The PACE Trial

An Explanation of the Published Results

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All questions, comments, and feedback is very welcome, and will be gratefully received.

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Preamble

This report is intended to explain and clarify the primary results of the PACE Trial. Special attention will be given to highlighting and clarifying: the results that have not been highlighted by the authors of the PACE Trial; the inaccurate reporting of the results in the Lancet and the media etc.; the results that are hidden within the data tables of the published paper; the important results that have not yet been released; and the widespread misinterpretations of the results.

One of the most prominent results of the PACE Trial is the average 'response rate' for the primary outcomes, of 13% for CBT and GET. This figure indicates the proportion of participants who responded to treatment, and achieved a minimum clinically useful improvement, attributable to CBT and GET. The primary outcomes were self-reported, and thus were subjective measures.

The 'Number Needed to Treat' for CBT and GET was determined to be 1 in 8 patients, for the primary outcome measures.

CBT was found to be clinically ineffective at reducing physical disability (as per the primary and secondary outcome results).

CBT and GET both failed to achieve a 'clinically useful' improvement in physical disability, when assessed by the only objective measure used in the PACE Trial, the 'six minute walking distance test'.

CBT and GET were found to be 'moderately effective' at improving self-reported 'fatigue'.

CBT and GET failed to reduce welfare benefit claims or private financial claims (insurance and pensions), or to increase employment for the PACE Trial participants, as per the separately published 'cost effectiveness' analysis.

This report is not intended to be a critique of the methodology of the PACE Trial, although many questions have been raised over many aspects of it. It is simply intended to clarify the data and the main analyses that are included in the published paper, and the associated 'cost effectiveness' analysis paper.

The PACE Trial

A summary of the main results and analyses included in the published paper

This is a summary of the main analyses of the primary outcomes, which were included in Table 3 of the published PACE Trial paper (1). For a more detailed explanation, and for some background, please continue reading, below the summary.

Response rates attributable to CBT and GET

The 'response rate' indicates the extra number of participants who responded to treatment (i.e. achieved a minimum clinically useful improvement) when CBT and GET were administered as a supplement to SMC. These results are based on the 'clinically useful difference' (CUD), and are outlined in Table 3 of the published paper ("Number improved from baseline").

Overall, the average response rate attributable to CBT/GET was 13% (NNT = 1 in 8)

This means that only an average of approximately 13% of the participants in the PACE Trial were shown to have responded to treatment with CBT and GET. This gives a 'number needed to treat' of 1 in 8 patients.

Details:

Number improved from baseline (Difference from SMC):

CBT (physical function)	**13%**	(NNT = 1 in 8)
CBT (fatigue)	**11%**	(NNT = 1 in 10)
GET (physical function)	**12%**	(NNT = 1 in 9)
GET (fatigue)	**15%**	(NNT = 1 in 7)

The average for all these primary results for CBT/GET was 13% (NNT = 1 in 8)

(NNT = number needed to treat)

Various other sets of unhelpful, misleading and/or inaccurate results have been promoted in various places (see the subheading: "Misinformation and The 'Normal Range'", below), but these results are one of the most useful demonstrations of clinical efficacy, and are taken from the main primary outcome analysis included in Table 3 of the published paper.

Clinical Effectiveness / Therapeutic Effect Size

Whereas the response rates, outlined above, show how many patients were reported to have responded to treatment, the clinical 'effect size' is based on average patient improvements.

The measure of 'clinical effectiveness' is an analysis of the primary outcomes included in the published paper. It indicates the clinical effectiveness of each of the treatments, as per a post-hoc analysis of the data (see below the summary for details). These results are based on the 'mean difference from SMC', which is included in Table 3.

CBT (physical function) = clinically ineffective (7.1 points improvement on a scale of 0 to 100.)
(CBT did not achieve a 'clinically useful difference' from SMC, when assessed using the SF-36 Physical Function primary outcome measure, and was thus found to be clinically ineffective at reducing physical disability. CBT had a 'small' effect size, as per the methodology of the PACE Trial paper.)

CBT (fatigue) = **moderately effective** (3.4 points improvement on a scale of 0 to 33)

GET (physical function) = **moderately effective** (9.4 points improvement on a scale of 0 to 100)

GET (fatigue) = **moderately effective** (3.2 points improvement on a scale of 0 to 33)

The threshold for a 'moderate' effect size (as applied to the 'mean difference from SMC', in Table 3) was defined as 0·5 of the SD of the primary outcome measures at baseline, which was 8 points for SF-36 physical function and 2 points for Chalder fatigue. This measure of the 'effect size' is a 'post-hoc' analysis of the primary outcome results, as it was not proposed in the Trial protocol (7)(28), but was included in the published paper after the proposed primary efficacy measure of a 'positive outcome', was abandoned.

Objective measures: The Six Minute Walking Distance test.

The 'six minute walking distance test', a secondary outcome measure, was the only objective measure used to assess the effectiveness of the therapies. Thus, it was an important measure of therapeutic effectiveness.

CBT failed to increase walking distances.

GET failed to achieve a 'clinically useful difference' from SMC (as per the 'CUD' defined for the primary outcomes): For GET, the 'mean difference from SMC', at 52 weeks, was 35.3m, whereas the CUD (0.5 of the SD of the mean baseline distances for the therapy groups) was 45m. Thus, the improvements in the GET group did not meet the threshold for a CUD.

So, CBT and GET were both found to be clinically ineffective therapies for reducing physical disability, when assessed using an objective measure, the six minute walking distance test.

Unpublished Data

Some essential data has yet to be published, as follows:

The 'recovery rates'; the ‘deterioration rates’ (as determined by an equivalent measure as the improvement rates); the ‘positive outcomes’ (as proposed in the trial protocol); and an analysis of the data using the ‘clinical important difference’ defined in the protocol.

Clearly the 'recovery rates' for CBT and GET will be less than 13%, as only 13% of the participants responded to treatment with CBT and GET.

The 'deterioration rates' are essential information for such an important clinical trial, because clinicians need to know what proportion of their patients will be harmed by the therapies, as well as how many might benefit, as explained by Guyatt et al (24), a paper cited in the published PACE Trial paper.

The Cost Effectiveness Paper

The PACE Trial’s cost effectiveness analysis has recently been published (25), and it showed that CBT and GET resulted in no significant difference to the number of patients receiving welfare benefits (income-related and illness/disability-related) or private financial payments (income protection insurance and private pensions.)

The number and proportion of participants claiming welfare benefits increased in every benefit category, for every therapy group, across the board.

There was also no significant change in the number of days of lost employment after treatment with CBT and GET, compared to the control group.

So, some revealing information to take from the cost effectiveness paper is that CBT and GET resulted in no significant difference to:

- The number of patients receiving welfare benefits (income-related and illness/disability-related) and private financial payments (income protection insurance and private pensions.)
- The number of days of lost employment.

Primary and Secondary outcome measures

Primary Outcomes

There were two 'primary outcome' measurements used in the PACE Trial, both of which used a questionnaire to assess the participants. These measures were both subjective self-reported health outcomes.

Chalder Fatigue:
The Chalder fatigue questionnaire assessed the symptom of 'fatigue', and used a scale of 0 to 33, where the lowest score indicates best health.

SF-36 Physical Function:
The other primary outcome, the Short Form 36 Physical Function subscale questionnaire (SF-36 physical function), measured 'physical function' or 'physical disability', and used a scale of 0 to 100, where a score of 100 indicates best health.

Secondary Outcomes

There were a number of secondary outcome measures included in the PACE Trial.

The Six Minute Walking Distance Test
The Six Minute Walking Distance Test was the only objective measure used in the PACE Trial, and is therefore one of the most useful measures to be used. The test measured the maximum distance that participants could walk in a six minute period.

Glossary

The PACE Trial – Published in the Lancet in February 2011
"*Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial.*"

CBT – Cognitive Behavioural Therapy
(In the PACE Trial, CBT was based on the hypothesis that CFS/ME is 'perpetuated' by a 'maladaptive' fear of exercise.)

GET – Graded Exercise Therapy
(In the PACE Trial, GET was based on the hypothesis that CFS/ME is 'perpetuated' by a 'maladaptive' avoidance of exercise, leading to 'deconditioning'.)

APT – Adaptive Pacing Therapy
(ATP was a novel therapy, created specifically for use in the PACE Trial, but failed to demonstrate clinical efficacy.)

SMC – Specialist Medical Care
(Used in the PACE Trial as a control, this program of medical care was tailored specifically for the PACE Trial. All the participants in the PACE Trial received SMC, and the SMC-alone group was used as a control group. SMC included educating patients to avoid extremes of activity and rest, and prescribed symptomatic medication, such as pain medication, when needed.)

CFS – Chronic Fatigue Syndrome

ME – Myalgic Encephalomyelitis

'Clinically useful' outcome / 'clinically useful difference'
This is the minimum level of improvement in health needed to demonstrate that a therapy has been clinically useful. This threshold was determined by the authors of the paper.

The PACE Trial

Background and Explanation of Results

Introduction

The PACE Trial, published in the Lancet in February 2011, was a multi-million pound UK government-funded research study, researching the effects of four potential treatments for CFS/ME, involving 641 patients. The treatments investigated were Cognitive Behavioural Therapy (CBT), Graded Exercise Therapy (GET), and Adaptive Pacing Therapy (APT). Specialist Medical Care (SMC) was used as a control.

The PACE Trial recruited secondary care patients, and excluded housebound patients, so the results do not apply to severely affected patients. (1)(16)

The study was divided into four therapy groups: SMC only; CBT with SMC; GET with SMC; and APT with SMC. The SMC-alone group was designed to be used as a control group, against which the other therapy groups were compared.

CBT failed to demonstrate a 'clinically useful' effect, in terms of improving 'physical disability', for the primary and secondary outcome measures. GET also failed to demonstrate a 'clinically useful' effect, in terms of improving 'physical disability', when assessed using an objective secondary outcome measure, but was considered to be 'moderately effective' at improving 'physical disability' in the self-reported primary outcome measure.

CBT and GET were both reported to be 'moderately effective' at reducing the symptom of 'fatigue', in the self-reported primary outcome measures.

The average 'response rate' (the proportion of patients who experienced a 'clinically useful' therapeutic effect) attributable to CBT and GET, for the primary outcomes, was approximately 13% for CBT and GET. This gives a 'Number Needed to Treat' of 1 in 8 patients. (See the detailed results above, and Table 3 of the published paper.) (1)

The Lancet (2) and the media (4)(5) have misreported a "30% recovery rate", however, no recovery data has yet been released. The MRC (6) has misreported a '60% rate of improvement', which they have incorrectly attributed to CBT and GET.

The actual result, for the primary outcomes, was an improvement rate, or 'response rate', of approximately 13% for CBT and GET, and a 'number needed to treat' of 1 in 8 patients.

This report is intended to set out and clarify the main results and analyses included in the PACE Trial paper. This is not intended to be a critique of the methodology of the PACE Trial, although many questions have been raised over many aspects of it. It is just intended to clarify the data and the main analyses that are included in the published paper.

Measures of a Positive Outcome

The main measures of therapeutic efficacy, for the primary outcomes, that were included in the published paper, were: the effect sizes of the primary outcomes; and the improvement rates for the primary outcomes. These are the most useful primary outcome analyses which are included in the published paper. Other 'secondary outcomes' and 'post-hoc' analyses were included in the published paper, some of which have been widely misunderstood and misinterpreted. The Six Minute Walking Distance Test, an objectively measured secondary outcome measure, was one of the most useful measures used in the PACE Trial.

The two primary outcome measures were the SF-36 Physical Function questionnaire (which measured self-reported physical disability) and the Chalder Fatigue questionnaire (which measured self-reported levels of fatigue.) It should be noted that both of these measures were self-reported, and therefore subject to bias, which was acknowledged in the published paper: "Masking of participants or clinicians to treatment allocation was not possible, and research assessors were also not masked. Primary outcomes were subjective and rated by participants. While this avoided investigator bias, it could be subject to other biases."

Thus it is helpful to look at, and analyse, the results of the only objective measure included in the PACE Trial, the 'six minute walking distance test', which assessed physical disability.

Levels of 'physical disability' and the symptom of 'fatigue' were measured separately. 'Fatigue' is a subjective symptom, whereas physical disability can be measured objectively, as was the case in the PACE Trial with the secondary outcome measure; the 'six minute walking distance test'.

The main measure of clinical effectiveness for the therapies was originally proposed to be a "positive outcome", as defined in the Trial protocol (7)(28), but this measure was subsequently abandoned in favour of a 'post-hoc' definition of a 'clinically useful difference' (CUD). The post-hoc measure of a 'CUD' has a substantially lower threshold for the therapies to be considered successful, and so places CBT and GET in a more favourable light than the proposed 'primary efficacy' measure of a 'positive outcome' set out in the protocol.

In the published PACE Trial paper, the (post-host) definition of the 'clinically useful' outcome (represented in the paper as the 'clinically useful difference' or 'CUD'), for the two primary outcome measures, was defined as 2 points on the Chalder Fatigue scale of 0 to 33, and 8 points on the SF-36 Physical Function scale of 0 to 100. The 'CUD' is a post-hoc analysis, and it differs from the abandoned 'clinically important difference' (CID) which was proposed in the Trial protocol (7)(28). The 'post-hoc' measure of a 'CUD' placed CBT and GET in a more favourable light than the protocol measure of a 'CID' would have done, as it uses a lower threshold to demonstrate clinical efficacy. Questions have been raised about whether the post-hoc definition of the CUD used the most appropriate statistical methodology (17). The 'CUD' was applied to the 'mean difference from SMC', in Table 3, and was defined as 0·5 of the SD of the primary outcome measures at baseline.

Every participant who improved by at least an amount defined by the CUD was considered to have clinically responded to treatment. If changes in health outcomes failed to meet the threshold of the CUD, then the therapy was not considered to be clinically useful (i.e. was considered to be clinically ineffective.)

Despite the authors abandoning the primary efficacy measure of a 'positive outcome' and the measure of a 'clinically important difference', as set out in the Trial protocol, and replacing them with a measure with a lower threshold for clinical effectiveness (the CUD), the primary results for CBT and GET were still far from impressive.

Response rates attributable to CBT and GET

This is an analysis of the primary outcomes, which is included in the published PACE Trial paper, in Table 3. The 'improvement rate', or 'response rate', indicates the extra number of participants who responded to treatment (i.e. achieved a minimum clinically useful improvement) when CBT and GET were administered as a supplement to SMC. These results are based on a (post-hoc) definition of a 'clinically useful difference' (CUD), and are outlined in Table 3 of the published paper ("Number improved from baseline").

Overall, the average response rate attributable to CBT/GET was 13% (NNT = 1 in 8)

This means that only an extra 13% of participants in the PACE Trial were shown to have responded to treatment with CBT or GET, when given as a supplement to SMC. This gives a 'number needed to treat' of 1 in 8 patients.

Details

Number improved from baseline (Difference from SMC):

CBT (physical function)	**13%**	(NNT = 1 in 8)
CBT (fatigue)	**11%**	(NNT = 1 in 10)
GET (physical function)	**12%**	(NNT = 1 in 9)
GET (fatigue)	**15%**	(NNT = 1 in 7)

The average for all these primary results for CBT/GET was 13% (NNT = 1 in 8)

(NNT = number needed to treat)

A note about the SMC control group

For the SMC control group, 58% (physical function) and 65% (fatigue) achieved a clinically useful outcome.

The SMC group was a 'control' group, so it is not legitimate to compare the results of CBT/GET with SMC, as if SMC was a normal therapy group. The SMC control group was designed for the PACE Trial to take account of natural fluctuations over time, and so any improvements seen in the SMC group might have taken place with no treatment.

Every participant in the PACE Trial received SMC. There was an SMC-alone group, and then, in the other therapy groups, APT, CBT or GET were used as a supplement to SMC.

The improvements attributable to CBT and GET were improvements over and above (i.e. in addition to) those for SMC, as CBT and GET were always used as supplements to SMC. Subtracting the results of the SMC-alone group from the results of the CBT+SMC and GET+SMC groups, gives us the results attributable to CBT and GET.

In strict technical terms, it should be said that an extra 13% of patients responded to treatment when CBT or GET were added to SMC.

Clinical Effectiveness / Therapeutic Effect Size

Whereas the improvement rates, outlined above, show how many patients were reported to have responded to treatment, the clinical 'effect size' is based on average patient improvements.

The measure of 'clinical effectiveness' is the main analysis of the primary outcomes that is included in the published paper. It indicates the clinical effectiveness of each of the treatments, as per a post-hoc analysis of the data. These results are based on the 'mean difference from SMC', which is included in Table 3

A 'moderate' effect size (determined in relation to the 'mean difference from SMC', in Table 3) was defined as 0·5 of the SD of the primary outcome measures at baseline, which was 8 points for SF-36 physical function and 2 points for Chalder fatigue.

The published PACE Trial paper declares that CBT and GET are 'moderately effective' therapies. However, when the data tables are studied closely, it becomes apparent that CBT failed to meet the threshold for a 'clinically useful' therapy, in relation to physical function (SF-36 physical function), one of the two primary outcome measures.

This means that CBT failed to demonstrate clinical usefulness, or clinical effectiveness, in terms of reducing physical disability. So, based on the results of the PACE Trial, it can be said that CBT is ineffective at reducing physical disability. The PACE Trial paper fails to highlight or discuss this result.

This primary outcome result, for CBT, was supported by the only other measure used to assess physical disability, the 'six minute walking distance test'. This was an objective secondary outcome measure which assessed physical disability. (The 'six minute walking distance test' was the only objective measure used in the PACE Trial, after the proposed actigraphy measurements were dropped from the Trial.) In the six minute walking distance test, CBT failed to improve walking distances beyond the improvements seen for SMC, when CBT was used as a supplement to SMC.

CBT was therefore found to be clinically ineffective at reducing physical disability, in all of the measures used.

So, for the primary outcomes, CBT was found to be 'moderately effective' only at reducing subjective symptoms of fatigue, and made no useful difference to physical disability.

GET was found to be 'moderately effective' for both the self-reported primary outcome measures (Chalder fatigue and SF-36 physical function), but failed to demonstrate a 'clinically useful' therapeutic effect when assessed using the objective six minute walking distance test.

It should be noted that the term 'moderate' in relation to a clinical 'effect size' (e.g. 'moderately effective'), is a technical scientific term, and does not necessarily reflect the use of the word 'moderate' as a lay person might use it.

The mean average improvements for CBT and GET (mean difference from SMC) were as follows:

CBT (physical function) = 7.1 points on a scale of 0 to 100 (clinically ineffective)

(The threshold for a CUD was 8 points for SF-36 physical function scores, thus CBT did not achieve a a 'clinically useful' outcome or a 'clinically useful difference' from SMC. The effect size was 'small', using the same methodology as the published paper.)

CBT (fatigue) = 3.4 points on a scale of 0 to 33 (moderately effective)

GET (physical function) = 9.4 points on a scale of 0 to 100 (moderately effective)

GET (fatigue) = 3.2 points on a scale of 0 to 33 (moderately effective)

The threshold for a 'CUD' was 8 points for SF-36 physical function and 2 points for Chalder fatigue, so the therapeutic effects for each measure did not go far beyond a CUD in any therapy.

(All of these results are taken from Table 3: Mean difference from SMC.)

Objective measures: The Six Minute Walking Distance test.

The ‘six minute walking distance test’, a secondary outcome measure, was the only objective measure used to assess the effectiveness of the therapies, after the proposed actigraphy measurements were dropped from the PACE Trial before publication, reportedly due to ‘inconvenience’ of wearing actometers for the participants.

In the six minute walking distance test, CBT failed to improve walking distances beyond the improvements seen in the SMC control group, when CBT was used as a supplement to SMC.

GET failed to achieve a ‘clinically useful’ outcome, as per the ‘CUD’ defined for the primary outcomes: For GET, the ‘mean difference from SMC’, at 52 weeks, was 35.3m, whereas the CUD (0.5 of the SD of the mean baseline distances for the therapy groups) was 45m. Thus, the improvements in the GET group did not meet the threshold for a CUD.

So, both CBT and GET were found to be clinically ineffective therapies for reducing physical disability, when assessed using the only objective measure used in the PACE Trial, the six minute walking distance test (a secondary outcome measure), using the same measure of a CUD as defined for the primary outcome measures.

The overall results were not impressive.

The median average SF-36 physical function score, for all adults in England, is 95 points (8). (This is on a scale of 0 to 100, where a score of 100 is the healthiest score.)

At the end of the PACE Trial, the average SF-36 physical function score for CFS/ME patients (after treatment with CBT+SMC and GET+SMC) was '58' points for both groups, which is substantially below the median average score for all adults in England, of 95 points. An SF-36 physical function score of '58' is possibly (this needs to be confirmed) within the poorest functioning 10 percent of the adult population (20), indicating severe disability.

This post-treatment average score of 58 points, for the CBT and GET groups, is worse than average patient scores for: 'Class I' chronic congestive heart failure patients, with a mean score of 79.2 (9); Hepatitis C patients, with a mean score of 79.3 (9); Osteoarthritis of the Hip patients, with a mean score of 62.4 (10); and rheumatoid arthritis patients, with a mean score of 62.3 (10).

The entry criteria for the PACE Trial was an SF-36 physical function score of 65, for which the PACE Trial literature described the associated symptoms as being 'severe' (19).

So although there were some 'clinically useful' (defined by the PACE Trial) average improvements in some of the PACE Trial measures, the end average results in all therapy groups were not impressive at all, as on average, patients still had substantial disability when assessed, a year after beginning treatment.

The PACE Trial paper, itself, even concludes:
"Our finding that studied treatments were only moderately effective also suggests research into more effective treatments is needed."

Objective measures.

For the objective six minute walking distance test, the improvements attributable to CBT and GET were even less impressive.

CBT resulted in no increase in the distance walked (after the improvements for the SMC group were taken into account), and GET failed to achieve a 'clinically useful' outcome, as detailed above.
So, CBT and GET were both found to be clinically ineffective, when assessed using an objective measure.

At the end of the PACE Trial (at 52 weeks), participants in the CBT group could walk 354m, and participants in the GET group could walk 379m, both far from what would be considered a healthy average walking distance.

By comparison, using other 'six minute walking distance test' studies: Healthy subjects (aged 55 to 75 years) can walk a mean average distance of 659m (41); Healthy elderly subjects (age 50 to 85 years) can walk 631m (42); Adults without chronic disease (age 40 to 80) can walk a mean average of 571m (43); Patients with Chronic Obstructive Pulmonary Disease can walk a mean average of 439m (44); And patients with class III stable chronic heart failure, can walk a mean average of 402m (45).

So, in the six minute walking distance test, patients with the 'moderate' classification for stable chronic heart failure, as categorised by the New York Heart Association (NYHA Class III), can walk further than the PACE Trial participants, on average, even after treatment with CBT+SMC and GET+SMC, when assessed on follow-up at 52 weeks.

Misinformation, and The 'Normal Range'

All the reports of a "30% recovery rate" (2), or of 30% “getting back to normal" (3), or even a "60% improvement rate" (6), as a result of treatment with CBT or GET, are simply incorrect.

The 'recovery' data has not yet been released, so there are not yet any 'recovery rates' available. Despite this, a glowing ‘commentary’, published in the Lancet (which misinterpreted its own PACE Trial paper), misreported a ‘30% recovery rate’ (2). The ‘recovery rate’, for CBT and GET, clearly must be less than the ‘response rate’ for CBT and GET, and so it must be less than 13%, and could possibly be substantially less than 13%.

The misreporting of a 'recovery rate' seems to have been based on a misunderstanding of the meaning of the so-called 'normal range' analysis.

The (post-hoc) 'normal range' analysis is purely a statistical tool, more appropriately known as a 'reference range', that can be used by researchers to help them understand their results, and in this case it does not indicate a 'normal' level of health as a lay person would understand the term 'normal', and it does not indicate a 'good' level of health, or even an ‘improvement’ in health, as will be explained below.

The 'normal range' post-hoc analysis used in the PACE Trial does not use a common methodology for a ‘reference range’, and seems to be quite meaningless, for a number of reasons.

To be within the 'normal range' a participant had to have an SF-36 physical function score of at least 60 points, which was a worse score than the upper threshold of the entry criteria for the PACE Trial of 65 points. So a patient could be recruited into the PACE Trial with a score of 65, and then could have deteriorated after treatment with CBT or GET to a score of 60, to then be declared as being within the 'normal range', and subsequently misreported in the media and the Lancet as having 'recovered'.

A person within the 'normal range' could also be ill enough to be recruited into the Trial, with SF-36 physical function scores between 60 and 65, so being within the ‘normal range’ does <u>not</u> (necessarily) indicate good health.

Also, a score of 60 clearly does not indicate ‘good health’, as the average scores for other illnesses demonstrate: 'Class I' chronic congestive heart failure patients, were assessed as having a mean average score of 79.2 (9); Hepatitis C patients, were found to have a mean average score of 79.3 (9); Osteoarthritis of the Hip patients, were found to have a mean average score of 62.4 (10); and rheumatoid arthritis patients, were found to have a mean average score of 62.3 (10).

According to normative data, an SF-36 physical function score of ‘60’ is possibly (this needs to be confirmed) within the poorest functioning 10 percent of the adult population (20). 25% of the adult English population have an SF-36 physical function score of 75 or lower (23).

It did not help to clarify the situation when one of the authors of the PACE Trial inappropriately talked of patients "getting back to normal" in a press conference (3). Clearly, without studying the paper in depth, anyone being told that patients were "getting back to normal", or were within the 'normal range', could easily misinterpret this as meaning a "recovery", as indeed it was misinterpreted by the media and the Lancet itself.

Any reports of "30%" of participants being within the ‘normal range’, or of "60%" improvement rates, as a result of CBT and GET, are misleading also because the changes in the SMC control group have to be taken account before the effects attributable to CBT and GET can be known. Once the effects seen in the control group are taken into account, then we see the primary results listed at the

top of this report. The authors know this (18), but we are still seeing these misleading figures being regularly misquoted, and misattributed to CBT and GET, including by the MRC and the Lancet, who should both know better. It is dangerous to promote inaccurate or misleading medical trial results.

As an example, using the 'normal range' analysis, the proportion of participants within the 'normal range' in the SMC group was 15%, so if this analysis had any merit, then the figures that apply to CBT and GET would be 15% (CBT) and 13% (GET). As explained above, the 'normal range' does not indicate an improvement in health, or 'good health', but this is yet another example of how the "30%" 'normal range' figure has been promoted unhelpfully.

As another example, the “60%” improvement rate that has recently been incorrectly and misleadingly attributed to CBT and GET by the MRC (6) is based on a ‘secondary’ ‘post-hoc’ analysis. It is based on the results for the proportion of participants who achieved a ‘CUD’ in both of the primary outcome measurements (as opposed to each of the primary outcome measurements.) However, the “60%” figure applies (approximately) to improvements seen for CBT+SMC and GET+SMC, and it does not indicate improvements attributable to CBT only or GET only. Once the improvements in the SMC control group (45%) are taken into account, then the improvements in this secondary post-hoc analysis are 14% attributable to CBT and 16% attributable to GET, giving a ‘number needed to treat’ of 1 in 7 patients.

A note regarding misinformation about Specialist Medical Care (SMC).

Specialist Medical Care (SMC) included advice about avoiding extremes of activity and rest, and included prescribing medication such as antidepressants, sleeping medication and pain medication where appropriate (7)(28).

At least one of the PACE Trial authors has talked about CBT and GET being more successful than SMC (11). But this assertion is incorrect, based on the results of the PACE Trial.

The SMC control group was not designed to test the effectiveness of SMC, as it was intended to be used as a control against which to test APT, CBT and GET.

CBT and GET were used always as a supplement to SMC, and then the effects of CBT+SMC and GET+SMC were tested against an SMC-alone group.

The incremental effects of CBT and GET could then be determined, by subtracting the results of the SMC-alone group from the CBT+SMC and GET+SMC groups.

This shows us the effectiveness of CBT and GET.

The effects of SMC-alone always exceeded the incremental effects of CBT and GET, so it is not correct to say that CBT and GET were more successful therapies than SMC, as has been done since publication (11).

What can be said, for example, is that CBT and GET had therapeutic value (where they did) when used as a supplement to SMC. Or that when CBT was used as a supplement to SMC, the combined effects of CBT and SMC were more effective (where they were) than SMC alone.

To demonstrate this further, 58% (physical function) and 65% (fatigue) of the SMC group achieved a clinically useful outcome, whereas the average improvement rates attributable to CBT and GET is 13%. This means that when CBT and GET were added as a supplement to SMC, an extra 13% of participants achieved a clinically useful outcome, compared to SMC alone, giving a ‘number needed to treat’ of 1 in 8 patients.

Unpublished Data

Some essential data has yet to be published, as follows:

The 'recovery rates'; the ‘deterioration rates’ (as determined by an equivalent measure as the improvement rates); the ‘positive outcomes’ (as proposed in the trial protocol); and an analysis of the data using the ‘clinical important difference’ defined in the protocol.

Clearly the 'recovery rates' for CBT and GET will be less than 13%, as only 13% of the participants responded to treatment with CBT and GET.

The 'deterioration rates' are essential information for such an important clinical trial, because clinicians need to know what proportion of their patients will be harmed by the therapies, as well as how many might benefit, as explained by Guyatt et al (24), a paper cited in the published PACE Trial paper.

A note about the diagnostic criteria used in the PACE Trial

All participants were recruited using the Oxford Criteria (13). The effects of the therapies were further analysed by sub-grouping the recruited Oxford Criteria participants, using a set of criteria by Reeves et al., published in 2003 (14), and a modified version of the London Criteria. (15) (It should be noted that the London criteria have never been published in a peer reviewed journal.)

The PACE Trial paper acknowledges that the Oxford criteria (used to recruit patients) are not an internationally recognised set of criteria, so the use of them to recruit patients to the PACE Trial raises questions about the quality and relevance of the results.

The Oxford Criteria (used to recruit patients) only requires unexplained chronic fatigue of definite onset, and no other symptoms are necessary, for a diagnosis. Therefore, the Oxford Criteria may select idiopathic chronic fatigue patients, or “Fatigue syndrome” patients (WHO ICD-10: ‘Neurotic, stress-related and somatoform disorders’: ‘Other neurotic disorders’: F48.0), who may respond differently to psychological interventions than CFS/ME patients (WHO ICD-10: ‘Other disorders of the nervous system’: ‘Other disorders of brain’: G93.3) selected using international criteria, such as Fukuda (CFS) (21) or the International Consensus Criteria (ME) (22).

Internationally recognised CFS/ME criteria (21)(22), require additional symptoms to be present (additional to fatigue), and are therefore more ‘exclusive’, or more ‘selective’, than the Oxford Criteria. The Oxford criteria are thus likely to define a more heterogeneous cohort, than internationally recognised criteria, and it is questionable whether the results of the PACE Trial can be extrapolated to a population of CFS/ME patients defined using internationally recognised criteria.

The authors say that by sub-grouping patients using the London criteria and the Reeves et al. criteria, they have demonstrated that CBT and GET work equally well with patients diagnosed using various criteria. However, best practise is to recruit patients using the sets of criteria intended to be investigated, so that distinct cohorts are investigated. Recruiting patients using one set of criteria and then sub-grouping using other criteria can lead to unexpectedly skewed results, or a set of results that does not represent a clear picture of events.

Michael Sharpe, author of the PACE Trial, on ABC Radio (NNT = 1 in 7)

To illustrate that the authors of the PACE Trial are fully aware of the most significant results of the PACE Trial, Michael Sharpe, one of the authors of the PACE Trial, stated on ABC radio, that the 'number needed to treat' (NNT) is 1 in 7, as follows:

Michael Sharpe on ABC National Radio, The Health Report. (26)
"We have a number needed to treat; I think it's about seven to get a clinically important treatment benefit with CBT and GET. What this trial isn't able to answer is how much better are these treatments than really not having very much treatment at all."

A 'Number Needed to Treat' of 1 in 7 patients, means that 7 patients need to be treated for a clinical response to be seen in 1 patient.

Obviously, this is very different to the "30%" figure promoted in the media, which would give a NNT of approximately 1 in 4.

Sharpe is possibly referring to a secondary post-hoc analysis, set out in the published paper, which demonstrates how many participants achieved a CUD in both primary outcome measures, as opposed to each of the primary outcomes. This secondary post-hoc analysis places the results for CBT and GET in a slightly more favourable light than the numbers who improved for each of the primary outcomes, as set out in Table 3 of the published paper (which gives an average NNT of 1 in 8 patients.)

Participants who improved in both primary outcomes: A secondary post-hoc analysis

To illustrate why the MRC is incorrectly referring to a 60% response rate (6), which they have wrongly attributed to CBT and GET, and why Michael Sharpe referred to a 'number needed to treat' (NNT) figure of "1 in 7" patients (26), it is necessary to look at a breakdown of a secondary post-hoc analysis, included in the PACE Trial paper.

This secondary post-hoc analysis looks at the number of participants who achieved a clinically useful outcome in both of the primary outcome measures (SF-36 physical function and Chalder fatigue), as opposed to those achieving a clinically useful outcome in each of the primary outcome measures, given in Table 3 of the PACE Trial paper.

An extract from the PACE Trial paper:

"A secondary post-hoc analysis compared the proportions of participants who had improved between baseline and 52 weeks by 2 or more points of the Chalder fatigue questionnaire, 8 or more points of the short form-36, and improved on both."

Proportion of participants who improved in both primary outcomes:

SMC alone 45%
SMC+CBT 59% (Difference from SMC = 14%)
SMC+GET 61% (Difference from SMC = 16%)

So the average for SMC+CBT and SMC+GET is 60%
(This is the result that the MRC has misused in a press release, incorrectly asserting that it is attributable to CBT and GET. Whereas, in fact, this figure includes the improvements seen in the SMC control group.)

When the improvements for the SMC group are taken into account, then the following results are apparent:

Improvements attributable to CBT = 14% (NNT = 1 in 8)

Improvements attributable to GET = 16% (NNT = 1 in 7)

Average for CBT and GET = 15% (NNT = 1 in 7) (This is the 'number needed to treat' figure, that Michael Sharpe used in the ABC Radio interview.)

This analysis is not a primary efficacy analysis, but it is a secondary post-hoc analysis which places CBT and GET in a slightly more favourable light than the figures from Table 3 of the published paper, which presents the primary outcome results.

Clinical Global Impression scores

For CBT and GET, the ‘clinical global impression’ results are supportive of the ‘response rates’ for the primary outcomes. (The ‘response rates’ indicate the proportion of participants who achieved a ‘clinically useful difference’, as defined by the published paper.)

For the ‘clinical global impression’ scores, the proportion of participants who recorded a ‘positive’ change’ for CBT and GET (the ‘difference from SMC’), was 16% for both CBT and GET, giving a ‘number needed to treat’ of 1 in 7 patients.

Details:

Table 5: Participant-rated clinical global impression of change in overall health

At 52 weeks:

Positive Change:

CBT 16% when compared to SMC. (Difference from SMC)
GET 16% when compared to SMC. (Difference from SMC)

Other Information

The FINE Trial

At the same time as the research for the PACE Trial was being carried out, another major UK government-funded medical trial was being carried out in the UK, on 296 primary care patients, including housebound CFS/ME patients. (Housebound patients were excluded from the PACE Trial).

Originally known as the 'FINE Trial' (27) (FINE = Fatigue Intervention by Nurses Evaluation), the study tested a CBT-based therapy, which included GET components, known as 'pragmatic rehabilitation'. This failed therapy was based on a hypothetical illness model of ‘deconditioning’.

Like the PACE Trial, the FINE Trial was also funded by the UK government's main research funding body, the MRC (Medical Research Council).

The results demonstrated that CFS/ME patients did not respond to CBT-based therapy or GET, when assessed at one year follow-up.

Unlike the PACE Trial, there was very little fanfare or media attention when the paper was published.

NICE guidelines

CBT and GET are the only specific treatments recommended for CFS/ME by NICE.

In the PACE Trial, only 13% of secondary care CFS/ME patients achieved a minimum clinically useful response to CBT and GET, when assessed using the subjective primary outcome measures. CBT was found to be clinically ineffective at reducing physical disability, in CFS/ME patients, when assessed using a subjective primary outcome measure (SF-36 physical function) and an objective secondary outcome measure (the six minute walking distance test.) GET was found to be moderately effective for the subjective primary outcome measures, and clinically ineffective at reducing physical disability when assessed using an objective secondary outcome measure.

In the PACE Trial’s cost analysis paper (25), it was shown that CBT and GET did not lead to a significant increase in employment rates, or a reduction in welfare benefit claims or private financial payments.

Much of the important data from the PACE Trial has not yet been released, such as: the deterioration rates (as a measure equivalent to the improvement rates); the recovery rates; and the ‘positive outcome’ rates. These will all have an impact on the interpretation of the results of the PACE Trial.

The FINE Trial also showed that CBT and GET are ineffective treatments for primary care CFS/ME patients (27).

It is questionable whether the most up-to-date evidence supports the current NICE guidelines.

Comment

A flawed hypothetical cognitive behavioural model of illness

The PACE Trial, published in the Lancet in February 2011, was a multi-million pound UK government-funded research study, researching the effects of four potential treatments for CFS/ME, involving 641 patients. The treatments investigated were Cognitive Behavioural Therapy (CBT), Graded Exercise Therapy (GET), Adaptive Pacing Therapy (APT), and Specialist Medical Care (SMC).

CFS/ME is categorised by the WHO, and the UK government, as a neurological disorder. However, the versions of CBT and GET, which were investigated in the PACE Trial, were based on a controversial cognitive behavioural model of CFS/ME which hypothesises that the illness is a 'reversible' psychosomatic condition, 'perpetuated' by a (maladaptive) 'fear of exercise' and a (maladaptive) 'avoidance of exercise' leading to 'deconditioning' (1) (32).

The results of the PACE Trial demonstrated that CBT and GET cannot be used to successfully treat or cure CFS/ME. Only approximately 13% of participants responded (achieved a minimum clinically useful outcome) to treatment with CBT or GET. This demonstrated that the hypothesis that CFS/ME is a psychological or psychosomatic condition, perpetuated by a fear of exercise etc., is unfounded.

It is not surprising that CBT and GET, as treatments for CFS/ME, remain controversial with patients while they are promoted as 'successful' treatments that 'reverse' the illness, or reverse disease progression. Such a model of disease is not supported by the evidence of the PACE Trial, in which 87% of participants were not shown to respond to treatment, and it is not supported by the anecdotal experiences of many patients, a substantial proportion of whom anecdotally report being harmed by CBT and GET in clinical settings (33).

Interestingly, based on information in the protocol, the authors of the PACE Trial, many of whom have a background in psychiatry and in promoting CBT and GET as treatments for CFS/ME, seem to have expected the results to show a 60% benefit for CBT and GET, and only a 10% benefit for specialised medical care (the SMC control group), but in fact, it was the opposite: Roughly 60% improved in the control group, and only approximately 13% improved as a result of CBT or GET.

Maybe the psychiatrists (the authors) had always mistakenly believed that their therapies were highly successful treatments, when in fact, the improvements seen in their patients were a result of natural improvements over time, as demonstrated by SMC control group in the PACE trial (58% and 65% improvement rates for SMC). The psychiatrists assert that CFS/ME patients have 'maladaptive' cognition and behaviour which 'perpetuates' the illness, but the PACE Trial gave us evidence that the psychiatrists, are in fact, mistaken about the treatments they offer and about the nature of CFS/ME.

It should be noted that the PACE Trial's deterioration rates for CBT and GET, as determined by an equivalent measure as the improvement rates, have not yet been released. Once the deterioration rates are released, the results for CBT and GET might confirm CFS/ME patients' anecdotal reports of harm from CBT and GET (33).

Harm from exposure to CBT and GET (33)(36) may be a result of 'post exertional malaise' or 'postexertional neuroimmune exhaustion', widely recognised to be a primary symptom of CFS/ME (34)(35). CFS/ME is reactive to activity or exertion (34), which is why patients often use 'pacing', to self-manage symptoms.

It should be noted that Adaptive Pacing Therapy (APT) was invented specifically for the PACE Trial and thus it was a failed attempt to devise a new therapy. APT is not the same as 'pacing', as recognised, and used, by many CFS/ME patients. If a form of pacing, recognisable to patients, was properly tested in a medical trial, then it might also confirm patients' anecdotal experiences, whereby a majority of CFS/ME patients anecdotally report finding 'pacing' beneficial for managing their symptoms (33).

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"In accordance with this criterion, the recovery rate of cognitive behaviour therapy and graded exercise therapy was about 30%—although not very high, the rate is significantly higher than that with both other interventions."

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http://www.meactionuk.org.uk/PACEpressconf.mp3
Conference was held at the Science Media Centre on the 17th February 2011
Professor Trudie Chalder stated:
"...if you think about the number of people who get back to normal levels of functioning and fatigue then you see twice as many people in the graded exercise therapy and cognitive behavioural therapy group improving and getting back to normal compared the other two groups."

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18 February 2011
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"About 30 per cent of patients given cognitive behavioural therapy (CBT) or graded exercise made a full recovery to normal levels of activity, the study found..."

(5) **The Independent**
18 February 2011
http://www.independent.co.uk/life-style/health-and-families/health-news/got-me-just-get-out-and-exercise-say-scientists-2218377.html
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Abstracts, oral presentations (appearing in session order)
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"We found that CBT and GET were more effective than APT and SMC"

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Paul McCrone, Michael Sharpe, Trudie Chalder, Martin Knapp, Anthony L. Johnson, Kimberley A. Goldsmith, Peter D. White.
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01 February 2006
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[Adults without chronic disease, aged 40 to 80 years, across seven countries = 571m]

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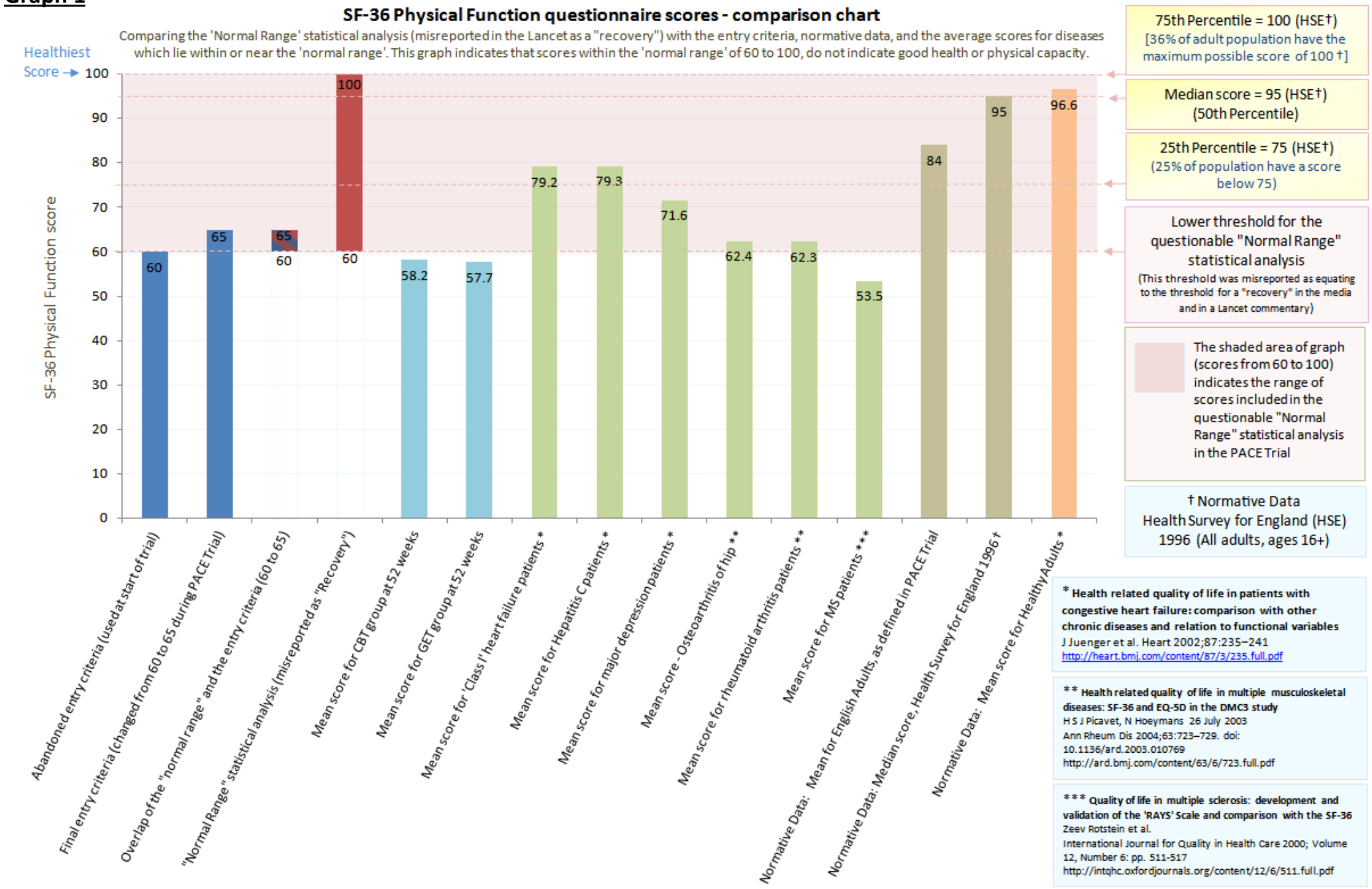
[Patients with class III heart failure = 402m]

Graph 1



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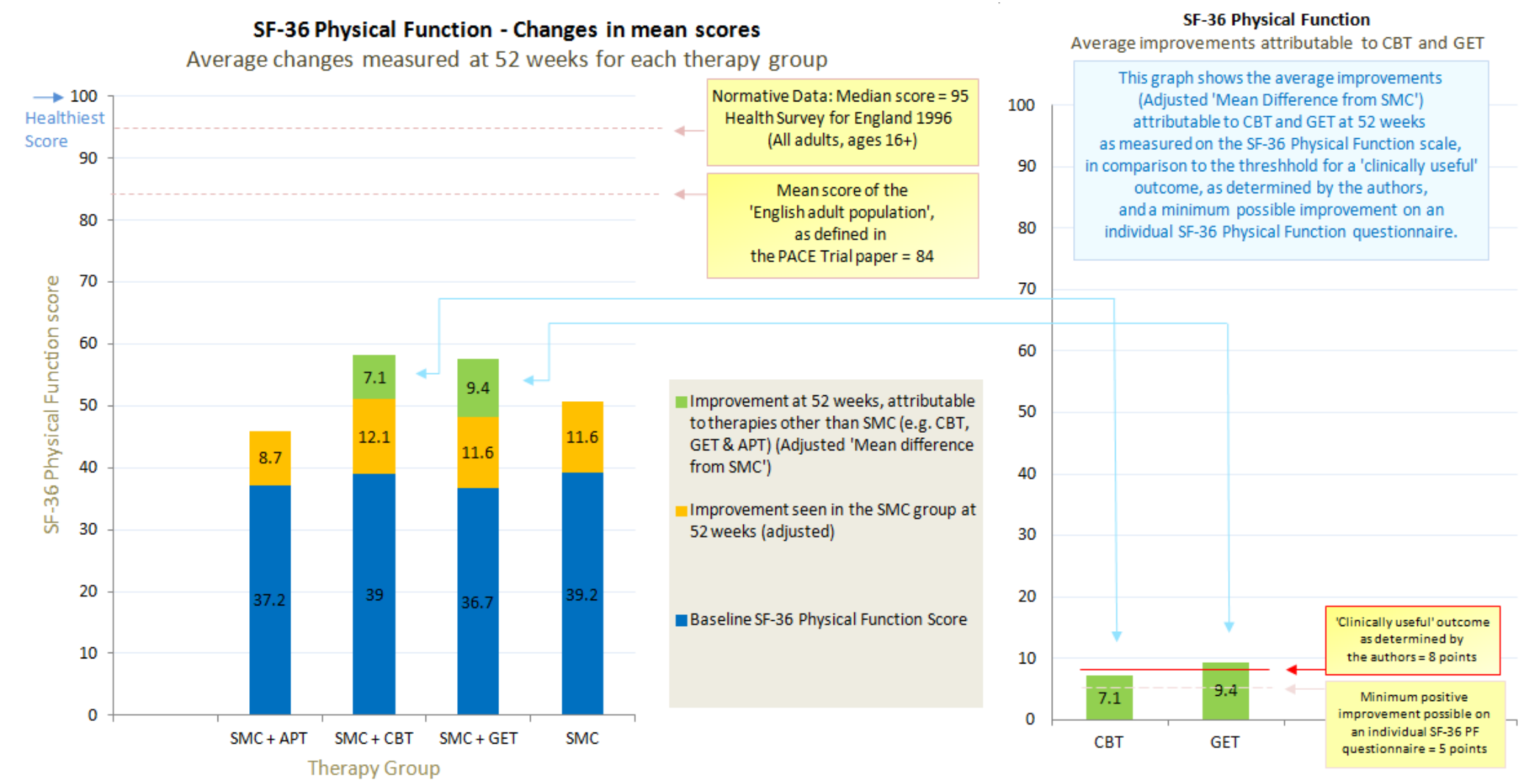
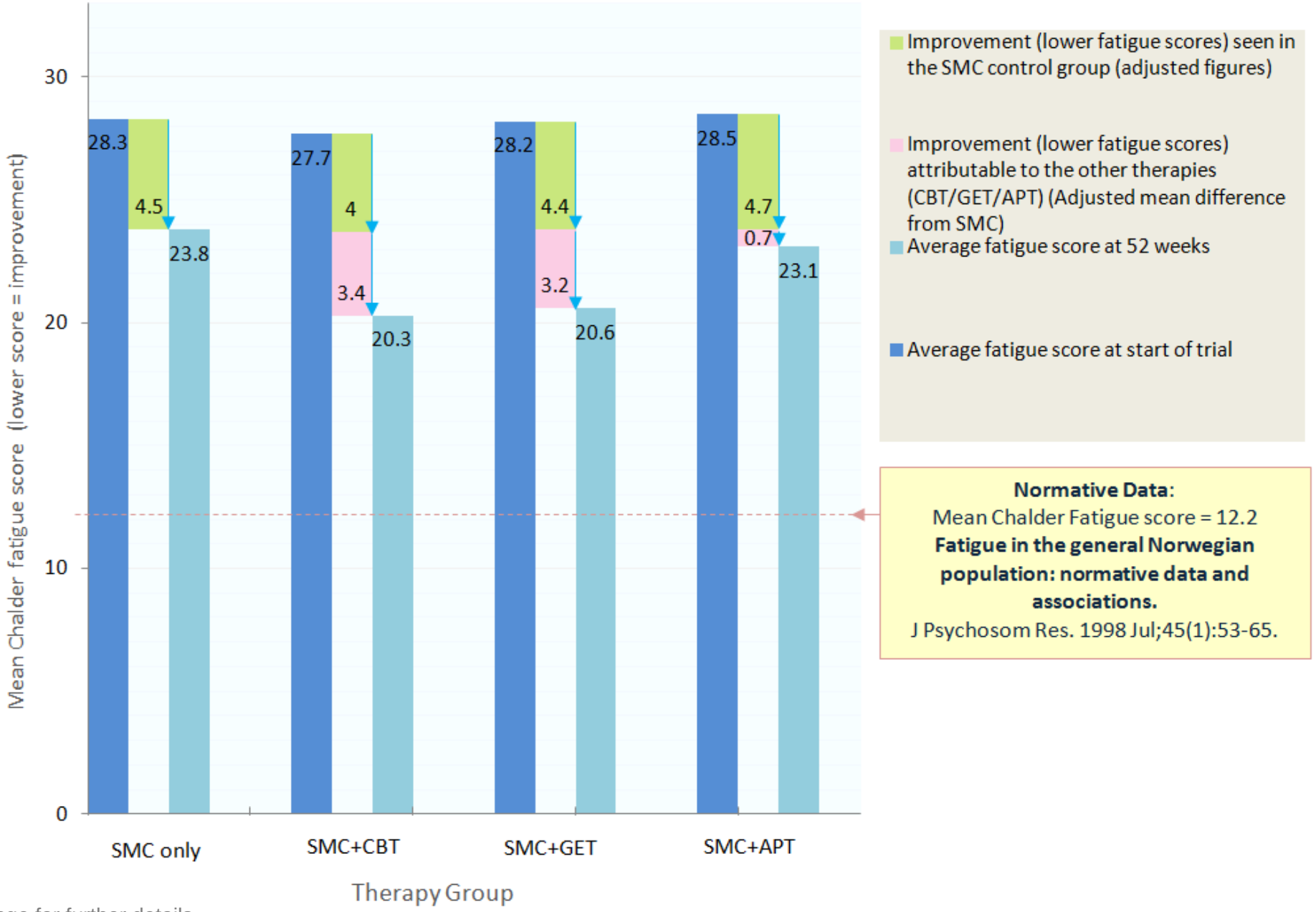
Graph 2


SF-36 Physical Function - Changes in mean scores
Average changes measured at 52 weeks for each therapy group
Healthiest Score
100
90
80
70
60
50
40
30
20
10
0
SF-36 Physical Function score
Normative Data: Median score = 95
Health Survey for England 1996
(All adults, ages 16+)
Mean score of the
'English adult population',
as defined in
the PACE Trial paper = 84
8.7
37.2
7.1
12.1
39
9.4
11.6
36.7
11.6
39.2
SMC + APT
SMC + CBT
SMC + GET
SMC
Therapy Group
Improvement at 52 weeks, attributable to therapies other than SMC (e.g. CBT, GET & APT) (Adjusted 'Mean difference from SMC')
Improvement seen in the SMC group at 52 weeks (adjusted)
Baseline SF-36 Physical Function Score
SF-36 Physical Function
Average improvements attributable to CBT and GET
This graph shows the average improvements (Adjusted 'Mean Difference from SMC') attributable to CBT and GET at 52 weeks as measured on the SF-36 Physical Function scale, in comparison to the threshhold for a 'clinically useful' outcome, as determined by the authors, and a minimum possible improvement on an individual SF-36 Physical Function questionnaire.
7.1
9.4
CBT
GET
'Clinically useful' outcome as determined by the authors = 8 points
Minimum positive improvement possible on an individual SF-36 PF questionnaire = 5 points

Graph 3

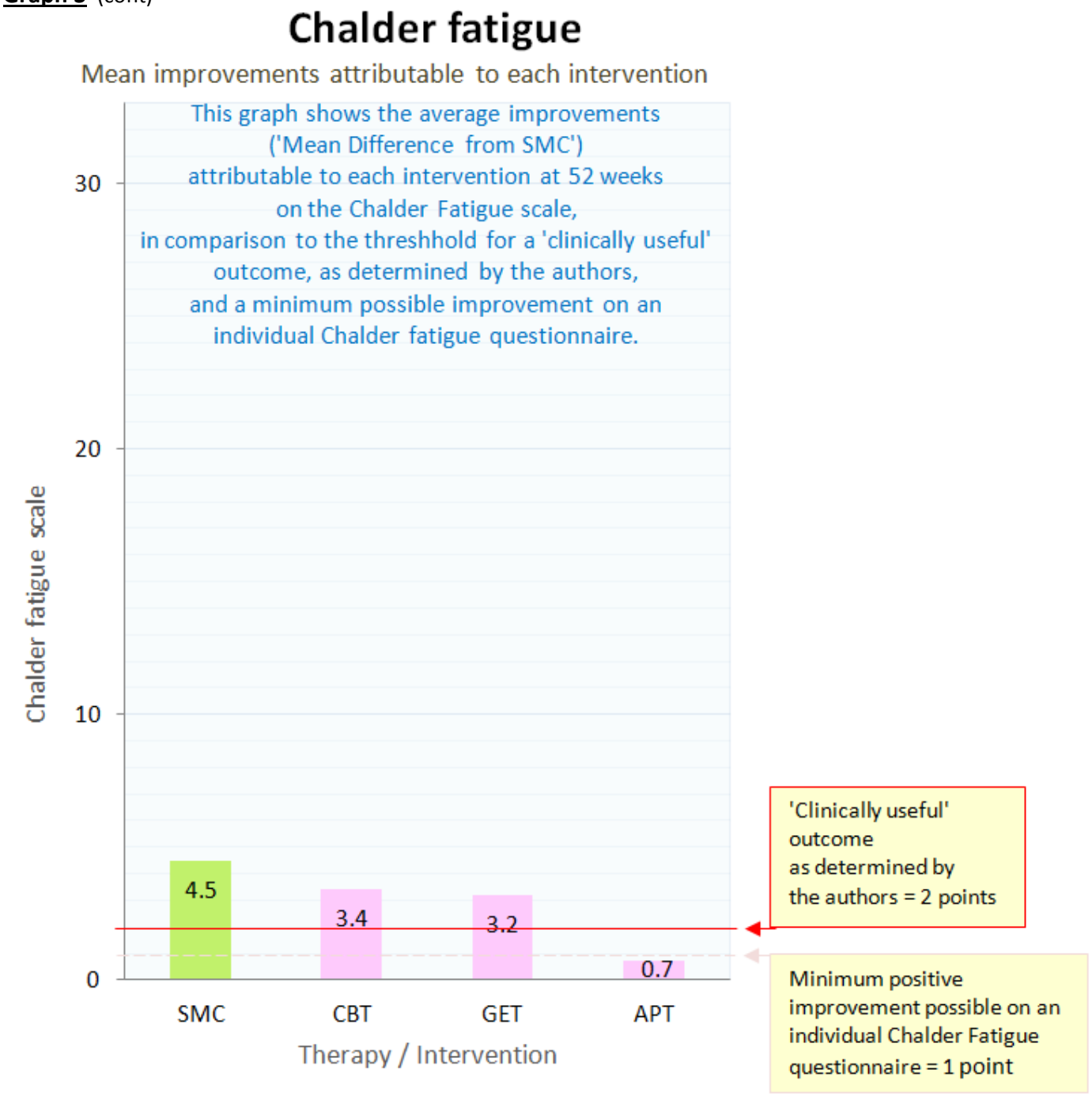
Chalder fatigue - Changes in mean scores for each therapy group

Graph showing the average improvements in Chalder Fatigue scores in the SMC control group and attributable to each intervention

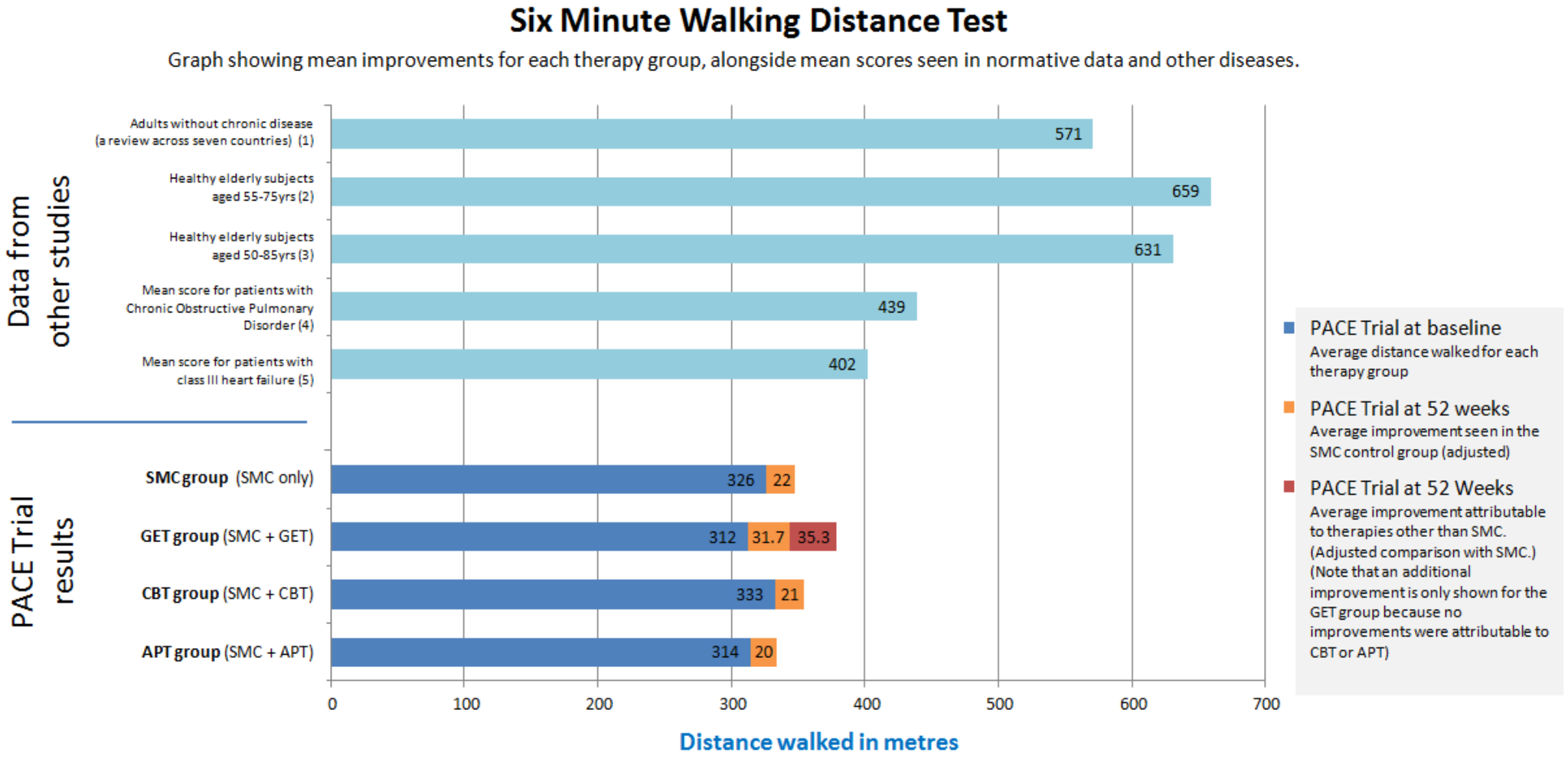


See next page for further details...

Graph 3 (cont)


Chalder fatigue
Mean improvements attributable to each intervention
This graph shows the average improvements ('Mean Difference from SMC') attributable to each intervention at 52 weeks on the Chalder Fatigue scale, in comparison to the threshhold for a 'clinically useful' outcome, as determined by the authors, and a minimum possible improvement on an individual Chalder fatigue questionnaire.
Chalder fatigue scale
30
20
10
0
4.5
3.4
3.2
0.7
SMC
CBT
GET
APT
Therapy / Intervention
'Clinically useful' outcome as determined by the authors = 2 points
Minimum positive improvement possible on an individual Chalder Fatigue questionnaire = 1 point

Graph 4



The most objective measure used in the PACE Trial to assess the effectiveness of the interventions, was the Six Minute Walking Distance Test.

The CBT group achieved no average improvement beyond the SMC control group.

The GET group made a small average improvement (35.3 m) beyond the SMC control group (adjusted difference from SMC) after 52 weeks.

The average distance that the GET group achieved, of 379m at 52 weeks, is still far from what might be considered a common healthy average distance, as shown in the graph.

Various other studies have measured reference values for the normal population, as shown in the graph for comparison. (Please see references below.)

See next page for further details...

Graph 4 (cont)

References:

(1) **The 6-min walk distance in healthy subjects: reference standards from seven countries.**
Casanova C, Celli BR, Barria P, Casas A, Cote C, de Torres JP, Jardim J, Lopez MV, Marin JM, Montes de Oca M, Pinto-Plata V, Aguirre-Jaime A; Six Minute Walk Distance Project (ALAT).
1 January 2010
European Respiratory Journal 2011 Jan;37(1):150-6. Epub 2010 Jun 4.
doi: 10.1183/09031936.00194909
http://www.ncbi.nlm.nih.gov/pubmed/20525717
http://erj.ersjournals.com/content/early/2010/06/04/09031936.00194909.full.pdf+html
Adults without chronic disease, aged 40 to 80 years, across seven countries = 571m

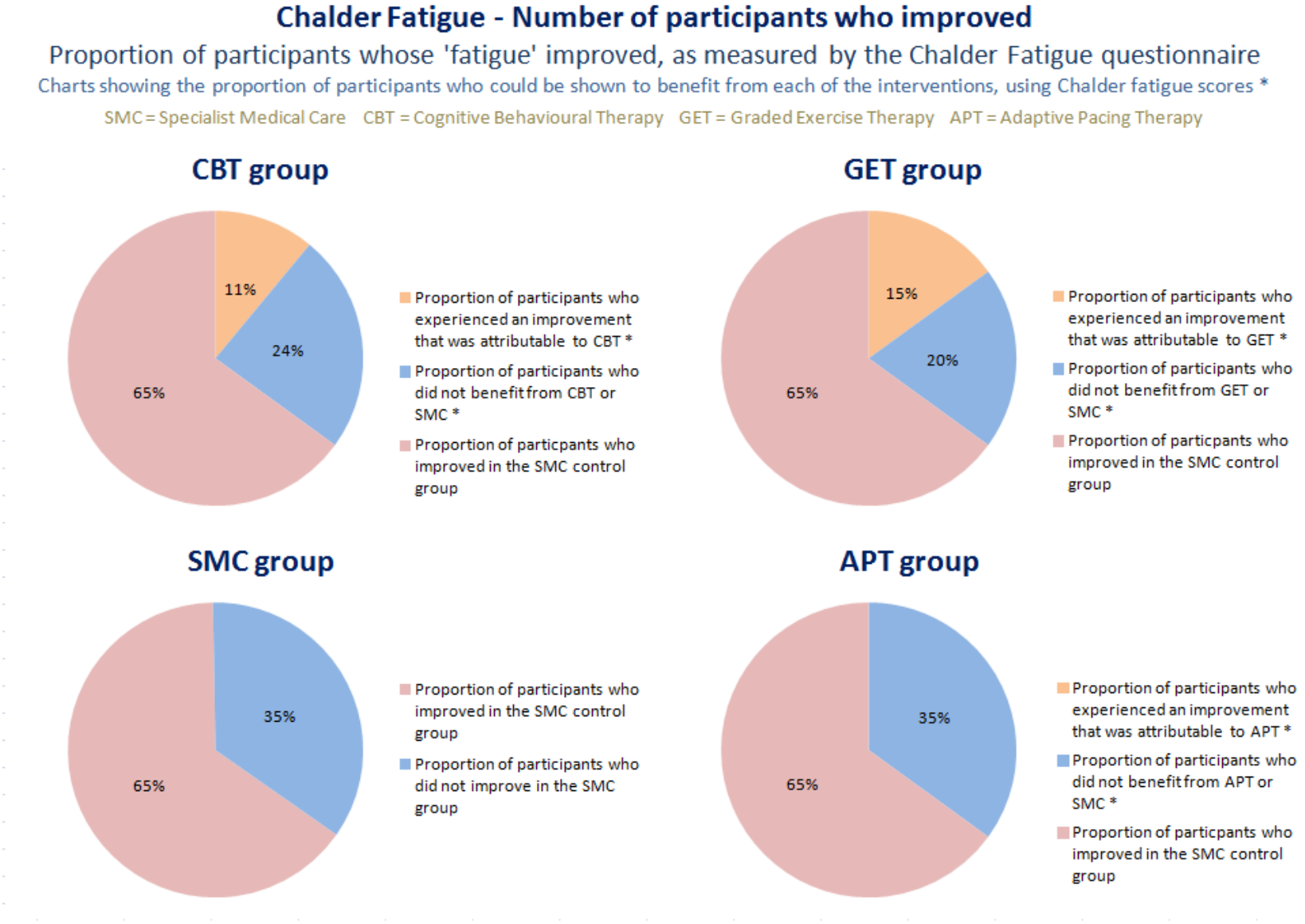
(2) **Six minute walk distance in healthy subjects aged 55–75 years**
Bernadine Camarri, Peter R. Eastwood, Nola M. Cecins, Philip J. Thompson, Sue Jenkins
Respiratory Medicine, Volume 100, Issue 4 , Pages 658-665, April 2006
http://www.resmedjournal.com/article/S0954-6111(05)00326-4/abstract
Healthy subjects aged 55-75yrs = 659m

(3) **Six minute walking distance in healthy elderly subjects**
T. Troosters, R. Gosselink, M. Decramer
Eur Respir J 1999; 14: 270±274
http://www.ersj.org.uk/content/14/2/270.full.pdf
Healthy elderly subjects (50-85 yrs) = 631m

(4) **Inspiratory Capacity, Dynamic Hyperinflation, Breathlessness, and Exercise Performance during the 6-Minute-Walk Test in Chronic Obstructive Pulmonary Disease**
José M. Marin, Santiago J. Carrizo, Manuel Gascon, Andres Sanchez, Begoña Gallego And Bartolomé R. Celli
Am. J. Respir. Crit. Care Med. May 1, 2001 vol. 163 no. 6 1395-1399
http://171.66.122.149/content/163/6/1395.full
Patients with Chronic Obstructive Pulmonary Disorder = 439m

(5) **Six minute walking test for assessing exercise capacity in chronic heart failure**
D P Lipkin, A J Scriven, T Crake, P A Poole-Wilson
British Medical Journal Volume 292 8 March 1986
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1339640/pdf/bmjcred00224-0015.pdf
Patients with class III heart failure = 402m

Graph 5



* These results are taken from Table 3 in the published paper:
"Number improved from baseline: Participants improved from baseline by two or more points for fatigue ..."
These charts show the proportion of participants who were shown to benefit from each of the interventions, and who improved by at least the minimum clinically useful amount, when assessed using Chalder fatigue scores, one of the two primary outcome measures.
For Chalder fatigue scores, a 'clinically useful' improvement was determined by the authors to be 2 points.
For APT, CBT and GET , these results are based on the 'difference from SMC', using SMC as the control group.
For APT, the 'difference from SMC' is not shown in the chart because it has a zero value.

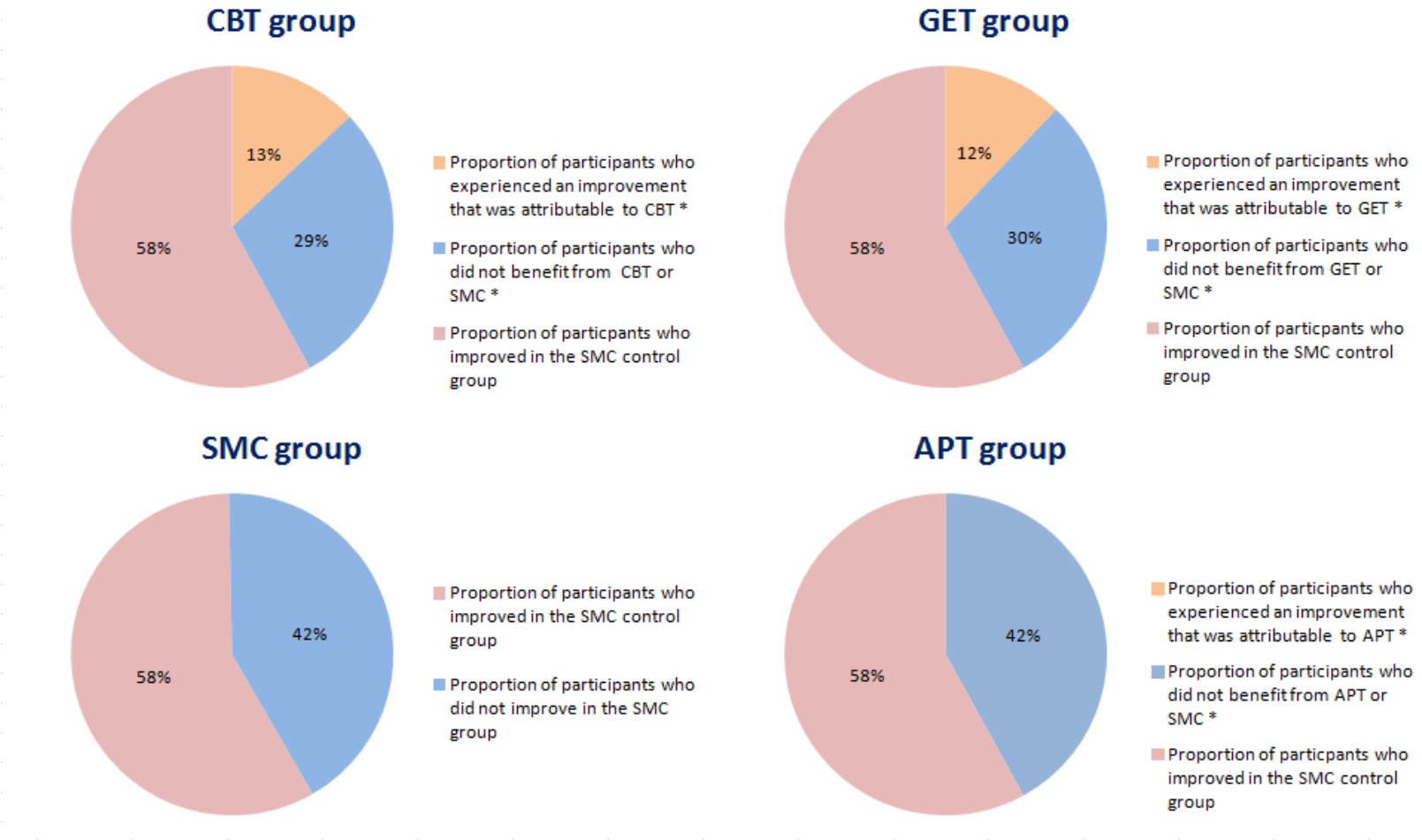
Graph 6

SF-36 Physical Function - Number of Participants who improved

Proportion of participants whose 'physical function' improved, as measured by the SF-36 Physical Function questionnaire

Charts showing the proportion of participants who could be shown to benefit from each of the interventions using SF-36 physical function scores *

SMC = Specialist Medical Care CBT = Cognitive Behavioural Therapy GET = Graded Exercise Therapy APT = Adaptive Pacing Therapy



* These results are taken from Table 3 in the published paper:
"Number improved from baseline: Participants improved from baseline by [...] eight or more for physical function."
These charts show the proportion of participants who were shown to benefit from each of the interventions, and who improved by at least the minimum clinically useful amount, when assessed using SF-36 physical function scores, one of the two primary outcome measures.
For SF-36 physical function scores, a 'clinically useful' improvement was determined by the authors to be 8 points.
For APT, CBT and GET , the results are based on the 'difference from SMC', using SMC as the control group.
For APT, the 'difference from SMC' has a negative value (-9 percent) and so an improvement is not indicated in the graph. (Fewer participants improved in the APT group than the SMC group.)

Graph 7

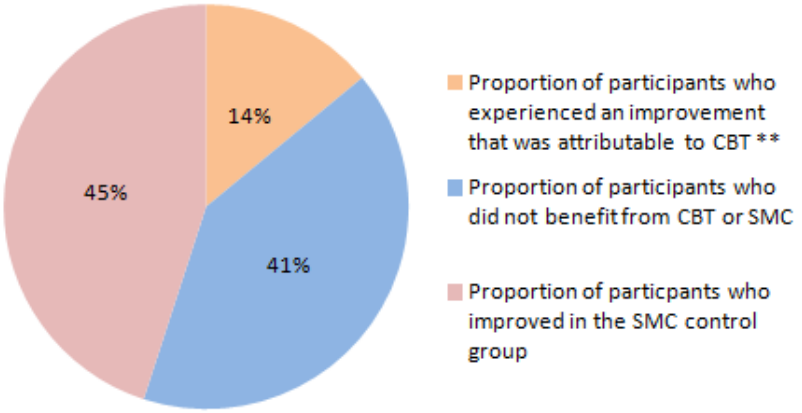
Number of Participants Who Improved

"secondary post-hoc analysis"

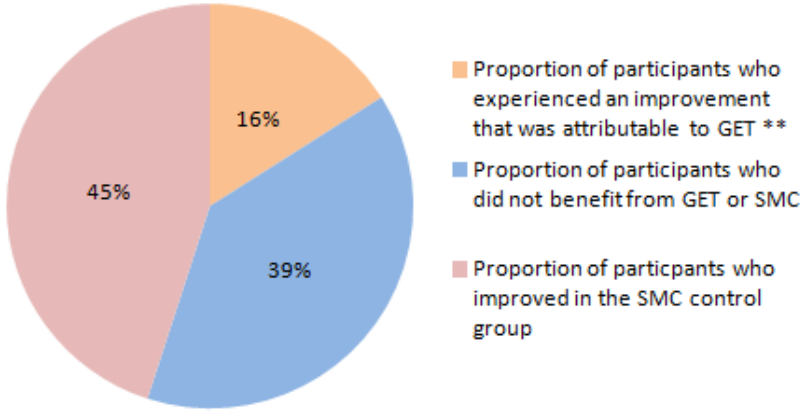
Charts showing the proportion of participants who could be shown to benefit in both of the primary outcome measurements (SF-36 physical function and Chalder fatigue) as a result of each of the interventions *

SMC = Specialist Medical Care CBT = Cognitive Behavioural Therapy GET = Graded Exercise Therapy APT = Adaptive Pacing Therapy

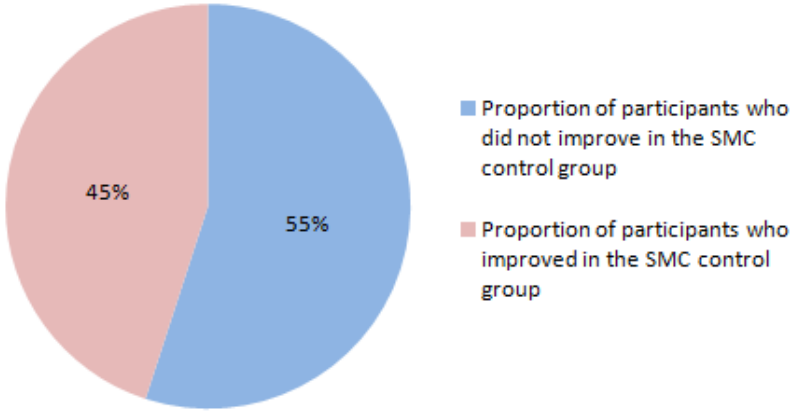
CBT group



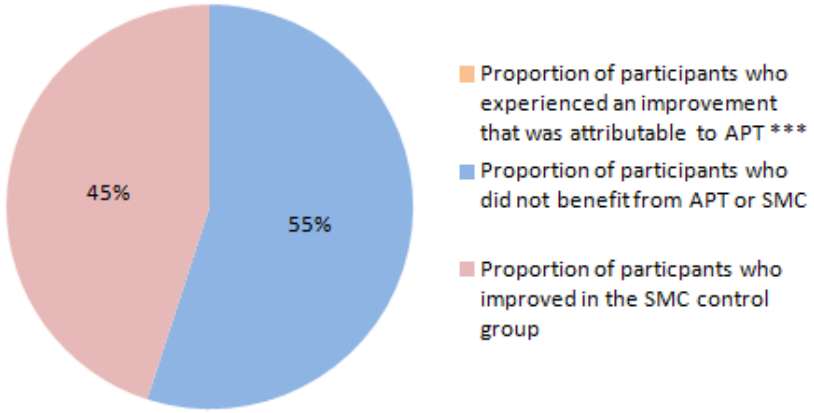
GET group



SMC group



APT group



* see over page for details

Graph 7 (cont)

* These pie charts show the proportion of participants who were shown to benefit from each of the treatments by at least a 'clinically useful' amount (as determined by the authors), for both of the primary outcome measures (both SF-36 Physical Function and Chalder fatigue). These results are based on a 'post-hoc' analysis which is presented in the published paper.

** For CBT and GET, the results are based on the 'difference from SMC', using SMC as the control group.

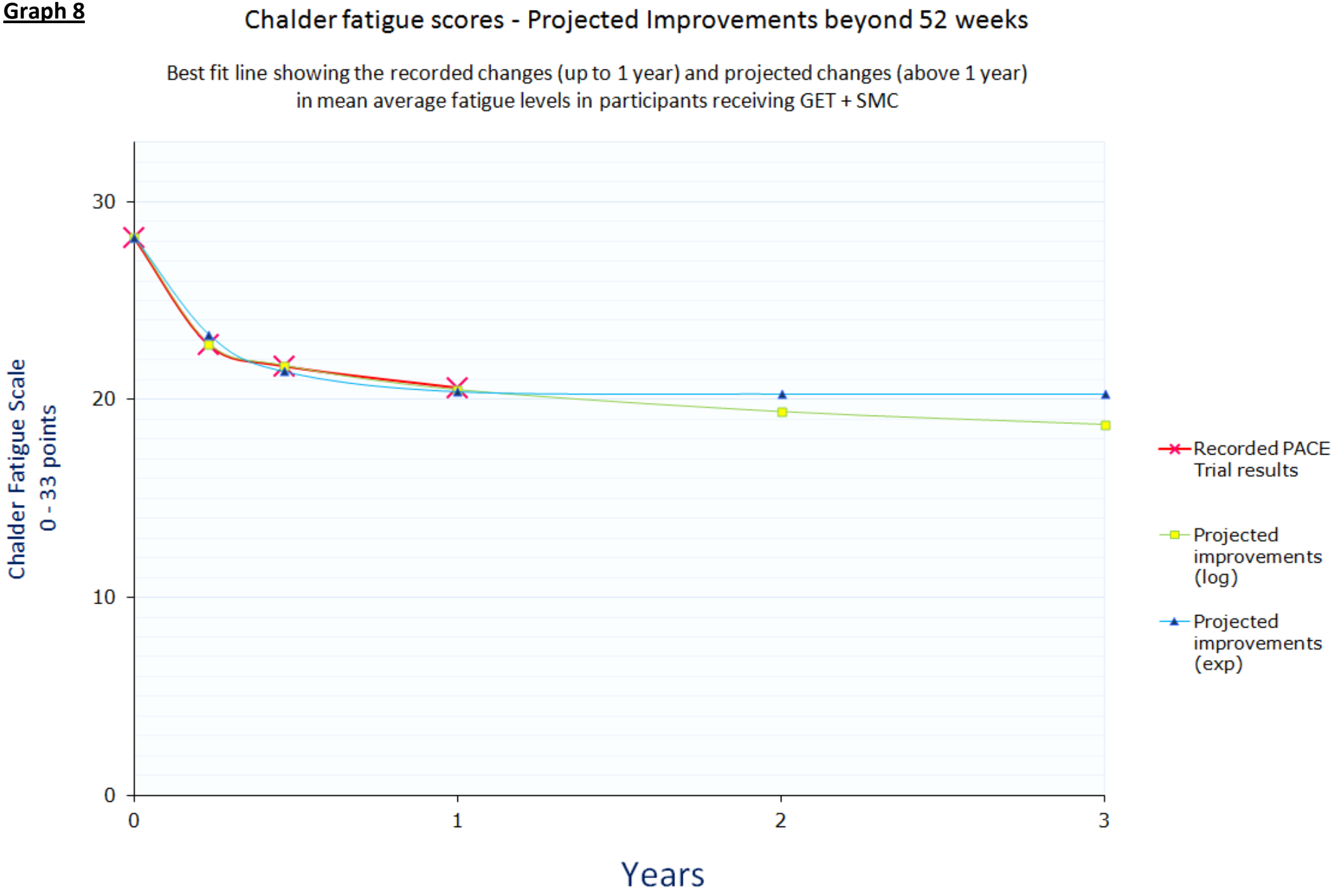
*** For APT, the 'difference from SMC' is not shown in the pie chart because it is a negative value (-3%).

Explanation from PACE Trial paper:

"A clinically useful difference between the means of the primary outcomes was defined as 0·5 of the SD of these measures at baseline, equating to 2 points for Chalder fatigue questionnaire and 8 points for short form-36. A secondary post-hoc analysis compared the proportions of participants who had improved between baseline and 52 weeks by 2 or more points of the Chalder fatigue questionnaire, 8 or more points of the short form-36, and improved on both."

"64 (42%) of 153 participants in the APT group improved by at least 2 points for fatigue and at least 8 points for physical function at 52 weeks, compared with 87 (59%) of 148 participants for CBT, 94 (61%) of 154 participants for GET, and 68 (45%) of 152 participants for SMC."

Graph 8

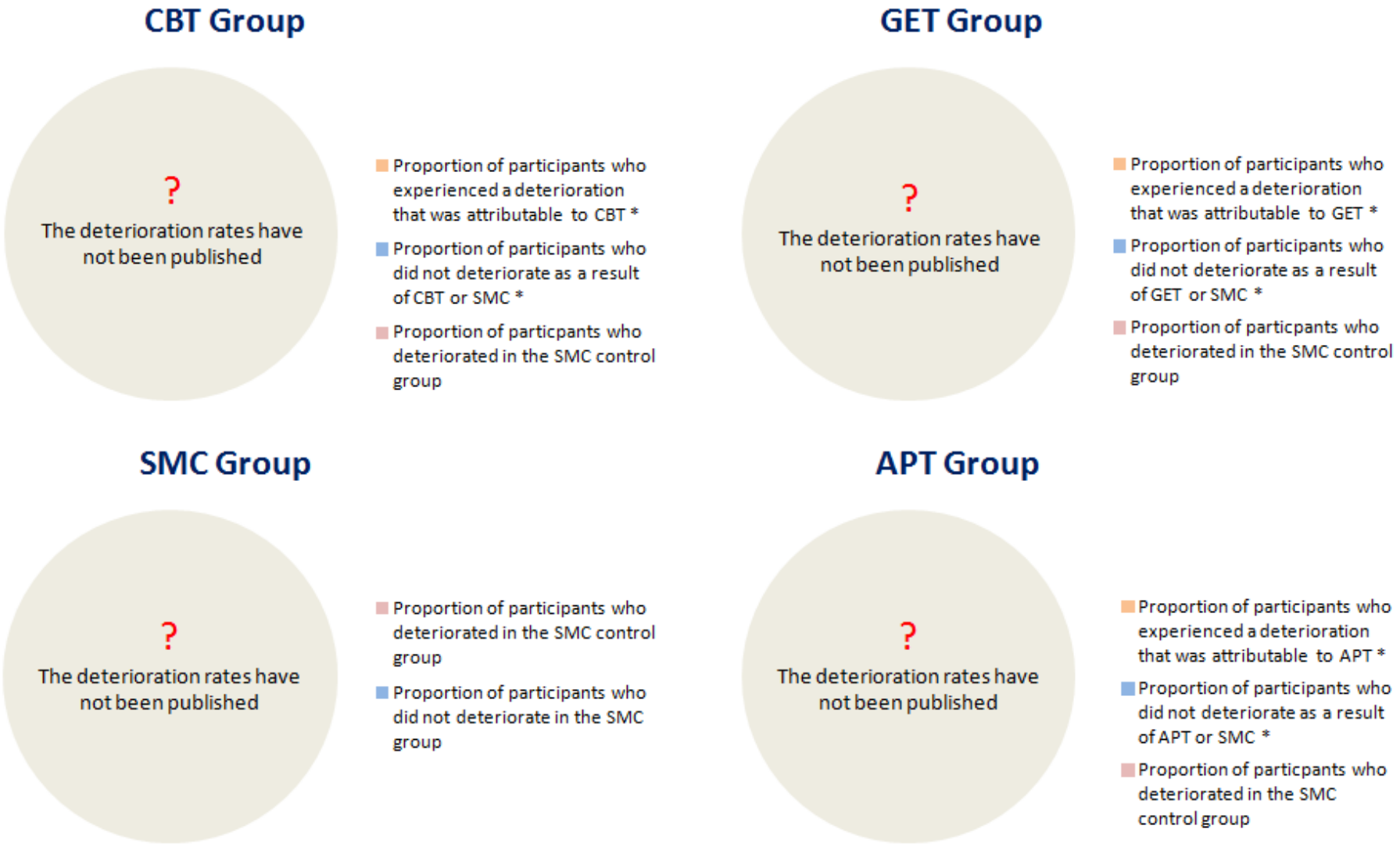

Chalder fatigue scores - Projected Improvements beyond 52 weeks
Best fit line showing the recorded changes (up to 1 year) and projected changes (above 1 year)
in mean average fatigue levels in participants receiving GET + SMC
Chalder Fatigue Scale
0 - 33 points
30
20
10
0
0
1
2
3
Years
Recorded PACE Trial results
Projected improvements (log)
Projected improvements (exp)

Graph 9

Deterioration Rates - Number of Participants who deteriorated

Charts showing the proportion of participants who deteriorated as a result of each of the interventions by the 'clinically useful difference' or more (at least 2 points for Chalder fatigue and 8 points for SF-36 physical function) *

SMC = Specialist Medical Care CBT = Cognitive Behavioural Therapy GET = Graded Exercise Therapy APT = Adaptive Pacing Therapy



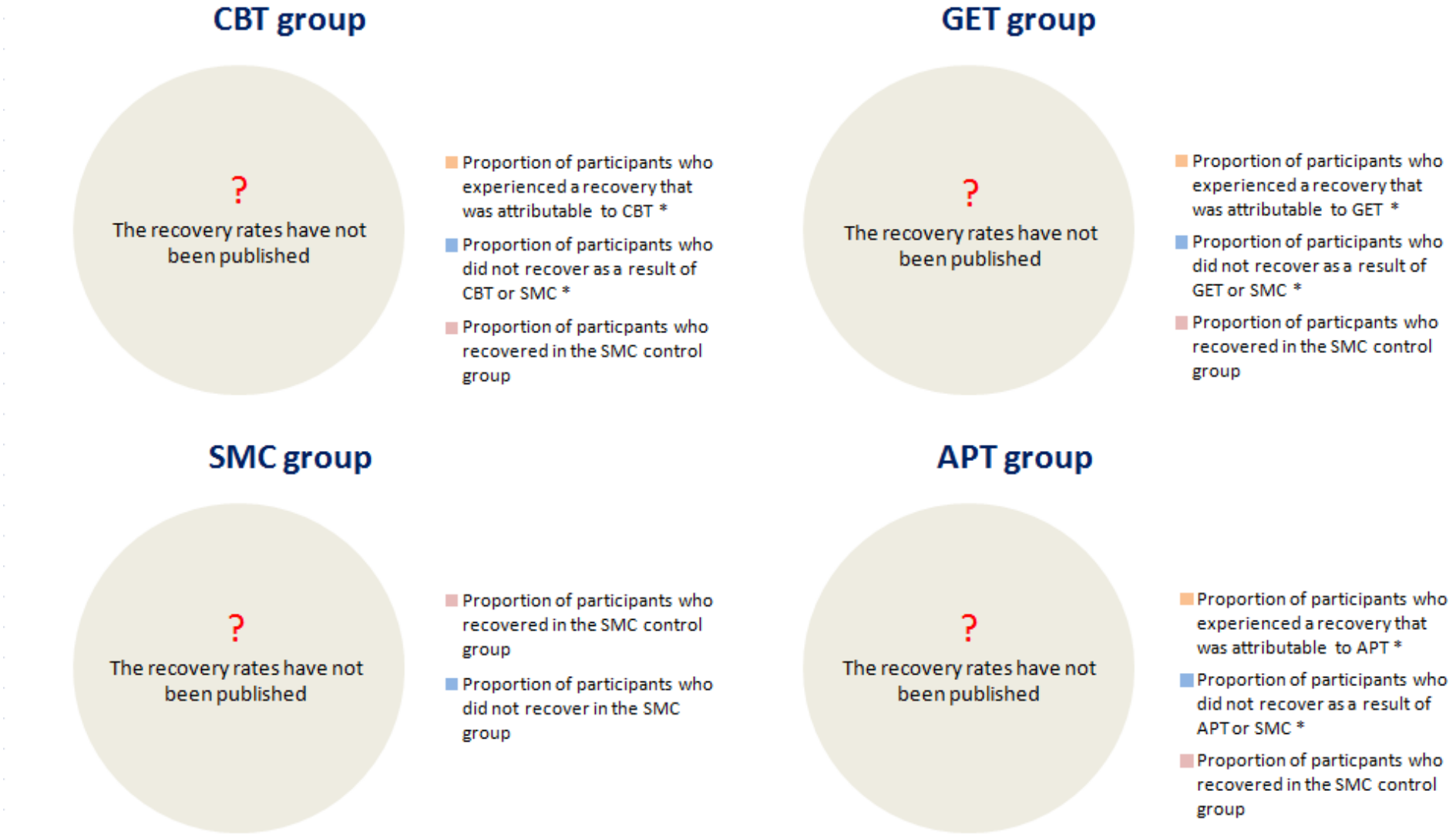
* To date, rates of deterioration, based on the same measures as the published rates of improvement (a 'clinically useful difference' or more) have not been published.

Graph 10

Recovery Rates - Number of Participants who Recovered

Charts showing the proportion of participants who recovered as a result of each of the interventions *

SMC = Specialist Medical Care CBT = Cognitive Behavioural Therapy GET = Graded Exercise Therapy APT = Adaptive Pacing Therapy



* To date, the recovery rates have not been published.