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Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Tom Kindlon
Information Officer (voluntary position)
Irish ME/CFS Association
PO Box 3075, Dublin 2, Rep. of Ireland
Tel: +353-1-2350965
E-mail: tkindlon@maths.tcd.ie or info@irishmecfs.org

ABSTRACT

Across different medical fields, authors have placed a greater emphasis on the reporting of efficacy measures than harms in randomised controlled trials (RCTs), particularly of nonpharmacologic interventions. To rectify this situation, the Consolidated Standards of Reporting Trials (CONSORT) group and other researchers have issued guidance to improve the reporting of harms. Graded Exercise Therapy (GET) and Cognitive Behavioural Therapy (CBT) based on increasing activity levels are often recommended for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). However, exercise-related physiological abnormalities have been documented in recent studies and high rates of adverse reactions to exercise have been recorded in a number of patient surveys. Fifty-one percent of survey respondents (range 28-82%, n=4338, 8 surveys) reported that GET worsened their health while 20% of respondents (range 7-38%, n=1808, 5 surveys) reported similar results for CBT.

Using the CONSORT guidelines as a starting point, this paper identifies problems with the reporting of harms in previous RCTs and suggests potential strategies for improvement in the future. Issues involving the heterogeneity of subjects and interventions, tracking of adverse events, trial participants' compliance to therapies, and measurement of harms using patient-oriented and objective outcome measures are discussed. The recently published PACE (Pacing, graded activity, and cognitive behaviour therapy: a randomised evaluation) trial which explicitly aimed to assess "safety", as well as effectiveness, is also analysed in detail. Healthcare professionals, researchers and patients need high quality data on harms to appropriately assess the risks versus benefits of CBT and GET.

Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

1. Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is increasingly recognised as an important worldwide health problem (1,2). Community-based epidemiological studies have shown it is more prevalent than previously thought and that it affects people of all races and socioeconomic groups (3-7). Illness intrusiveness is high with patients having poor health-related quality of life (8,9). Given that average onset is at an age when people should be at their most productive, its economic impact is substantial with total direct and indirect costs in the USA estimated at 18.7 to 24 billion dollars annually (10-13). There is a lack of consensus on many issues, including what causes the illness, what it should be called, how it should be defined, and whether it is one condition or many (14-31).

One of the most contentious views in the field of ME/CFS is the suggestion that gradual increase of activity or exercise will substantially improve or even reverse the condition (32-34). Proponents of Graded Exercise Therapy (GET), Graded Activity Therapy (GAT), and Cognitive Behavioural Therapy (CBT) programs which involve graded exercise/activity for ME/CFS often point to the efficacy that has been reported in the literature (35-41). Prior studies suggest that approximately 40% of those who received CBT experienced lower fatigue levels post-intervention in contrast to 26% in usual care, while those receiving GET experienced both lower fatigue levels as well as improved self-rated physical functioning. Although a small number of trials have shown some benefits over the long term, most of the efficacy data are from trials that did not involve long-term follow-up (35,36,42-45). Other non-pharmacological interventions have also been proposed, with some showing efficacy in trials (46-53).

Although RCTs of CBT and GET have generally shown average improvements on the measures reported (which is not the same as meaning no individual deteriorated on these measures), one recently published randomised controlled trial (RCT) of a "[m]ultidisciplinary treatment combining CBT, GET, and pharmacological treatment" found that, at 12 months, there was a statistically significant decline in physical function compared to baseline when measured by the Medical Outcomes Study Short-Form questionnaire (SF-36) physical function subscale and that pain was significantly worse when measured by both the SF-36 bodily pain and the pain subscale of the Stanford Health Assessment Questionnaire (HAQ) (54). There was also a statistically significant increase in the total number of the following co-morbidities: fibromyalgia, sicca syndrome, endometriosis/dysmenorrhea, dysthymia, thyroid dysfunction, multiple chemical sensitivity, and irritable bowel syndrome.

Many patients, as well as some clinicians and researchers, disagree that CBT and GET should be routinely recommended at this time believing, amongst other reasons, that safety issues have not been properly addressed (55). Using a generic definition of "harms", the harms associated with

GET (or CBT) could be defined as the "totality of possible adverse consequences of GET (or CBT)" (56). Breau and colleagues constructed a more detailed definition when looking at harms in the urological literature (57) that could also be applied: "any undesirable event that occurred during the trial that had a deleterious impact on morbidity, mortality, quality of life or increase in the use of resources. Harm could be a primary or secondary outcome and could also be referred to as adverse event, side effect, complication, toxicity or safety." The purpose of this paper is to explore issues of safety for ME/CFS patients in regards to GET and the form of CBT that involves scheduling increasing activity and/or exercise.

2. Exercise and the measurement of the effects of exercise programs

It is well recognised that exercise can have beneficial effects for many in society. Exercise is recommended not only as an important component of maintaining good health and preventing disease but also suggested as an adjunct treatment for a host of chronic medical conditions. However, exercise can also cause harm (58). As Cooper and colleagues note (58), "like pharmaceutical therapies, prescribing exercise as therapy, an activity that is gaining in acceptance throughout the medical community, must be predicated on understanding the risks and benefits of exercise as thoroughly as possible."

Given the limited understanding of exercise pathophysiology in ME/CFS, it is difficult to formulate a definition of safe and effective exercise that confers the benefits of being active without causing harm. The effects of exercise in ME/CFS, although not fully understood, have been examined in several studies. A number of physiological abnormalities have been detected with exercise in individuals with ME/CFS (59,60), including metabolic disturbances, modified gene expression, decreased cognitive reaction times, impaired cellular ion channel functions, and immune dysfunction. For example, the Pacific Fatigue Laboratory, using the commonly accepted American Medical Association disability guidelines, found that 48% of 203 CFS subjects would be classified as moderately to severely impaired based on peak oxygen uptake (VO_2 max) during cardiopulmonary exercise testing (CPET) (61). Furthermore, even among those participants who were not impaired or mildly impaired during initial testing, repeated testing 24 hours later yielded, on average, a 22% decline in VO_2 max (62). This is unique and significantly different from other chronic diseases where VO_2 max initially can be low but is reproducible on repeated CPET (61).

In another study, Light and colleagues compared the effect of moderate exercise on patients with CFS and controls (63). These investigators found that after the exercise, CFS patients showed enhanced gene expression for receptors detecting muscle metabolites and for both the sympathetic nervous and immune systems; many of these changes correlated with symptoms of physical fatigue, mental fatigue, and pain. Given the range of abnormalities that have been found with exercise in ME/CFS subjects, it would not be unexpected if programs encouraging increased physical activity resulted in adverse reactions for some patients.

Indeed, observational studies have shown that physical exertion of various intensities can provoke a diverse array of symptoms in ME/CFS such as fatigue, light-headedness, muscular/joint pain, cognitive dysfunction, headache, nausea, physical weakness, trembling/instability, insomnia, and sore throat/glands (64,65). These symptoms are not uncommon and can last days, if not weeks, for some individuals (65). In 2006, an audit of adult specialty ME/CFS rehabilitation (CBT/GET) clinics in Belgium (clinics that had been set up following a request from the Minister of Social Affairs (66)) found that, compared to before treatment, about one-third of participants reported worsening of their pain, concentration, and sleep after CBT/GET (67,68).

It should be noted that randomised controlled trials (RCTs) of GET and CBT have tended to assess fatigue primarily, so it is unclear whether other symptoms have regularly been exacerbated in such trials. Furthermore, the instruments used to measure fatigue often suffer from ceiling/floor effects so it is not possible to ascertain whether some participants experienced a worsening of their fatigue (69-71). Moreover, factor analysis has shown that fatigue in ME/CFS is multidimensional and so other scales, such as the ME/CFS Fatigue Types Questionnaire (MFTQ), may be required to capture the different fatigue-related sensations and symptoms experienced by patients with the condition (72).

3. Direct reports of adverse reactions by patients

3.1. The value of patients' self-reported data

Generally, in medicine, the documentation of adverse reactions to pharmacologic and non-pharmacologic treatments has almost entirely been based on reports from researchers and clinicians. However, Basch has contended that an accurate portrait of patients' subjective experiences cannot be obtained from clinicians' and researchers' documentation alone: "A substantial body of evidence [shows that] clinicians systematically downgrade the severity of patients' symptoms, that patients' self-reports frequently capture side effects that clinicians miss, and that clinicians' failure to note these symptoms results in the occurrence of preventable adverse events" (73). Given this information, a system for reporting adverse events to treatments would ideally involve the collection of data from patients as well as health care professionals.

3.2. Qualitative and quantitative data about harms from GET and CBT

Currently, assessing the harms of non-pharmacologic treatment relies mainly on anecdotal data (74).

Discourse within the ME/CFS patient community is replete with reports of adverse reactions from those who undertook exercise programs. Some members of the Irish ME/CFS Association have reported not just temporary increases in ME/CFS symptoms but also long-term decreased

levels of functioning. This was explicitly recorded in a United Kingdom 25% ME Group survey where the authors noted that some participants had made clear that they had not been severely affected before undertaking a GET program (75). This was echoed in a subsequent survey by the same group (76):

- *"I participated in Graded Exercise therapy via the <name of a ME/CFS specialist unit>. This lead to a relapse, at home, and made me unable to sit upright for 1 year due to pressure in my head, and chest pain. I then relapsed and ended up in my local NHS Hospital in a cardiac care unit."*
- *"Graded Exercise Therapy worsened me dramatically and I have no doubt had been a large factor in my being severely affected after 20 years."*
- *"I worked with a physiotherapist, who also had no experience of M.E. I began to seriously deteriorate, and 4 months in, suffered a major relapse. I had a kind of undiagnosed 'stroke', collapsed, and became incapable of looking after myself. When I went to the hospital I could walk 100 yd., feed, wash and dress myself. When I left I could not weight bear at all, had no leg muscles to speak of, and needed two people to transfer me on and off the toilet and in and out of bed. I had little use of my hands and was totally bed bound. I could not tolerate sitting upright against the pillows, conversation was beyond me, and I could barely manage to feed myself by picking up food in my hands -- cutlery was out of the question. Nine years later I have improved, but I'm still bed bound.*

One recently published study found that there was a trend for both CBT ($p=0.088$) and GET ($p=0.02$) (received before diagnosis) to be risk factors for severe illness at follow-up (77). In addition, the risk for a related modality, physiotherapy ($p=0.0009$), was significant at an α-threshold of 0.0036. It is important to point out that this was a self-report retrospective survey, rather than a prospective longitudinal study, and thus has similar limitations to other surveys, as itemised in section 3.3. Also, the sample sizes were relatively small. Of those reporting therapies before diagnosis, there were 415 individuals with mild illness and 84 with severe illness (at follow-up); 18 mild cases and 8 severe cases reported using CBT while 23/11 and 35/20, respectively, reported receiving GET and physiotherapy.

High rates of adverse reactions following GA/GE programs have consistently been reported in large patient surveys in various countries over the last two decades (see Table 1) (75, 77-85). Participants in these surveys were asked about the effect of GET and a myriad of treatment and management strategies on their health. The data has been pooled in Table 2, with the mean of worsening for GET/GAT and CBT respectively amounting to 51.24% (range: 28.1-82%) and 19.91% (7.1-38%) of subjects. The percentages of subjects adversely affected in Table 2 are not low; in comparison, an average of 2.58% (of 5894) subjects reported that "pacing" worsened their health.

3.3. Limitations of survey data

Some researchers have been dismissive of the survey results, contrasting them with what they see as the safety that has been proven in RCTs and suggesting the discrepancy might be due to

improper implementation of GET outside of RCTs. Even if safety had been shown in RCTs, which is debatable given there appears to be scope for improvement in the reporting of harms (see sections 4 and 5), it has been observed in other medical domains that outcomes from routine practice may be more relevant than the "artificial" environment of a clinical trial (86, 87). Moreover, a subgroup analysis of a GET survey performed by Action for M.E./AYME and published in 2008 (82) found that there was no statistically significant difference in the rate of people saying they were made worse from engaging in GET under a "NHS specialist" (31.27%, 111/355) compared to the rest of those reporting such an outcome from GET in another scenario (33.02%, 70/212).

Secondly, in eight of the surveys, categories of harm have been collapsed into single categories such as "harmful", "made worse", "disimproved with treatment" and "deterioration". In two of the surveys, two levels of severity of the harms were available to respondents: "somewhat worse" and "a lot worse". Although it is somewhat unsatisfactory to not have more details about adverse events, participant-rated clinical global impression (CGI) change scores, which use similar language, have been used as both primary and secondary outcome measures in RCTs of non-pharmacologic interventions for ME/CFS (44, 49, 88-92). The current survey data and CGI change scores can be subject to recall and other biases as they are dependent on the participant having an accurate memory of how they were overall before the therapy and making an accurate global comparison.

Thirdly, survey respondents may not be representative of all who undertake CBT and GET, resulting in either an over- or under-estimate of harm. People who have been harmed by GET or CBT may be more inclined to fill in treatment surveys or join patient groups. Members of ME/CFS patient groups may also satisfy more restrictive definitions for ME/CFS (which may correspond with less response to GET/CBT), have been sick for a longer period of time (79, 85), or be more severely affected. On the other hand, some of the most disabled subset of patients may not be able to respond to the survey. People who actively seek out support organizations or fill in surveys may have higher levels of general education (93, 94). Compared to the general ME/CFS population, these individuals might be less likely to be harmed by a therapy not only because of cautions about exercise and CBT/GET issued by patient groups but also because they have the confidence to challenge prevailing ideas about treatment that do not seem to be working for them.

Fourthly, there may be differences in the content of the therapies received. For example, the first Cochrane Review of CBT for CFS distinguished between two forms of CBT offered (95):

> *"The way in which modification of thoughts, beliefs, rest, and activity was attempted was used to delineate two 'types' of CBT. 'Type A' attempted to increase activity and reduce rest time in a systematic manner, independent of symptoms, towards 'normal' levels. 'Type B' attempted to tailor the patient's rest and activity towards levels which were compatible with the limitations imposed by the disorder. Therefore, type B CBT did not explicitly attempt to increase the*

patient's physical or psychological capacity beyond improving their ability to 'cope' with their disabilities.

Even within 'type A' and 'type B' protocols, as well as within GET programs, there can be heterogeneity in the components of the interventions (e.g., when activity levels should be decreased, maintained, or increased and by how much; the intensity of the exercise; the frequency per week, etc.). Consequently, harms-related data from one study may not be fully applicable to another. In an editorial on the reporting of psychological interventions in general, Marks highlights how there can be many differences between programs that appear superficially to be similar (96). Practitioners themselves can alter the program they offer over time. In a manual published in 2006, the influential team at Radboud University Nijmegen Medical Center described how their CFS program had changed from the one assessed in an earlier RCT (32,97).

The newer approach involved dividing patients up into two groups, the so-called "relatively active" and "relatively passive", and giving different advice to each group. The new protocol for "relatively passive" patients was quite intense (32): "So, for example, the first day the patient has six 1-minute walks, the second day six 2-minute walks, the third day six 3-minute walks, and so on. The aim is a total build-up of 5 minutes a week for each walk a day." The therapy usually offered in the UK does not divide patients in this way (41). Exactly what constituted GET or CBT for each survey respondent was not made explicit. It would have been ideal if we had data available on the activity/exercise performed by each survey participant; however, as discussed later in Section 5.4, even data taken from RCTs has generally been of a poor quality in terms of measuring the actual activity. These differences in focus, type, and execution of GET and CBT might at least partly explain the wide range of means in Table 2.

Differences in the content of interventions may also explain the large difference in the rate of harms reported between GET and CBT. So, for example, some therapists may employ the aforementioned "type B" CBT which does not involve scheduling graded increases in activity. Also, at least one set of authors have pointed out that many clinicians using CBT principles in practice "add a host of interventions that are not specific for CBT" (98), for example measures "target[ing] pain, sleep problems and emotional distress [...] stress management techniques, experiential group discussions, family support and so on (see e.g. 99 [i.e. Pardaens et al., 2006])." Due to there being effectively more interventions involved in the CBT, participants may focus less on exercise/activity between sessions.

Finally, there may be possible problems with pooling data in this way since there might be some overlap among surveys (i.e. an individual filled in more than one survey) and since there was inconsistent wording across surveys. However, looking at absolute figures, if one were to just combine one of the UK surveys (80) with the Norwegian-language study from Norway that was published 8 years later (84), there is likely to be very little, if any, overlap. Between the two surveys, approximately 1100 respondents reported being made worse by a graded exercise programme.

Despite these reservations, the consistently high rates and absolute numbers of adverse reactions coupled with the potentially disabling effects of GET and CBT reported in these surveys are concerning and need to be investigated more thoroughly.

4. Guidelines for the reporting of RCTs and application to ME/CFS RCTs

4.1. CONSORT randomized controlled trials statements

The CONSORT (Consolidated Standards of Reporting Trials) Group is an international organization of experts in the methodology of clinical trials that was formed in 1993 due to concerns regarding inadequate reporting of RCTs. The Group created a 25-item checklist (100) of essential points that should be included in all publications of RCTs to "enabl[e] readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results." (101) Specific suggestions from the CONSORT statement include sufficiently detailed interventions such that it is able to be replicated by other researchers, blinding of participants and researchers as appropriate, and tracking participant withdrawals. CONSORT is endorsed by over 50% of the core medical journals listed in the Abridged Index Medicus on PubMed (102).

Since publication of the initial CONSORT guidelines, extensions for specific areas have been prepared, e.g. for acupuncture interventions (103,104) and, more recently, for non-pharmacologic treatment interventions (105). Reporting in general has been shown to improve since the publication of CONSORT guidelines with some reviews demonstrating improvements in particular areas such as weight loss intervention studies and acupuncture (106-109).

4.2. Poor reporting of harms in RCTs, particularly for non-pharmacological interventions

Evidence across various medical domains suggests the reporting of harms in clinical trials has been especially inadequate and receives less attention than efficacy outcomes (110-113). As one group of authors noted, "Reporting harms may cause more trouble and discredit than the fame and glory associated with successful reporting of benefits" (114). Breau also observed that, in general, "[t]rialists may not evaluate adverse outcomes because they believe the safety of the intervention has already been established. However, this assumption is often invalid since the adverse effects of an intervention may differ depending on the indication or population subjected to treatment" (57).

To help remedy this, the CONSORT group issued a statement extension in 2004 focusing on harms (56). This extension consisted of a 22-item checklist that researchers should consider in the process of designing, carrying out, and publishing their studies. The checklist includes "clarify[ing] how harms-related information was collected", "list[ing] addressed adverse events with definitions for each", and "describ[ing] for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment" (56).

Harms reporting for nonpharmacologic RCTs is generally inferior to that for pharmacologic RCTs. A study focusing on the reporting of harm in RCTs of mental health interventions found that no report of nonpharmacologic treatment trials adequately reported harms (115). Another group of researchers compared the reporting of harm in pharmacologic (n=119) and non-pharmacologic (n=74) RCTs of treatments for rheumatic disease (74). Pharmacologic treatment reports included information related to harms more often than nonpharmacologic treatment reports. This information consisted of collection methods, blinded assessment, reporting of adverse events, causal relationship between the treatment and adverse events, withdrawals due to the events, and severity of the events. A greater proportion of the space in the results section was allocated to harms in pharmacologic than nonpharmacologic treatment reports. These differences remained with adjustment for sample size, medical area, funding, and multicenter trials. Fewer than half of the nonpharmacologic treatment trials assessed reported any harm-related data at all. The authors commented (74):

> *"Presupposed lower toxicity profiles of nonpharmacologic treatment, such as exercise therapy, complementary and alternative medicine, and behavioral interventions, could explain a lower interest in the evaluation of adverse events. However, most therapy entails the risk for adverse events, including serious events."*

The aforementioned CONSORT statements provide a framework against which to evaluate the quality of RCTs. Reporting of harms from trials of nonpharmacologic trials should be as systematic as the reporting recommended for pharmacologic trials.

4.3 Quality of reporting of harms in ME/CFS RCTs

RCTs of CBT and GET for CFS have been found lacking in their reporting of harms by the Cochrane Collaboration, a multinational independent network of medical professionals, researchers, and policymakers. For all five RCTs of GET that the Collaboration examined in 2004, no data for adverse effects was documented in any of the trials (36). However, the CONSORT statement on harms (56) notes that "it is important to report participants who are non-adherent or lost to follow-up because their actions may reflect their inability to tolerate the intervention." Perhaps this may partially explain the finding of a trend for a higher dropout rate in GET as compared to the control group in the studies assessed in the Cochrane review (Analysis 1.3). Thus the Cochrane reviewers concluded that (36) "studies of higher quality are needed that involve different patient groups and settings, and that measure additional outcomes such as adverse effects, quality of life and cost effectiveness over longer periods of time."

The Collaboration similarly reviewed RCTs of CBT for CFS in 2000 (95) and performed an update in 2008 (35). Out of 14 separate RCTs examined, only one had any data to assess patient acceptability and none of the studies had good quality data related to adverse effects. In the

"Selective outcome reporting" subsection of "Risk of bias in included studies", the Collaboration authors wrote (35): "Whilst Lloyd 1993 collected data concerning the adverse effects of DLE injection, data referring to adverse effects of psychological treatment was not systematically presented by any study." Drop-out rates averaged 16% across studies but definitions for what constituted "drop-outs" varied and reasons for attrition were not detailed; a third of the studies had drop-out rates over 20%. The authors finished by asserting that future studies should incorporate data on adverse effects and acceptability among other outcome measures.

In 2006, a systematic review by Chambers and colleagues of the same set of GET trials and most of the same CBT studies echoed similar concerns (38), "There is limited evidence about adverse effects associated with behavioural interventions. Withdrawals from treatment in RCTs suggest that there may be an issue but the evidence is often difficult to interpret because of poor reporting."

5. Considerations for future research

5.1 Recognize heterogeneity of patients with a diagnosis of ME/CFS

A complication in the ME/CFS field is the heterogeneity of patients who might have the diagnosis of ME or CFS (22,31). Interventions such as GET and CBT may be associated with lower rates of harms for some groups of patients but with much higher risks for others. Indeed, the authors of one recent paper recommend that some patients should not participate in GET at all: "the use of GET in the management of CFS is in serious doubt, and there stands a need to develop a method of identifying which patients respond poorly to physical exercise and should be advised to avoid GET" (116).

The various diagnostic criteria for ME and CFS may pick out groups of patients with different symptomatology, functional impairment and psychiatric comorbidity (117-119). Some criteria require post-exertional symptoms (23,24,29,30,31); others take a polythetic approach where such symptoms are optional (25,26). At least one set of criteria do not mention them at all and could be described as criteria for chronic fatigue (27). There are wide variations in the prevalence rates for CFS depending on how it is defined. Population studies in the US using the Fukuda criteria give estimates of 0.2-0.4% (6,7) while the figure for the empiric criteria is 2.5% (28,120). It is clear from these figures that whether somebody is classified as having CFS largely depends on the criteria used.

Given that fatigue, cognitive dysfunction and sleep problems can be part of depressive disorders (121), some fear that some patients who satisfy criteria that do not specify post-exertional symptoms may have primary depression (122-124). A model that is the basis for CBT trials was found to adequately represent chronic fatigue secondary to psychiatric conditions but not CFS (125,126). Moreover, it has been shown that satisfying the Fukuda CFS criteria (25) was the most powerful predictor of poor response to either GET or CBT in those with fatigue (127).

Investigators may add specific criteria that may affect the generalisability of results. For example, one study testing GET for CFS excluded those with “appreciable sleep disturbance” problems (88) despite the fact that in the region of 90% of those with CFS have such symptoms with sleep (128,129).

More severely affected patients have often been excluded from trials for ME/CFS. Indeed, a review reported that "No severely affected patients were included in the studies of GET”, adding that “the balance between effectiveness and adverse effects of interventions may be different in more severely affected compared with less severely affected” (38). Some clinicians employ this factor in their practice, giving different recommendations based on severity. Ho-Yen stated that he does “not recommend an emphasis on greater activity until a patient feels 80% normal” (130) while Lerner “prohibits” exercise (131,132) until CFS patients score 7 on his Energy Index Point Score [meaning a person who does not need to nap during the day, is up from 7AM to 9PM, can work a sedentary 40-hr/ week job, and do light house-keeping] saying “if you exercise before that you're going to go backwards" (133).

Some researchers have examined whether certain biological markers might predict the efficacy of CBT/ GET. Roberts and colleagues found that hypocortisolism predicted a poor response to a CBT program designed to increase activity levels (134). These results are consistent with findings reported by Jason and colleagues (135) who found, in a study of four non-pharmacologic interventions (including CBT and an exercise program), that those with abnormal baseline cortisol did not improve over time. In a follow-up paper (136), it was reported that baseline measures including immune function, activity levels, sleep status and past psychiatric diagnosis significantly differentiated those participants who demonstrated positive change over time from those who did not. CFS subjects with a dominance of the Type 2 over the Type 1 immune response, as indicated by the patterns of lymphocyte subset distributions, did not improve over time.

“At risk groups” may not be clearly defined by single variables so multivariate analyses may be required. A recent exploratory study using latent class regression (LCR) explored the Chalder Fatigue Questionnaire outcome data from 236 CFS patients as defined by the Oxford criteria (27) who had received CBT at a specialist CFS clinic in the UK (137). It found that participants could be divided into 4 classes with one class predicting a poor response to CBT outcomes. We were not given data on all 38 possible predictors but this class was characterised by more frequent weight fluctuation, physical shakiness and pain, and had higher anxiety and symptom focusing scores compared to the other classes (137).

Given how frequently increased physical activity is recommended in healthcare settings, there should be an added impetus to characterise those who might be at increased risk of harm from following such recommendations.

5.2. Make detailed instructions of interventions easily accessible

The CONSORT statement on the reporting of RCTs (100) suggests that researchers describe "the interventions for each group with sufficient details to allow replication, including how and when they were actually administered." The CONSORT Extension for Trials Assessing Nonpharmacologic Treatments re-emphasises this (105):

> *"authors [should] allow interested readers to access the materials they used to standardize the interventions, either by including a Web appendix with their article or a link to a stable Web site. Such materials include written manuals, specific guidelines, and materials used to train care providers to uniformly deliver the intervention."*

Such materials have often not been available when RCTs have been published in the ME/CFS field. Consequently the programs offered in clinical practice may not be the same as those assessed in clinical trials and may have different rates of harms associated with them.

As alluded to in section 3.3, Marks has highlighted how there can be many differences between psychological interventions that can appear superficially to be similar (96). Manuals can be long and detailed so it can be useful if investigators can summarise the active components of interventions and contrast them with other therapies being assessed. One example of this is exemplified in Table 1 ("Shared and distinct activities among treatment groups") of the Jason et al. (2007) trial of four non-pharmacologic interventions for CFS (49).

If intervention details are not present, it can be difficult for readers and reviewers to classify therapies correctly. In the PACE Trial, the GET intervention was guided by the principle that, "[p]lanned physical activity and not symptoms are used to determine what the participant does" (33); similarly "[i]t is their planned physical activity, and not their symptoms, that determine what they are asked to do"(33). In contrast, in adaptive pacing therapy, "activity is planned and then modified in the light of its effect on symptoms"(33). If one looks at the exercise prescription used in the Wallman et al. (91,138) study from Australia, it appears perhaps more like the latter program: "on days when symptoms are worse, patients should either shorten the session to a time they consider manageable or, if feeling particularly unwell, abandon the session altogether" (138). Given the low rate of harms reported in the survey data for pacing in contrast to GET (Table 2), it may be that interventions that involve the principles of pacing may have lower rates of harms associated with them and should be analysed separately in reviews.

5.3 Develop a system to track adverse effects

Some GET and CBT studies have included general statements, like "no adverse event attributable to CBT was reported", or have simply counted the number of subjects who did not complete a study with scant details (35,38). CONSORT regards "using generic or vague

statements" as insufficient reporting so both they and others have suggested several strategies to counter this practice (56, 74, 139).

Researchers should state in the study methods section why harms data were omitted if no data was collected. For those studies where it will be collected, researchers should contemplate setting up a system before study initiation to systematically track adverse effects as passive surveillance of harms (i.e. spontaneous reporting) leads to fewer recorded adverse events than active surveillance (140). Different methods of ascertainment can produce different reporting incidences. For example, one study found that patient diaries yielded higher rates of Adverse Drug Reactions (ADRs) than other forms of assessment (113). Open-ended questions may yield different information, both quantitatively and qualitatively, than structured questionnaires (141). If the latter are used, researchers should ideally be ready to make the questionnaire accessible and to explain why it was selected or how it was constructed.

Pooling of data from various studies is often required to investigate signals of adverse events. Abstracts should contain the existence of harms-related data (including no adverse events) to help facilitate appropriate database indexing and information retrieval.

Investigators should also consider: defining adverse events; recording the nature/frequency/severity of events (and the definition used to define severity); noting whether an event led to subject withdrawal; stating whether harms appraisement was done blindly and its timing; making explicit the rationale behind whether or not to attribute an event to an intervention, and noting who did the attribution. Only if such detailed data collection is attempted can a complete picture emerge of the benefits versus risks of proposed interventions.

5.4 Monitor intervention implementation and compliance using objective measures of activity

The CONSORT extension for RCTs of non-pharmacological interventions suggests that "details of the experimental treatment and comparator as they were implemented" be reported. One example given is of an exercise intervention where not only the mean sessions of exercise attended by participants are noted but also the minutes exercised (105). The rationale behind this suggestion is to demonstrate that the interventions are reproducible and were carried out as intended, without contamination of treatment either by research staff treating participants unequally and/or with different/ additional unintended protocols or by participants choosing to treat themselves differently. Furthermore, it has long been recognised that adherence to medication regimens can be poor; objective tools such as Medication Event Monitoring System (MEMS) devices have shown that self-reported measures tend to inflate reports of compliance (142-5). Without data on implementation and adherence, claims that an intervention is safe are questionable.

There are reasons to believe that compliance to interventions might be problematic. The distinction between an exercise program and a Graded Exercise (GE)/ Graded Activity (GA)

program for CFS is that, for the latter, a participant is not supposed to decrease exercise (or activity) levels based on his or her symptoms. As a GET expert described, "if [after increasing the intensity or duration of exercise] there has been an increase in symptoms, or any other adverse effects, they should stay at their current level of exercise for a further week or two, until the symptoms are back to their previous levels" (146). One has to wonder how many patients would dutifully comply with counterintuitive instructions to maintain a higher activity level for 7-14 days in the face of new or worsening symptoms. If participants did comply, their level of activity on completion should increase substantially; however, a review of three studies using objective measures found only a small increase in total activity levels at assessment subsequent to treatment, and a similar level of increase was recorded in those who had undertaken no intervention (147).

Another reason that some might feel measuring compliance is important is that some researchers have hypothesised that personality factors such as higher “action proneness” (“the extent to which one is oriented toward direct action and achievement”) might make people vulnerable to ME/CFS (148,149). Theoretically, this might affect proper adherence to programs with high “action prone” individuals potentially being more likely to increase activities or exercise prematurely, leading to exertional symptoms. However, these personality studies were retrospective, performed after subjects were ill, and thus are subject to recall bias. Additionally, when the same team actually recorded “action-proneness” levels, using the "Vragenlijst voor Habituele Actiebereidheid" (Questionnaire for Habitual Action-proneness) (HAB), they found a score of 17.75 (SD6.21) and 20.23 (SD4.65) in CFS patients before and after a multidisciplinary group treatment respectively (150). Both these sets of scores are lower than the Dutch norm of a mean of 29.4 (SD6.5), derived from 316 industrial workers (148). It is thus unclear whether people with CFS should be seen as having high “action-proneness” or not after they become ill. It is also unclear whether being “action-prone” would lead to more or fewer adverse reactions from activity programs: people who are “action prone” might in fact be more compliant with treatment than the average subject if their interpretation of “action” or “achievement” is to adhere to therapist recommendations. Nevertheless, for some, given possible concerns about the theoretical effect of personality factors on compliance, this might be a sufficient reason to seek to measure the activity that was actually performed.

In general, implementation of Graded Exercise (GE) or Graded Activity (GA) programs by therapists and adherence to them by patients has not been rigorously assessed. No RCT of such a therapy for ME/CFS, to my knowledge, has measured the intervention using objective measures of activity. Some trials have employed participant self-report of activity but several studies have found that activity questionnaires do not correspond well with objective measures (151-153). As one set of researchers explained, "the subjective instruments do not measure actual behaviour. Responses on these instruments appear to be an expression of the patients' views about activity and may be biased by cognitions concerning illness and disability" (152). In fact, non-ME/CFS exercise studies have shown that activity interventions can influence participants to overestimate physical activity when compared to objective measures (154-7). This seems particularly relevant

in the context of GET and GET-based CBT which are designed to change patients' attitudes about activity.

Documenting the type of, intensity of, and frequency of exercise/activity sessions in GE/GA programs is also needed. When assessing the safety of pharmaceuticals, dosage is important: a drug may be safe at one dosage but quite dangerous at a higher dosage. There seems to be no reason to view GE and GA differently. For example, a pilot study by Meyer et al. of high- and low-intensity exercise for fibromyalgia, a condition that has considerable overlap in symptomatology with ME/CFS (158,159), required participants to complete and post weekly activity logs (160). An examination of the returns found very poor compliance with the assigned exercise programs, leading the researchers to reassign participants to the high- and low- intensity groups based on the actual activity levels recorded in their logs. Interestingly they found that there was a difference ($p<0.05$) between the groups on the Fibromyalgia Impact Questionnaire, with scores improving from baseline in the low-intensity exercise group but deteriorating in those who had performed high intensity exercise.

Assessments of the effects of activity in ME/CFS as discussed in Section 2 may involve higher levels of activity than the intensity of activity and exercise in some GET and CBT programs (161-172). However, a gentle walking test, where participants with CFS covered on average 558m (0.35 miles) at a reported average speed of 0.9m/s (2 miles/hour), resulted in a statistically significant worsening of fatigue, pain, sore throat, and general health perception (64). Moreover, when Van Oosterwijck et al. (2010) assessed a short, self-paced and physiologically limited exercise bout lasting just 5 minutes on average at a mean workload of only 46 Watts, there was a worsening of the ME/CFS symptom complex post-exercise (173). Given the problems individuals with ME/CFS have experienced with aerobic programs, one set of clinicians have suggested exercise needs to be performed at below the anaerobic threshold (174). To be able to satisfactorily assess any differences in adverse events or outcomes between various programs, investigators need to collect good information on the activity or exercise performed.

Beyond merely showing compliance with interventions, objective measures can also test the claims that CBT and GET have been shown to lead to recovery in CFS (175,176) – indeed that recovery should be seen as an achievable goal in months rather than years (177). However, since we do not have data on patients attempting a normal level of activity in a ME/CFS trial, we do not know the level of risk associated with patients attempting to achieve such a level of activity. Given the ceiling of activity (178) that has been recorded in ME/CFS, higher levels of adverse reactions seem possible at or close to this "dosage" of activity or exercise.

Good quality compliance data could help answer many questions. With non-pharmacologic interventions such as GET and CBT, objective measures of activity, through use of devices such as actometers or pedometers, should be utilized to confirm compliance and to assess any increase that was achieved, e.g. the percentage increase in activity in comparison to baseline levels. There should be careful documentation of sessions attended as well as type, duration, frequency, and intensity of activity.

5.5 Evaluate for harms using objective measures

In pharmacologic trials, subjects are monitored for harm not only through interviews, patient questionnaires, and clinical examinations but also with objective measures such as blood tests assessing kidney function, liver metabolism, or any other anticipated adverse effects of the medication. Non-pharmacologic interventions in contexts outside of ME/CFS are also monitored similarly. During supervised exercise post-heart surgery, healthcare staff ask patients if they have symptoms such as shortness of breath or chest pain (possible signs of the heart not receiving adequate oxygen), take patients' blood pressure/ heart rate regularly, and observe for abnormal heart rhythms using portable monitors. If symptoms occur or abnormalities are seen, staff might ask patients to stop exercising or decrease the intensity/ duration of exercise.

The effects of exercise on ME/CFS are not yet fully elucidated to the degree it is in coronary heart disease but there are existing objective measures that that have been utilized to document symptoms experienced by ME/CFS subjects with exercise. Aside from using repeated cardiopulmonary exercise testing to measure fatigue/ energy metabolism as mentioned in section 2, standardized tests such as the CalCap reaction time component and the Stroop Word/Color Test could be used to monitor for any deterioration in cognitive function (171,179). Polysomnography could be used to examine changes in sleep patterns. Serum cytokine measures are another possible avenue to monitor exercise effects: Light recently showed that post-exercise symptoms (mental fatigue, physical fatigue, pain) in ME/CFS subjects were correlated with persistently high levels of certain cytokines compared to healthy controls (60). Furthermore, in a small subset of patients who developed CFS after documented infection with parvovirus B-19 and subsequently treated with intravenous immunoglobulin, Kerr and colleagues demonstrated that recovery from CFS symptoms including post-exertional malaise correlated strongly with normalization of cytokine levels (180).

Researchers should consider utilizing these or exploring other objective measures. If specific objective measures correlating with exercise/ activity-associated symptoms are established, these could be monitored to determine the intensity, frequency, type, or duration of activity that could be safely tolerated by an individual with ME/CFS and customized treatment plans could be constructed.

5.6 Measure non-physical harms / patient-oriented outcomes pertaining to quality of life

Aside from any possible "direct" biological harm from increased activity/exercise, other "indirect" harms, such as psychological, social, and economic harms (181), are also possible. The magnitude of a harm can be judged by the effect it has on someone's ability to pursue life goals and the duration of this interference (182). A distinction can be made between interfering with minor (e.g. visit a museum, meet friends, vacation, etc.) and major (e.g. attend school,

work, have children, etc.) life goals. GET and GA-based CBT programs involve large commitments of time and energy which might interfere with the pursuit of both minor and major life goals by some participants. Given the post-exertional symptoms that are part of ME/CFS (59,183), effects may not just be experienced during the activity sessions and since such programs may not involve an increase in total activity levels, other activities are presumably being substituted for (184). This could put a strain on individuals with ME/CFS in terms of their ability to perform other roles, like employee, student, partner, and/or parent.

Even if eventually an increased total activity level was achieved, there is likely to be a transitory period where a reduced amount of time and energy is available for other aspects of one's life. This could potentially lead to increased social isolation and, in particular, the break-down of relationships (i.e. have a long-term, rather than just temporary, effect). Outside the ME/CFS arena, it has been recognised that psychosocial treatments can have negative effects on family functioning (185).

In terms of education, a student's academic performance could suffer due to the cognitive problems which can occur post-exercise (171,179): they might underperform or fail exams, or simply fall too far behind and drop out.

In the employment realm, an employee might lose their job because an employer was not satisfied with their performance. In Belgium, an audit of five rehabilitation centres for CFS that involved CBT and GET (66-68) found that the average hours working decreased at conclusion and at follow-up six months later compared to the start. In addition, more people (10%) decreased the number of hours they worked than increased (6%). In fact, when one notes that only 27% were employed before the program, it means 37% (=10/27) of the participants decreased how much they worked (which would have included stopping). A Dutch study of CBT reported better results, with the number of hours worked increasing from a mean (median) of 9.4 (0) hours to 11.4 (0) hours (186). No data was available on the number of people whose hours worked had decreased; however, the mean (median) number of contract hours (cf. hours actually worked) decreased from 16.2 (10) hours to 14.9 (7) hours.

So, even if it were the case that there were no biological harms associated with GET and CBT, individuals with ME/CFS or their physicians could believe that the potential for these secondary or indirect harms might mean that the treatment is not suitable for a specific individual at a particular time.

As is often the case when harms are being recorded, specific checklists may need to be developed that assess some iatrogenic effects – in this case non-biological harms. Spontaneous reporting of harms may not pick up some unintended consequences. Additionally, a greater use could be made of patient-oriented outcome measures. Some might claim that the SF-36 questionnaire (187) would be suitable. However, criticisms have been made that it covers few fields of functional limitation and that several questions cover the same field (two items on "stairs" and three items on "walking") (188). These five questions make up 50% of the physical

functioning subscale which is sometimes used on its own in ME/CFS trials. Given the nature of GE/GA/CBT programs, this may not be a suitable tool to measure functional impairment when assessing such interventions.

ME/CFS studies have found apparent improvements using this subscale without any actual increase in total physical activity (184,189) or a difference with the control group on this instrument was recorded despite no difference in actigraphy (147,190-192). A similar phenomenon has been observed with fatigue scales where an improvement in (self-reported) fatigue scores did not correspond with increased activity (147,184,189,192). Indeed, a recent systematic review of patient-reported outcome measures (PROMs) confirmed that the quality and acceptability of those that have been used in ME/CFS studies as "limited ... [as] [c]lear discrepancies exist between what is measured in research and how patients define their experience of CFS/ME. Future PROM development/evaluation must seek to involve patients more collaboratively to measure outcomes of importance using relevant and credible methods of assessment."(193)

5.7 Follow subjects for a longer period post-intervention

Only one study of CBT was recorded by the Cochrane Collaboration as having a follow-up of over 1 year – it involved just 53 patients (35). Similarly, among GET trials reviewed by the same group, the longest period of follow-up was 1 year post-intervention, leaving the authors to comment that there is a need for more long-term follow-up data from GET studies (36).

As was pointed out in subsection 5.4., a ceiling of activity appears to exist for at least some ME/CFS patients (178). During a trial, an individual may be able to increase the quantity or intensity of exercise up to a certain level without experiencing significant adverse effects, particularly if they are substituting this activity for other activities in their lives (184). However, one cannot necessarily extrapolate from such data that patients can use the same program to safely work their way up to a normal, or pre-ME/CFS, level of functioning, because of the ceiling of activity nor that, post-study, they will be able to maintain gains. This point was illustrated in a case study of a graded activity intervention (192):

> *"[T]his patient largely overcame his initially reported fear of triggering symptom exacerbations. Yet his concern about exceeding the maximum prescribed weight lifting levels appeared to be realistic because scheduled attempts to exceed these levels consistently triggered symptom flare-ups. In addition, the work-related 4-week relapse revealed an apparent upper limit on his ability to work. This suggests that eradication of a fear-based activity avoidance will facilitate functional improvements up to a point, beyond which a more biologically based mechanism of symptom generation may be involved."*

With harms from some pharmaceutical treatments, some adverse reactions may only occur following a certain number of "doses" of the treatment or take a relatively long period to

manifest. Similarly, given some of the mechanisms through which exercise might cause harm in ME/CFS (59,194,195), adverse reactions may not become apparent with short-term treatment or follow-up. Since the full recovery rate from ME/CFS, in general, is 5% over a decade (196), many patients have been ill for longer than 5 years (79,85), and ME/CFS is known to be a remitting-relapsing condition (197), it would behove researchers investigating this condition to design studies with longer term follow-up (38).

5.8 Check for clustering/therapist effects

Therapist effects could be assessed to see whether certain types of results, whether positive or negative, cluster with specific centres or therapists (198). If, for example, a particular intervention were associated with a low rate of significant harms with all therapists except one individual, that might suggest an intervention had less potential for harm than if the effect were more uniform. Alternatively, if a significant rate of harms were recorded with most of the therapists except a small number or those in a particular centre, interesting information might be able to be gleaned from investigating how the treatments were executed differently. However, the importance of the issue for GET and GA-based CBT for ME/CFS is uncertain. One recent paper reviewed the results of 374 CFS patients who received CBT with 12 therapists (3 clinical psychologists and 9 nurses with specialist CBT training) (199). The variance explained by therapists, when demographic covariates were accounted for, was 0% for fatigue and under 2% for disability. A review of therapist effects in general found that manualized therapies tend to produce smaller therapist effects (200).

5.9 Interpret results of studies taking into account previous studies

Discussion sections should place trial results within the context of prior and current ongoing research. CONSORT suggests that "[i]nterpretation [be] consistent with results, balancing benefits and harms, and [that] other relevant evidence", including that which does not support the study the paper is based on, should be considered (100). Furthermore, researchers are encouraged to "contrast the results on harm…with observational data from spontaneous reporting, automated databases, case-control studies, and case reports" (56). The qualitative and quantitative harms data presented in Section 3 of this paper have existed for several years yet has rarely been mentioned in prior CBT or GET trials. RCTs play an important role in medical research, but their results should not be overemphasized to the exclusion of basic research and other clinical studies that may offer pertinent evidence to advance the field.

6. PACE Trial – A model of excellence in harms reporting?

Within a week of receiving initial comments about this paper from reviewers, the *Lancet* published the PACE Trial, a multi-centered randomised trial in the United Kingdom comparing

specialist medical care (SMC), GET+SMC (hereafter GET), CBT+SMC (hereafter CBT), and SMC combined with a form of adaptive pacing therapy (APT) (hereafter APT) as treatment for ME/CFS (90). The form of CBT evaluated in PACE aimed to "change the behavioural and cognitive factors assumed to be responsible for perpetuation of the participant's symptoms and disability" based on the "fear avoidance theory of CFS"; this included "making collaboratively planned gradual increases in both physical and mental activity" (90). The trial set out to not only assess efficacy but also look at harms with outcome measures in the protocol paper designated as "efficacy measures" or "adverse outcomes".

The PACE Trial brought the reporting of harms in trials of non-pharmacologic interventions in the field of ME/CFS to a new standard: compared to prior GET/ CBT studies, the PACE researchers made available their interventions and protocols online and in published resources, put forth some effort to establish a system of tracking adverse effects, and provided greater detail about serious adverse events and reactions (SAEs and SARs). This transparency of PACE researchers is to be praised and allows researchers to understand, evaluate, and replicate the trial prudently. However, there remain some concerns about how harms data were collected, interpreted, and reported and many of the considerations delineated in Section 5 could still be applied to PACE and future trials; some of these are discussed below.

From online and published protocols, harms surveillance appears to have been active in the sense that a harms detection system was set up but potential anticipated adverse events were not specifically solicited by research staff and left open-ended (201,202). Therapists had the most contact with participants but it is unclear what their role was in terms of reporting harm. The manuals indicate that research nurses (RNs) were responsible for monitoring adverse events (AEs) at 12, 24, and 52 weeks as well as when a participant dropped out of the trial. While some examples were given to nursing staff regarding what was a SAE, RNs were still required to use their clinical experience to decide what constituted a SAE and how severe of an impact a "non-serious" adverse event could have. If an RN assessed the AE as an SAE, was unsure whether it was a SAE or was concerned about the event generally, he/she was advised to seek the opinion of other professionals.

Information conveyed to participants may influence whether certain symptoms were reported and participants' interpretation of them. Both GET and CBT models are based on a model of inactivity/ deconditioning as the major driver in perpetuation of CFS symptoms (34). Thus, patients were informed that a range of symptoms were due to inactivity. While some, such as changes in muscle function or reduced tolerance to activity, are well-recognized consequences of physical inactivity (although whether deconditioning could explain all muscle abnormalities in ME/CFS is debatable [21,63,169,179,203-216]), other symptoms, such as visual/ hearing changes, regulation of body temperature, and impairment of mental functioning, are more questionable. Patients were also told to "consider increased symptoms as a natural response to increased activity", that "most people with CFS/ME felt either 'much better' or 'very much better' with GET", and that "the benefits of continuing with cognitive behaviour therapy makes overcoming the difficulties worthwhile" (34).

Simultaneously, therapists were told that adverse effects of GET were "due to inappropriately planned or progressed exercise programmes" without mention of what these effects were and were instructed to encourage patients to focus on their symptoms less (33). This sort of priming could easily lead to instances of symptoms not being reported. Previous research has demonstrated that questionnaires, and especially interviews, addressing sensitive topics, including physical activity, are susceptible to social desirability response bias (154-157,217). Participants consciously or unconsciously (self-deception) present inaccurate information about themselves to conform to what they believe the researcher expects. Participants may also worry that their performance or demeanor during the trial might negatively influence their physician's treatment of them (the consent form included release of information to patients' regular healthcare providers) and receipt of disability benefits. Thus, given the way information was conveyed to both patients and therapists, it is possible that there may be underreporting of adverse effects.

SAEs and SARs were sub-divided into the following categories in the final report (218):

> *"a) Death; b) Life-threatening event; c) Hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included), d) Increased severe and persistent disability, defined as a significant deterioration in the participant's ability to carry out their important activities of daily living of at least four weeks continuous duration; e) Any other important medical condition which may require medical or surgical intervention to prevent one of the other categories listed; f) Any episode of deliberate self-harm."*

Details of all the SAEs were combined – notation such as superscripts could have been used so readers could identify which arm of the trial the participants had been in, as recommended by the CONSORT guidelines. For SARs, these were divided up by intervention along with the assessment of whether it was felt each individual SAR was associated with the intervention. Given the large number of participants (n=640), the number of SARs was relatively small: APT [2], CBT [4], GET [2] and SMC alone [2]. Apart from one SAR in the SMC arm ("Worse CFS symptoms and function" (category d) which was rated as "probably related"), all the other SARs were rated as "possibly related" [to the intervention]. The SARs listed for CBT were "Episode of self harm" (category f), "Low mood and episode of self harm" (e & f), "Worsened mood and CFS symptoms" (d) and "Threatened self harm" (e); for GET, the SARs were "Deterioration in mobility and self-care" (d) and "Worse CFS symptoms and function" (d).

What adverse events are deemed to be serious or to be causally related to the interventions may be debatable. For SAE/ SAR category (d), some researchers, clinicians, and patients might argue that if a management program resulted in impairing a participant's ability to function for a lesser amount of time than 4 weeks continuously, that it should be still considered a serious event. For example, many workplaces would not tolerate an employee who was out on sick leave for a week or two at a time on a few occasions yet this would not be deemed a serious event due to the lack of sensitivity of these criteria.

In contrast to the low number of SAEs and SARs, a large number of what were classed as "non-serious adverse events" (APT: 949, CBT: 848, GET: 992 and SMC: 977) were recorded amongst the 640 participants; virtually everyone had at least one adverse event (APT: 96%, CBT: 89%, GET: 93% and SMC: 93%) but we are not given any information about what these events were, whether certain events were a one-time occurrence or recurrences for a given participant, or when the event occurred, important factors suggested by CONSORT (56). This meant that of the 3774 adverse events (AEs) recorded in the trial, we were given both the intervention and details of the event for 0.26% (=10/3774) of them. Given that this was a trial of non-pharmacologic therapies (cf. surgical and pharmacological interventions) on a group of individuals with an average age of less than 40 throughout the trial, who could not have a range of medical and psychiatric disorders and who were deemed capable of participating in an outpatient exercise program, more information on adverse events would have been desirable, particularly if the investigators want to claim, as they did in the Lancet paper, that the interventions were "safe" (27,41,90,218,219).

The protocol stated that an "operationalised Likert scale of the nine CDC symptoms of CFS" would be used as a secondary outcome measure (201,219). This potentially could have given useful information on whether there were deteriorations in particular symptoms. Unfortunately, in the final paper, we were only given information on the "chronic fatigue syndrome symptom count" and the presence or absence (i.e. not the Likert scores) of two symptoms: "Poor concentration or memory" and "Postexertional malaise." Sleep scores were reported separately, using the Jenkins sleep scale; however, no information on pain symptoms was presented despite the importance of such symptoms in the condition (7,85,128,220-222) and existing findings of increased pain following activity and exercise testing (60,63-65,173). It might also have been useful to allow participants to rate the severity of adverse events outside those of the nine CDC symptoms. It is also unclear how safety monitoring staff determined which events were causally related to the interventions. If safety monitoring staff believe that GET or CBT is safe to begin with, they might not be as vigilant about monitoring adverse events or attributing them to the interventions.

The researchers did not explain why they changed or did not report on pre-specified adverse outcomes from the 2006 PACE Final Protocol. Originally, adverse outcomes were defined as a "score of 5-7 on the self-rated Clinical Global Impression" (PCGI) or a drop of 20 points on the SF-36 physical function score (187) from the prior measurement (201). By the time the Lancet paper was published, "serious deterioration in health" is defined as (90):

> *"a short form-36 physical function score decrease of 20 or more between baseline and any **two** consecutive assessment interviews;[ref] scores of much or very much worse on the participant-rated clinical global impression change in overall health scale at **two** consecutive assessment interviews;[ref] withdrawal from treatment after 8 weeks because of a participant feeling worse; or a serious adverse reaction." [bolding by author]*

The *Lancet* paper does not include data on those participants with a PCGI score of 5 ("a little worse") and instead this rating is combined with "no change" and "a little better" to form the category "minimum change". We are also not given information about participants whose SF-36 PF score (187) dropped by 20 points from the previous measurement. Instead, a serious deterioration now necessitates a change from the baseline score at two consecutive assessment interviews. Given that there are 12 weeks between the first and second assessment and 26 weeks between the second and third assessment and that the baseline scores for the four arms of the trial all averaged below 40, a participant's score would on average need to sustain a drop of more than 50% of their function over a period of at least 12 weeks to qualify as a serious deterioration in health. Another effect of this change is that any declines after 24 weeks would not be counted as there is only one more assessment, at 52 weeks, after 24 weeks.

At the same time, the change required for a participant to be considered improved was modified between the time that the final PACE protocol was published and publication of the trial and sustainment of improvement was only needed between baseline and one other assessment (i.e. 52 weeks) to qualify as clinically significant.

> *"A clinically useful difference between the means of the primary outcomes was defined as 0.5 of the SD of these measures at baseline,[ref.] equating to 2 points for Chalder fatigue questionnaire and 8 points for short form-36.*

The justification for using the threshold of 0.5SD threshold comes from a 2002 paper by Guyatt et al. but Guyatt also points out that the same threshold could be used for deteriorations (223); unfortunately data on such deteriorations (e.g. participants who declined 8 points on the SF-36) are not given. Likewise, if it was felt one could not be confident a deterioration had occurred based on a measurement at one point in time, it suggests one should also probably not be confident a participant has "improved" (the phrase in the paper) using one time point. In the paper, Guyatt refers to another group of researchers who had used a similar definition in a trial comparing temozolomide and procarbazine for recurrent glioblastoma multiforme (223); they required that improvement in quality of life had to continue for two assessment points to be considered clinically significant (224). As was discussed in section 5.6, PROMs need to be further developed in the ME/CFS field (193): this would give better information on what should be considered "important" changes. In the meantime, it would seem reasonable if there was consistency in the reporting of improvements and deteriorations, with symmetrical clinically useful differences scores and time periods unless there are clear rationales given to do otherwise.

Another major issue with PACE is the lack of detail about implementation of the interventions and participant compliance. Participant compliance was considered to be adequate if a participant attended 10 (out of a maximum of 15) therapist sessions but the contents of those sessions are not described in the Lancet paper. Audio- and videotapes of participant-research staff contact and rating of participant compliance by therapists were executed but these are indirect measures. PACE CBT and GET manuals directed at therapists and participants give very detailed instructions how to establish baselines and goals, how/ when to increase activity/ exercise, and how to manage setbacks; in addition, participants are to maintain an activity record.

For example, CBT participants are to set specific activity goals that incorporate the type of activity, how long the activity will last, and how frequently they plan to perform the activity e.g. "To walk for 15 minutes daily" or "To do gardening x 3 per week for half an hour."

When they reach certain milestones, like achieving their targets 75% or more of the time, they are advised to increase their activity. Likewise, GET participants are to start with gentle stretches and light exercise that they can maintain for 5 days out of a week. Once they reach that level, they are then to increase the duration of that activity up to 30 minutes a day at which point, therapists can begin to increase the level of intensity as measured by heart rate. Ideally, objective measure of correct implementation of the assigned intervention or good compliance via actigraphy, heart rate monitors, etc. or direct observation of activity/ exercise by research staff would be preferred but in absence of this, detailed reporting from participants' activity logs would have been helpful to assess compliance and confirm that participants did indeed receive the intervention as intended. There is no mention in the paper of whether participants achieved their target goals, exercised an increased amount via increased duration/ frequency/ or intensity, or maintained/ increased activity despite symptoms.

A possible alternative to the use of motion sensors during treatment would have been their use as an outcome measure: given the nature of the CBT and GET interventions being assessed, over the course of 12 months, with good compliance one would expect reasonably large increases in activity levels, particularly if an individual was coming from a low baseline. Unfortunately, although the investigators initially planned to employ them on completion and indeed took a week of measurements at baseline, they were dropped as an outcome measure in the final protocol (225). The only objective outcome measure reported in the Lancet paper, the 6 minute walking distance (6MWD), could conceivably be used for a similar purpose (90). Data was available for only 72% of participants; for other outcomes, data was presented for 89%-94% of participants. Reasons for this difference are not given. The CBT group only increased from an average 6MWD of 333m to 354m, the same change as the SMC group; the GET cohort went from 312m to 379m, or an (adjusted) increase of 35.3 metres compared to SMC. Both sets of figures make one wonder what percentage of participants had a high rate of compliance, especially when the final 6MWDs were still much lower than 644m, the predicted value for an age- [39 years] and gender-matched [77% female] cohort of average height [176.5cm (male), 163.1cm (female)] (226,227). Decreases on such objective measures could also give useful information on adverse events.

There is much to recommend in the PACE Trial with regard to its reporting of harms; however, there are also important omissions which could be improved upon in future trials. White el al. do mention that they "plan to report ... moderators and mediators, whether subgroups respond differently, and long-term follow-up in future publications" (90). I look forward to reading these papers and hope that they will consider reporting or sharing the data from their important trial with other researchers to respond to the points raised by this paper.

7. Other issues

Due to the length of this paper, some other issues of relevance have not been broached: (i) differences in regulatory requirements for pharmacologic and non-pharmacologic interventions with no equivalent to post-marketing surveillance for interventions of the latter type; (ii) lack of litigation concerning harms of GET or CBT leading to less focus on, or concerns about, harm; (iii) conflicts of interest (COIs) and how they might affect harms reporting; and (iv) the possibility that cognitive biases, beliefs, attitudes and behaviours of investigators and healthcare professionals might influence the reporting of adverse events. Also, there has not been space to cover some of the possible effects, such as coercion of patients to participate in GET or CBT, that poor reporting might produce.

8. Conclusion

It is hoped that this paper will lead to a greater focus on the reporting of harms in ME/CFS, not just those that might be associated with GET or CBT, but from any posited treatment. Interventions should not be presumed to be harmless when there exists evidence of potential harm and there have not been well-planned systematic methods to track and assess harms both within and outside trials. Potential strategies to improve reporting of harms are summarized in Table 3. ME/CFS research should at least conform to standards being recommended for the majority of medical research while taking into account the unique features of the disease, such as its relapsing-remitting nature. Moreover, in the ME/CFS field, comparisons are often not made just within the classes of pharmacologic interventions and non-pharmacologic interventions but also between pharmacologic and non-pharmacologic treatments (38). False conclusions could be reached that a non-pharmacologic intervention is “safer” than a pharmacologic agent if harms-related data was collected more rigorously for the latter (87).

Individuals with ME/CFS can face many challenges and have not always been treated as well as they should have been by healthcare professionals (76,122,228-232). Many feel that their symptoms have been downplayed and their negative experiences of some treatments ignored. This can lead to a mistrust of the medical profession. Furthermore, healthcare professionals who strive to help their patients cannot do so without assessing risks versus benefits for each intervention they prescribe. To do this suitably, they need good data on harms. Greater vigilance for harms could restore patient trust and assist clinicians in adhering to the maxim, "Primum non nocere" (first, do no harm).

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Conflicts of Interest:

I am the Information Officer and Assistant Chairperson of the Irish ME/CFS Association. All my work for the organisation is voluntary (i.e. unpaid).

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Table 1: Reporting of Harms in 9 Patient Surveys (1 of 5)

Study	Year	Country	Sample	Results for GET, GAT and CBT
M.E. Action [78] (a)	**1990**	**UK**	**N=695**	**"Graded exercise programme"** (n=127): **Harmful: 49.6% (63)** No effect: 13.4% (17) Useful: 37.0% (47)
C.F.I.D.S.* Assoc. of America [79]	**1999**	**USA**	**N=820**	**"Graded exercise (starting slow, increasing gradually as tolerated)"** (n=462) (b) **Harmful: 28.1% (130).** No effect: 11.0% (51) Helped a little: 36.8% (170) Helped a lot: 24.0% (111)
Action for M.E. [80]	**2001**	**UK**	**N=2338** (c)	**Graded exercise (n=1212):** **Made worse: 50% (606†)** No Change: 15% (182†) Helpful: 34% (412†) **Cognitive behavioural therapy** (n=285): **Made worse: 26% (74†)** No Change: 67% (182†) Helpful: 7% (412†)
25% M.E. Group [75]	**2004**	**UK**	**N=437** (d)	**Graded exercise Therapy** (n=170): **Made worse: 82% (139†)** (Other figures not located)

(a) The charity, M.E. Action, was subsequently renamed Action for M.E.

(b) This survey also asked a question about: "*Cognitive behaviour therapy (specify group or individual counselling) .....*". There were no other questions about counselling or other "talking therapies" so the therapy under discussion does not seem to be well-defined. For completeness, here are the data: (n=160) Harmful: 10.0% (160), No effect: 23.8% (38), Helped a little: 37.5% (60), Helped a lot: 30.0% (48)

(c) Additional Information: Circulated to 7529 Members (Response rate: 31%). 710 (30.4%) of respondents "currently severely affected" Gender: 81% Female, 19% Male. Age: 10% were aged under 18. "Age at onset: 39% were aged between 26 and 40 at the time of onset of M.E. 38% were aged between 41 and 65 at time of onset."

(d) Additional Information: Response rate: 66%. Severity: Group caters for patients in lowest quartile i.e. most severely affected
*C.F.I.D.S. = Chronic Fatigue and Immune Dysfunction Syndrome, a synonym for ME/CFS
† These figures are estimates based on the percentages

Table 1: Reporting of Harms in 9 Patient Surveys (2 of 5)

Study	Year	Country	Sample	Results for GET, GAT and CBT
Koolhaas et al. [81]	**2008**	**Netherlands**	**N=100** [e]	**Cognitive Behavioural Therapy** (n=100): [f] **A lot worse: 29% (29)** **Somewhat worse: 9% (9);** No change: 30% Somewhat improved: 15% (15) Considerably improved but not recovered: 15% (15) Entirely Recovered: 2% (2)
Action for M.E./ Association for Youth with M.E. [82]	**2008**	**UK**	**N=2763** [g]	**Graded exercise Therapy or Graded Activity (since 2005)** (n=699): **Made worse: 34% (238†)** No Change: 21% (147†) Helpful: 45% (315†) **Cognitive Behavioural Therapy (since 2005)** (n=?††): **Made worse: 12%** No Change: 38% Helpful: 50%

[e] Additional Information: Participants who had undertaken CBT. Questionnaire posted on various internet newsgroups. Age: Mean: 39 (S.D.: 11.8) Gender: Female: 84%; Male 16% Doctor gave diagnosis of ME/CFS: 98% Treatment last 6 months or longer: 64%
[f] Translated from the Dutch: Cognitive Behavioural Therapy = Cognitieve gedragstherapie; A lot worse = Sterk verslechterd; Somewhat worse = Iets verslechterd; No change = Gelijk gebleven; Somewhat improved = Iets verbeterd; Considerably improved but not recovered = Behoorlijk verbeterd, maar niet genezen; Entirely Recovered = Volledig hersteld.
[g] Additional Information: Gender: Female: 81.89% Male: 18.11%.
Ethnic Origin: White British: 97.0%, Asian British: 0.48%, Black British: 0.22%, Caribbean: 0.15%, Chinese: 0.07%, Indian: 0.07%, Pakistani: 0.04%, Other: 1.96%
Age now: 0-11 years: 0.85%, 12-17 years: 6.26%, 18-25 years: 11.18%, 26-40 years: 20.56%, 41- 65 years: 54.04%, 65+ years: 7.11%.

† These figures are estimates based on the percentages
†† The number is not given - from a graph that the 12% figure comes from, the sample size for CBT is approximately 600-700

Table 1: Reporting of Harms in 9 Patient Surveys (page 3 of 5)

Study	Year	Country	Sample	Results for GET, GAT and CBT
Veer et al. [83]	**2008**	**Netherlands**	**N=412** [(h)]	**Graded Activity/Exercise Therapy** (n=142): [(i)] **"Disimproved following treatment" 33.1% (47)** "No impact" 23.9% (34) "Improved following treatment" 43.0% (61) **Cognitive Behavioural Therapy** (n=115): **Disimproved following treatment 27.0% (31)** No impact: 42.6% (49) Improved following treatment: 30.4% (35) Other (related): Physiotherapy (n=203): Disimproved following treatment 21.2% (43) No impact: 41.9% (85) Improved following treatment 36.9% (75) Psychotherapy (not CBT), Psychological support (n=169): Disimproved following treatment 5.9% (10) No impact: 60.9% (103) Improved following treatment: 33.9% (57) Participation at a rehabilitation centre (n=40): Disimproved following treatment 20.0% (8) No impact: 35.0% (14) Improved following treatment: 45.0% (18)

[(h)] Additional Information: Participants from 3 patient organisations: (Steungroep ME en Arbeidsongeschiktheid, the ME/CVS Vereniging and the ME/CVS Stichting) (CVS=CFS) Total respondents = 412 (completed questionnaires) "Circulated to: 740 Net response rate: 55.7%

[(i)] Translated from the Dutch: Graded Activity/Exercise Therapy = begeleide opbouw van activiteiten; Disimproved following treatment = Effect: Het ging daarna slechter; No impact = Geen effect; Improved following treatment = Effect: Het ging daarna beter; cognitieve gedragstherapie (CGT) = Cognitive Behavioural Therapy; fysiotherapie = Physiotherapy; psychotherapie (niet CGT), psychologische begeleiding = Psychotherapy (not CBT), Psychological support; opname in revalidatiecentrum = Participation at a rehabilitation centre

Table 1: Reporting of Harms in 9 Patient Surveys (4 of 5)

Study	Year	Country	Sample	Results for GET, GAT and CBT
Bjørkum et al. [84]	**2009**	**Norway**	**N=828** (j)	**Graded Training** (n=620): (k) **"Deterioration": 78.7% (488)** "No change": 8.2% (51) "Helpful": 13.1% (81) **Cognitive Behaviour Therapy** (n=311): **Deterioration: 7.1% (22)** No change: 36.0% (112) Helpful: 56.9% (177)

(j) Additional Information: Participants from 2 Norwegian patient organizations (ME-association and MENiN)
Circulated to 2060 Members (Response rate: 40.2%). Gender: Female: 84.2% (697); Male: 15.8% (131)
"Age: Mean 43.7 years (SD: 12.6)."780 persons (94.2%) said that they had filled out the questionnaire themselves.
Only persons that had officially received the diagnosis post-viral/chronic fatigue syndrome (ICD-10: G93.3) could participate
(k) Translated from the Norwegian: Graded Training = Gradert trening; Deterioration = Forverring; No change = Ingen effect; Helpful = Nyttig; Cognitive Behaviour Therapy = Kognitiv atferdsterapi

Table 1: Reporting of Harms in 9 Patient Surveys (5 of 5)

Study	Year	Country	Sample	Results for GET, GAT and CBT
M.E. Association [85]	**2010**	**UK**	**N=4217** [I]	**Graded exercise Therapy** (n=906): **A lot worse: 33.1% (300)** **Somewhat worse: 23.4% (212)** No change: 21.4% (194) Improved: 18.7% (169) Greatly improved: 3.4% (31) **Cognitive Behavioural Therapy (n=997)**: **A lot worse: 7.9% (79)** **Somewhat worse: 11.6% (116)** No change: 54.6% (544) Improved: 27.0% (269) Greatly improved: 11.6% (116) Other: Physiotherapy (n=862): A lot worse: 15.7% (135) Somewhat worse: 17.2% (148) No change: 36.7% (316) Improved: 27.0% (233) Greatly improved: 3.5% (30) Hydrotherapy (n=275): A lot worse: 13.1% (36) Somewhat worse: 13.5% (37) No change: 32.0% (88) Improved: 37.5% (103) Greatly improved: 4% (11)

[I] Additional Information: Online respondents: 3494 (23% members), Paper respondents: 723 (97% members). Country: 92% UK, 1% Rep. of Ireland, 7% Elsewhere. Age: 11-20 years: 5%, 21-35 years: 24 %, 36-50 years: 35 %, 51-65 years:30%, 65+ years: 6%. Gender: Female: 78%. Male 22% Length of illness: Less than a year: 8%, "2 to 5 years" (sic): 28%, "6 to 10 years": 20%, More than 10 years: 44%. Effect of illness on health: mildly: 28%; moderately: 57% severely: 15%

Table 2. Pooled Data of Harms from GET, CBT and Pacing reported in Surveys

Therapy	Sample Size	Harms[a] (N)	Mean rate of harms (%)	Range
Graded Exercise Therapy (GET) (or similar terms)[b]	4338	2223	51.24%	28.1 - 82%
Cognitive Behavioural Therapy (CBT)[c]	1808	360	19.91%	7.1 - 38%
Pacing (or similar terms)[d]	5894	152	2.58%	0.2 - 9.3%

[a]This includes any degree of harm e.g. both *"somewhat worse"* and *"a lot worse"* from the ME Association survey [85].
[b]Taken from [75,78-80,82-85]; [c]Taken from [80,81,83-85]; [d]Taken from [79,80,83-85]

Table 3. Potential Strategies to Improve the Reporting of Harms in ME/CFS

Setting	Strategy
Clinical trials	▪ Recognize heterogeneity of ME/CFS study participants ▪ Systematically track adverse events ▪ Use blinded raters ▪ Develop checklists for possible harms and combine them with spontaneous reporting ▪ Use instruments that are appropriate for ME/CFS cohorts ▪ Assess possible psychological, social, and economic harms ▪ Use objective outcome measures ▪ Monitor a range of symptoms, not just fatigue ▪ Record level of activity and check for intervention compliance using objective measures of activity ▪ Monitor study withdrawal rates and reasons ▪ Follow subjects for longer periods post-intervention ▪ Check for clustering/therapist effects ▪ Interpret results of studies taking into account previous studies
Surveillance outside of trials	▪ Establish a surveillance system for harms associated with non-pharmacologic treatments that allows both patient and healthcare staff submissions ▪ Collate existing and future reports from clinicians and patients ▪ Educate clinicians about possible harms and encourage them to report any adverse events
Publications	▪ Make available intervention details via appendices, web-based materials ▪ Adhere to common standards for trial reporting ▪ Observe international standards for disclosing conflicts of interest (COIs) recognizing that financial connections with entities that pay disability claims may constitute a COI in ME/CFS

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