An illness in Crisis: The Subtleties That Led To The PACE Trial And Its Impact On ME/CFS

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Abstract

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a contested illness with no diagnosis. Treatment typically consists of symptom management. This spurred interest in finding ways to help patients with ME/CFS to find new ways of improving and helping them recover. The PACE trial tested and found that Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET) were effective therapy options for ME/CFS. However, this trial had a lot of controversies attached to it for various reasons, like methodology changes and misrepresenting results that made the results look more favorable. This trial led to adverse outcomes for ME/CFS patients, impacting their lives and how the illness is seen. However, what isn't frequently discussed are the various aspects that potentially influenced the lead-up and decision-making of the trial. The biopsychosocial model of ME/CFS and its reliance on the psychological part, the researcher's prior research and potential allegiance to CBT and GET, and researchers having free rein to make their own research decisions without critique all played subtle roles in leading to the trial and its outcome. By exploring these different factors, one can see these factors and how to prevent that for future ME/CFS studies and other contested illnesses, restoring trust toward researchers.

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Table of Contents

Chapter 1: ME/CFS and The World of A Contested Illness

The Contested Illness Life

Let's begin with a story. Paul was an avid worker who enjoyed traveling, having new experiences, and enjoying life. However, while working abroad, he started to get sick. These started small: headache, stiff neck, flu-like symptoms. Eventually, it worsened to the point where they had to stay inside and rest for weeks. Tests revealed nothing, and Paul's boss thought he suffered from depression. As Paul continued getting worse, he saw a new general doctor who told him that Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), which he thought he had, didn't exist and that therapy and antidepressants were the answer. Paul refused medicine but agreed to therapy. Despite dealing with the disease, his employer told him he must continue seeing a therapist to use sick days, doubting his illness. The therapist diagnosed him with Post-viral Fatigue Syndrome, another way of saying ME/CFS, giving Paul an answer that isn't pills or psychiatric claims. While Paul still suffers, managing the illness gives him a chance to regain some of his life. This is the true story of someone who started suffering from ME/CFS in 1998 (M.E. Support, 2017). It tells the story of what patients deal with when it comes to contested illnesses or illnesses with no empirical evidence. In this case, it's ME/CFS.

Illnesses are unique. When it comes to diseases, we might catch something less serious, like a cold, or something more severe, like the flu, bacterial infection, or chronic condition. However, something that most illnesses have in common is that there are objective ways to diagnose them. A bacterial infection might be determined through specific blood tests, or gastrointestinal diseases might be found through stool tests. Although they affect other body parts, they still have objective ways of being diagnosed that are accurate to the medical profession (Abbott, 1988). Doctors use these objective results, something they can see and

analyze, to show their authority regarding these illnesses and their control in the medical profession to patients (Abbott, 1988; Friedson, 1988). However, some don't fall into those categories.

Contested illnesses are illnesses with no official diagnosis and are uncertain, leading to them being in a gray area (Dumit, 2006). In other words, these illnesses might not be seen as real illnesses by the medical profession because there's no "proof" through tests and examinations, but patients and their experiences say it is a problem (Dumit, 2006; Barker, 2008). The medical establishment might see these illnesses as fake or exaggerated. There's also the doctor vs. patient aspect, with doctors believing their conclusion because of the lack of evidence and patients believing they have an illness (Barker, 2008; Conrad et al., 2016). Some contested illnesses are Gulf War Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, and ME/CFS. These illnesses are challenged because no test or examination gives doctors clues as to what is ailing patients.

These issues can make patients feel out of control and ignored by medical professionals (Dumit, 2006). These patients must fight for their illnesses in an institution where medical professionals have more control (Abbott, 1988; Friedson, 1988). Since doctors have more control, they use that authority and power and limit patients' input. Doctors tend to focus more on objective evidence, like tests, than subjective evidence, like how patients feel. However, by minimizing patients' experiences, doctors ignore these patients and say that a test is more important than experiences. Contested illnesses are seen as medical by patients but aren't that way by doctors. There has been a struggle for contested illnesses to be medicalized because they aren't seen as authentic medical issues.

Those with contested illnesses who refuse to be fitted into an objective framework will "remain the undeserving sick of our society and our health service" (Chainey, 2016, para. 5). The

medical establishment believes that patients shouldn't deserve treatment if they can't fit into an objective view. These patients face numerous difficulties regarding their contested illnesses, feeling that the profession failed them.

However, one of the biggest struggles that patients with contested illnesses face is their illness being seen as psychological. These patients were told, as one patient put it, that it's "all in my head, there is no pain, you just imagine there is" by their physician who was just out of medical school (Barker, 2008, pg. 27). These claims invalidate their experiences, push them away, and could worsen their illness.

Patients with contested illnesses being offered therapy or denied treatment because their doctor has a psychological view can spread that to the public. With that comes the risk of the stigma often associated with psychological treatment, either because they don't think it will help them, have cultural reasons that stop them, or some other factor (Hirai et al., 2015). They must deal with their illnesses being minimized by the medical profession and the stigma that comes with it being psychological and not physical.

The World of ME/CFS

An example of a contested illness that has been controversial is ME/CFS. ME/CFS is a chronic condition characterized by unexplained recurrent or chronic periods of severe fatigue, present for at least six months (Sharpe et al., 1991; Castell et al., 2011). Other debilitating symptoms include delayed post-exertional fatigue and neurological symptoms that reduce activity and function (Spander and Allen, 2018). These aren't set criteria, as one of the controversies regarding ME/CFS is that different standards can be used (Spander and Allen, 2018). While research and funding involving ME/CFS have continued to increase in the past few decades, there are still a lot of unknowns about the illness.

Why is ME/CFS regarded as a contested illness? Its symptoms are vague and can appear for other diseases, making it difficult to determine if it's because a patient has ME/CFS or another illness. Doctors are less likely to believe what a patient is saying without objective proof. Instead, doctors must rely on various criteria that patients must meet, whether the CDC, Oxford or another type (Sharpe et al., 1991; Malouff et al., 2008). Researchers have explored using a blood test to determine if a patient has ME/CFS (Esfandyarpour et al., 2019). Despite this, no blood or other test can currently diagnose the illness.

Other diseases with symptoms resembling those with ME/CFS consist of sleep disorders, pain disorders, multiple sclerosis, or even side effects of certain drugs (Devasahayam et al., 2012; Sampson, 2020). This can lead to patients being misdiagnosed, which can harm those patients who are not getting the proper treatment and are being ignored.

These risks are one of the reasons why ME/CFS criteria were created. They ensure that the patient meets the more accepted symptoms and minimize the risk of being misdiagnosed. Multiple criteria can be used. Two examples of these used in most studies testing the efficacy of treatment for ME/CFS are the CDC and the Oxford criteria (Sharpe et al., 1991; Malouff et al., 2008). The CDC criteria have changed over the years. The one described below is the Institute of Medicine (IOM) criteria from 2015. It determines whether a patient has the three characteristic symptoms of ME/CFS. The first is a substantial reduction or impairment in the ability to engage in pre-illness activity, lasts longer than six months, and has severe fatigue. The second is a post-exertional malaise which consists of symptoms worsening after physical, mental, or emotional exertion that can last days, weeks, or longer. The third is unrefreshing sleep; the patient doesn't feel better after sleeping. It also states that either cognitive impairment, problems with thinking and executive function, or orthostatic intolerance (patients unable to maintain an upright posture)

must be present (Institute of Medicine, 2015). While there are other symptoms of ME/CFS, these are the ones that the IOM determined as the main symptoms, supported by the CDC.

The Oxford criteria are like the IOM criteria in that it heavily emphasizes fatigue as the primary symptom, along with other symptoms like mood swings and sleep disturbances. It also includes excluding ME/CFS, like those with conditions that can produce chronic fatigue, mental disorders, eating disorders, etc. (Sharpe et al., 1991). While there are other criteria, like Fukuda and Canadian Consensus, the Oxford and IOM are often used in research studies for ME/CFS. These criteria are based on patient's subjective experiences and how doctors categorize them.

If ME/CFS is misdiagnosed, it can have drastic consequences for the patient. The disease can lead to dangerous outcomes where the patient is housebound or confined to their beds for up to decades (Chainey, 2016). This is an even bigger problem and risk because ME/CFS's recovery rate is around 5% (Cairns and Hotopf, 2005). Since there's no cure for ME/CFS and treatment tends to consist of rest and medication that can alleviate some symptoms like depression stemming from ME/CFS, recovery from the illness can be seen as due to chance. These treatment options mean that ME/CFS patients need all the support they can get; otherwise, their journey will be very different and challenging.

Patients with ME/CFS have to live with the disease and make lifestyle changes that accommodate the presented limitations. One such patient is Eleanor, who contracted COVID in July of 2021 and dealt with numerous symptoms like fatigue, muscle pain, fever, etc. Later recovered, but she still felt some lingering effects like shortness of breath and difficulty concentrating. Those effects worsened over time to the point that she had constant brain fog, more fatigue, and difficulty making decisions and choices. In January 2022, she was diagnosed with ME/CFS, with post-COVID symptoms parallel to the illness, requiring her to learn to live

with her symptoms, take medication, and fit breaks into her schedule not to push herself. Due to her diagnosis and cultural upbringing, she has dealt with the stigma of ME/CFS being seen as a mental illness and non-existent if it isn't physical while learning to live with ME/CFS (Eleanor, 2022). In her story, it's unknown where her illness came from, but most likely, it was due to COVID. She had to adjust to life with the disease and counter those downplaying her illness.

Another patient is Andrew, a physician who suddenly got ME/CFS. However, despite symptoms not going away, they were minimized, being sent to a "shrink" who claimed their symptoms came from being anxious and depressed. After receiving his ME/CFS diagnosis, he felt heard and understood and realized that he must pace himself not to have his symptoms appear stronger. While he had a robust support system from family and friends, he saw and understood that others, including medical professionals, can belittle those with the illness (Andrew, 2018). In Andrew's story, he was brushed away due to claims that his symptoms were psychological, an outcome that those with ME/CFS hear frequently. Again, the lack of support can dramatically affect a patient with the illness and provide a more difficult road to recovery. As a medical physician, he has gone through and understands the effects of ME/CFS and what those patients must go through, something that many physicians can't claim.

The final patient is Liz, who first got sick on April 15th, 1991, with a fever and upper respiratory infection that nothing helped. She didn't get out of bed for over two years due to headaches, muscle aches, severe fatigue, sensitivity, and more. It took her a year to be diagnosed with ME/CFS. Despite slowly improving after those first two years of being bedridden and getting an apartment, she was forced to return home and be supported by her parents. For 27 years, she has spent most of it in bed, with no improvement in treatment options or getting better over time and having to deal with stigma (Liz, 2018). Liz had a more extreme version of

ME/CFS, being confined to a bed for most of her life and having to adapt to that and the support she needed.

What all three of these patient stories of ME/CFS have in common are the drastic changes that the illness can force upon patients. The lives of these patients changed completely, from being forced to add breaks to manage symptoms to being unable to move for days. The stigma that sticks to the illness also means patients need support.

The medical relief a patient with the illness could seek is not easy to look for since medical professionals can disagree with patients. Medical professionals have control over diagnosis and treatment, so they can prevent patients from getting what they need. All this added to the fact that ME/CFS doesn't have a cure, shows that there needs to be a push for new potential treatments. Some believe that patients with ME/CFS suffer due to their beliefs about the illness and its effects, leading to less movement and a fear of doing anything, making their bodies worse. This led to one of the suggested treatment options for ME/CFS: Cognitive Behavioral Therapy (CBT).

The History, Use, and Dangers of Cognitive Behavioral Therapy

CBT can be thought of in different ways. One way to think of CBT is as a combination of cognitive therapy approaches integrated with behavioral techniques (Dozois et al., 2021). There are a set of principles that underlie CBT treatment. These principles set the foundation for CBT and what cognitive behavioral therapists focus on and use to help patients. The first principle states that psychological problems are partly due to the wrong or unhelpful ways of thinking a person creates for themselves (APA, 2017; Hazlett-Stevens and Craske, 2005). People have dysfunctions in learning and processing information, leading to faulty thoughts. The second principle states that these problems are partly due to learned unhelpful behavior patterns (APA,

2017; Hazlett-Stevens and Craske, 2005). People reinforce these bad habits and behaviors, making them challenging to break and change. This directly leads to the third principle, which states that these problems can be resolved by teaching people how to cope better, providing relief and symptom management (APA, 2017; Hazlett-Stevens and Craske, 2005). The unhelpful behavior learned can be unlearned, improving the patient's life. The patient learns new behaviors that positively affect them while seeing the negative of their old behavior.

There's a lot of focus on how the mind thinks, understands, processes, and interprets a situation, surroundings, and more to change thinking into something positive through various strategies. CBT uses this information to steer patients away from their current thinking and into noticing and changing their thinking.

CBT came about from a combination of Behavioral Therapy (BT) and Cognitive Therapy (CT) (Eysenck, 1959; Ellis, 1962; Beck, 1970). BT can be thought of as the idea that psychological treatment should eliminate unadaptive behavior and enhance adaptive behavior (Rachman, 2015; Eysenck, 1959). Meanwhile, CT focuses more on the importance of internal events or what goes through a person's mind (Blackwell and Heidenreich, 2021; Beck, 1970). These internal events include dysfunctional thoughts, belief systems, and conditional and unconditional assumptions. It took a more cognitive approach to understanding the inner workings of a person's mind and how their thoughts and beliefs impact decision-making. It focuses on understanding the thought process of patients, untangling it, and fixing it.

CT tries to show a difference between thought and external reality (Ellis, 1962; Beck, 1970). According to Beck, CT focuses on four types of thinking that lead to various problems. The first is arbitrary inference, where the patient draws a conclusion with little to no evidence or the evidence suggests the opposite of their thinking. The second is overgeneralization thinking,

where the patient uses a single decision to generalize multiple scenarios and outcomes. The third is magnification thinking, where the patient exaggerates the meaning or significance of an event. The fourth is cognitive deficiency thinking, where the patient ignores or fails to use their own experience to guide themselves and how they reach conclusions (Beck, 1970). These four types of thinking have in common that they all lead to continued reinforcement of what the patient is thinking. The combination of CT and BT led to CBT, which focuses on cognitive activity, how it affects and changes a patient's behavior, and how that can be remedied (Clark, 1986). Cognitive concepts were absorbed into BT to give more tools for cognitive therapists to work with (Rachman, 2015).

CBT has high efficacy and is used for various mental conditions like panic disorders, specific phobias like agoraphobia, anxiety disorders, depression, and eating disorders (Hazlett-Stevens and Craske, 2005). This efficacy is likely because CBT changes people's way of thinking into something that can better help them. This makes CBT today a highly effective therapy option seen as a gold standard in the field (Olatunji et al., 2010). Its low cost, lack of intrusiveness, rapid results, and the ability to be used in various illnesses and disorders are some reasons for it being highly regarded (Olatunji et al., 2010).

However, while CBT is seen as an effective treatment, some controversies surround it. One of the main controversies is that it can be suggested as a treatment option for those with contested illnesses. This suggestion can downplay their condition and give them a treatment that doesn't relate to their disease. One example of this for ME/CFS was the story from Andrew, who was told to go see a "shrink" and said that his symptoms were depression and anxiety rather than ME/CFS. Other patients have also been told that their illness is in their heads and not real (Barker, 2008). These claims have led to the controversial history between ME/CFS and CBT in

that CBT has been seen as a treatment option, but activists are against the idea. The same goes for Graded Exercise Therapy (GET), which has patients gradually expose themselves to more exercise to build up their energy levels (White et al., 2011). Graded exercise therapy can be given to patients when they stop exercising and being active due to illness, pushing their bodies into an inactive state. This state would lead to a patient believing their illness is worsening due to inactivity. In the state of ME/CFS, it has been seen as harmful because it forces patients to become more active despite symptoms (Twisk and Maes, 2009).

There is also Adaptive Pacing Therapy (APT), which focuses on helping patients adapt to the disease and teaching them about their limited energy (White et al., 2011; Action for ME, 2019). With APT, it's believed the illness is organic and not changed by behavior. APT can be seen as similar to GET, but the main difference is that GET has patients continuing to push themselves to improve their activity despite symptoms. At the same time, APT acknowledges that there's a limit patients won't be able to pass. APT is not seen as controversial in the ME/CFS community. Many ME/CFS activist groups encourage pacing as one of the best treatments for the illness since it acknowledges patients' limitations and teaches patients how to work around them (Action for ME, 2019; CFS/ME Working Group, 2002).

This past led to a study testing whether CBT and GET were effective behavioral treatment options for ME/CFS. CBT and GET were seen as treatment options that became more popular with researchers as a route for tackling ME/CFS. The study and the subtleties that led to it, including how medical professionals saw ME/CFS, how researchers unconsciously align themselves to the treatment they know, and how some questionable research decisions impacted the lives of ME/CFS patients and how the illness is seen. Introducing these different ideas show the various factors that led to the study and the aftermath it caused, showing why these areas

need to be focused on more when it comes to research concerning illnesses and behavioral treatment to learn from and prevent it from happening to future unknown diseases.

Chapter 2: The PACE Trial Improvement and Recovery from ME/CFS Results

The Positive and Negative History of ME/CFS in Research

There is a lot of controversy regarding research for ME/CFS and any indication that the disease is psychological. Specifically, studies claiming that CBT and GET are effective have been perceived as harmful by the community (Friedberg, 2016). Why was CBT seen as potentially effective for ME/CFS? A reason is due to research that claimed that illness belief played a role in prolonging fatigue states, including ME/CFS (Nijrolder et al., 2008). Specifically, some research believed CBT was adequate based on the fear avoidance theory of ME/CFS, which states that their symptoms are due to their fear of engaging in activities that lead them to not engage in them. (White et al., 2011). Why was GET seen as potentially effective for ME/CFS? Some believed that GET could help patients be conditioned to be fitter by increasing their activity and effort (White et al., 2011). Patients work to reverse the deconditioning of their lack of exercise and activity. Based on the belief that a lack of exercise was the leading cause of ME/CFS, CBT and GET were seen as therapy options.

Researchers have tested whether CBT and GET were helpful for ME/CFS (Butler et al., 1991; Sandler et al., 2016; Wiborg et al., 2010). These studies had patients get CBT, GET, or both and looked at whether they improved with therapy. Those studies showed improvements for patients who got those therapies compared to a control group. For example, Butler et al. 1991 gave 32 ME/CFS patients who had been ill for a mean of five years CBT. 22 out of 27 patients who completed CBT reported feeling better or much better. They also showed better physical function in areas like their ability to work after treatment (Butler et al., 1991). Wiborg et al., 2010 analyzed three studies that tested CBT for ME/CFS. They showed that, after getting CBT,

participants reported lower fatigue that was still significant after controlling for physical activity (Wiborg et al., 2010). Sandler et al., 2016 found that using both GET and CBT improved self-reported fatigue scores, lower mood disturbances, and greater physical functioning. This was sustained during follow-up 24 weeks after treatment started (Sandler et al., 2016).

However, those studies had results that had limits on those claims. Butler's study was uncontrolled, non-blinded, and non-randomized, potentially compromising the results (Butler et al., 1991). For Wiborg, they found that while CBT reduced fatigue, it didn't do anything to improve the physical function of ME/CFS patients (Wiborg et al., 2010). ME/CFS can decrease patients' physical function to the point where they become bed-bound. Improvement in fatigue but not in physical function provides a limited benefit.

Another study, a meta-analysis of exercise therapy for ME/CFS from 1999, showed evidence for the effectiveness of GET and CBT. GET was seen through an analysis of eight studies as significantly more effective than regular medical treatment. It was also seen as more effective than pacing, or APT. Comparing GET to CBT showed no difference in effectiveness (Larun et al., 2019). However, the meta-analysis showed that all studies looked at are at a high risk of performance and detection bias due to a lack of blinding. They also raise concerns about the risk of preference regarding selective reporting, with six out of the eight studies showing unclear to high risk (Larun et al., 2019). While these studies support these therapy treatment options, the results can bring concerns and contradictions.

There was also criticism about studies that showed the effectiveness of CBT and GET. They were criticized for issues like too small of sample size, being too selective, or using different outcome measures (White et al., 2007). These issues are problematic in research because a low sample size can affect a study's trustworthiness (Wicherts et al., 2016). Smaller

sample sizes can work to the researcher's advantage. This mix of results for CBT and GET showed that there was a need for a study that would be powerful and big enough to make a better attempt at solving the question of whether either or both can be effective options for ME/CFS. This study would better examine what CBT and GET can offer and whether they can be provided as an official treatment for the illness. This could add more to an unknown disease (Dumit, 2006).

The PACE Trial 2011 Paper - Improvement Results

This study was called the Pacing, graded Activity, and Cognitive behavioral therapy: a randomized Evaluation (PACE) Trial (White et al., 2007; White et al., 2011; White et al., 2013). The study aimed to determine whether psychological treatment, like CBT, is an effective way to help individuals suffering from ME/CFS, providing more straightforward answers to researchers and the public (White et al., 2007).

The PACE Trial was publicly funded by numerous British government agencies, including the UK Medical Research Council (Sharpe et al., 2019). It showed that government agencies also wanted to find an effective treatment for ME/CFS. In this case, it was behavioral therapy. The trial had a high cost, around $6.4 million, to run (Torjesen, 2018). The study was also preregistered, meaning the authors posted information like their rationale, methodology, and analysis plan before collecting data (White et al., 2007; ISRCTN, 2003). By preregistering for the PACE trial, the authors attempted to be transparent and honest about how the trial would be conducted.

There is a lot of importance in preregistering a study as it creates transparency and accountability. Preregistering ensures much of an experiment is decided before it's conducted and isn't changed without rationale (Foster and Deardorff, 2017). This guarantees that aspects of

a study that could be modified are set, and researchers could go back to a preregistration to replicate it in detail. Any changes must be explained in detail and under increased scrutiny. This would also prevent changes to make results look better.

The PACE trial was one trial that spanned numerous research articles. The protocol to establish the methodology, analysis plan, etc., was released in 2007 (White et al., 2007). This showed their choices, rationale, and how they selected participants. The trial's outcome, which answered whether CBT and GET improved ME/CFS in patients, wasn't reported until 2011 (White et al., 2011). Whether patients recovered from ME/CFS 52 weeks after starting the trial and how many weren't written until 2013 (White et al., 2013).

The PACE trial had four treatment groups: APT, CBT, GET, and specialized medical care (SMC) alone. The three therapies were in addition to SMC (White et al., 2011). SMC included patients getting care from doctors specializing in ME/CFS, consisting of information regarding the illness, generic advice like resting, and symptomatic pharmacotherapy for issues like insomnia, pain, or mood. APT, adapting to the disease and knowing about energy limits, was the second treatment group. Based on the fear avoidance theory of ME/CFS, CBT was the third treatment group. The final treatment group was GET, based on deconditioning and exercise intolerance for ME/CFS. Patients in each treatment group got manuals that explained more. CBT and GET were based on prior studies of ME/CFS, APT was based on previous descriptions of the therapy and support from the UK ME community, and SMC used a general manual of information on ME/CFS and medicine if symptoms are present (White et al., 2011).

Patients were recruited from six outpatient specialist ME/CFS clinics over three years. Participants were screened for eligibility using the Oxford criteria of ME/CFS (Sharpe et al., 1991). As stated in Ch. 1, the patient's primary symptom is disabling fatigue, with other

symptoms like an affected physical and mental function and fatigue being present for a minimum of six months and more than 50% of the time. It makes no distinction between mild and severe fatigue. Other aspects include it not being life-long, having other symptoms like myalgia (muscle pain), mood swings, sleep disturbances, and not having other conditions that can cause chronic fatigue (Sharpe et al., 1991). This criterion was made by a group of researchers led by Michael Sharpe, one of the principal researchers for the PACE trial. While the Oxford criteria were used as the eligibility indicator, participants were also assessed at baseline with the international criteria for ME/CFS and the London criteria (White et al., 2007). The international criteria require four or more symptoms like persistent fatigue for six or more months, post-exertional malaise lasting more than 24 hours, lack of sleep, a new type of headache, etc. (Reeves et al., 2003). The London criteria require post-exertional fatigue, poor memory, fluctuating symptoms, no depression or anxiety, and lasting six or more months (Dowsett et al., 1994). Despite these two criteria, they were not used to determine whether a participant entered the trial.

Various survey instruments were used in addition to the Oxford criteria to select those eligible for the trial. The first was the Chalder Fatigue Questionnaire (CFQ), a list of 11 questions designed by various experts on physical and mental fatigue to measure fatigue, not focusing on one illness like ME/CFS (Chalder et al., 1993). It is seen as reliable and valid to quantify fatigue. Participants answer with a one if it applies to them or a zero if it doesn't. That leads to a maximum score of 11, so patients, according to the trial, had to score six or higher to meet the eligibility to enroll in the trial (White et al., 2011). The second instrument used was the short form-36 physical function (SFPF) subscale, which focuses on understanding how a patient can physically function. This includes questions regarding bodily pain scales, role limitations due to physical causes, and other factors. It is seen as a detailed examination of patients and their

physical health (McHorney et al., 1993). This scale is out of 100; a participant had to score 60 or less to enter the trial (White et al., 2007). However, 11 months after the trial began, the threshold was upped to 65 to increase recruitment rates (White et al., 2011).

The PACE trial excluded participants unable to attend hospital appointments (White et al., 2011). Patients with ME/CFS have limits, as shown by the criteria stating severe fatigue as the main symptom. Extreme fatigue as the primary symptom would increase the likelihood that a patient cannot go to a hospital to attend an appointment. Excluding those patients could remove more severe cases of ME/CFS. This could result in scores more representative of ME/CFS patients with a mild to moderate case of the illness. This could be because the researchers believe the treatment options would work better for mild to moderate patients than for severe. These criteria ensured those in the trial had the highest likelihood of having ME/CFS, getting the most accurate data possible. After these assessments, participants were randomly assigned to their treatment groups. However, due to the nature of the trial, participants, therapists, and doctors couldn't be blinded to which condition they were allocated (White et al., 2011). For example, a participant getting CBT couldn't be blinded to that fact, nor could the therapist. This is an issue that's problematic in all therapy.

The therapists used in each treatment were trained by "therapy leaders," one for each therapy, who had extensive experience with ME/CFS treatment (White et al., 2011). These trained therapists held individual therapy for patients each week for the first four weeks, then every two weeks afterward until week 23. At week 36, there was an additional, final "booster" therapy session for all treatments minus SMC alone. Meanwhile, patients got at least three sessions with doctors during the 12 months for SMC. Additionally, the researchers recorded extra information like the session itself, how many sessions per participant, if they withdrew,

dropped out, etc., to inform their analyses of patients who didn't complete the trial (White et al., 2011).

The PACE trial had two primary outcome variables. These variables were used to determine whether patients improved from their baseline assessment. Assessments regarding patients' ME/CFS treatment were taken at week 12 mid-therapy, week 24 immediately post-therapy, and week 52. This was done face-to-face, and the patients self-rated the measures to keep observer bias to a minimum due to the lack of masking in the trial (White et al., 2011). The authors believed self-rated measures were the most efficient way of getting responses. They were the CFQ and the SFPF scales, as mentioned earlier. The CFQ was modified to have each question scored 0-3, where the lowest score is the least fatigue (Chalder et al., 1993). According to the researchers, the modification was to "more sensitively test our hypothesis of effectiveness" (White et al., 2011, pg. 827). This meant that the range of potential outcomes was 0-33, as there were 11 questions in the questionnaire. The SFPF subscale was the same as described above (White et al., 2011; McHorney et al., 1993). Alongside their two primary variables, they also had other secondary variables, like severe adverse effects (White et al., 2011). While these secondary variables had results and were also important, the main results of importance were the two primary outcomes: physical function and fatigue.

Their analysis included 641 participants split into four groups of 160 participants, except CBT, which had 161 participants (White et al., 2011). A reason for the number of participants was to address prior studies' small sample size issue and reduce the risk of misleading results. Despite the large sample size, there were a lot more participants who were excluded for other criteria. Specifically, 2,517 participants were excluded for various reasons, like if they didn't meet the Oxford criteria for having ME/CFS, even if they had a clinical diagnosis of the illness,

to keep results specific to the Oxford criteria (White et al., 2011). This continued until the researchers stopped looking for more participants.

The trial predicted that APT would be more effective than SMC alone, CBT and GET with SMC would be more effective than APT with SMC, and CBT and GET with SMC would be more effective than SMC alone. All these predictions state that the therapy would reduce fatigue, physical disability, or both after 52 weeks (White et al., 2007). They found that participants improved more from their baseline assessment with CBT than with APT and SMC alone. The same goes for GET compared to APT and SMC alone. There was no difference between APT and SMC alone (White et al., 2011). The trial also looked at which treatment option resulted in more participants having normal fatigue and physical function ranges. The typical person feels the normal range regarding their fatigue and physical function. Fatigue was defined as less than the mean of adult attendees to UK general practice plus one standard deviation (SD), making a CFQ result of 18 or less count as normal fatigue. Physical function was defined as equal to or above the mean scores of the UK working-age population minus one SD, making the SFPF result of 60 or more count as normal physical function. More participants were within normal ranges after CBT than APT or SMC. The same goes for GET compared to APT or SMC (White et al., 2011). APT compared to SMC resulted in no difference (White et al., 2011). These results show that CBT and GET, when added to SMC, successfully reduced fatigue and improved physical function more than APT and SMC or SMC alone.

The results don't support pacing in the form of APT as a first-line therapy for ME/CFS (White et al., 2011). Despite pacing being pushed by activists, the authors claim that it isn't practical. The authors also claimed that the results could be generalized to ME/CFS patients who meet alternative diagnostic criteria as long as fatigue is the main symptom (White et al., 2011).

In other words, as long as patients have fatigue as their primary symptom, they can be prescribed CBT or GET as treatment.

One limitation of the trial was that SMC could vary between patients (White et al., 2011). What counts as standard care isn't universal, so there would be some differences between patients seeking treatment. Another limitation was excluding patients who could not go to a hospital to attend appointments. Some accommodations were made for patients, like telephone visits. Yet more could've been made, like home visits or video visits, to include those who couldn't go to a hospital. A third limitation counters what the PACE researchers said: that the results could be generalized to other ME/CFS criteria. While fatigue tends to be the main symptom, the specific criteria chosen was Oxford. They also said those with a clinical diagnosis of ME/CFS but who didn't meet the Oxford criteria were omitted. By selecting the Oxford criteria, some participants who fulfilled different criteria were excluded from the trial, meaning there will be a limitation in generalizing the results to other criteria. This is a problem inherent in all clinical trials. Lastly, SMC wasn't as closely monitored as alternatives (White et al., 2011).

Lastly, there were conflicts of interest in the PACE trial. The conflicts of interest from researchers in the PACE trial included paid consultancy work for certain companies, working for the government that funded the trial, working for insurance or health companies, and receiving royalties from publishing companies (White et al., 2011). Despite these conflicts of interest, there isn't any evidence they played any role in the outcome of the results. The authors see the trial as the first extensive one to see whether behavioral treatment can be effective for ME/CFS, and the results show that it is. Although all therapy treatments were in addition to SMC, the trial heavily promoted the idea of ME/CFS being treated by a primarily therapy-driven treatment.

The PACE Trial 2013 Paper - Recovery Results

The PACE trial concluded that behavioral treatment could effectively reduce fatigue and improve physical function for ME/CFS patients. Another question that the researchers wanted to answer was whether those treatment options helped patients recover from ME/CFS (White et al., 2013). Improvement and recovery are two different outcomes. One merely reduces symptoms, while the other puts them into remission when no symptoms appear. That was the definition the researchers used for recovery (White et al., 2013). The researchers had this focus based on the low recovery rate of ME/CFS, showing the need for treatment (White et al., 2013). The study, done in 2013, followed up 52 weeks after randomization on patients to see if they recovered from what they call the patient's "current episode" of the illness (White et al., 2013). The current episode means their bout of ME/CFS that was present during the PACE trial. As the 2011 paper showed, they predicted that CBT and GET would lead to the highest recovery rates (White et al., 2013).

Everything about the 2013 paper was identical to the 2011 paper and the 2007 protocol that underscored the PACE plan. The only exceptions were the primary outcome variables. As mentioned earlier, the researchers explained that the CFQ scale was changed to a scale of 0-3 instead of a bimodal scale of 0-1 (White et al., 2011). That wasn't the only change regarding the CFQ. The other change was the normal range for fatigue which they determined to be 18 or less out of 33 (White et al., 2011). This differs from their original plan, which considered the normal range to be three or fewer out of 11 (White et al., 2007).

The researchers, as mentioned earlier, changed the eligibility threshold for the SFPF scale in the 2011 paper from below 60 to below 65 to find more participants (White et al., 2011). Another change was made after data collection but before data analysis regarding the physical function scale. The normal range of fatigue was set to a score of 60 or higher, while the initial

analysis plan had the normal range of fatigue set to a score of 85 or higher, a drastic change (White et al., 2007; White et al., 2013). The reason for these two outcome variables is because of their use in prior trials testing CBT and GET for ME/CFS (Malouff et al., 2008). All these changes, however, were approved by the relevant committee (White et al., 2011).

There was also a final variable used to determine the recovery rate of participants called the Clinical Global Impression (CGI), a measure of overall health change (White et al., 2013; Guy, 1976). In the initial analysis plan, a score of 1 (very much better) out of a scale of 7 meant recovery, while the modified method had a score of 1 and 2 (much better) out of a scale of 7 as meaning recovery (White et al., 2007; White et al., 2013). These three variables meeting the normal range, not meeting the Oxford criteria, and not meeting the international criteria for ME/CFS and London criteria for ME counted as clinical recovery for a participant (White et al., 2013). After running the data, 21% of participants met the criteria of recovering from ME/CFS after either CBT or GET, compared to 7% for SMC and 8% for APT (White et al., 2013). This supported their hypothesis that CBT and GET for ME/CFS made a statistically significant difference in the recovery rates compared to APT and SMC.

One limitation of this was that the PACE trial researchers didn't have an agreed measure of recovery (White et al., 2013). In other words, they believed that the self-rated scores could be a flawed measure of recovery, but objective measures like whether patients returned to work were also insufficient. However, that argument was countered by the researchers saying that subjective results are better than objective results, providing an example that objective measures of physical activity correlate poorly with subjective measures (White et al., 2013; Wiborg et al., 2010). Another limitation was that more data for CBT and GET were missing compared to APT and SMC. 11% of GET and CBT participants were missing data compared to 6% for APT and

SMC. They didn't mention what data was missing. However, they claimed that the missing data wasn't enough to change any results since all but 33 participants out of 640 contributed some data. They also mentioned changing their recovery analysis plan before analyzing the data (White et al., 2013). Their reasoning for the SFPF scale change was that with the original recovery threshold of 85, over half of the UK working population would be out of range. Their reasoning for the CFQ change was that the average fatigue for UK adults was around 14 out of 33, so one SD higher would be 18, making it below the normal range (White et al., 2013). While they explained their reasoning for it, they acknowledged that it could have impacted their final result. Lastly, they noted that recovery past 52 weeks isn't sure (White et al., 2013). They mentioned ways to keep the recovery past 52 weeks, including more sessions or behavioral treatment over the internet (Castell et al., 2011; White et al., 2013).

The PACE trial, and the recovery follow-up, supported the notion that behavioral treatments such as CBT and GET are effective for ME/CFS. However, while on the surface, the trial may look fine with some questionable decisions, looking more closely at aspects like changing the criteria for the primary outcome variables and the researchers' continuous framing of the illness as a psychological one shows that the PACE trial was dangerous and misleading. This brought about fights between researchers supporting the PACE trial and its findings and those who saw the PACE trial as a dangerous precedent that would cause harm and consequences to ME/CFS patients being subjected to these treatment options.

Chapter 3: Aftermath of PACE: Opposing Sides and Viewpoints

Researchers' Point of View on PACE

The PACE trial article released in 2011 showed that CBT and GET improved patients with ME/CFS overall fatigue and physical function (White et al., 2011). The recovery paper showed increased recovery for those who got GET and CBT compared to other treatments (White et al., 2013). Despite these results, there were differing opinions on what to think about the results. Some people disagreed with it and thought it was a dangerous paper that ignored important information, minimized patients' experiences, and ignored the biology behind the illness. Others believed the trial was a gold standard that went above and beyond to find a treatment option for a disease debated for years.

Let's start with researchers who had a more mixed reaction. Some saw the benefit, and others saw problems with it. The researchers that disagreed with the trial had multiple disagreements. First, they felt that, despite the PACE trial not finding much harm from GET, the results and researchers didn't focus on the damage GET can bring patients. For GET, the trial focused on the term "fear avoidance of exercise," which states that patients' ME/CFS worsens because they have an irrational fear of exercise (White et al., 2011, pg. 825). However, articles have shown that the fear avoidance theory for ME/CFS isn't supported (Gallagher et al., 2005; Geraghty et al., 2019). For example, one study found that ME/CFS patients compared to control were more fatigued, had more sleep disturbances, more self-reported physical disabilities, and more perceived exertion on the treadmill (Gallagher et al., 2005). The study results showed patients feeling worse than the control group despite doing the same exercise. Patients being scared to continue exercising is not why they suffer from the illness. While the trial mentioned any severe effects, researchers feel the risk was minimized. Researchers have also claimed that

GET doesn't help people with the illness return to their daily lives (Vink and Vink-Niese, 2022). This is based on updated guidelines from the National Institute for Health and Care Excellence (NICE), which state that GET and CBT should not be recommended to those with ME/CFS (NICE, 2021). While the trial claimed that there were few serious adverse effects from the treatment options, researchers see it differently.

Another primary reason some researchers were critical of the PACE Trial was the methodology changes and lack of transparency in the immediate aftermath of the trial and years later (Feehan, 2011; Kewley, 2011; Kindlon, 2011a;, Shepherd, 2017). The methodology change was criticized for making the results look more favorable than the original plan outlined in the trial protocol (White et al., 2007). Numerous researchers called for the journal to independently review the trial methods and results, as patients' trust has been lost (Shepherd, 2017; Torjesen, 2018). An independent review would give researchers more information on the decisions made and their impact, which could rebuild the trust of ME/CFS patients that the trial's results affected. Queen Mary University of London (QMUL), which hosted the PACE trial, refused to release the data despite the study being preregistered and publicly funded (Torjesen, 2018; Wilshire et al., 2018). Preregistered and publicly funded research should be accessible to all, especially researchers. The university refused to release the data for privacy reasons, but the data, once released, was anonymized, making the privacy argument moot (Wilshire et al., 2018).

Connecting with the methodology changes was a lack of transparency that researchers have voiced (Matthees et al., 2016; Tuller, 2017; Wilshire et al., 2018). The PACE trial authors have consistently given vague or no explanations for their decisions regarding their methodology, nor have they rebutted against the criticism (Kewley, 2011; Mitchell, 2011; Tuller, 2017). For example, the trial researchers found only 20% of patients met the definition of

improvement with the original analysis plan they did when QMUL released the trial data after the court case outcome. However, despite the drop from 61% improvement under the revised plan to 20% for the original method, the researchers claim that it doesn't alter the outcome or efficacy (Tuller, 2017). The massive drop didn't affect the researchers, despite showing that their controversial revised plan had favorable results.

Another example is that, with the revised analysis plan, 81 out of the 641 participants in the trial met the SFPF recovery threshold at baseline. However, the trial researchers instead claimed that no patients met the SFPF and CFQ criteria, even though nobody stated otherwise (Tuller, 2017). Instead of focusing on and addressing the issue of 81 patients being recovered on the SFPF scale, the trial researchers ignored and focused on something else.

If the researchers had discussed these criticisms, much of the controversy could've been prevented. This still leaves the question of whether the changes were made for a reason backed up by evidence or for better results.

Those that agreed with the results of the PACE trial, on the other hand, have very different arguments. The main views stated by those who supported the findings were that the trial should be considered a great work of science and something to support (Lancet, 2011; Macloed and Issar-Brown, 2017). The criticism that has come towards the researchers was unexpected considering the making of the trial itself (Lancet, 2011). This has been followed by researchers claiming that criticism of the trial is minor and from a vocal minority (Macloed and Issar-Brown, 2017). The supporters pushed back on the idea that the trial was badly designed and claimed it was conducted with high scrutiny.

This group of supporters included the journal where the trial was reported in 2011. They disagreed with the criticism and called it an "active campaign to discredit the research" (Lancet,

2011, pg. 1808). The journal claimed that those criticizing the results are "ignoring the findings of this rigorously conducted work" and that rather than the trial researchers forming their opinion about the intended outcome, the critics have done that (Lancet, 2011, pg. 1808). They claimed that good research is being attacked. Although research is meant to be open to discussion and critique, even if harsh, those supporting the trial have been making rebuttals in unique ways that seem to ignore what the criticism states.

The journal's support is like that of other researchers who focused on the benefit of the trial for the illness and bringing change. This also included the PACE trial researchers who have released numerous articles refuting critiques of the trial (White et al., 2011b; White et al., 2017). Lastly, researchers supporting the findings argue that there has been research in the past that supports the results (Butler et al., 1991; Whiteside, 2004; Wiborg et al., 2010). These articles show that CBT and GET are effective for ME/CFS; the trial results confirm that. It increases patients' durability and helps them work through their fear of exercise. Both groups, those who criticized and supported the trial's results, provided explanations to support their reasoning. Those criticizing the trial focused on the methodology changes and the lack of transparency shown throughout it and afterward. Those supporting the trial focused on the evidence shown and that it was backed up by prior research but ignored the transparency issues.

Media and Patient Point of View of PACE

Now let's move on to how the media saw the trial results. When the improvement results were released in 2011, the media soon picked up on it. Specifically, they focused on the positive outcome that the trial showed: CBT and GET are effective in helping patients improve from ME/CFS (Mann, 2011; Kelland, 2011). They zeroed in on those patients' improvement compared to APT or SMC alone. They also supported that with quotes from medical

professionals, including one who said they use “graded exercise, antidepressants, and CBT when possible” to treat patients with ME/CFS (Mann, 2011, para. 11). However, these news articles didn’t focus much on the potential criticism that can come from the trial, like the harm of exercise (Twisk and Maes, 2009). The positive spin continued in the future, with another article mentioning how patient belief about exercise can make ME/CFS patients worse (Siddique, 2015). This spin regarding patient belief brings worry, with the medical advisor for the ME association saying that it can make people believe that ME/CFS is psychological because of how the results are presented and the media (Siddique, 2015). The media had a more positive interpretation of the trial, but critics focused on the numerous problematic aspects.

Patients primarily saw numerous problems with the trial and criticized it. The first problematic aspect of the trial critics focused on immediately after its release was the depreciation of how ME/CFS is seen and felt. Specifically, with its results, the trial made ME/CFS seem like an easy illness to recover from with exercise. Let’s use CBT in the PACE trial. Chapter One explained that CBT aims to turn maladaptive thoughts off and teach patients better practices to help them. However, the PACE trial didn’t follow that. Specifically, the trial recommends using a form of CBT that challenges patients’ beliefs that they have a physiological illness limiting how they physically function (Rehmeyer, 2016). It suggests fighting against the patient’s belief that it’s a physical illness. How would ME/CFS patients feel if they were constantly told that their disease and experience weren’t physical but due to fear? Patients believe it’s a physical illness, but a therapist using CBT modeled from the trial would make another claim that says it’s due to a more psychological fear of exercise.

The trial made ME/CFS patients distrust the medical profession, research, and the public. It is known that many ME/CFS patients question doctors due to how the medical profession sees

it as a contested illness and downplays it (Blease et al., 2017; Dumit, 2006). This distrust comes primarily from the bullying of ME/CFS patients who try to fight back against the suggestion that they get CBT or GET. This even extends to parents fighting for the right to make medical decisions for their children with ME/CFS. For example, one mother describes how her daughter was forcefully taken by police, doctors, and a social worker because she didn't want her daughter to get psychological treatment for ME/CFS (Harding, 2010). Despite being returned to her mother soon after, the mother claimed her daughter was completely different (Harding, 2010). Patients with ME/CFS are seen as problematic when they don't want psychological treatment. What's the solution people came up with? One solution is forcefully giving them treatment whether they like it or not, as happened to this mother's daughter.

This bullying is rampant among ME/CFS patients, with them frequently describing having negative experiences with medical professionals regarding their illness. ME/CFS support groups come together to support one another in dealing with the disease, but also because most have had bad experiences with medical professionals. This is either because they were given lousy treatment, laughed at, or criticized for using items like mobility aids (Chainey, 2016). ME/CFS patients have many stories of how the medical profession wants to continue seeing them in a bad light. Other researchers also bully ME/CFS patients and critics of the PACE trial. For example, a researcher named Malcolm Macloed criticized those attacking the trial by mentioning that ME/CFS and the PACE trial are like what is seen when people compare autism to vaccinations (Macloed and Issar-Brown, 2017). While he doesn't elaborate, I would guess that he means a vocal minority tries to claim that vaccines cause autism. According to this idea, the same can be said for the PACE trial: a vocal minority claims that good research causes problems. It belittles and makes critics of the trial be seen as evil individuals trying to impact science

negatively. Bullying patients and other critics would only fester more distrust for the trial because people would see that they are getting their opinions shot down instead of discussing them.

The resulting data was the final problematic aspect of the trial that was noticed and criticized by both patients and researchers alike. One troubling aspect of the resulting data is that the analysis plan was changed. Another aspect was the lack of focus on objective measures that would have provided more information on treatment effectiveness. There was also criticism that the outcome variable doesn't tell the whole story and only focuses on what patients feel (Feehan, 2011; Kewley, 2011; Stouten et al., 2011; Kindlon, 2011a; Mitchell, 2011; Tuller, 2015). For example, Tom Kindlon mentioned that the trial didn't use "actometers" to determine physical activity patterns or how active patients are (Kindlon, 2011a). However, the trial didn't use this information, questioning whether patients were more active (Kindlon, 2011a). The only objective test, the 6-min walking distance test, also showed minimal improvement for CBT and GET, giving more evidence doubting the effectiveness of these treatments in improving physical activity (Kindlon, 2011a). The objective measures would provide results that could have a lower chance of being tainted by bias, but the lack of focus on them was a sticking point to those criticizing the trial. Another part of this criticism is the lack of data on the original analysis plan (Feehan, 2011). The researchers should've done both and compared them to show their changes' affected the outcome.

The Real Results of The PACE Trial

The raw data not being available to the public was one of the significant issues of the PACE trial. Despite the article's release in 2011, there was no way for anyone to get the raw data to run their own analyses to verify the results shown in the article. This meant that researchers

couldn't verify and replicate the results in the article, which is essential when many studies aren't easily replicable (Ioannidis, 2005; Geraghty, 2017). This is even though the trial was publicly funded and preregistered (Torjesen, 2018; ISRCTN, 2003). In my opinion, a publicly-funded trial using taxpayer money should be released transparently to let people know that the research performed with their money wasn't modified in a way that will change the outcome.

The original researchers didn't release the data due to privacy reasons. However, as it was a publicly funded trial, an ME/CFS patient named Alem Matthees filed a Freedom of Information Act (FOIA) request to get the raw data. This started a five-year court battle that, in the end, forced QMUL, the university that conducted the trial and held the data, to release it in an anonymized form (Queen Mary University of London v. The Information Commissioner and Alem Matthees, 2016). They spent 250k pounds to try and keep the raw data hidden, which is confusing considering if the data was anonymized, why was privacy a concern? With anonymity, researchers still get the data to analyze while patients won't have confidentially broken. However, despite the data being released, it wasn't the entire dataset, as certain variables weren't included. Specifically, stratification variables such as treatment center, therapist, and presence of depression included in the primary outcome analysis for the 2011 paper were not included in the FOIA dataset released (Wilshire et al., 2018).

This goes back to the criticism patients, activists, and researchers gave on why the original researchers weren't transparent. Transparency is essential in studies as it gives people a sense of trust in the results. Without that transparency, people are left to come to their own interpretations of the results and whether that's the results the data shows or what the researchers concluded. No transparency means follow-up exploratory analyses or tests that weren't reported cannot be redone, leading to further harm. This is especially a problem with the PACE trial,

which influenced health guidelines for ME/CFS making CBT and GET the primary treatment option for those with the illness based on the results (White et al., 2017). Decisions with significant implications need transparency for confirmation. The National Institute of Health has guiding principles for ethical research, and two stand out concerning PACE. One states that research should have scientific validity in the form of a good study design. The second states that research should have independent reviews to verify its claims (NIH, 2016). In the case of the PACE trial, those principles would've been followed by not changing their methodology and having the raw data released so independent researchers could support or refute their claims. The trial didn't follow those ideas of transparency.

While the PACE trial authors admitted to changes in their methodology and analysis plan, they didn't explain them in a way others understood (Feehan, 2011; Kewley, 2011), which meant that the raw data was necessary to reach accurate conclusions. Once the data was released, it allowed researchers to verify the results of the PACE trial and conduct the original protocol analyses. Now there was the possibility to see the impact the methodology changes made on the results.

One of the biggest criticisms regarding the PACE trial was its redefined methodology and analysis plan that impacted how the results were presented (see Figure 1). Specifically, the most significant criticism comes from how the PACE trial researchers changed the criteria for a patient to count as recovered regarding fatigue and physical function. They changed the Chalder Fatigue Questionnaire from a bimodal response (0 or 1) and a $\leq$ 3 out of 11 requirement to a Likert 0 to 3 response scale and a $\leq$ 18 out of 33 requirement (White et al., 2011; White et al., 2013; Matthees et al., 2016; Wilshire et al., 2018). The bimodal scale could present problems because patients can quickly score high. However, a change to the scale shouldn't be made mid-

trial without presenting the original and changed version to show the difference. Yet the change doubled the range of normal fatigue. Let's use an example of a participant's score for the CFQ. Using the bimodal scale, let's say the participant got a 5 out of 11 on the primary outcome variable. In other words, they didn't meet this criterion to count as recovered from ME/CFS. Now let's say this same participant got the same score as the bimodal counterpart in another universe where they used the 0 to 3 scale. For the same score to appear between the different scales, the bimodal score needs to be multiplied by 3. This would result in the participant scoring 15 out of 33. However, with this score, the participant did meet the criteria for having recovered from ME/CFS since they were below the normal range of fatigue, which was 18 or less. This hypothetical patient would've counted as recovered for that trial criteria using the revised scale, which shows the drastic change made mid-trial.

The second primary outcome variable was the physical function scale. They changed that from a score of >85 to count as recovered to a score of >= 60 (White et al., 2011; White et al., 2013; Matthees et al., 2016; Wilshire et al., 2018). This change was controversial because it allowed 13% of participants to enter the trial even though they met that qualification to count as recovered (Matthees et al., 2016). This doesn't answer whether they clinically recovered, but they did on that variable.

	Definition A: Specified in trial protocol	Definition B: Used in published reports
Overall Improvement	Minimum score of 75 on the 100-point SF-36 physical function scale *or* a score increase of 50% or more.	At least an 8 point increase in the 100-point SF-36 physical function scale.
	Of the 11 fatigue items on the Chalder Fatigue Questionnaire (CFQ), three or fewer rated as worse/much worse than prior to illness OR the total items rated worse/much worse dropped by at least a 50%.	At least a 2 point decrease on the 33-point CFQ (Likert scoring method).
Recovery	Minimum score of 85 on the 100-point SF-36 physical function scale.	Minimum score of 60 on the 100-point SF-36 physical function scale.
	Of the 11 items on the CFQ, three or fewer rated as worse/much worse than prior to illness.	Maximum score of 18 on the 33-point CFQ.
	Overall health self-rated as "very much better" on the Clinical Global Impression scale [50].	Overall health self-rated as "much better" or "very much better" on the Clinical Global Impression scale.
	The final "caseness" criterion was met if the patient no longer fulfilled: The Oxford case definition of CFS; the CDC criteria [51]; AND the London ME criteria [52]. (As determined by a non-blinded assessor).	The revised "caseness" criterion was met if ANY of the following applied: a) the patient did not meet the standard Oxford case definition; OR b) on the CFQ, they rated less than six of the 11 fatigue items as being worse than prior to illness; OR c) their SF-36 Physical Function score was greater than 65.

Figure 1: The criteria used for a participant to count as improved, as used in the 2011 article (White et al., 2011) and the one used for a participant to count as recovered, as used in the 2013 article (White et al., 2013). A comparison between the original protocol plan vs. the revised plan. From Wilshire et al., 2018.

Furthermore, multiple researchers pointed out that certain secondary variables and objective data weren't reported. Changes to the primary outcome variables also weren't explained (Mitchell, 2011; Kewley, 2011). There was also vagueness in how the trial identified patients, with the primary marker being unexplained fatigue over the past six months. While there were other criteria, all mentioned unexplained fatigue. However, "unexplained fatigue over the past six months" is vague. Coupled with the lack of information on how all three criteria were used, this can potentially lead to the inclusion of people who don't have ME/CFS (Tuller, 2011). While the trial did use two scales and three criteria, there's confusion about the purpose of the CDC and London criteria. While the Oxford criteria were used for trial inclusion, the same wasn't explicitly mentioned for the other two. If all three were used, it could've been a more secure method of preventing those without the illness from being included.

The PACE trial focused on subjective data like the primary outcome variables based on patients' answers. This can impact results because they're getting the thoughts of patients, which is good. However, objective results, like whether they continued to go to work, how many hours

they worked, and their physical activity, gives a clearer picture of the effectiveness of the treatment options (Kindlon, 2011a; Kewley, 2011). Past research showed that improving patient experience doesn't mean improving activity (Wiborg et al., 2010). An improvement in activity would've been expected if patients showed they got better.

The trial also didn't focus as much on the potential harm from the treatment options. Numerous researchers have pointed out the mixed results on how harmful CBT and GET are (Twisk and Maes, 2009; Wiborg et al., 2010; Kindlon, 2011a; Kindlon, 2011b). CBT and GET, especially GET, have been shown to have mixed effectiveness in prior research. That same research has also demonstrated GET to be harmful to patients. Patients' bodies are being pushed farther than they should. There are fewer claims of harm regarding CBT due to the nature of that therapy (Kindlon, 2011b). However, ME/CFS activists and researchers asked the question of injury after the release of the trial's improvement results.

The trial also put a psychological lens on the disease (Shinohara, 2011). For example, the trial focused on the fear avoidance theory for both CBT and GET (Wilshire et al., 2018). Patients avoid exercise because they fear it, which causes ME/CFS. However, no evidence supports that claim (Gallagher et al., 2005). There were concerns about how patients were told to complete certain aspects of the trial or told about them (Wilshire et al., 2018). Patients were told to ignore their symptoms for a year and repeatedly told it was due to fear. Then they were told to answer how they felt about their illness. They might answer because they've been in the trial for close to a year and want to show something came out of it (Rehmeyer, 2016). There was also the concern that participants in the trial were primed during treatment to expect improvement through manuals of the treatment options that consistently praised them (Wilshire et al., 2018).

Researchers, like Wilshire, brought up concerns that aspects of the trial or how participants were told to answer were said in a way that would bias them to show what the researchers wanted, especially if it came from an authoritative voice like researchers. The trial used CBT and GET manuals given to all patients in their condition. These manuals had phrases that could be seen as priming patients to expect good results from those options. For example, the CBT manual stated that it's "a powerful and safe treatment which has been shown to be effective in... CFS/ME" (Wilshire et al., 2018, pg. 9). For GET, the manual stated it's "one of the most effective therapy strategies currently known" (Wilshire et al., 2018, pg. 9). These phrases can lead to worrying results because it can prime the patient's subjective outcome variables to lean towards those claims. Prior research has shown that demand characteristics, the case where patients report improvements based on what they believe the researcher wants, is a significant reason why psychotherapy results show that a specific therapy works when it doesn't (Lilienfeld et al., 2014). With subjective-only measures, putting those phrases into manuals could prime them to respond favorably.

These concerns prompted independent researchers to analyze the raw data obtained after the court case. The first was Alem Matthees, a ME/CFS patient who was part of the court case to get the data. He and other researchers used the PACE trial's original analysis plan from the 2007 protocol for both an intention-to-treat and available case analysis. Intention-to-treat would include all randomized participants, even if they were lost to follow-up. Available case excludes those lost to follow-up. The PACE trial used an available case analysis which Matthees worried would overestimate the effects of the treatment options (Matthees et al., 2016). The new analysis by Matthees and colleagues using the original protocol showed that recovery with CBT was 7% and GET 4%, neither statistically better than SMC, which was 3%. This is compared to the

analysis used in the trial, which found CBT and GET at 22% and SMC at 7% (Matthees et al., 2016) for both intention-to-treat and available cases. There was an increase of over 3x for specific treatment options when comparing the original and revised analysis plan. While certain variables used as part of the trial results weren't available for Matthees and colleagues, they believed it wouldn't make a difference in the final result showing that the treatment options weren't effective. Matthees and colleagues ended by mentioning that researchers who conduct their own research shouldn't be able to make drastic changes like modifying the analysis plan without proper oversight, as was done in the PACE trial. Those drastic changes can severely impact the results.

Another researcher, Wilshire and colleagues, who looked into the trial data, found new results for fatigue and physical function improvement and similar results for recovery. Regarding fatigue and physical function improvement from baseline, the trial's revised analysis plan showed 59% of CBT patients and 61% of GET patients that improved. However, their revised analysis plan also meant that 45% of SMC alone patients improved (White et al., 2011; Wilshire et al., 2018). The analysis plan conducted by Wilshire, which uses the original protocol analysis, showed that 20% of CBT patients, 21% of GET patients, and 10% of SMC alone and APT patients improved (see Table 1) (Wilshire et al., 2018). This is a decrease of nearly 40% for CBT and GET and close to 40% for SMC alone and APT, showing the difference that the analysis plan revision had in improving the results. The original analysis plan would've shown no significance, while the revised plan showed a statistically significant difference. Similar results were obtained when the analyses were conducted with participants who missed outcome results at 52 weeks and were removed, showing 11% SMC alone, 22% CBT, and 21% GET improvement (see Table 1) (Wilshire et al., 2018).

	PACE Trial Result (using modified analysis plan)	Wilshire et al. 2018 Result (using original analysis plan mentioned in PACE protocol)
ME/CFS fatigue and physical improvement using APT	64 out of 153 participants (42%)	10% of participants
ME/CFS fatigue and physical improvement using CBT	87 out of 148 participants (59%)	20% of participants
ME/CFS fatigue and physical improvement using GET	94 out of 154 participants (61%)	21% of participants
ME/CFS fatigue and physical improvement using SMC	68 out of 152 participants (45%)	10% of participants
ME/CFS recovery using APT	12 out of 149 participants (8%) - trial recovery	3% of participants (using available case analysis)
ME/CFS recovery using CBT	32 out of 143 participants (22%) - trial recovery	7% of participants (using available case analysis)
ME/CFS recovery using GET	32 out of 143 participants (22%) - trial recovery	4% of participants (using available case analysis)
ME/CFS recovery using SMC	11 out of 150 participants (7%) - trial recovery	3% of participants (using available case analysis)

Table 1. Table of results for what was reported in the PACE trial using their modified analysis plan and what was reported by Wilshire et al., 2018 using the protocol-specified PACE trial analysis plan. Wilshire et al., 2018 didn't give specifics on number of patients, only percentages, so only those are reported.

As for the recovery results, Wilshire got the same results that Matthees and colleagues obtained with the intention-to-treat analysis. The available case analysis explained above showed similar results: 8% for CBT, 5% for GET, and 3% for SMC alone (Wilshire et al., 2018). The overall results show that, had the trial researchers followed their original analysis plan, the results would've been less impressive. There wouldn't have been any statistically significant result showing effective treatment options for ME/CFS. This also includes finding no evidence of long-term benefits despite the original authors making that claim in a future article (Chalder et

al., 2015; Wilshire et al., 2018). As numerous patients and researchers mentioned, the authors should've compared their modified analysis results to the original analysis plan.

Furthermore, Wilshire and colleagues raised concerns about why evidence like returning to work wasn't required by patients, which is vital in determining what recovery is to a patient (Wilshire et al., 2018). A patient can submit a form showing they have recovered from ME/CFS, but have they recovered if they can't walk to work or stay out of bed for longer than a few days? These concerns lead to no justification for the change in the analysis plan. One argument in defense of the change stated that there was no agreed definition of recovery, meaning that the modification can be as effective as the original (Chalder et al., 2017). However, if there were no agreed definition, wouldn't the preregistered one be the most effective since it was decided and set (Wilshire et al., 2018)? Due to all this, Wilshire concluded that there's no evidence to claim that behavioral treatments are effective treatment options for ME/CFS.

The articles released after obtaining the raw data of the trial brought answers to the significance of the change and how much they can be trusted. According to these recent articles, the PACE trial showed no effect for behavioral treatments. It misinformed patients, researchers, and governments in creating expectations that didn't pan out. The consequences this has had on patients dealing with bullying or abuse have run rampant (Coyne, 2017; #MEAction, 2019).

The original researchers, however, have refuted the claims made by Wilshire and colleagues and believe that their analysis using the original protocol misinterprets the results (Sharpe et al., 2019). Other researchers believe that the new revelations about the PACE trial shouldn't be focused on as heavily as they still are (Rehmeyer, 2016). Simon Wessely, president of the UK Royal College of Psychiatrists, summarized his thoughts on the lack of recovery from the PACE trial using the original analysis plan by saying, "OK folks, nothing to see here, move

along please" (Rehmeyer, 2016, para. 40). Despite showing null results with the initial protocol analysis, some researchers ignore those results.

The PACE trial had numerous dangerous effects, including making the ME/CFS community wearier of the medical profession and treatment options. The subtlety of how behavioral treatments for ME/CFS can be effective in some form, maybe as an add-on, has disappeared in the aftermath of the trial. There's a separation between thinking it's a brain or a body illness rather than a mix. Relating to that is the harm when researchers believe one factor contributes to a disease rather than multiple. By focusing on just one aspect rather than all of them, you only get one side of the story, so you only apply one part of a solution. That solution might not work if the whole story is taken into account. The PACE trial focused on the psychological basis, ignoring other parts and creating a model that doesn't represent the illness.

Chapter 4: The Biopsychosocial Model of ME/CFS and The Risks of It from PACE

The History of the Biopsychosocial Model

The PACE trial was built on numerous studies that showed the potential effectiveness of behavioral treatments (Butler et al., 1991; Malouff et al., 2008; Wiborg et al., 2010). However, these studies are criticized for putting a psychological lens on the illness. Those studies focused solely on CBT as the primary treatment rather than having medicine as a treatment for ME/CFS and CBT alongside it. The PACE trial had its conditions alongside SMC, which included medication if the patient needed it but didn't find a significant result in improvement or recovery (White et al., 2011; White et al., 2013). This includes the original analyses (Matthees et al., 2016; Wilshire et al., 2018). While there seems to be no proof that CBT could be effective in any form for ME/CFS, the studies that tested them have been criticized for numerous design issues that complicate their results (Twisk and Maes, 2009). This leaves the question of whether CBT could be effective for ME/CFS as an add-on treatment while focusing on what the patient needs, which tends to be the biological factor. It could look into the illness from new angles and determine new treatment routes that can be effective depending on the patient. However, this isn't very easy because CBT and GET are frequently seen together when discussing ME/CFS. This is despite researchers believing CBT could be considered harmless for the illness since it's a talking therapy. At the same time, GET is a harmful therapy due to forcing patients to push themselves with exercise (Twisk and Maes, 2009). This is further shown by patient stories that primarily focus on the harms of GET, as the stories mentioned above. CBT could be a useful treatment option for ME/CFS, but the PACE trial and their reliance on framing the illness as psychological affected that potential and how some see that treatment option. A multi-faceted

approach to ME/CFS could better help patients by supporting the idea of behavioral treatment for ME/CFS and other treatment options like biological ones when available. However, it's affected by the same thing that was problematic for the PACE trial: an over-reliance on a psychological viewpoint for an illness and pushing other aspects away. The PACE trial focused heavily on one part rather than all elements that could affect a patient's outcome.

This approach is called the biopsychosocial (BPS) model. This model was created by George Engel and stated that illness is not just based on one factor but multiple factors. Specifically, the disease is based on, determined, and should be treated based on its biological, psychological, and sociological aspects and the patient (Engel, 1977; Engel, 1980; Suls and Rothman, 2004; Geraghty and Blease, 2019). A better understanding of this model is with a hypothetical example. Let's say someone has a chronic gastrointestinal illness. This illness is biological because some tests and surgeries can determine if a patient has it, and there's medicine to treat it long-term. The disease is also psychological because stress and other complications that affect a person's mental state can cause the illness to have a longer flare-up. The condition is also sociological because the food a person eats can determine whether a patient has an upset stomach or other intestinal complications that cause temporary discomfort. This patient is low-income, meaning they can't make healthy choices as often, leading them to get food that causes that discomfort. This gastrointestinal illness has multiple factors that impact and affect how a patient lives with the disease. This is what the model is trying to state. This approach can also have some similarities to the idea behind disability studies: a disability can come from both biological and social aspects (Ferguson and Nusbaum, 2012). Let's say a patient is in a wheelchair. There's the biological aspect because they might have a bodily illness that puts them in that condition, and they take medicine to treat it. There's the psychological aspect because a

wheelchair patient might feel isolated, anxious, or depressed because of their illness and state. Lastly, there's the social aspect because their lives could be made more difficult because of societal norms or the way infrastructure is set up, like a lack of accessibility options (Lawthers et al., 2003). An illness shouldn't be approached from one angle but from multiple angles since each has its own influence.

Engel introduced the BPS model in response to the biomedical model, which states that illness is from biological abnormalities (Deacon, 2013). He believed that the biomedical model didn't focus enough on illness's psychological and sociological aspects as much as it should (Engel, 1977; Engel, 1980). The biomedical model concentrate on just one part of the illness and ignores other aspects that could also play an important role. By focusing on multiple aspects of disease and not on only one part, physicians can learn more about the patient and how their condition is influenced, giving more information that can be used for diagnosis and treatment. Engel believed that the biomedical model focuses too much on proof that a patient has a disease and ignores the patient and their attributes as a person (Engel, 1977; Engel, 1980). It ignores behavioral and psychological data that can be useful. The PACE trial was also accused of ignoring patients and their experiences (Kindlon, 2011a). The biomedical model has physicians focusing only on a patient's biological part and illness. It focuses on all aspects of a human, like their social, biological, and psychological state. The biopsychosocial would fix that by telling physicians to focus on all three factors rather than just one.

The BPS model has continued to gain traction in research, with more articles released yearly that contain the topic (Suls and Rothman, 2004). This is especially important as research shows how psychological and sociological factors like stress, emotions, and social support have been shown to play essential roles in the progress and management of certain diseases

(Andersen, 2002). The BPS model has continued to shape research and theory on health and the development of health psychology (Friedman and Alder, 2007). This traction also includes expanding the model to incorporate different ideas, like understanding how all three factors interact and how that impacts disease (Lehman et al., 2017). This attempt to expand the model comes from the belief by some researchers that the model tends to ignore interpersonal dynamics (Lehman et al., 2017). The effects of actual or perceived social contacts on health tend to be ignored or put at a lower priority. Aspects like family members, work environment, etc., are being ignored in research concerning the BPS model despite evidence of those sociological factors' effects on people's health (Repetti et al., 2002; Reblin and Uchino, 2008). Researchers have been pushing for more priority on that aspect which is lacking in a lot of research that uses the model despite the benefits those aspects can have in health (Lehman et al., 2017). The PACE trial was also guilty of this. The trial ignored the model's social state by not considering social aspects like whether patients returned to work or tried to integrate themselves into society during and after treatment (Wilshire et al., 2018). These aspects are essential for determining whether treatment for a debilitating disease like ME/CFS worked, as claimed. However, that information was left out, which gave an incomplete picture of how the sociological state is impacted and how behavioral treatments change that.

The Criticisms of the Biopsychosocial Model in The Context of PACE

The BPS model, like any model, is not without its share of criticism. It has been described as flawed or problematic by researchers for numerous reasons. One of these flaws is that the model isn't a model but an unproven theory that is continuously being pushed despite the lack of a framework (McLaren, 1998). The model can instead be seen as an emotive case for more humanity and less technology in medicine (McLaren, 1998). The model was created

without a way to prove it adequately. The multiple aspects of illness for the model are seen as complex in that the information is scattered and probably has no relation to one another (McLaren, 1998). Even if the data from those different angles could be put together, it doesn't mean it will give relevant information to help physicians better understand patients and their illnesses. If a physician has the information to make out one aspect of the model, it doesn't mean it can be used to make out the other aspects, weakening the model.

Another flaw in the model is the claim that it can be seen as an eclecticism model. In this case, the BPS model isn't rigidly set to a single set of assumptions but instead takes multiple styles or ideas to gain insights into a problem (Ghaemi, 2009). It fails to provide convincing evidence to resist the biomedical model (McLaren, 1998; Ghaemi, 2009). Engel specified that more information to help physicians is always better (Engel, 1977). However, that's not always the case scientifically and doesn't provide as much benefit as claimed (Ghaemi, 2009). This flaw comes from the BPS model focusing on the three illness factors but forcing physicians to focus on them without explaining how to use that information or what to prioritize based on the patient. The answer could be a case-by-case scenario, but the model doesn't specify that, instead seeming stitched together with some gaps on how it would work.

A third flaw with the model is the criticism that studies using the model for diseases don't focus on all aspects of the model equally (Suls and Rothman, 2004). In a test of 70 studies regarding the BPS model from the Health Psychology journal, 66 focused on the psychological, 39 on the biological, and 37 on the social aspect (Suls and Rothman, 2004). Studies tend to ignore some parts of the model while prioritizing other elements, specifically the psychological aspect. This includes the PACE trial, which focused on the psychological component and neglected the potential biological causes of ME/CFS (Green et al., 2015). This includes forcing

patients to take treatments they don't want to but have to because there are no other options (UK Parliament, 2018). This can harm patients because it focuses on only one component and pretends that another element is not as essential or non-existent.

Furthermore, critics of the BPS model for ME/CFS believe it's too narrow and doesn't consider the patient's experiences (Geraghty and Blease, 2019). Incorporating a BPS model into ME/CFS can end up hurting patients like the psychological aspect of the model has done (Twisk and Maes, 2009; Kindlon, 2011b; Vink and Vink-Niese, 2022). Patients being hurt doesn't benefit anyone and only makes those same patients weary of coming back.

It also doesn't help that doctors are encouraged by others, including UK health authorities, to apply the BPS model and primarily give psychotherapy treatments (Deary et al., 2007). These supporters tend to make numerous recommendations based on the model. One suggestion is not to diagnose a contested illness to prevent "unhelpful illness behaviors" (Salmon et al., 1999). ME/CFS patients are stopped from being able to get the necessary support they need under the model, going against its goals of it. Patients with ME/CFS are left without a needed diagnosis, which is crucial for them and helps them get the required treatment. A diagnosis is a validation of what they have; without it, they're left with few alternatives for treatment and support. Another recommendation they give is not to provide exhaustive tests to prevent a drain on medical resources and prevent patients from getting access to the sick role so easily for ME/CFS (Geraghty and Blease, 2019). In other words, ME/CFS patients should be scrutinized more closely to prevent unnecessary diagnoses.

The Impact of PACE and Its Psychological Push

The continuous framing of ME/CFS as a psychological illness can amount to a negative stereotype about ME/CFS patients. The PACE trial showed this despite objective tests not being

significant alongside those psychological treatments. How the study was designed and presented also showed this. Furthermore, the trial created manuals geared to the idea that CBT and GET are effective treatments rather than staying as neutral as possible (Wilshire et al., 2018). Prior research has shown a lack of effectiveness for CBT and GET for ME/CFS. Focusing on the psychological basis of the model doesn't change those results.

This includes the media playing a role in influencing how CBT or GET are seen for ME/CFS and the illness itself. Those who read those stories or articles are then given a possibly biased viewpoint of the illness or treatment options rather than neutral facts. In one story from The Guardian, a patient got a combination of CBT and GET for their ME/CFS and fully recovered, speaking highly of the treatment options and the evidence to support the claims that they can be effective for the illness (Marchant, 2016). They also spoke about how the illness can and should be thought of as one of the biological and psychological states. They aren't separate but intertwined for the illness, as mentioned by Peter White, one of the PACE trial researchers (Marchant, 2016). The article was trying to get people to understand ME/CFS from a biological and psychological standpoint. It was trying to strike a balance between both sides.

In another scenario, there was a negative spin on ME/CFS. In this case, it wasn't by the media but by researchers affiliated with ME/CFS but not by PACE. They claimed that the illness is a "meme" and is spread in a meme-like fashion (Collings and Newton, 2014). This article immediately got criticized for its claims, with researchers claiming that it's offensive and appalling to those with the illness, especially as it comes from researchers in the ME/CFS field (Chowdhury, 2014). This article from these researchers paints a negative view of the illness, believing it to be hype and more than it should be, downplaying patient experiences.

A third scenario negatively spins CBT and GET for ME/CFS (NICE, 2021; Vink and Vink-Niese, 2022). After it was revealed that behavioral treatments aren't adequate for ME/CFS, the guidelines regarding how they should be treated were modified to show that. This stopped the claims of the effectiveness of those treatments. With these three scenarios, CBT, GET, and ME/CFS are all seen in various ways. One shows a neutral, factual, and scientific-driven point of view on how to showcase it. Another showed the personal preference of some that ME/CFS isn't an actual disease and is instead more of a meme disease. A third showed a bias towards the psychological basis of the illness. These opinions expand to the media and other researchers differently, exposing the difference between those who believe in ME/CFS in one way and those who believe in it differently.

The media can play a role in the information it gives. It can give one side while equally giving or neglecting the other side. Researchers also play a role in their contributions that impact how others see health. These contributions affect how others see these treatment options and the illness in the public eye.

That hasn't stopped the researchers from making those claims, and, despite being disproved numerous times, the trial hasn't been retracted. Despite that, the trial results were proven misleading. The NICE guidelines that caused a lot of harm to patients, like those described earlier, were retracted and replaced with new policies that explicitly state CBT and GET should not be given for ME/CFS (Vink and Vink-Niese, 2022; NICE, 2021). However, the damage had already been done. The ME/CFS community is more guarded against claims of their illness, especially claims that it's psychological. Science should be sound and verified before it's used for consequential policy decisions like changing guidelines for an unknown disease (IJzerman et al., 2020). A policy decision shouldn't be continued when researchers disprove one

of its pillars. The PACE trial should've verified that its results were accurate. Verification is essential for a study of this scale and implication since it can drastically change a person's life, as shown in the two patient stories showing the guideline effects on their lives with ME/CFS. Otherwise, it can create ideas of effectiveness for treatment that aren't true.

Another idea that the PACE trial did not entertain as much was whether behavioral treatments like CBT could be used alongside non-psychological treatment, like as an add-on. It could be a balance of giving psychological and biological treatment rather than just one or the other. The PACE trial gave SMC to each group. However, SMC didn't consist of medicine unless necessary for aspects like depression. The PACE trial had SMC that consisted primarily of information about ME/CFS and best practices, which wouldn't be the same as having a behavioral treatment like CBT alongside biological medicine. At least now, there is a significant problem regarding the possibility of a biological treatment for ME/CFS. There aren't any effective biological treatments, and treatment can consist of anything from diet changes to supplements and medicine for depression or anxiety. Due to these numerous issues, the PACE trial and its outcome created two groups: those that believed in psychological therapy for ME/CFS and those who were against it. There was no discussion of an in-between.

One of the significant aspects of ME/CFS is that patients have to make numerous lifestyle changes to accommodate their new status. For example, in the story of Eleanor in Chapter 1, she was diagnosed with ME/CFS after a COVID infection, having to deal with ME/CFS social stigma but also learning to pace herself alongside medicine. Otherwise, she would have to deal with post-exertional symptoms, which can last (Eleanor, 2022). This is part of life for those with ME/CFS. To prevent the dangerous fatigue that comes with ME/CFS, those with the illness have

to focus on their limits and not push past them, something supported by the Action for ME charity organization (Action for ME, 2019).

Despite the idea of pacing in the ME/CFS world, the PACE trial limited the push of that belief with their claims that CBT and GET are effective options for ME/CFS (White et al., 2011). They said that APT wasn't adequate for ME/CFS despite being modeled off pacing therapy and created for the trial in conjunction with those with ME/CFS (White et al., 2007; White et al., 2011). This led to the claims supported by the NICE guidelines for ME/CFS that CBT and GET should be the primary treatment options. Due to this, patients suffered because it pushed focus away from having their disease be seen from a biological standpoint. It turned the focus into making ME/CFS be seen as something more psychological, as the PACE trial claimed with their results (White et al., 2011; White et al., 2013). This psychological standpoint had negative consequences regarding patients and their experiences with the illness, as well as how the medical profession treated them after the PACE trial changed the recommendations for ME/CFS from NICE (Vink and Vink-Niese, 2022). It made the lives of patients worse.

For example, one patient was discussed during a 2018 UK Parliament meeting on the impact of the PACE trial on patients. Carol Monaghan, a member of parliament (MP), discussed the story of a 12-year-old patient. The patient was given GET treatment for their ME/CFS, leading to higher inflammation, pain, and headaches. However, these complaints fell on deaf ears as the ME/CFS specialist claimed that since the child could still "limp into my office," they were fine and needed to continue exercising. Due to having to take GET for a year, they developed Juvenile Idiopathic Arthritis due to their body's overactive immune system, leading the child's toes to get permanently swollen from abnormal bone growth due to inflammation (UK Parliament, 2018). Following the NICE guidelines of prescribing CBT or GET for ME/CFS, this

child was continuously told to take the treatment despite adverse effects. They were repeatedly told to continue exercising. However, it only worsened their ME/CFS, permanently affecting them. The guidelines affected this child's life in a way that will leave them with health problems for the rest of their life.

Another patient was discussed during a UK parliament meeting in early 2019. Carol Monaghan talked about this patient who was eight years old. The child became ill at that age, and their parents were told to get GET for their child or have child protection proceedings against them if they refused. The child continued to deteriorate in condition throughout the therapy. At age 15, the child was allowed to be placed back home and have her name taken off the "at-risk" register for child protection. However, due to the forced GET treatment, she is bedridden, paralyzed, and unable to feed or wash (#MEAction, 2019). This patient was forced to continue taking GET despite the harmful effects being shown. Despite that, the specialist followed the guidelines, and now this patient's life has been permanently altered. The PACE trial assisted in getting the policies to prefer CBT and GET for ME/CFS with their results despite the future proof that it was wrong. Numerous researchers and even UK MPs pushed for a guideline change to no longer recommend those options (#MEAction, 2019).

These two stories show how the PACE trial negatively affected ME/CFS patients, especially children. The stories showed what can be considered severe effects of treatment. The PACE trial also had results on those, with 8% of those getting GET having severe reactions like hospitalization (White et al., 2011; Wilshire et al., 2018). These results from the trial could've given evidence that GET may have been dangerous to some patients. As described earlier, the trial and its requirements may have allowed those with milder versions of ME/CFS to enter the trial and prevented severe patients from entering. These choices could've prevented the trial from

seeing these patients where the treatment was severely harmful. These patients and their stories show they dealt with permanent destruction to their bodies and lives. These are only the stories that have been told. There's no way of knowing how many others were impacted by the PACE trial and the changes it made to how ME/CFS should be seen and treated.

Medical professionals should acknowledge that ME/CFS is an unknown illness rather than attempting to devise a solution that won't work, like a psychological one. Doctors must also recognize that treatments might not work and shouldn't be forced upon patients. Doing otherwise decreases and impacts trust in the scientific research process and how patients see medical professionals. A potential reason the PACE trial researchers had such a significant psychological push could be their belief that it could work or because they wanted it to work under any circumstances due to their prior research on ME/CFS. Their allegiance to the treatments given and the PACE trial could've brought about the results and the pushback afterward, showing a more significant problem of how trustworthy researchers can be.

Chapter 5: The Role of The Allegiance Effect and Questionable Research Practices with PACE

The Allegiance Effect, Its Power, and Its Impacts

The allegiance effect refers to the personal confidence in a specific or preferred treatment's superiority over others (Luborsky et al., 1985; Thase, 1999; Tolin, 2010; Dragioti et al., 2015; Boccaccini et al., 2017). Researchers are meant to have a neutral view of their study and outcome. However, some researchers might prefer one treatment option over others before analysis. For example, a researcher researching CBT for decades could subconsciously ignore the potential that options other than CBT would be effective when designing and analyzing data due to their history of CBT research. Researchers will have a preferred treatment option, potentially impacting results as they have an allegiance to that option, leading to more significant treatment effects that favor the preferred treatment (Dragioti et al., 2015). A meta-analysis of 30 studies showed researchers had allegiance to some treatment options and that allegiance typically resulted in the preferential option having a 30% higher effect than articles that didn't have allegiance (Dragioti et al., 2015). The PACE trial researchers could be considered committed to behavioral treatment options considering some had a history of attempting to use those options for ME/CFS (Butler et al., 1991). Furthermore, those same researchers continued criticizing those who critiqued the PACE trial (Chalder et al., 2017; White et al., 2017; Sharpe et al., 2019), further showing a potential allegiance to those treatment options. While this makes it sound like researchers are intentional, it's almost always an unconscious bias. However, this can introduce systematic biases that can cause problems by showing support for treatment that might not be replicated in the future (Leykin and DeRubeis, 2009). This effect and its outcomes can negatively impact research by giving misleading results.

This effect is even more substantial if the experimenter with an allegiance trained the therapists or made the methods, with a relative odds ratio of around 2.2, showing that this exposure was associated with higher odds of the preferred outcome (Dragioti et al., 2015). This revelation is concerning in the context of how CBT and GET were designed to be used for PACE. The researchers developed the manuals used for CBT and GET, and the way they were intended for the study was based on prior studies, some of them being conducted by the researchers (White et al., 2011). The researchers wrote the manuals for CBT and GET, while APT was designed with an ME organization, and SMC was designed with sound medical practices. The researchers' unconscious bias about CBT and GET could've been gearing participants to give more positive results about CBT and GET.

The possibility of allegiance can increase through decisions that eventually help the researcher reach significant results for the treatment they want. One way the allegiance effect shows is through inconsistencies in research design (Boccaccini et al., 2017). As mentioned numerous times, the PACE trial was tainted by many inconsistencies in research design, such as their exclusion criteria, treatment conditions, primary outcome variables, and data analysis plan (Matthees et al., 2016; Wilshire et al., 2018). These inconsistencies and the researchers' prior research experience lead to concerns that the trial was designed in ways that pushed those treatment options. It could've raised the possibility that pushing those options would've led to more improvement and recovery over the other options. Supporting this is that allegiance effects can happen due to the positive expectations of the researcher's favored treatment approach (Boccaccini et al., 2017). Researchers who are optimistic about a particular treatment would want to see that come back true. With all the risks it can bring to research, the allegiance effect has invalidated some studies (Jacobson, 1999). One example is a study comparing insight-

oriented marital therapy (IOMT) to behavioral marital therapy (BMT) (Snyder and Wills, 1989). They found that IOMT led to a lower divorce rate compared to BMT. However, this effect was because BMT was never adequately tested. One of the researchers, Wills, who wrote the manuals for both therapies, was never trained in BMT. They were trained and had practiced only in IOMT, leading to the results being compromised by this fact (Jacobson, 1999). While this wasn't the intention of both researchers, unconsciously, there was a push for the results to benefit IOMT due to the choices made. The effect can change the results of studies in ways that make them doubtful.

The allegiance effect also relates to researchers who don't publish results inconsistent with their loyalties or expectations (Luborsky et al., 1999). If the results the researchers want don't appear, the results might not appear in general. The PACE trial authors were accused of not including or discussing non-significant results that could impact how the results can be seen (Kindlon, 2011a). Those non-significant results could've downplayed the significant effects, so removing them kept the focus on how effective the treatment options were.

Another way that allegiance effects can manifest is through conflicts of interest the researcher has (Lexchin et al., 2003). A hypothetical researcher could have an interest due to working for a specific company to get certain results that will benefit the company. A conflict of interest can lead to an allegiance to a particular treatment option, giving results that can be misleading.

Allegiance effects can also come from the expertise of a research team (Luborsky et al., 1985; Thase, 1999). If a research team are experts on one particular treatment, allegiance effects could happen for that option. Due to their prior experience with CBT and GET for ME/CFS, the PACE trial researchers could be considered experts in those treatment avenues for the illness.

This could've led them to make the decisions they did for the trial, leading to the outcomes. However, this argument that expertise causes allegiance has been refuted by the argument that allegiance effects could reflect honest differences in researchers regarding treatment options (Hollon, 1999). While this denies the idea of intentional deception, the allegiance could still be there and be detrimental to the research.

Allegiance effects can also be more likely if multiple researchers for one study have the same allegiance. The PACE trial had researchers who had researched CBT and GET for years. These researchers focused on similar ideas, which could lead to allegiance to those ideas. The PACE trial also used manuals for CBT and GET that were created from prior studies, some of which they conducted (White et al., 2011). With all these indications, the chance of allegiance towards CBT and GET can increase.

A recent study in a non-ME/CFS context found that as the allegiance toward CBT increases, CBT's effectiveness also increases (Tolin, 2010). However, CBT was still significantly more effective when controlling for researcher allegiance than other treatment options. While allegiance effects amplify CBT effectiveness, CBT remains more effective than other therapy options. Many comparative psychotherapy trials tend to be conducted by those who have a mild allegiance to the favored therapy, potentially affecting results. Yet the significance of CBT compared to other treatments can't be attributed solely to researcher allegiance (Tolin, 2010). As for whether the same case can be made for CBT for the treatment of ME/CFS is unknown.

The allegiance effect considers whether researchers conduct a study from a neutral scientific or a personal viewpoint. The PACE trial authors may have had an allegiance to CBT and GET due to their prior experience and expertise, leading to their choices. The authors

ignored the scientific viewpoint, ignoring their protocol and favoring different ideas. They took what could be seen as a more personal viewpoint on ME/CFS based on their past experiences with the illness and the behavioral treatments. Specifically, that experience with the disease was more of the psychological basis of the condition (Butler et al., 1991). Allegiance effects might have pushed the PACE trial results and analysis changes more.

The Questionable Side of Research

But how much can research allegiance be used to create misleading studies? These could be caused by bad actors in research who make research decisions that could be questionable, increasing the likelihood of personal viewpoints. The freedom that researchers have to design studies in their ways can negatively affect research and science. The same can go for studies based on ME/CFS, like the PACE trial, with all its questionable decisions that have been dissected and criticized. How can this be prevented? A step in the right direction would be determining what makes a bad research study and whether those affected the PACE trial.

The PACE Trial was controversial partly due to how they made their methodology and analysis decisions. The claim was that these changes influenced the outcome of the data to be more favorable to the effectiveness of CBT and GET for ME/CFS. These changes are part of a bigger problem in research: researchers making decisions that are not good practices. These issues intertwine with the allegiance effect and could lead to results that benefit one treatment.

Let's start with a p-value which usually defines a significant result in research, typically set at 0.05 or 5% to support an effect or say there wasn't (Banks et al., 2016). The cutoff of 0.05 is traditional, but some articles have a value lower than that due to choice or correction, the latter being to prevent false positives due to repeated testing (Tintle et al., 2020). While p-values signify when a result is significant, errors can occur based on the choices of a researcher.

Research that has its significance determined by a p-value is called Null Hypothesis Significance Testing (NHST). While it is commonly used, there is criticism that NHST has problems, making it a less favorable option. These common criticisms relate to how NHST is sensitive to sample size, false positives and negatives which is when a researcher finds an effect that isn't there and doesn't see an effect when there is one, respectively, and how it is misunderstood and abused when used, leading to less trust in results (Levine et al., 2008). Researchers have too much freedom in designing and analyzing a study. It makes it easier for researchers to falsely find evidence for an effect than to find evidence that there isn't one correctly (Simmons et al., 2011). This is because of the choices researchers make, like selectively reporting hypotheses with significant results, ignoring specific non-significant results, cherry-picking fit indices in modeling, and presenting post-hoc as if they were always going to be performed. Some might report a p-value near 0.05, like 0.054, as < .05 instead of = .05 (Simmons et al., 2011; John et al., 2012; Banks et al., 2016). These choices make modifications that ignore certain aspects of the data that impact how others see it.

These choices are called researcher degrees of freedom. Researchers must decide how to run and analyze their experiments with little questioning (Simmons et al., 2011; Wicherts et al., 2016). Another way of describing these decisions is as Questionable Research Practices (QRPs), where the choices a researcher makes can be seen as valid but could have negative consequences and give a false picture of data (Banks et al., 2016). These choices include how many participants are for an experiment, how to exclude participants, what statistical test to use, the significance cutoff, and whether corrections or further testing is required (Simmons et al., 2011). A researcher's decision can be seen as a regular decision with no consequences or one that creates misleading results. One example of QRPs is p-hacking, collecting or selecting data and

analyses until non-significant results become significant (Wicherts et al., 2016). This is a considerable concern in the field because, with p-hacking, many published results can be seen as false positives and can't be verified. The PACE trial was accused of selectively reporting significant results and applying incorrect corrections to their test, making the p-value cutoff higher than it should've been (Wilshire et al., 2018). While NHST is commonly used, there are issues with it, and the choices researchers make can affect the outcome of using that testing method. They can make these choices and create their rationale for it that some might look at and see as enough justification. Another example is the PACE trial analysis plan change, which gave a recovery rate over 3x the original plan (Wilshire et al., 2018). QRPs allow researchers to make decisions they see fit for themselves, potentially influencing the results.

QRPs are also common in research. A study of 64 articles found that 6 had little to no evidence of QRPs, while the other 58 had more severe evidence. These include data manipulation, selective reporting of results, and more (Banks et al., 2016). Some of the most common QRPs are things that the PACE trial was accused of, like data manipulation and reporting significant results while downplaying or not reporting non-significant results. Moreso, they didn't report actometer data showing how much physical activity patients had, which is objective (Wilshire et al., 2018; Kindlon, 2011a). These choices give the story the researchers want to tell, but not all. With what the PACE trial tested for and its potential to change lives, the fact it used numerous QRPs is a cause for concern.

All this flexibility leads to the potential for biases, impacting the outcome and how the study is reported. The PACE trial shows that researchers could spotlight significant results despite not reporting non-significant results with equal information. The researcher can also introduce these biases because they want to find a significant effect, either because journals want

only those results or their belief that they aren't in a "null field" (Simmons et al., 2011; Ioannidis, 2005). With the flexibility available, researchers could decide to make changes or selectively report results, which researchers have openly admitted to in the past (John et al., 2012). If psychology researchers engage in questionable research practices, this can lead to people trusting their misleading results. The same can be said for the PACE trial.

Another research issue has to do with conflicts of interest, as mentioned in Chapter 5. Much research, like in the biomedical world, has conflicts of interest, primarily financial interest (Krimsky et al., 1998). These conflicts of interest are mentioned so that other researchers know about influences, and the results can be scrutinized. The PACE trial also had conflicts of interest with some authors (White et al., 2011a; White et al., 2013). Despite that, no evidence says those conflicts impacted the results shown in the paper.

All these vulnerabilities appearing in these choices are problematic as they can create more favorable results. These results would benefit them when it comes to publishing in journals with a history of rejecting null results (Rosenthal, 1979; Simmons et al., 2011). These favorable results might not be replicated without the QRPs or other factors. The PACE trial had no significant effects when performed with the original analysis plan (Matthees et al., 2016; Wilshire et al., 2018). These problems can become even more critical regarding studies with government policy implications (IJzerman et al., 2020). These vulnerabilities can create results that don't represent who it will impact, as the PACE trial did with NICE recommending CBT and GET for the illness. The impact of the PACE trial on patients was drastic, showing the harm these flexibilities can cause to those the research is meant to help.

The choices these bad actors make, their QRPs, can impact people that rely on reliable results. The changes can be made to sound plausible and then be proven false, affecting trust.

These researchers release articles that make claims with misleading evidence. As mentioned, some of those articles are retracted (Ritchie, 2020; Brainard and You, 2018). While watchful eyes and journals stop some, that doesn't help the trust lost. This happened with the PACE trial, which negatively affected the confidence of those with ME/CFS. They only told one side of the story and used numerous QRPs that have been criticized for coming to their conclusions. Correcting these issues and showing the truth showed that the PACE trial was wrong and that the researchers' choices resulted in favorable results.

A study should be vetted if it will make policy guidelines or other medical decisions, like the PACE trial. It shouldn't be used if it's misleading, as it can be consequential for patients. Studies that make choices like those made by PACE can mislead their audience, especially those who use that information to make decisions. It can make claims that others will use without knowing that those claims are false, like what the PACE trial did with their claims. That claim spread and was used on patients, resulting in harm to patients.

Bad actors and their QRPs in research articles can lead to outcomes that affect people, influence agencies, and more (Banks et al., 2016). These issues and criticisms from research, like selective reporting and certain analysis decisions, can be prevented. With how common these practices are, there need to be ways to solve them to prevent cases like the PACE trial and the impact it had from happening with another contested illness in the future.

If bad actors aren't stopped, a scenario similar to what happened after the PACE trial will follow with a different illness, isolating patients and changing the treatment landscape. Solutions and safeguards to ensure research is done correctly are needed to prevent something like this from happening.

Chapter 6: How to Stop Bad Research Practices and Prevent PACE

How to Prevent Bad Research

Solutions to bad actors can stop their research from becoming ingrained into science. These solutions can help the scientific community to build trust between each other and the public by showing correct and valid results. It can push to increase trust oversight from researchers and journals (Simmons et al., 2011). With more supervision, journals can catch more bad articles, as has been the case in recent years (Brainard and You, 2018).

The first solution that can be used to stop bad actors in research is replication, the process of researchers performing a previously done study exactly as mentioned to obtain the same result (Ritchie, 2020; Wicherts et al., 2011). Researchers cannot follow the exact steps the original paper did, or the results obtained conflict with the initial results (Ritchie, 2020; Geraghty, 2017). Many areas have a replication crisis, including psychology, where the PACE trial treatments are based (Geraghty, 2017; Nuijten et al., 2013). People focus on the significance of the results rather than the researcher's choices in terms of their methods and analysis plan (Ioannidis, 2005; Nuijten et al., 2013). Replication is essential because it safeguards research, especially in the face of the current replication crisis. Suppose the results are replicated in the future by other researchers using the same methods and plans as the original author. In that case, that study can be regarded as more trustworthy because the results are the same. If the results aren't replicated, the study could be doubted. If there's any reason to doubt the results, the authors can perform a replication themselves or ask other researchers to do it to verify the results (Simmons et al., 2011).

A replication wasn't done with the PACE trial, but a re-analysis of the original plan showed the difference in results. If replication was done following everything the original

authors did with the initial analysis plan, it could give more evidence to determine what went wrong with the PACE trial. However, that replication wasn't done since the raw data wasn't released for years. Replication requires access and transparency. Without either, replication can't easily happen. Access and openness show that the researchers trust the results since they believe it will be confirmed if another researcher attempts it. Without it, the article can only be taken at face value, preventing a more in-depth look from confirming the results.

Despite the benefit of replication, there is an issue with its effectiveness. The number of research articles being released has increased in the past (Brainard and You, 2018). Due to that, many articles could be ignored or lost, not being replicated due to the number of articles available (Wicherts et al., 2011). With so many articles being released, replicating most is impossible, making it an option that could best be used for articles that can have a bigger impact.

Another solution to stop bad actors is to have them focus on the odds of finding an effect and be transparent about that. This safeguard allows work to be more closely scrutinized if the chance of finding an effect is low but still found, leading to replication for confirmation of the results. Researchers could be required to determine how likely they can find an impact, leaving other researchers to decide how to take the results (Ioannidis, 2005).

A third solution to stop bad actors is to push journals to accept null results in research rather than focusing on significant results only (Simmons et al., 2011; Ioannidis, 2005; Rosenthal, 1979). Journals ignoring or rejecting articles because of the number of non-significant results could pressure researchers to use QRPs to get significant results to have their research published. With journals not publishing non-significant results, the field is seen as always having an effect, creating the expectation of one. This is the file drawer problem in research, where null results are forgotten, and significant results are prioritized, creating pressure (Rosenthal, 1979;

Simonsohn et al., 2014). Accepting null results means that analyses and entire papers are not discarded. The research field will have significant and non-significant results to improve discussion between researchers. In the PACE trial, the authors didn't focus on non-significant results or explain why that was the case and what it meant. Journals being more open to null results could allow a future experiment similar to PACE to include and explain null results equally to significant ones. Science doesn't have to be significant, and not all research needs to show an outcome.

A fourth solution is to give more retractions. As mentioned earlier, retractions are articles removed due to misleading information, misguided results, errors, ethical violations, etc. (Fang and Casadevall, 2011). Research should be held to the highest standard, or it will negatively affect the scientific community (Azoulay et al., 2015). If an article isn't given a retraction but gives misleading information, other researchers will see the claims and might use that to make their hypotheses. By increasing retractions, authors get punished and deal with the social stigma that comes with it, while journals remove misleading articles that impact trust in science (Brainard and You, 2018). An increase in retractions due to better oversight by researchers and journals could push researchers to reconsider choices that might cause them to commit bad practices. While retractions aren't that common, averaging about four retractions for every thousand papers, it has increased in years past (Brainard and You, 2018). This solution shows promise and more oversight can stop more bad articles.

An issue with retraction is whether the journal wants to pursue the matter. With the PACE trial, the journal resisted investigating the trial and results, going so far as to criticize those attacking the trial (The Lancet, 2011). Journals have to be more vigilant in stopping and retracting lousy research. After five years, the PACE trial was caught with its misleading results,

but it had already significantly impacted the ME/CFS world and how people see and treat it. Furthermore, it has never been officially retracted. Another issue with retractions is how they can impact the journal and the author. Many stigmas can be associated with a retraction, both the researcher and the journal (Brainard and You, 2018). This could make them more restrictive on when and how often they do retractions.

These solutions can stop bad actors but require the contribution of multiple individuals and groups. Each solution has its downsides that can be exploited. These solutions can help to prevent bad actors from impacting science at a grand scale, as the PACE trial did. However, while these solutions are to stop bad actors, it doesn't try to help researchers improve or help prevent them from becoming bad actors. Improving and pushing for better research practices can lower the rate of QRPs and improve people's trust in research.

How to Promote Good Research

One suggestion to improve research practices is to fix the ambiguity problem of data collection and analysis. These guidelines can help researchers limit their decisions that can be deemed influential to the results. It could give researchers a standard to work off. These rules state that researchers must decide their rule for terminating data collection before it starts, have 20 observations per group or provide a justification for why they didn't reach 20, list all the variables collected in a study and not just the significant ones, report all experimental conditions and not just those that succeeded, report statistical results on the data with and without exclusions decided on to see how it impacted the data, and showing results without covariates if the results included it (Simmons et al., 2011). These suggestions could've been helpful for the PACE trial, stopping the researchers from selectively focusing on significant results and being more transparent.

Tips were also provided for reviewers and journals. These suggestions state that reviewers and journals should ensure that authors are transparent, allow imperfections and stop making everything significant, have authors show their results weren't from arbitrary analytical decisions, and require a replication if the author's justification for data collection and analysis aren't compelling (Simmons et al., 2011). These suggestions can provide a second layer of protection to stop bad research practices and encourage good ones. The PACE trial was criticized for giving a lousy rationale for its methodology changes (Tuller, 2017). These suggestions would've pushed the journal to ask the authors to, at the very least, perform the analysis with their original plan to show the comparison.

More suggestions for researchers and journals include looking for red flags that might make an article less likely to be true. These red flags include if the study is too small, which leads to less statistical power and variable results, small effect sizes, too much flexibility on analysis, designs, or definitions, not using a common standard like a randomized controlled trial, having financial or other interests which can lead to prejudice, and if a study is in a scientific field that has a lot of publicity at the moment (Ioannidis, 2005). The PACE trial was criticized for its flexibility and not adhering to a common standard (Wilshire et al., 2018). Looking for red flags would encourage researchers to look at their research and find ways to fix or explain them to be transparent and honest.

Another suggestion for promoting good research practices is preregistering a study, as mentioned in Chapter 2. Open Science Framework (OSF) is a known place where researchers preregister their study and agree to upload their data and code for other researchers (Foster and Deardorff, 2017). Preregistering provides transparency, openness, and trustworthiness since the researchers are opening their study to anyone. Other researchers would have all the information

needed for replication and verification. While preregistration is a crucial suggestion that can be useful, safeguards must be in place to ensure that authors follow through and are honest about changes. The PACE trial was preregistered (ISRCTN, 2003; White et al., 2007). Despite being preregistered, they didn't release the raw data or any information like rationale, analysis scripts, etc., until they were later forced to. Preregistration is helpful only if researchers follow its principle. While these tools to stop bad research are useful, they all require safeguards to confirm that they are being followed. If not, they are nothing more than empty suggestions that researchers can choose whether to follow or not.

Chapter 7: How to Prevent PACE in The Context of Long COVID

The Status of ME/CFS

Those with contested illnesses like ME/CFS must trust their doctors to do the right thing. Without that trust, patients can feel like they aren't feeling heard, safe, understood, or cared for by the medical profession. This is what happened with the PACE trial. It made recommendations that negatively impacted how those with the illness saw the medical professionals and agencies meant to help them. Furthermore, impactful health guidelines that affect millions shouldn't be based on a single study with no replication or backups.

The PACE trial brought about changes that weren't backed up by valid data. While debates in research are meant to foster discussion and new ideas, the arguments regarding the PACE trial were more for the future of ME/CFS treatment. However, despite the numerous articles that disproved the results of the PACE trial, lingering problems remain. Specifically, the researchers of the PACE trial have started to push the claim of the effectiveness of GET and CBT for long COVID, trying to extend into that field (Tuller, 2022).

The solutions presented previously to stopping bad actors and suggestions for improving research practices can help teach researchers to improve. If followed, they could've prevented PACE from reaching the outcome it did. All the methodology changes, preregistration, data release, etc., would've been explained and followed to avoid adverse outcomes. These changes to research practices can not only help future ME/CFS studies to build trust but also to studies in science generally to be trustworthy. The PACE Trial was tainted by many bad decisions that changed how those patients see research on their illness. It refused to consider a biological basis, had numerous research mistakes that harmed the results, and impacted the future of ME/CFS and its research. For example, one grant-giving organization, the Patient-Led Research Fund for

Long Covid, gives grants to those researching the effects of Long COVID on ME/CFS. They mention that "other studies not eligible for funding are studies into therapies that have already been well-evaluated in similar cohorts, do not result in positive outcomes, and are known to cause harm, including studies that use graded exercise therapy and cognitive behavioral therapy" (Patient-Led Research Fund, 2022). While there can be other reasons for this decision, the primary decision can be due to numerous studies that showed the lack of effect that CBT and GET had on ME/CFS and the harm they can bring (Gallagher et al., 2005; Twisk and Maes, 2009; Matthees et al., 2016; Wilshire et al., 2018). Future studies that look into ME/CFS concerning Long COVID that are looking for funding, at least from this grant, will have to agree not to use the funding to test those options due to the lack of effect. Researchers and ME/CFS patients want to see that the treatment results for their illness are based on fact and not tainted by decisions that can't be transparently explained. While those treatments can be helpful for other diseases concerning ME/CFS and now, Long COVID, they aren't popular and are looked down on (Patient-Led Research Fund, 2022).

The Long COVID-ME/CFS Connection

While many patients recovered from COVID in a few days or weeks, some didn't fully recover (Mayo Clinic Staff, 2022; CDC, 2022). They continue to have lingering symptoms reminiscent of their COVID infection. Specifically, long COVID is the signs, symptoms, and conditions continuing after a COVID-19 illness lasting four weeks or longer. Long COVID includes symptoms of COVID like fatigue, post-exertional malaise, lung symptoms like coughing, neurological symptoms, muscle pain, digestive issues, etc. (CDC, 2022; Mayo Clinic Staff, 2022). This is especially true since Long COVID can be considered a contested illness, appearing a while after the COVID-19 pandemic. It can affect multiple systems and have a

relapsing pattern and progression or worsen over time with a risk of serious harm in the future since it lasts months or years. It's not just one condition but can overlap multiple conditions with different risks and outcomes per patient. (CDC, 2022).

Long COVID sounds like many different conditions, so it isn't easy to figure it out. There's also no definitive laboratory test that helps one determine whether they have it (Mayo Clinic Staff, 2022). While there are tests for COVID, there's nothing for Long COVID. While there are specific indicators of the likelihood of it, like a past infection, medical conditions, and no vaccination, it's up in the air. There are even suggestions that factors like gender, ethnicity, socioeconomic status, and more can impact the likelihood that one gets Long COVID and how long they deal with symptoms (Subramanian et al., 2022). The CDC even states that it can be confused for ME/CFS or other "poorly understood chronic illnesses" due to their symptom similarities (CDC, 2022). The symptom that connects Long COVID to ME/CFS the most is fatigue, a hallmark of ME/CFS.

Just like ME/CFS, there are controversial takes for Long COVID. These controversial opinions form a different belief of where the symptoms come from or whether it's even Long COVID. For example, one article suggests that Long COVID could be a syndrome like post-intensive care syndrome or other respiratory symptoms while acknowledging that Long COVID is an actual illness (Mahese, 2020; Gaffney, 2022). Healthcare professionals have doubts about attributing everything to Long COVID, which could affect how patients feel. This problem has been mentioned numerous times in the ME/CFS world. This leads to patients giving their experiences but being ignored, affecting how they see medical professionals.

Another article suggests that beliefs of having a COVID-19 infection could create a perception of illness or create maladaptive health behaviors like reducing physical activity and

making patients experience Long COVID symptoms (Matta et al., 2021). While the authors claim that they aren't saying Long COVID doesn't exist, that's what some people took the claims to mean, especially those who believe that COVID might not be a severe illness (Reuters Fact Check, 2021). It shows that misinformation is a powerful weapon that can impact diseases without much information on their origins. This has happened in the past with ME/CFS, with researchers claiming it's not real or a "meme" that feeds off spreading common symptoms, as mentioned in Chapter 4. Furthermore, the statement by the researchers bears similarity to the claim that ME/CFS is not so much a biological illness but a psychological one.

That statement has been bounced around constantly in the ME/CFS world. It is also being bounced off in the Long COVID world. One of the reasons for that is the similarity that Long COVID bears to ME/CFS. For example, one study found that 72% of patients six months after COVID experience Post-Exertional Malaise (PEM), feeling unwell after exertion, a hallmark symptom of ME/CFS (Davis et al., 2021). Two of the three requirements for diagnosing ME/CFS are present in Long COVID patients. Due to a lack of diagnostic tests for either illness, it's up to a healthcare professional's opinion, taking in medical history and what the patient experiences. ME/CFS and Long COVID patients have dealt with hostile reception when describing their subjective experience to medical professionals. This is despite the evidence that subjective patient experience can provide more evidence of a serious medical problem (Roth and Gadebusch-Bondio, 2022). Medical tests can be wrong or not as informative, so doctors also consider what a patient says.

ME/CFS has existed for decades, and COVID started appearing only after March 2020. There's also the fact that Long COVID is more accepted in the public eye and the medical world than ME/CFS (Roth and Gadebusch-Bondio, 2022). Factors like social media have turned Long

COVID from something initially hidden and ignored into something that can't be overlooked or dampened down. Patients can tell their stories online and come together, forcing medical professionals to acknowledge that Long COVID is real and not fake (Roth and Gadebusch-Bondio, 2022). ME/CFS had this but didn't spread as much because that factor wasn't around then, leading it to be more hidden and fought against. This also pushed back against the initial claim that Long COVID doesn't have a biological basis, similar to the allegations against ME/CFS.

The Future of Long COVID and ME/CFS With PACE In the Background

Long COVID is at a critical stage which can either make it an illness where a biological cause is there but still unknown or go down the consequential route of ME/CFS in the claims it's psychological. Some are already making the psychological claim for Long COVID. A professor who had long COVID said he recovered by using pacing, a popular form of therapy recommended for ME/CFS by the ME Association. However, he heavily emphasized Long COVID being psychological-based and placing a connection between that belief and how ME/CFS is seen. That led to criticism of his illness and psychological claims, with many ME/CFS patients and activists disagreeing with them (Roth and Gadebusch-Bondio, 2022). Another article discussed Michael Sharpe and his claims that Long COVID comes from biological, psychological, and social factors. The best treatment, according to Sharpe, for Long COVID currently is "psychologically informed rehabilitation" (Newman, 2021). His comments were criticized for believing that Long COVID is in the mind, like the claims for ME/CFS. Michael Sharpe was, and still is, one of the principal investigators of the controversial PACE trial that found CBT and GET as effective treatment options for ME/CFS. He now claims psychological treatment is best for Long COVID.

As I mentioned, some are making claims about long COVID very similar to those made for ME/CFS. This includes the controversial statements regarding Long COVID being seen as psychological. We can see how that claim turned out for ME/CFS and the division created between the community and anyone who makes that claim. The same thing can potentially happen with Long COVID, so it's helpful to look back to the instances that led to the PACE trial, what happened during it, and the aftermath to prevent a mistake like that again. As we know, Long COVID is a potentially severe illness that we won't know the full extent of for a long time. It's best to prevent the same mistakes that plagued ME/CFS from happening to Long COVID and give patients a voice to participate in their illness. ME/CFS didn't fully get that opportunity, and it created irreparable harm to the community and the disease itself. If Long COVID is seen the same way and something similar to the PACE trial is done for it, a lot of irreparable harm can happen that will be bigger. Looking at ME/CFS as a case study can help guide ways to make sure patients are heard, valid claims are made, and studies give correct evidence to support a statement. We can't change what happened with ME/CFS, but by using ME/CFS, we can fix the mistakes of it in the path of Long COVID.

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