Draft minutes of PACE team meeting of 7.6.02

1. Those present

[redacted]

2. Apologies

[redacted]

3. Note

[redacted] and [redacted] feed-back summaries had previously been circulated and were used as back-ground papers to the meeting. [redacted] also spoke to [redacted]'s summarised feed-back email.

4. Previous minutes

These were accepted with the correction that [redacted] was Principal rather than Chief Medical Adviser [redacted].

5. Funding

[redacted] had spoken recently to [redacted], and [redacted] had emailed [redacted] earlier in the week. A letter from [redacted] to [redacted] was in the post, but the news did not look promising, especially with the likely policy paralysis that normally follows the arrival of a new Secretary of State. We agreed not to mention the DWP bid beyond one line, unless further positive news was received.

6. Biomarkers

[redacted] Concern was expressed regarding recruitment if a blood test was incorporated. We agreed to add a sentence regarding a voluntary extra consent for a single blood test at baseline for possible studies involving gene assays, with [redacted]'s group, making it clear that this was a separate study.

7. 3 versus 4 arms

This was the major change of design since the last meeting. A fourth arm would allow an examination of the efficacy of pacing, and also allow comparison of all three interventions with treatment as usual (TAU), in case we find that all 3 interventions are equally efficacious. Although 4 arms would mean that more subjects would be required, and recruitment might suffer (subjects not being offered a "treatment"), we agreed that the fourth arm would make the study more worthwhile.

8. The questions being asked

The original question of interest had been whether CBT or GET were more efficacious, predictors and process of effective treatment. [redacted] pointed out that the study was not sufficiently powered to adequately answer the first question, of comparative efficacy between CBT and GET, although some estimate of an answer

might be possible with the number of subjects we contemplated studying. Various questions were put forward, such as comparing a combined CBT and GET versus pacing. After discussion we agreed the following five questions...

Are CBT and GET more efficacious than pacing?

Is pacing more effective than TAU?

(Are there trends of efficacy from TAU to pacing to CBT, and TAU to pacing to CBT?)

What are the important predictors of efficacy in general and with specific interventions?

What is the essential process of effective treatment: Change in beliefs or behaviour, or both?

What are the relative cost-effectiveness and cost-utility of the interventions?

9. Power analysis

We noted [redacted]'s view that power would be increased by using interval primary outcome variables, but we were concerned as to how such results (ie of change in an interval variable such as fatigue) might be interpreted. Particularly since we wished the study to be sufficiently powered to examine process and predictors, we agreed to power the study on the basis of categorised measures of the two primary outcome measures. These are the Chalder 11 item fatigue scale with a 3/4 score threshold, and the physical function sub-scale SF-36 self-rated questionnaire, with 74/75 score threshold, which is approximately one standard deviation below the mean score for the UK adult population of working age (Jenkinson et al, 1997). Change in these scores would be a secondary outcome. Depending on these exact figures of these variables from previous trials, but without allowing for drop-outs, [redacted] estimated that this would mean approximately 125 subjects per treatment group, or 500 subjects in total, before allowing for drop-outs.

[redacted] and [redacted] agreed to send [redacted] the summary data on the Chalder scale and SF-36 physical function sub-scale scores from their previous RCTs so that [redacted] could do the definitive power analyses on the two variables.

10.Interim analysis

We agreed that there would be no need for a planned interim analysis, since no treatment was found to do harm in previous RCTs. This was particularly the case since we would pay particular attention to employing trained therapists, whom we would then carefully train regarding the treatments for CFS, and would carefully supervise.

11.Measures of harm

In recognition of the AfME survey findings that significant proportions of surveyed members reported CBT and especially GET as "harmful" when given in undescribed clinical settings, we agreed that it was important to measure harm carefully, and include it as an important secondary outcome. Apart from already included fatigue and function measures and the CGI change score, we also agreed to include Likert scale scores of improvement and deterioration of each of the nine CDC symptoms of CFS criteria. We agreed to add a sentence covering this to the protocol. Furthermore, we agreed that when a subject dropped out of treatment, there would be a detailed clinical assessment (along with a research assessment, if

possible), if necessary at home, so that any subject who "took to their bed" would not be forgotten, but would received a domicilliary assessment and the necessary help would be offered.

12.Treatment as usual (TAU)

We were concerned to minimise the effect of TAU on recruitment and on artificially minimising differences between groups. We agreed to adopt the following strategies:

[redacted] *will consider differential recruitment into TAU, so that less subjects are required, particularly since we are only interested in efficacy in the TAU group.*

TAU subjects will be placed on the waiting list for their treatment of choice following the end of the study (12/12).

TAU will include any symptomatic pharmacotherapy, including mineral replacements and vitamins, if thought to be indicated by the clinician, but would exclude specific endocrine (eg hydrocortisone), immune (eg immunoglobulins and inosine pranobex) or other putative specific pharmacotherapies (eg NADH).

The clinical approach of TAU (ie pharmacotherapy) will be applied to all 4 arms of the trial.

Clinician advice in TAU will be limited to expressions of ignorance of the correct lifestyle approach to CFS, consistent with the reasons for us doing this trial in the first place. This will be summarised in a leaflet given to all TAU subjects.

13.Pacing

[redacted]'s draft manual was well received, and [redacted] was thanked for his efforts to define pacing in the absence of a published manual. We noted that there was a limited literature, which mainly came from the chronic pain field. The meeting heard that [redacted] was happy with this current draft in principle, in that it answered his specific concerns regarding previous attempts to define pacing.

We then had a wide-ranging discussion about how it would be delivered. There was a difference of opinion regarding whether it should be delivered in the same or smaller number of sessions as CBT and GET. One view was that we should control for non-specific elements of therapy by having 14 sessions, and that our results would be criticised if we had fewer sessions, if pacing was shown to be less effective than both CBT and GET. The other view was that we should define it (including fewer sessions) in the way that [redacted] defined it, since this was essentially a policy of illness self-management, and therefore the sessions themselves were less relevant. At the meeting we agreed that 6 sessions on a monthly frequency would be appropriate.

Revisions to the content of the draft manual were also suggested. We agreed that it was important to make pacing as credible as possible to [redacted] members, while keeping it clearly different from GET and CBT.

We agreed that revisions to be incorporated included:

Explicit understanding of the "battery" model of finite energy to be used wisely

Clearer definitions of rest
Avoidance of boom and bust
Relaxation therapy
Alternating (not switching!) between physical, cognitive and emotional exertions, by serial tasking
Learning self-empowerment and control by learning to respond to bodily symptoms
Telephone help-lines
Appropriate self-help books

We agreed that [redacted] would take a revised manual [redacted] and take soundings (and/or run a focus group) on it by next Friday 14th if possible, or early in the week after if more time were needed.

[*Added note: [redacted] and [redacted] in discussion after the meeting were not yet convinced that less sessions for pacing was sufficiently justified. Why should we fix 14 sessions for two interventions and have less sessions for a third intervention with which the first 2 interventions would be compared? Not many therapies/approaches in medicine are more effective with less dose. Comments please to [redacted]]*

14.CBT and GET flexible versus fixed number of sessions

The current protocol had changed from its previous fixed number of sessions for CBT and GET in order to allow some examination of the [redacted] 4 session only therapy, as well as to allow the cost-effective analysis to have a more realistic and wider variance (see [redacted]'s feed-back). This was criticised for not controlling for non-specific elements of therapy, and a minimum number of sessions recommended. We noted that subjects would vote with their feet anyway, and thus there would in any case be a difference in the number of sessions. In the end, we agreed to go back to the original 14 sessions for both these interventions.

15.Predictors

We agreed to include only those factors for which there is reasonable published evidence as predictors of outcome with treatment. This would exclude chronic widespread pain and the specific Illness Perception Questionnaire itself.

16.Process variables

We agreed that this question was important and it made the 10 week assessment necessary. We agreed that we wanted to know the essential mechanism of change necessary in effective treatment. This might be change in beliefs (CBT), behaviours (GET and pacing), or both. We agreed to include 5 variables of interest:

(1) fitness
(2) activity
(3) the belief that symptoms mean that harm is being done
(4) the belief that activity/exercise mean that harm is being done
(5) the belief that careful control of activity enhances recovery

We would analyse this by repeated measures ANOVA.

[redacted] *agreed to send* [redacted] *a measure of fearful cognitions.*

17.Pathway of care for research subjects

We noted the importance of having one caring person "looking after" a subject throughout the project, particularly in the TAU group, where there was no added therapist beyond the clinician. One way to help this would be to make the research assistant (RA) a nurse by discipline, and have them take a subject through the study, doing assessments and passing them over to the therapist, so that misadministration was minimised. This would unblind them, so that the outcome assessments would not be masked. Some thought the unblinding was inevitable when the RA and therapists were working together, often in the same building. We did not have time to resolve this.

Therefore, views would be welcome to [redacted].

18.Other centres

We were concerned about recruiting sufficient subjects in the time available, particularly since we had now agreed to a 4 arm trial. We noted that the MRC would be particularly worried if it believed that recruitment was an issue. [redacted]'s opinion was that the more centres involved the better the chances of success of the trial, particularly if it made our samples more heterogeneous, such as having more provincial representation. Although more centres would increase costs, this was less of a concern than not delivering the trial. [redacted] reported that the Royal Free hospital's CF clinic were interested. [redacted] had also contacted [redacted] in Liverpool. Another possible centre was Cardiff.

We agreed to review the number of centres needed after the definitive power analysis was made by [redacted]. *In the meantime* [redacted] *agreed to contact possible new centres.*

19[redacted]'s and [redacted]'s other feed-back

These suggestions were all accepted apart from the composite primary outcome measure, lowering the age of subjects to 16, and the number of sessions of therapy.

20.Other issues

We noted that there was insufficient time to address several other important issues. These included:

A more detailed criticism of the protocol
Practical arrangements for running the trial
CTU arrangements and randomisation procedure
Named involvement of [redacted]
Staff required for research and therapy
Funding of therapists
Training and supervision arrangements
TSC and DMEC membership
Ethical approval (please note that 5 centres would allow us to go for a single Multi-centre Research Ethics Committee approval)

We agreed to respond to [redacted] *and deal with these issues by email and phone.*

END

[redacted]