participants to provide an overall measure of fatigue and associated symptoms; the higher the score the more severe the fatigue.
24.	What is the SF36 physical function scale?	This 10 item scale measures different aspects of physical ability, and was scored by trial participants to provide a measure of overall physical function; the lower the score the more severe the disability.
25.	Why did you omit actigraphy as an outcome measure?	Actigraphy is a measure of physical activity, measured by a wrist watch sized accelerometer, worn around the ankle continuously for a week. Before we started the trial, we were advised that the number and scope of the outcome measures were too great and that it might reduce the proportion of participants making it through to the end of the trial. Actigraphy was the obvious measure to reject because of its burden in time and effort required by participants. The patient charity advising us agreed that this would be sensible.
26.	Did you measure any other outcomes?	Among many other measures, participants rated the change in their overall health, overall ability to function, mood and sleep. We also measured how far the participant could comfortably walk in six minutes.
27.	Why did you change the analysis plan of the primary outcomes?	A detailed statistical analysis plan was written, mainly by the trial statisticians, and approved by the independent Trial Steering Committee before examining the trial outcome data. This is common practice in clinical trials. We made two changes: First, as part of detailed discussions which took place whilst writing the statistical analysis plan, we decided that the originally chosen composite (two-fold) outcomes (both % change and the proportions meeting a threshold) would be hard to interpret, and did not answer our main questions regarding comparative efficacy. We therefore changed the analysis to comparing the actual scores. Second, we changed the scoring of one primary outcome measures – the Chalder fatigue questionnaire – from a binary (0, 1) score to a Likert score (0, 1, 2, 3) to improve the sensitivity to change of this scale. These changes were approved by the independent Trial Steering Committee, which included patient representatives.
28.	Why haven't you reported all the outcome data from the trial?	We plan to publish all the outcome data from the trial, but could not fit this all in to the main paper. We chose which outcome data to report in the main paper on the basis of clinical relevance and before we analysed the data to make sure our choice wasn't affected by knowing

		the results.
29.	Did you analyse the data by intention to treat?	Broadly yes. An intention to treat (ITT) analysis means that the data from *all* participants are included in the analysis. Since only 10 out of 640 (1.5%) participants had no outcome data at all (and they were spread across all four treatment arms), doing an ITT analysis would have made very little difference to the results.
FINDINGS		
30.	What did the PACE trial show?	Both cognitive behaviour therapy (CBT) and graded exercise therapy (GET), when combined with specialist medical care (SMC), were more effective in reducing fatigue and improving physical functioning than adaptive pacing therapy (APT) when combined with SMC, and SMC alone. Approximately 12 out of 20 patients made a clinically useful reduction in fatigue and improvement in functioning with either CBT or GET compared to about 8 out of 20 with APT and 9 out of 20 with SMC. Twelve months after starting in the trial, 3 out of 10 participants were within normal population ranges for both fatigue and function, following CBT and GET, which were approximately twice as many participants than after APT and SMC. This means patients were more able to do things we all take for granted such as carrying shopping, or walking up a flight of stairs. This level of improvement is what we would expect in the treatment of other chronic disabling conditions. Being within the normal population range for these two outcomes does not necessarily mean the patient had recovered from CFS, so we are analysing separately the numbers of patients who recovered after treatment.
31.	How effective were CBT and GET?	We concluded that CBT and GET were more effective than APT and SMC and that the size of the effect was *moderate*. We drew these conclusions on the basis of the size of their effect compared with APT and SMC and the proportions of participants who made a clinically useful reduction in fatigue and improvement in functioning.
32.	Why did CBT and GET have similar effects? Is it just the effect of seeing a therapist?	Both CBT and GET were better than APT, so this suggests it was not simply due to the benefit of seeing a therapist. The better outcome may have been due to the active rehabilitative approach common to both CBT and GET, which encourages people gradually to do more. However, we are now analysing in more detail what makes these treatments work, and will report this.
33.	Would CBT and GET given together be more effective, or do they work better when given separately?	The PACE trial was not designed to answer these questions; this may be a topic for future research.
34.	Were the treatments safe?	We measured the safety of all the treatments in five separate ways, and found no significant differences in any of these measures among the different arms of the trial. We concluded that all these treatments are safe so long as they are delivered by similar healthcare professionals, who are trained and supervised to deliver these treatments in a similar way to the PACE trial.
35.	Does APT not work?	A minority of people who received APT did improve, but no more than the proportion who received SMC by itself. The majority of patients who received APT reported that they were satisfied with their therapy.
36.	How is it possible that APT had the most satisfied group of patients but was the least effective therapy?	Satisfaction with a treatment is based on lots of things, such as how helpful the person found their therapist, and does not necessarily relate to its effectiveness. Patients can be satisfied that their therapist did their best, without the therapy itself improving symptoms and disability.
37.	Did poor delivery of APT account for the findings?	We know the therapists delivered APT to a high standard and that APT was delivered as planned because of:

		1. The high rates of patient satisfaction, 2. Recorded therapy sessions were consistent with the therapy manual, 3. The quality of the therapeutic relationships between patients and therapists, which were independently assessed, were as good with APT as with other therapies. This suggests that it was the content of the therapy that was less effective, not the therapists or how it was delivered. It seems as though the adaptive nature of APT is not as effective as the rehabilitative approach common to both CBT and GET.
38.	How do we know that the results were not biased in any way?	Bias means that the results were not correct because of a limitation in the methods. There are many forms of bias: 1. *Bias in design and conduct of the trial:* The trial was subject to independent scrutiny by both a Trial Steering Committee and a Data Monitoring and Ethics committee throughout, and was conducted to the highest standards. A patient charity, Action for ME, helped to design, implement and oversee the study throughout its existence. 2. *Outcome measurement bias:* This might have occurred because the research assessors knew which treatment each participant had received. However, as the participants rated the main outcomes themselves, any measurement bias would have been determined by participants themselves. One reason may have been different expectations of treatments. We measured expectations before treatment and the highest expectations were in those about to start APT and GET, with less expectations of improvement in those about to receive CBT. This makes patient rating bias an unlikely explanation of the results: 3. *Bias in assessing safety outcomes:* These were reported by participants themselves, and finally assessed by independent scrutineers, so this is unlikely. 4. *Bias in the analysis:* The statistician who analysed the main results did not know which outcome data referred to which treatment, so this is unlikely. Whilst it is never possible to completely eliminate all bias in trials we are confident that the findings of the trial were not substantially affected by bias.
IMPLICATIONS		
39.	Will the results have an effect on policy?	The 2007 NICE guidelines recommend both CBT and GET. The PACE trial results were reviewed by NICE in 2011, and it was concluded that there was currently no need to change this advice.
40.	Why did NICE recommend the treatments before now?	More evidence was available to support the effectiveness of CBT and GET than for other treatments. However that evidence was limited to small trials, and the recommendation remained controversial. PACE is a large scale clinical trial (with 641 participants), which has provided definitive evidence of effectiveness and safety.
41.	Does the effectiveness of CBT indicate that CFS is a psychological condition?	No. The effectiveness of cognitive behaviour therapy (CBT) as a treatment for CFS does not make assumptions about the nature of the illness. Pigeon-holing CFS as either physical or psychological is not helpful as many if not all illnesses have elements of both. CBT is used widely to manage many medical conditions such as arthritis, heart disease and chronic pain. There is also evidence that CBT can have an effect on the body. For instance it has been recently found to reduce repeat heart attacks in people who have had a first attack. This is because CBT helps to change behaviour, which in turn changes the

		functioning of the body.
42.	How have you found a treatment to be useful when we do not know the cause of CFS?	There are very many examples in medicine where a treatment is developed for an illness before the cause of the illness is known. For example: quinine treating malaria, or digitalis (from the foxglove) helping heart failure. Treatments sometimes help in reversing the factors that keep someone unwell rather than addressing original causes. Digitalis is an example of that. CFS and ME are extremely debilitating and therefore there is a real need for treatment now. We are open minded about what research into the condition's causes will reveal; in the meantime the PACE trial shows that CBT and GET can make a difference to patients' lives today
43.	Do the treatments give value for money?	Our health economic analysis will be reported in a separate paper. It is important to think about the costs of these treatments to the National Health Service as well as the costs of the illness to patients' families and society in general due to the costs of caring for patients, and some patients' inability to work.
44.	If patients continued treatments for longer would they continue to get better?	The PACE trial was designed to measure benefits of five months of therapeutic treatment. We cannot predict the effects of continued treatment from this study.
45.	Do the effects of these treatments last?	We will have followed up participants long-term (for 2.5 years) and therefore will be able to make a better assessment of whether the positive effects shown in the trial are long-lasting. Previous studies have shown that the effects of both CBT and GET do last.
46.	Some patients didn't improve: was it worth it?	Since approximately 6 out of 10 patients improved after either cognitive behavioural or graded exercise therapies, the results of this study are encouraging. But, as with many treatments in most areas of medicine, there will be patients who do not respond to treatment. This underscores the need for continued research into this area.
47.	What would you say to participants who didn't get better?	After participation in the trial, if patients did not improve, they were offered further or alternative treatments; we hope this would happen in clinical practice.
48.	Are the CBT and GET widely available on the NHS?	NICE currently recommends these treatments, but their availability varies across the UK. We hope that the results of this trial will inform practice throughout the UK and abroad.
49.	Who funded the PACE trial?	Large trials like this are expensive and it is common for funding to be shared between different public sector bodies including charities with an interest in finding the best treatments for a debilitating condition. The PACE trial was primarily funded by the Medical Research Council as well as the Department of Health for England, The Scottish Chief Scientist Office and the Department for Work and Pensions. CFS and ME are a priority research area for the MRC. The MRC's decision to fund this trial was based on detailed peer review of the grant application, including the fact that there was a lack of high quality evidence to inform treatment, and in particular on the need to evaluate treatments that were already in use and for which there was insufficiently strong evidence from randomised controlled trials to support their effectiveness.
Main results available for free download, once registered with the Lancet at no charge: *Lancet,* 377,9768, 823-836, 5 March 2011		