The Relationship Between Sleep and Fatigue in Chronic Fatigue Syndrome

A thesis submitted to The University of Manchester for the degree of Doctorate in Clinical Psychology (ClinPsyD) In the Faculty of Medical and Human Sciences

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The Relationship Between Sleep and Fatigue in Chronic Fatigue Syndrome
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Abstract
This thesis has been prepared in a paper based format and includes an empirical paper, a systematic review and critical reflection. As a whole, the thesis focuses on the importance of sleep in Chronic Fatigue Syndrome (CFS). The systematic review is prepared for submission to ‘Sleep Medicine Reviews’. The empirical paper is prepared for submission to the ‘Journal of Consulting and Clinical Psychology’.

Paper 1 is a systematic review and narrative synthesis of the current evidence for the effectiveness of Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) on sleep in CFS. Eight studies were found and their methodological quality varied. To understand heterogeneity in findings, information regarding intervention delivery, including the presence of sleep management components, methodology and sleep outcome measures was extracted and synthesised. We conclude that GET can improve sleep, when delivered by experienced therapists in outpatient settings. The evidence for CBT on sleep is limited, moreover, at present we know little about the effectiveness of adding sleep management components to interventions. We suggest that sleep outcomes used previously have not been sufficiently comprehensive and sensitive to measure change in sleep difficulties experienced in CFS. Implications for further research are discussed.

Paper 2 presents an empirical study examining the relationship between sleep and fatigue in CFS using a daily diary approach. Sleep was measured objectively using actigraphy, and subjectively, using sleep diaries, in order to test which parameters better predict next-day fatigue. We also examined whether negative mood could mediate these relationships and whether subjective sleep variables were predicted by pre-sleep arousal. Using multilevel modelling, we found that subjective sleep, and not objective sleep, predicted next-day fatigue and these relationships were partially mediated by negative mood on waking. Pre-sleep cognitive and somatic arousal predicted subjective sleep variables including sleep efficiency and quality. Based on these findings, we suggest that interventions targeting subjective sleep, such as CBT for insomnia, may be useful in improving experiences of fatigue in CFS.

Paper 3 is a critical reflection on the systematic review and empirical research, and on the process as a whole. Strengths and weakness of Paper 1 and Paper 2 are discussed, in addition to consideration of their contribution to wider research, and clinical practice.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Acknowledgements

This thesis would not have been possible without those who took part, and I am very grateful for their time and effort. Thank you to my supervisors Professor Alison Wearden and Dr Simon Kyle for their enthusiasm, support and guidance throughout the research and write up. Thank you also to my field supervisor, Dr Gill Fairclough, and to the CFS team at Salford Royal for their support with recruitment. I’d also like to thank Dr Richard Emsley for guidance regarding the design of the project and statistical analyses. Thank you to my fellow trainees; Laura Maxon for assisting with quality assessment, and Jasper Palmier-Claus for teaching me how to use Stata.

On a personal note, thank you to my husband James for supporting me throughout the process.
Paper 1: Systematic Review

Do Evidence Based Interventions for Chronic Fatigue Syndrome Improve Sleep? A Systematic Review and Narrative Synthesis

Written for publication in: Sleep Medicine Reviews (See Appendix 1 for author guidance)

Word Count: 8021 (Including references, tables and figures)
Summary

Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) are the current evidence based treatment approaches for Chronic Fatigue Syndrome, with substantial research supporting their effectiveness in reducing fatigue and functional impairment. However, little research has focused on the effectiveness of these treatments on sleep, despite high reported sleep disturbance in CFS. This review used a narrative synthesis approach which aimed to 1) Systematically identify and summarise the current evidence for the effectiveness of CBT and GET in improving sleep; 2) Consider factors influencing effectiveness, including incorporation of sleep management techniques within interventions; and 3) Consider the appropriateness of sleep outcome measures used within studies. Eight studies were eligible for inclusion. We found that that GET interventions can improve sleep but this effect is inconsistent across studies. For CBT the evidence is limited with only one of two evaluations demonstrating sleep-related improvements. We conclude from existing research that we know little about the effects of including sleep management components within CBT and GET interventions. We suggest that sleep outcomes used previously have not been sufficiently comprehensive and sensitive to measure change in sleep difficulties experienced in CFS. Implications for further research are discussed.

Keywords: Chronic Fatigue Syndrome; Sleep; Cognitive Behavioural Therapy; CBT; Graded Exercise Therapy; GET; Narrative Synthesis
**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>APT</td>
<td>Adaptive Pacing Therapy</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive Behavioural Therapy</td>
</tr>
<tr>
<td>CFS</td>
<td>Chronic Fatigue Syndrome</td>
</tr>
<tr>
<td>CFIDS</td>
<td>Chronic Fatigue and Immune Dysfunction Syndrome</td>
</tr>
<tr>
<td>GET</td>
<td>Graded Exercise Therapy</td>
</tr>
<tr>
<td>ME</td>
<td>Myalgic Encephalomyelitis</td>
</tr>
<tr>
<td>PR</td>
<td>Pragmatic Rehabilitation</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
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</tbody>
</table>
Introduction

Chronic fatigue syndrome (CFS) is a condition characterized by severe and persistent unexplained fatigue with a definite onset and a duration of longer than six months [1,2]. For a diagnosis to be made, the fatigue experienced has to substantially impact daily activities [1,2]. A high proportion of patients experience sleep difficulties, including poor sleep quality, difficulties initiating and maintaining sleep [3,4], and perceiving sleep to be unrefreshing [5,6].

Despite high reported levels of sleep disturbance, to our knowledge no study has evaluated the effectiveness of sleep-specific interventions in this group. This lack of focus on sleep is problematic because from a patient perspective, poor sleep is viewed as exacerbating daytime symptoms [7] and models of CFS posit that sleep disturbance is one factor involved in maintaining both biological and psychological symptoms associated with CFS [8]. Moreover, a recent empirical study found that poorer subjective sleep predicted increased following day fatigue in CFS [9], suggesting that improving sleep is likely to be beneficial as a target in CFS interventions.

At present, Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) are the recommended treatments for CFS [10] and a recent large Randomised Controlled Trial (RCT) supported their effectiveness in reducing fatigue and improving physical functioning [11]. CBT for CFS aims to formulate and modify unhelpful cognitive and behavioural responses to symptoms that may perpetuate the condition. This includes challenging unhelpful thoughts and beliefs, reducing symptom focus, and behavioural change [12]. GET aims to gradually increase physical activity without a specific focus on cognitive factors.

1 See Paper 2
This approach is based on the understanding that avoidance of activity and physical deconditioning may perpetuate CFS symptoms [12].

Although substantial research has evaluated the effectiveness of CBT and GET for improving fatigue and functioning, their effectiveness for improving sleep has been less studied. However, both CBT and GET are thought to positively impact sleep, and may do so through different mechanisms. For GET, a gradual increase in regular exercise may improve perceived sleep quality, as has been demonstrated in insomnia [13] and non-clinical samples [14]. It has also been suggested that exercise can improve sleep in CFS by reducing muscle tension and relieving stress [15]. For CBT, perceived sleep may improve via a number of different mechanisms including improved general mood and anxiety management strategies. Sleep specific techniques, including sleep hygiene can also be added to both GET and CBT in line with guidance for CFS in both the UK and US [10,16]. When there is a focus on sleep, CBT can also modify unhelpful beliefs that increase preoccupation and worry about sleep, which itself can exacerbate sleep difficulties.

Although CBT and GET are understood to improve sleep, evaluation studies have not focused on improving sleep as a primary aim. However, a recent Cochrane review [17] of GET for CFS did include sleep as an outcome and included three RCTs that had examined sleep as secondary outcomes. A meta-analysis of these findings showed that GET had a significant positive effect on sleep but that there was heterogeneity in the size of this effect [17].

Although the Cochrane review provided initial information about the effects of GET on sleep, factors contributing to the heterogeneity in findings remain unknown. It is likely that differences between studies related to the delivery of GET interventions, including the
incorporation of sleep management approaches, and characteristics of the samples, contributed to differences in findings. However there has not previously been an attempt to summarise how these factors might influence the effectiveness of GET on sleep. Additionally, the extent to which differences in the measurement of sleep outcomes contributed to variations in findings is also unclear. Moreover, the effect of CBT for CFS on sleep has not, to our knowledge, been evaluated systematically.

It has been suggested that when there is inconsistency between findings of effectiveness studies, such as the effects of GET on sleep, a narrative synthesis approach can be used to understand heterogeneity in outcomes [18]. This approach aims to systematically assess the strength of current evidence and the conclusions that can be drawn [19]. Therefore, in order to further understanding of the effects of GET and CBT on sleep, this review used a narrative synthesis approach to:

- Identify GET or CBT intervention studies including sleep as an outcome in order to summarise the current evidence for CBT and GET on sleep in CFS
- Consider factors influencing the effectiveness of these interventions, including intervention delivery and whether sleep management strategies have been explicitly included
- Describe how sleep has been measured as an outcome within included studies
Method

Search strategy

To identify relevant studies, one researcher (C.R.) conducted searches in Medline (PubMed), PsycInfo (Ovid), Embase (Elsevier), Web of Science (Thomson Reuters) and CINAHL (Bbso). Two sets of search terms were combined using “AND” to produce a comprehensive search within each database. The first set of terms identified CFS literature by including “chronic fatigue syndrome” and CFS. “Myalgic encephalomyelitis” was included as this is used within the UK due to being preferable to some patient groups. “CFS/ME” was included as it is used within the UK by both professionals and patient groups. “CFIDS” (Chronic Fatigue and Immune Dysfunction Syndrome) was included as it is preferred by patient groups within the US [20]. Finally “Post-viral fatigue syndrome” was included as this is sometimes used if patients develop the condition following a viral infection. The second set of search terms identified treatment or intervention studies within the CFS literature by including “cognitive behaviour”, “cognitive behavioral”, “cognitive behaviour”, “cognitive behavior”, “CBT”, “graded exercise”, “graded activity”, “exercise therapy”, “treatment”, “intervention” and “trial”. Databases were searched from inception up to and including March 2015, although because the first working case definition of CFS was not published until 1988 (Holmes, Kaplan and Gantz, 1988), all search results were found to be published after this date.

The results of the searches were exported to reference management software and merged to identify duplicates. Titles were reviewed and if there was an indication that the article was related to treatment evaluation in individuals with CFS, abstracts were reviewed. If the
abstract suggested that the study was relevant the full text was acquired and assessed against inclusion and exclusion criteria. The study selection process is shown in Figure 1.

Criteria for inclusion of research articles

Studies evaluating interventions based on the principles of CBT and/or GET were included providing they incorporated at least one outcome relating to sleep. Sleep outcomes could include sleep-related questionnaire measures, sleep diaries and objective sleep parameters. As the literature in this area is limited, we included all types of evaluation study designs including RCTs, uncontrolled trials and case studies\(^2\). Only studies including adults (aged 18 or over) meeting the Oxford and/or Fukuda [1,2] diagnostic criteria for CFS were included. Only full text articles published in English were included.

Quality Assessment

In order to assess the quality of included studies, the Downs and Black [21] checklist was used (Appendix 2). This has been highlighted as one of the ‘best’ tools for evaluating both randomised and non-randomised intervention studies [22]. The checklist has 27 items assessing study reporting, external validity, and internal validity including bias and confounding and has good inter-rater reliability [21]. Item 14, regarding participant blinding to intervention, was removed as this was not relevant to the current review. Item 27 relating to power was also omitted due to sleep being a secondary outcome within included studies, and therefore any power calculations were not based on sleep outcomes, and were therefore not considered relevant. For the current review, quality assessment for

\(^2\) See Paper 3 for reflections on the inclusion criteria
each of the studies was assessed by two researchers independently. Agreement between researchers was found to be $\text{Kappa} = 0.872$ (p < 0.001). Inconsistencies were then discussed and consensus was reached between researchers (Appendix 3).

**Extraction of sleep management components**

Information regarding sleep components within interventions was extracted from published research articles and any published trial intervention manuals. The presence of sleep components based on extracted information was rated by consensus between two authors (C.R. & S.D.K) using the following definitions:

- **Sleep hygiene**: Instructional advice to sleep management including keeping consistent bedtime and wake times, avoiding napping, avoiding caffeine, alcohol and stimulating activities prior to sleep, and ensuring a comfortable sleeping environment.
- **Education regarding circadian desynchronisation**: Educational information about circadian rhythms, factors that can disrupt rhythms, and resulting symptoms.
- **Stimulus Control**: Instructional advice to maintain associations between the bedroom and sleep, using the bed only for sleep and leaving the bedroom when unable to sleep.
- **Relaxation techniques**: Teaching specific techniques such as ‘progressive muscle relaxation’ aimed at increasing skills in relaxation prior to sleep. General advice regarding increasing ‘relaxation time’ or ‘relaxing activities’ was not included.
- **Managing worry prior to sleep**: Cognitive strategies including problem solving and thought challenging.
- **Cognitive restructuring**: Modifying unhelpful beliefs about sleep using cognitive strategies and behavioural experiments.
• Sleep restriction advice: Instructional advice to restrict the amount of time spent in bed in order to improve sleep efficiency.

• Dealing with oversleeping: Instructional advice to reduce total sleep time in those with hypersomnia.

Data Synthesis

Findings were combined and summarised in line with guidance for completing a narrative synthesis [19]. This included considering how CBT and GET interventions might influence sleep and presenting all available evidence. Differences in findings and how the methodology, delivery of the intervention, inclusion of sleep management strategies, and the sample used might influence effectiveness were considered and summarised. Conclusions that can be drawn based on the quality of included studies were also evaluated [19]. As part of the synthesis, quantitative data regarding effect sizes, and the methodological quality of included studies was also provided in order to fully describe the current evidence. The standardized mean difference (SMD) was used as a measure of effect size and was calculated for studies providing follow up data (beyond assessment immediately post-treatment). The SMD expresses the size of the intervention effect and is calculated based on differences between group means for intervention and control groups at follow up, relative to the variability observed in that study.
Results

Study Selection

Searches of the databases and reference lists yielded 1390 titles and abstracts after duplicates were removed. A total of 256 full text articles were reviewed for eligibility, and eight studies were eligible for inclusion. The study selection process is shown in Figure 1.

Figure 1. Flow chart of the study selection process

- Records identified through database searching (n=2475)
- Duplicates excluded (n=1085)
- Records screened by title/abstract (n=1390)
- Irrelevant papers (n=1134)
- Full text articles assessed for eligibility (n=256)
- Full text articles excluded (n=248):
  - Included age <18 (n=30)
  - Not published in English (n=11)
  - Intervention not based on principles of CBT or GET (n=137)
  - Sleep not included as an outcome (n=59)
  - Not an evaluation study (n=10)
  - Samples not defined by Oxford or Fukuda criteria for CFS (n=1)
- Studies included in the review (n=8)
Description of studies included within the review

Characteristics of the eight included studies are shown in Table 1. Included studies were four RCTs [11,23,24,25], one pilot study with randomisation [26], one non-randomised trial [27], and one case study [28]. The remaining study was an uncontrolled follow up of an included RCT [29].

Studies varied considerably in their quality, ranging from scores of 8 to 25 of a possible 26 (mean score = 18). The two large RCTs [11,25] scored highly, indicating high study quality and a low risk of bias. As expected, these studies scored more highly than non-randomised and pilot studies included [2,27]. The case study [28] scored poorly, as although it provided a detailed description of the participants and methods, the nature of this design allowed for a high risk of bias.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Design</th>
<th>Description and duration of intervention (number of participants)</th>
<th>Control condition/ Comparator (number of participants)</th>
<th>Mean age, % female</th>
<th>Length of follow up</th>
<th>Sleep outcomes</th>
<th>Summary of reported sleep outcomes at follow up</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulcher &amp; White (1997)[23]</td>
<td>RCT</td>
<td>12 weeks of individual graded exercise sessions (29)</td>
<td>12 weeks of individual flexibility sessions (30)</td>
<td>37.2, 74%</td>
<td>Post treatment/ 12 weeks after baseline</td>
<td>Pittsburgh Sleep Quality Index (PSQI)</td>
<td>No significant difference in ratings of sleep difficulties following treatment, compared to controls</td>
<td>19/26</td>
</tr>
<tr>
<td>Lopez et al. (2011)[26]</td>
<td>Pilot study (with random allocation)</td>
<td>12 week group cognitive behavioural stress management programme(CBSM;44)</td>
<td>Half day psycho-education seminar on CBSM (25)</td>
<td>45.9, 88.4%</td>
<td>Post treatment/ 12 weeks after baseline</td>
<td>CDC Symptom Inventory for CFS – self report ratings of sleep problems and unrefreshing sleep</td>
<td>Ratings of the frequency, but not the severity of unrefreshing sleep reduced significantly in the CBSM group compared to controls.</td>
<td>18/26</td>
</tr>
<tr>
<td>Powell et al. (1999)[28]</td>
<td>Case Study</td>
<td>Pragmatic rehabilitation (PR) sessions incorporating elements of CBT &amp; GET Participant 1 – 60 sessions over 24 months Participant 2 – 55 sessions over 27 months</td>
<td>None</td>
<td>20.5, 100%</td>
<td>30 &amp; 33 months after baseline</td>
<td>Jenkins at al. sleep scale</td>
<td>Ratings of sleep problems decreased from near the maximum possible score (18 &amp; 19/20) to 0 following treatment for both participants.</td>
<td>8/26</td>
</tr>
<tr>
<td>Powell et al. (2001)[24]</td>
<td>RCT</td>
<td>Individual patient education to encourage graded exercise (PR). Three treatment levels: Minimum— 2 sessions (37) Telephone—2 sessions plus telephone contact (39) Maximum— 7 sessions(38)</td>
<td>Standardised medical care (34)</td>
<td>Min 34, 76% Tel 32, 85% Max 33, 82% SMC 34, 71%</td>
<td>3, 6 &amp; 12 months after baseline,</td>
<td>Jenkins at al. sleep scale</td>
<td>Intervention groups showed significant improvements in ratings of sleep difficulties, compared to standardised medical care at 3, 6 and 12 months.</td>
<td>20/26</td>
</tr>
<tr>
<td>Author (year)</td>
<td>Design</td>
<td>Description and duration of intervention (number of participants)</td>
<td>Control condition/Comparator (number of participants)</td>
<td>Mean age, % female</td>
<td>Length of follow up</td>
<td>Sleep outcomes</td>
<td>Summary of reported sleep outcomes at follow up</td>
<td>Quality rating</td>
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<tr>
<td>Powell et al (2004)[29]</td>
<td>Uncontrolled follow up</td>
<td>As above</td>
<td>None – control participants from earlier RCT were offered PR intervention</td>
<td>As above</td>
<td>2 years after baseline</td>
<td>Jenkins at al. sleep scale</td>
<td>Sleep improvements appeared to be maintained at follow up although statistical analysis for the sleep outcome was not reported.</td>
<td>18/26</td>
</tr>
<tr>
<td>Thomas et al. (2006)[27]</td>
<td>Non randomised trial</td>
<td>10 sessions of individualised multi-convergent therapy combining elements of CBT, GET and adaptive pacing therapy (12)</td>
<td>10 sessions of relaxation therapy (14), No intervention controls (9)</td>
<td>MCT 46.7, 67% Relaxation 45.7, 71.4% Control 46.2, 67%</td>
<td>10 weeks and 6 months after baseline</td>
<td>Smith at al. Sleep questionnaire</td>
<td>There were a significantly greater number of participants whose sleep was rated as improved in the MCT group, compared to the relaxation and control groups.</td>
<td>11/26</td>
</tr>
<tr>
<td>Wearden et al. (2010)[25]</td>
<td>RCT</td>
<td>10 sessions of individual nurse led pragmatic rehabilitation sessions including elements of CBT &amp; GET (95) in addition to GP treatment as usual</td>
<td>10 sessions of nurse led supportive listening (101), GP treatment as usual (100)</td>
<td>44.6, 78%</td>
<td>20 weeks &amp; 70 weeks after baseline</td>
<td>Jenkins at al. sleep scale</td>
<td>PR group showed significant improvement in ratings of sleep difficulties at 20 weeks, but not at 70 weeks compared to control conditions</td>
<td>25/26</td>
</tr>
<tr>
<td>White et al. (2011)[11]</td>
<td>RCT</td>
<td>24 weeks of individual CBT sessions (161), or individual GET sessions (160) each in combination with standardised specialist medical care</td>
<td>Up to 15 sessions of standardised specialist medical care (160), alone or in combination with 24 weeks of individual adaptive pacing therapy APT(159)</td>
<td>38, 77%</td>
<td>12, 24 and 52 weeks after baseline</td>
<td>Jenkins at al. sleep scale</td>
<td>CBT and GET groups showed significantly improved ratings of sleep difficulties, compared to APT and specialist medical care groups.</td>
<td>25/26</td>
</tr>
</tbody>
</table>
Description of Interventions

Included studies differed considerably in their treatment approaches. Two RCTs evaluated GET interventions over 12 weeks [23], and 24 weeks [11] respectively.

Two studies evaluated interventions derived from a CBT approach [11, 26]. One study evaluated formal individual CBT sessions over 24 weeks [11], and one piloted a 12 week cognitive behavioural stress management group [26]. We did not find any studies evaluating sleep focused CBT interventions.

Four studies combined aspects of GET and CBT within a Pragmatic Rehabilitation (PR) intervention [24,25,28,29]. PR includes education to encourage graded increases in activity based on an understanding of CFS encompassing physiological dysregulation maintained by behavioural and cognitive factors. The first PR study [28] was a case study of two patients completed over a two year period. The Powell et al. [24] study and its two year follow up [29], evaluated PR delivered in different doses, namely in two face-to-face sessions with or without telephone support, or the same intervention delivered over seven face-to-face sessions. The final study evaluated the effectiveness of 10 sessions of individual nurse led PR sessions [25].

The remaining, non-randomised, study evaluated a ‘Multi-Convergent Therapy’ approach which was described as combining aspects of CBT, GET and adaptive pacing therapy [27].
Description of control and comparative conditions

Three studies had more than one comparator delivered over the same duration. One RCT evaluated CBT, GET, and an adaptive pacing intervention, each in addition to specialist medical care [11]. During analyses, CBT and GET were compared against adaptive pacing therapy and against specialist medical care alone [11]. In another RCT a PR intervention, in addition to GP treatment as usual, was compared against nurse led supportive listening with equivalent contact (in addition to GP treatment as usual), and with GP treatment as usual alone [25]. The remaining, non-randomised, study compared an intervention combining aspects of CBT, GET and adaptive pacing therapy with controls receiving relaxation sessions or no intervention [27].

For studies with one control group only, one RCT compared GET against equivalent contact within flexibility sessions [23]. One RCT evaluated a PR intervention (in different doses) against standardised medical care [24]. A pilot study compared a 12 week cognitive behavioural stress management programme with a half day seminar on the same approach [26]. The remaining case study did not include a control condition [28].

Description of participants

A total of 1249 participants meeting the Oxford or Fukuda criteria for CFS participated in the eight included studies. The mean age of participants across studies was 39.6 (SD= 9.1), and the mean proportion of females across studies was 77.7% (SD=10.4). For six of the studies, interventions were provided on an outpatient basis requiring patients to be mobile enough to attend sessions [11,23,24,26,27,29]. Two studies evaluated interventions delivered by home visit and telephone contact [25,28] and in one of these studies 11% of
participants were non ambulatory and would have had difficulty attending outpatient appointments [25]. Within the included case study the two individuals who participated were described as severely affected and requiring the use of wheelchairs prior to intervention [28].

Five of the studies had no sleep-related participant exclusion criteria [11,25,26,27,28]. One of the studies offered treatment to patients who had had ‘symptomatic insomnia’ prior to participation, and included participants only if that insomnia had been treated successfully and they still met the criteria for CFS [23]. One study (and its follow up) excluded patients who were ‘taking other treatments including antidepressants’ which although not specified further would presumably exclude patients taking medications for sleep [24,29].

Sleep management components within interventions

Information regarding sleep components was extracted from each article, and for two studies from published trial intervention manuals [11,25]. Included studies varied substantially in the extent to which they reported including sleep management techniques. Table 2 shows extracted sleep components within interventions.
Table 2: Sleep components within included interventions

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Intervention</th>
<th>Sleep hygiene</th>
<th>Education re: circadian desynchronisation</th>
<th>Relaxation techniques</th>
<th>Managing worry prior to sleep</th>
<th>Cognitive restructuring</th>
<th>Sleep restriction</th>
<th>Dealing with oversleeping</th>
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</thead>
<tbody>
<tr>
<td>Fulcher &amp; White (1997)[23]</td>
<td>GET</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez et al. (2011) [26]</td>
<td>CBT</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powell et al. (1999)[28]</td>
<td>PR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas et al. (2006)[27]</td>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wearden et al. (2010)[25]</td>
<td>PR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Description of sleep-related outcome measures

Five included studies used the Jenkins et al. [30] sleep scale as an outcome measure [11,24,25,28,29]. This contains four items relating to initiating and maintaining sleep, and unrefreshing sleep, rated on the frequency of each difficulty during the past month, with higher scores indicating increased frequency. One study [23] used the Pittsburgh Sleep Quality Index (PSQI) [31], which is a comprehensive measure of sleep problems including difficulties initiating and maintaining sleep, poor sleep quality, use of medication and the impact of sleep problems on daytime functioning. One included study [26] used the Centre
for Disease Control Symptom Checklist for CFS [32], which contains four items measuring the frequency and severity of unrefreshing sleep and ‘sleeping problems’ using Likert style responses. The remaining study [27] used the Smith et al. [33] sleep questionnaire which “classifies sleep abnormality based on reported average sleep duration and difficulties initiating and maintaining sleep” [27]. No studies used sleep diaries or objectively measured sleep parameters as outcomes.

Effect sizes for sleep outcomes

Where appropriate data were available, the standardised mean difference (SMD) between treatment and control groups at follow up was calculated as a measure of effect size. For two studies [28,29], SMD could not be calculated due to the absence of control conditions. For one study, insufficient data were provided and authors could not be contacted for clarification [27]. For another, the nature of the outcome measure meant that interquartile range was reported rather than standard deviation [23] and therefore SMD could not be calculated.

Effect sizes (SMD) were calculated for studies including appropriate follow up data. For the Lopez et al. [26] study, post treatment data were provided by authors but follow up data were not available due to this being a small pilot study, and consequently data provided were not deemed comparable to follow up data from the large RCTs included. In the Powell et al [24] study, the PR intervention was delivered at 3 doses, and for the purpose of this review the SMD was calculated for the maximum intervention (7 sessions) only. For the two studies where there was more than one control group [11,25], specialist medical care or GP treatment as usual was used to calculate SMD due to these being more similar and comparable to control groups used in other included studies.
For three studies (evaluating four interventions) follow up data were provided and used to calculate SMD as shown in Table 3 and Figure 2. Within all four of these studies, the Jenkins sleep scale [30] was used, with lower scores indicating improvements in sleep.

### Table 3: Follow up data used to calculate SMD

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Follow up (weeks)</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powell et al. (2001)[24]</td>
<td>PR</td>
<td>52</td>
<td>38 Mean 7.1 SD 4.9</td>
<td>34 Mean 11.5 SD 5.5</td>
<td>-0.847 (-1.330, -0.365)</td>
</tr>
<tr>
<td>Wearden et al. (2010)[25]</td>
<td>PR</td>
<td>70</td>
<td>81 Mean 12.32 SD 5.61</td>
<td>90 Mean 13.18 SD 5.71</td>
<td>-0.152 (-0.453, 0.149)</td>
</tr>
<tr>
<td>White et al. (2011)[11]</td>
<td>CBT</td>
<td>52</td>
<td>161 Mean 9.9 SD 5.3</td>
<td>160 Mean 11 SD 5</td>
<td>-0.214 (-0.433, -0.006)</td>
</tr>
<tr>
<td>White et al. (2011)[11]</td>
<td>GET</td>
<td>52</td>
<td>160 Mean 9 SD 4.8</td>
<td>160 Mean 11 SD 5</td>
<td>-0.408 (-0.630, -0.187)</td>
</tr>
</tbody>
</table>

**Figure 2: Plotted SMD at Follow Up with 95% Confidence Intervals**
**Narrative Synthesis**

*Current evidence for the effect of CBT and GET on sleep*

Within our review only two studies evaluated ‘pure’ GET interventions, and these produced contradictory findings with one finding that GET can significantly improve sleep [11] and one reporting no effect [23]. However, the latter study excluded participants experiencing insomnia symptoms unless these could be successfully treated prior to participation. This may explain the intervention having no effect on sleep given that the sample were not experiencing sleep difficulties prior to intervention.

Four included studies [24,25,28,29] evaluated a PR intervention encouraging graded exercise based on an understanding of CFS that included cognitive and behavioural factors. PR includes education around sleep rhythms and sleep hygiene advice. Two high quality RCTs evaluated PR on sleep. One showed that PR can be more effective at improving sleep than standardised medical care at post treatment, and at follow up, with participants’ sleep continuing to improve in the 12 months post treatment [24]. In contrast, the other RCT found that PR did not significantly improve sleep at 70-week follow-up (although a significant improvement in sleep immediately post intervention was reported) [25]. There are several possible explanations for this finding, including that the intervention was delivered via home visit, allowing the inclusion of more severely affected participants and who as a consequence may be less responsive to intervention [25]. Moreover, the intervention was delivered by trained non-specialist nurses, and not by experienced therapists which may have contributed to the non-significant findings [25]. In contrast, in the earlier PR trial [24] and case study [28] where sleep improvements were observed, the
intervention was delivered by an experienced therapist who had developed this treatment approach.

Within the remaining study that included GET, CBT and adaptive pacing therapy in combination, it was reported that the intervention improved ratings of sleep [27]. However, it was not clear how ratings of sleep had been calculated making it difficult to draw conclusions based on this finding, particularly given that this was a small non-randomised trial with a risk of bias.

Interestingly, all four interventions including GET (alone or in combination) that report significant improvements in sleep, also report including sleep hygiene advice within their interventions [11,24,27,28]. This suggests that GET interventions including sleep hygiene advice can be effective at improving sleep. However, because of the limited research in this area, it is unclear how much the addition of sleep hygiene advice to GET interventions enhances their effectiveness on sleep or whether other aspects of GET aid sleep. The latter may be more likely given that there is limited evidence for the effectiveness of sleep hygiene advice for those experiencing sleep problems [34].

In terms of the current evidence regarding the effect of CBT on sleep, we found only one high quality RCT that evaluated CBT and GET separately, and examined sleep as an outcome [11]. The individual CBT sessions delivered over 24 sessions within this study incorporated comprehensive sleep management approaches. At one year follow up, significant improvements in sleep were seen compared to controls receiving specialist medical care [11]. This suggests that providing this comprehensive sleep management approach within CBT for CFS may improve sleep. However, within this study it appeared that the treatment effect size for GET was larger than the effect size for CBT at follow up,
suggesting that GET may have a greater effect on sleep over a one year period. However, CBT and GET were not compared directly to one another within analyses, making it difficult to draw conclusions about their relative effectiveness.

In a different study, CBT focusing on stress management did not have a significant effect on sleep [26]. However, within this study, sleep difficulties were measured as part of a broad CFS symptom measure, with the frequency and severity of ‘sleep difficulties’ rated on single four point Likert scales. Consequently these ratings may not have been a sensitive measure of change in sleep difficulties following intervention. Moreover, this was a small pilot study with a high risk of bias, and therefore conclusions that can be made based on this study are limited.

Measurement of sleep outcomes

All included studies used self-report measures of sleep difficulties. Most used the Jenkins et al. [30] Sleep Scale on which difficulties with initiating and maintaining sleep, and unrefreshing sleep (URS) are rated based on their frequency within the past month. This measure however does not assess the severity of these difficulties, their duration beyond one month, or whether they are problematic or distressing to the individual, and consequently may not provide a comprehensive and sensitive indicator of change. One study used Likert style ratings of the frequency and severity of sleeping problems and URS within a CFS symptom checklist [32]. Although such ratings provide a useful general assessment of symptoms, as was intended within this study, they are not likely to form a sufficiently comprehensive measure of sleep difficulties, particularly given that a number of difficulties were rated within one ‘sleep problems’ item, limiting the validity and reliability of these ratings. Only one study [23] used a more detailed and comprehensive measure of
sleep difficulties, the PSQI [31]. This instrument has good psychometric properties and has been recommended for assessing sleep disturbance as an outcome within intervention studies [35]. Unfortunately however, the sleep-related exclusion criteria used limit the conclusions that can be made about the effect of the intervention on sleep problems from this study.

Discussion

This review highlighted that only eight studies have evaluated the effects of CBT and GET on sleep, and that these studies varied markedly in their methodological quality. Only three studies provided high quality evidence from which robust conclusions could be drawn and only one of these studies evaluated CBT. We found that no studies had aimed to examine the effects of interventions on sleep as a primary outcome. This lack of focus on sleep is problematic given a high proportion of individuals with CFS report difficulties with sleep and because sleep problems are hypothesised as being involved in the maintenance of the condition [8].

The current evidence for the effect of GET and CBT on sleep

In our review, GET interventions differed in their effect on sleep with the two included studies showing opposing findings, although this may reflect methodological limitations in one of these studies [23]. The other high quality trial did however clearly show that GET can have a significant impact on sleep at one year follow up [11].

Our review also showed that a PR intervention which combines elements of GET and of CBT can have a significant effect on sleep, but that the size and durability of the effect appears
to depend on the delivery of the intervention and the characteristics of participants. In one study, PR delivered in secondary care over seven outpatient sessions by an experienced therapist significantly improved sleep and that these treatment gains were maintained to one year follow up [24]. However, the same intervention delivered by specially trained general nurses did not significantly improve sleep at follow up which may reflect the therapists being less experienced and that the intervention was provided by home visit, and to more patients recruited from primary care, some of whom were more severely affected [25].

Taken together, the findings of the GET and PR interventions show that interventions based on GET principles can be effective at improving sleep in CFS but in line with what was reported in the a recent Cochrane Review [17], this positive effect is not consistent across studies. We have highlighted that improvement in sleep outcomes may depend on factors such as the characteristics of the sample, inclusion criteria, and the content and delivery of the intervention itself.

Evidence examining the effectiveness of CBT on sleep is limited with only two studies evaluating CBT interventions. Moreover one of these studies was a small preliminary study which may not have been sufficiently powered to detect changes in sleep outcomes, particularly given that they were not the primary focus of the research [26]. The other study, a large high quality RCT, demonstrated that CBT had a positive impact on sleep which perhaps reflects that the intervention included a fairly comprehensive sleep management component [11].

The White et al. [11] trial was also the only study which evaluated the effects of CBT and GET on sleep separately and it was found that both these treatments significantly improved
ratings of sleep at follow up. In this trial however, CBT and GET were delivered over 24 sessions which may not to be representative of the current provision for CFS which in the UK has been described as “patchy at best” [36]. Therefore even in areas where a specialist CFS service is available, it is unlikely that all patients could be offered this level of service input due to practical and financial service constraints.

*Inclusion of sleep management approaches within interventions*

Although sleep management techniques are recommended as part of symptom management guidance in both the US and the UK [10,16], this review highlighted that the inclusion of sleep management techniques within interventions has varied. Due to this variation and because of the small number of studies available, it is unclear whether incorporating sleep management components within CBT and GET enhances their effectiveness. This is an area requiring further research.

Our review also found that to date, there has not been a published evaluation of sleep focused interventions, such as CBT for insomnia within CFS. As a consequence, we do not currently know the effects of targeting sleep specifically in this patient group. Future research could aim to establish whether such interventions may be useful in this group given the high levels of reported sleep disturbance, and the perceived importance of sleep in the maintenance of the condition.

*Measurement of sleep outcomes*

Within included studies, sleep outcome measures used were not adequately comprehensive and sensitive. This may reflect the fact that sleep was a secondary outcome
in all studies identified. Only one study [23] used a comprehensive self report measure of sleep in the form of the PSQI, which provides a comprehensive measure of self-reported sleep disturbance [35] and has previously been recommended for use within CFS [37].

Further studies should aim to use comprehensive measures, such as the PSQI to assess the effects of interventions on different aspects of sleep in CFS. In addition, specific measures of difficulties associated with CFS, such as unrefreshing sleep, which is reported by up to 95% of CFS patients [6] should be used to capture improvements in this difficulty specifically [e.g.38]. These measures would however require validation within the CFS population.

White et al. [11] demonstrated that both CBT and GET can improve sleep, however it is likely that these interventions improve sleep through different mechanisms. It is also possible that CBT and GET can impact different aspects of sleep but because the sleep outcome measure used in this trial produces a global score of sleep difficulties, it is not possible to determine whether this is the case. Further research using more detailed measures could provide further information about the aspects of sleep that can be improved by CBT and GET for CFS.

Our review did not identify any studies that used sleep diaries to provide self reports of sleep as outcome variables. Sleep diaries have been recommended as a useful way to prospectively assess treatment effects within insomnia research [35,39] and provide reliable data due to being less susceptible to memory bias than retrospective reports over a longer duration. Furthermore, it has been found recently that subjective sleep measured by sleep diaries, can predict following day fatigue in CFS [9]. Therefore, because of the association with fatigue, subjective sleep is likely to be a useful target for intervention and can be captured effectively by sleep diaries.
We also identified that in the CFS field, no intervention studies used objective recordings of sleep, such as polysomnography or actigraphy to measure sleep-related outcomes. It has been highlighted that despite substantial research investigating sleep in CFS, there is no strong evidence for objective sleep disturbance [40]. Objective measures of sleep are therefore likely to be of limited utility as outcome measures, although they may provide useful information, as well as helping to rule out undetected other sleep disorders.

The lack of focus on sleep as an outcome reflects the wide ranging impact of CFS and the consequent complexity in measuring treatment response, with primary outcomes often focusing on fatigue and physical functioning [41]. Within the CFS field there is debate around the appropriateness of condition specific, domain specific and generic measures [41] which is beyond the scope of this review. However, it is clear that the inclusion of sleep outcomes, using detailed and comprehensive measures is necessary in order to fully examine the effects of CBT and GET on sleep.

This review has highlighted a number of additional areas in need of further research. Firstly, further research should establish whether the addition of sleep management components to CBT and GET may enhance their effectiveness on sleep. The likelihood of establishing this will be improved by studies providing explicit descriptions of intervention content, including sleep components, within trial manuals [42]. The effectiveness of sleep-specific interventions in this patient group should also be evaluated. Within such research, including sufficiently comprehensive measures of sleep designed to capture commonly reported sleep difficulties in CFS could also establish the types of difficulties that can be treated using CBT and GET. Moreover, given recent findings that subjective sleep predicts
following day fatigue in CFS [9], the role of sleep as a potential mediator of the effects of CBT and GET on fatigue in CFS should be explored further.

Practice Points

- Sleep management components are recommended for use in CBT and GET interventions for CFS. However in previous research the inclusion of these techniques has varied markedly.
- The limited current evidence suggests that GET interventions incorporating sleep hygiene advice can improve sleep, if the intervention is delivered by experienced therapists to CFS patients experiencing sleep difficulties.
- The limited evidence suggests that CBT delivered individually over 24 sessions incorporating comprehensive sleep management components can improve sleep. However whether sleep improvements could be seen in fewer sessions or in group settings is unclear.
- Sleep outcome measurement in the CFS field has not been sufficiently comprehensive to fully capture changes in the sleep difficulties experienced by this group, or the aspects of sleep that may improve following intervention.

Research Agenda

Further research should aim to:

- Establish whether the inclusion of sleep specific components within CBT and GET enhances their effectiveness on sleep
- Evaluate whether sleep specific interventions, such as CBT for insomnia, may be beneficial in this group
- Use comprehensive sleep outcome measures that reflect sleep difficulties experienced within the condition
- Explore the role of perceived sleep as a potential mediator of the effects of CBT and GET on fatigue in CFS
References


[12.] PACE trial management group (2010) CBT and GET Therapist Manuals. ISRCTN54285094

of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine, 6(3), 270.


*Citations marked with an asterisk are included within the review.*
Paper 2: Empirical Research

Subjective but not objective sleep predicts next-day fatigue in chronic fatigue syndrome: A daily diary study

Written for publication in: Journal of Consulting and Clinical Psychology (For author guidance see Appendix 4)

Word Count: 6856 (Including references and tables)
Abstract

**Objective:** This study aimed to examine the relationship between subjective and objective measures of sleep, and next day fatigue in chronic fatigue syndrome (CFS), and investigate the potential mediating role of negative mood on this relationship. We also sought to examine the impact of pre-sleep arousal on perceptions of sleep. **Method:** Using a daily diary approach, 27 participants meeting the Oxford criteria for CFS completed sleep diaries and multiple daily ratings of symptoms and mood over six days. Objective sleep was estimated nightly over the same period using actigraphy. **Results:** Multilevel modelling revealed that subjective sleep variables, namely sleep quality, efficiency and perceiving sleep to be unrefreshing, predicted following day fatigue levels, with poorer subjective sleep related to increased fatigue. Lower perceived sleep efficiency and perceiving sleep as unrefreshing predicted reduced variance in fatigue across the following day. Negative mood on waking partially mediated these relationships. Increased pre-sleep cognitive and somatic arousal predicted self reported poor sleep. Objective estimations of sleep however, were not found to predict following day fatigue. **Conclusions:** Our findings are the first to demonstrate that nightly subjective sleep predicts next-day fatigue in CFS, and identify pre-sleep arousal and negative mood on waking as key variables in this relationship.

**Public Health Significance Statement:** This study suggests that sleep specific interventions, targeting perceived sleep and negative mood on waking, in addition to existing CFS-focused cognitive behavioural interventions may improve fatigue in CFS

**Keywords:** Chronic fatigue syndrome; CFS; Sleep; Daily Diary Study
Introduction

Chronic fatigue syndrome (CFS) is a condition characterized by severe and persistent fatigue of more than six months duration, which has a substantial impact on daily activities (Fukuda et al., 1994). Difficulties with sleep are commonly reported, with up to 95% of patients experiencing unrefreshing sleep (Nisenbaum et al., 2003; Jason et al., 1999). Difficulties with initiating and maintaining sleep, and poor sleep quality are also highly prevalent in this group (Morris, Wearden & Battersby, 1997; Neu, et al., 2007).

Despite high levels of reported sleep difficulties in CFS, two recent reviews have concluded that there is minimal evidence for objectively measured sleep impairment (Mariman et al., 2013; Jackson & Bruck, 2012). This suggests a discrepancy between perceived and objective sleep. Research within the field of insomnia has consistently demonstrated a similar discrepancy; with patients overestimating wakefulness during the night and underestimating total sleep time, compared with polysomnography-measured sleep (Perlis et al., 1997). Pre sleep arousal has been found to negatively impact perceived sleep in insomnia populations, contributing to this inconsistency. Within CFS, it is not known whether a similar effect can be seen but it has been suggested that the discrepancy between objective and subjective sleep highlights the importance of psychological factors on sleep perception in this group (Mariman et al., 2013).

From a patient perspective poor sleep can be distressing and is viewed as difficult to manage (Gotts et al, 2015). Patients also perceive poor sleep to exacerbate symptoms and negatively impact on daytime functioning (Gotts et al, 2015). In line with this, the cognitive behavioural conceptualisation of CFS suggests that disturbed sleep, in addition to a number of other factors, may be involved in the maintenance of both physical and psychological symptoms associated with CFS (Deary, Chalder & Sharpe, 2007).
Despite the perceived impact of poor sleep on daytime symptoms and functioning, very few studies have examined this relationship empirically. A recent study provided initial evidence by examining the relationship between perceived sleep, measured using sleep diaries, and fatigue (Gotts et al., 2015). Increased duration of reported waking after sleep onset (WASO) significantly predicted increased fatigue severity. However, fatigue was measured at a single time point only and as a result may have failed to capture the fluctuating nature of fatigue in CFS. Moreover, as this study only included self-reported sleep it does not illustrate whether a similar relationship exists between sleep measured objectively and fatigue. This is an important limitation given the discrepancy between objective and subjective sleep variables highlighted in CFS (Mariman et al., 2012). Due to these limitations the relationship between sleep and fatigue in CFS remains unclear.

In fibromyalgia, which has considerable overlap with CFS (Aaron, Burke & Buckwald, 2000), research using prospective designs and daily self-report measures have examined relationships between sleep and symptoms such as pain and fatigue. This has allowed researchers to demonstrate the complexity of these relationships. For example, one study found that a significant relationship between pain and next day fatigue was fully mediated by subjective sleep quality, as measured by sleep diaries (Nicassio, Moxham, Schuman & Gevirtz, 2002). To date however, no study has utilised a similar design to examine the relationship between sleep and fatigue in CFS and it remains unknown whether sleep parameters predict next-day fatigue.

Therefore building on previous research and using a prospective daily diary approach, the current study aimed to examine the relationship between subjectively and objectively measured sleep and next day fatigue in patients with CFS. We included self-reports of sleep quality and efficiency using a sleep diary alongside objective estimations of sleep in the form of actigraphy, to determine which parameters better predict following day
fatigue. In order to provide a thorough assessment of fatigue, multiple daily assessments were included, which allowed comparisons both within and between participants enabling a close examination of the relationship between sleep and next day fatigue (Myin-Germeys, Oorschot, Collip, Lataster & van Os, 2009). The impact of pre-sleep cognitive and somatic arousal as potential predictors of subjective sleep quality and efficiency was also assessed, in line with associations seen in insomnia (Tang & Harvey, 2003). As distress is known to exacerbate the experience of symptoms in CFS (Deary et al., 2007), negative mood on waking was examined as a potential mediator of the relationship between sleep and next-day fatigue.

Method

Procedure

All participants were recruited from a specialist multidisciplinary CFS service in the United Kingdom. Ethical approval was gained from the local NHS Regional Ethics Committee (Appendix 5). Patients were eligible to take part if they had a diagnosis of CFS made by a medical professional, and if they self-identified as experiencing difficulties with sleep, including difficulties with initiating and maintaining sleep, and unrefreshing sleep. Patients were excluded if they had another sleep disorder or if they were currently taking hypnotic medications. Eligible patients were identified by members of the clinical team and study information containing the contact details of the researcher was given to potential participants, either by post or during clinical contact (Appendix 6 & 7). A total of 280 information sheets were administered, the majority of which were sent by post to patients on a waiting list for psychological therapy within the service.

Those who were interested in participating were asked to contact the researcher directly. Following initial contact, a meeting was arranged to discuss the study procedures,
complete screening measures and to gain informed consent (Appendix 8). On the day of this meeting participants began their six-day participation in the study, during which period the researcher was available for contact by telephone and email.

**Screening Measures**

Prior to participation demographic information was collected and participants were screened using a checklist to ensure that they met the Oxford Criteria for CFS (Sharpe et al., 1991). Information on current medications was also collected to ensure participants met inclusion criteria.

The Brief Sleep Interview (Wilson et al., 2010) was used to screen participants for possible sleep disorders other than insomnia prior to participation. This consists of five lead questions assessing the possible presence of narcolepsy, sleep breathing disorder, periodic limb movement disorder/restless leg syndrome, circadian rhythm disorders and parasomnia. Additional supplementary questions are asked if any of these sleep disorders are suspected following a positive response to the lead question. If there was any uncertainty about including potential participants, decisions were made by consensus in the research team.

In addition to the above screening measures, a number of additional measures were also included in order to fully describe the current sample in terms of sleep variables, anxiety, depression and fatigue:

The Sleep Condition Indicator (Espie, Kyle, Hames, Gardani, Fleming & Cape, 2014) was administered to measure ongoing sleep difficulties. It comprises eight questions reflecting sleep latency and wake after sleep onset (WASO) duration, sleep quality, duration of difficulties with sleep, concern about sleep and daytime dysfunction attributed to poor
sleep. Participants are asked to rate each of these domains on a typical night in the last month using a five-point scale with lower scores indicating greater difficulties in each domain. The SCI produces a score of 0 to 32, with scores less than 16 indicating probable insomnia disorder (Espie et al., 2014). The SCI has good levels of internal consistency (α=0.865) and concurrent validity (correlation with Pittsburgh Sleep Quality Index, Buysse et al., 1989, r=-0.734), and has shown to be a sensitive as a measure of treatment outcome. We measured attitudes and beliefs about sleep using the Dysfunctional Beliefs and Attitudes about Sleep Scale: Brief Version (DBAS16; Morin et al., 2007), a validated questionnaire comprising 16 statements. These items measure four domains including consequences of insomnia, worry about sleep, sleep expectations, and medication. Items are rated on a 10-point Likert scale ranging from 0 (strongly disagree) to 10 (strongly agree). Total scores are averaged to produce a mean item score, with a cut-off of 3.8 indicating clinical levels of dysfunctional beliefs about sleep (Carney et al., 2010). The DBAS-16 has been found to be reliable, as evidenced by adequate internal consistency (α = 0.77) and temporal stability (r = 0.83).

Levels of symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) which contains 14 items, assessing two subscales of anxiety and depression. Items are rated on a four point scale from 0-3 (not present – substantial), and a total score on each subscale is calculated. A score of 11 or more indicates clinically significant difficulties. The HADS is commonly used in CFS studies, and has good internal consistency (mean Cronbach α > 0.8 for both subscales) and concurrent validity (agreement with clinician ratings of anxiety: r = 0.54 and depression: r = 0.79).
To measure fatigue the Chalder Fatigue Scale (Chalder et al., 1993), a widely used 11-item measure of mental and physical fatigue severity, was administered. The 11-item version has been found to be valid and reliable when used with CFS patients (Morriss, Wearden & Mullis, 1998). Bimodal scoring was used with a score of 1 given for items rated ‘more than usual’ or ‘much more than usual’. Items rated as ‘no more than usual’ or ‘less than usual’ were given a score of 0. Total scores could range from 0 to 11, with scores of 4 or more indicating clinical caseness.

**Daily Diary Design and Measures**

**Actigraphy**

To provide objective measures of sleep, participants were instructed to wear a CamNtech MotionWatch 8 actigraph watch, a lightweight and unobtrusive device similar to a wristwatch. The device includes a digital accelerometer which enables, based on movement, the differentiation of probable sleep and wake states for each 60 second period of recording. Participants began wearing the device at 6pm on the day of their meeting with the researcher, and wore this continuously over the following six days. Participants were also asked to press the event marker on the device when they got into bed at night, and when they got out of bed the following morning. The following objective sleep variables were extracted, using CamNtech MotionWatch 8 software: total sleep time, sleep efficiency (proportion of time in bed spent asleep) and sleep fragmentation index (reflecting time spent mobile during the sleep period). Actigraphy has been shown to have good agreement with polysomnography recorded sleep parameters (Kushida et al., 2001).
Daily Diaries

Participants were asked to record their subjective experiences of sleep by completing the waketime version of the Consensus Sleep Diary (CSD; Carney et al., 2012) each morning on waking. The CSD was developed through collaboration between experts within the insomnia field with patient input, with the aim of standardising subjective sleep measurement. The CSD asks questions about bed-time, latency to fall asleep, duration of WASO, and rising time. From this self-reported data, perceived total sleep time and sleep efficiency can be calculated. Perceived quality of sleep during the previous night is rated on a five point scale from ‘very poor’ to ‘very good’. An additional item taken from the extended version of the CSD was included, also rated on a five-point scale, which measured the extent to which participants felt ‘refreshed’ or ‘rested’ on waking.

Participants completed two additional visual analogue scale (VAS) items measuring perceived pre-sleep cognitive arousal (“As you were trying to go to sleep last night, did thoughts keep running through your mind?”) and somatic arousal (“As you were going to sleep last night, did you experience a jittery, nervous feeling in your body?”). Scales ranged from ‘very little’ to ‘very much’. These items were adapted from a previous daily diary study examining sleep in chronic pain (Tang et al., 2012), and are similar to items on the Pre Sleep Arousal Scale (PSAS; Nicassio et al., 1985).

In order to measure symptoms, participants were asked to complete the Daytime Insomnia Symptom Scale (DISS; Buysse et al., 2007) at four time points during each day; on waking, 12noon, 6pm and at bedtime. The DISS is a validated measure designed for daily diary studies to characterise daytime insomnia symptom levels in real-time. It consists of 20 items, has four subscales and has been validated within normal sleepers and patients with
primary insomnia previously. For the current analyses the fatigue subscale was derived for each time point by summing scores on items measuring the extent to which participants felt ‘sleepy’, ‘fatigued’ and ‘exhausted’, providing the primary outcome measure within the study. A negative mood score was derived by summing scores on items measuring feeling ‘sad’, ‘tense’, ‘anxious’, ‘stressed’ and ‘irritable’ completed each morning on waking. Each item is rated on a VAS scale from 0 (very little) to 100 (very much).

Participants were asked to record the time that they completed the sleep diaries and each of the symptom ratings. Any data points completed more than one hour outside of the requested time point were excluded from analyses.

**Participants**

Forty-two individuals contacted the researcher with an interest in participating. Seven were not eligible to take part due to suspected additional sleep difficulties including sleep phase shift disorder (2), restless legs syndrome (2), sleep apnoea (2) and night terrors (1). Four were excluded due to taking hypnotic medications, and one due to uncertainty around their CFS diagnosis. Three individuals were too unwell or withdrew prior to participating.

Twenty-seven eligible participants completed the six-day study period. Their mean age was 49.7 (SD=12.5) and 24 (89%) were female. Eighty-nine percent of the sample defined themselves as White British, two as Black British, and one as being from a mixed White and Black Caribbean ethnic background. Twenty six and 22% were in employment full time and part time respectively, 37% were unable to work due to ill health, and the remaining 15% were retired. The mean illness duration of the sample was 141 months (SD= 144 months). Descriptive information on the initial validated measures is shown in Table 1.

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3 See Paper 3 for a discussion of data collected but not used in current analyses
Table 1: Descriptive information from initial measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean</th>
<th>Standard Deviation</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Chalder Fatigue Scale</td>
<td>8.8</td>
<td>3.6</td>
<td>85.2%</td>
</tr>
<tr>
<td>HADs Anxiety</td>
<td>9.8</td>
<td>5.3</td>
<td>42.3%</td>
</tr>
<tr>
<td>HADs Depression</td>
<td>8.4</td>
<td>4.3</td>
<td>30.8%</td>
</tr>
<tr>
<td>SCI</td>
<td>8.6</td>
<td>4.0</td>
<td>96.2%</td>
</tr>
<tr>
<td>DBAS</td>
<td>6.2</td>
<td>1.3</td>
<td>100%</td>
</tr>
</tbody>
</table>

In terms of condition management, 37% of the sample were currently undertaking some form of self-directed activity management, and a further 19% had received input from a health care professional regarding managing activity. Fifteen percent had received graded exercise therapy and 11% had previously received CBT. In terms of medication, 15% were taking SSRIs and 8% were taking tricyclic medications. No participant had undergone sleep focused therapy, but three participants (11%) had previously received sleep hygiene advice from a health care professional.

**Statistical Analysis**

All analyses were performed in Stata version 13 (Stata corporation, 2013). First, the main outcome variables, mean fatigue across each day, and variability (standard deviation) in fatigue across each day were calculated for each participant. These were included in further analyses if participants had completed at least three of the four daily symptom ratings.

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4 See Paper 3 for a discussion of this finding
5 The use of standard deviation as a measure of fatigue variance is discussed in Paper 3
As fatigue mean scores and variability across the day were used as outcomes, the daily diary design had a 2-level hierarchical structure, with days nested within participants. Multilevel modelling was used to account for the clustering in outcomes within participants, and all analyses were performed using maximum likelihood estimation, which accounts for missing data under a missing at random assumption.

In the first models, subjective sleep efficiency, quality, and feeling refreshed, were entered as predictors with fatigue mean levels and variability as outcomes, using separate models for each outcome. To account for possible confounding, illness duration at baseline was included as an additional covariate in each of the models. Separate models were then used to examine objective sleep variables; total sleep time (TST), sleep efficiency (SE) and sleep fragmentation index as predictors of next-day fatigue. Models examining whether pre-sleep cognitive and somatic arousal predicted sleep variables associated with fatigue were also examined.

To test the effect of negative mood on waking as a potential mediator of the relationship between subjective sleep and fatigue, we used the difference in coefficients approach\textsuperscript{6}, as outlined in Bolger and Laurenceau (2013). This involved first examining whether subjective sleep variables predicted negative mood on waking. Following this, the direct effect of subjective sleep variables on next day fatigue when negative mood on waking was added as a variable, is compared to the total effect when negative mood is not in the model. The difference between these two effects is an estimate of the indirect effect.

\textsuperscript{6} Limitations of this method are discussed in Paper 3
Results

Descriptive Sleep Data

All 27 participants completed the six-day study period and completion rate for fatigue ratings was 95.7%. Descriptive information on nightly subjective ratings of sleep, derived from sleep diaries and objective measurements from actigraphy are shown in Table 2.

Table 2: Descriptive sleep data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data type</th>
<th>Mean</th>
<th>Min</th>
<th>Max</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset latency (mins)</td>
<td>Subjective</td>
<td>34 mins</td>
<td>0 mins</td>
<td>180 mins</td>
<td>39 mins</td>
</tr>
<tr>
<td></td>
<td>Objective</td>
<td>33 mins</td>
<td>0 mins</td>
<td>295 mins</td>
<td>42 mins</td>
</tr>
<tr>
<td>Total sleep time (mins)</td>
<td>Subjective</td>
<td>428 mins</td>
<td>120 mins</td>
<td>635 mins</td>
<td>103 mins</td>
</tr>
<tr>
<td></td>
<td>Objective</td>
<td>459 mins</td>
<td>247 mins</td>
<td>655 mins</td>
<td>81 mins</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>Subjective</td>
<td>73.7%</td>
<td>20.7%</td>
<td>99.0%</td>
<td>16.2%</td>
</tr>
<tr>
<td></td>
<td>Objective</td>
<td>81.1%</td>
<td>45.7%</td>
<td>95.3%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Sleep fragmentation index</td>
<td>Objective</td>
<td>26.7</td>
<td>2.5</td>
<td>87.1</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Preliminary Analysis

Prior to beginning the main analyses, illness duration was examined as a predictor of the main outcome variables, to determine whether illness duration might confound the relationship between sleep and fatigue. For fatigue mean outcomes, illness duration was not a significant predictor (coefficient=0.013, p=0.515). For variance in fatigue, illness duration was found to be a significant predictor (coefficient=-0.016, p=0.027), with longer illness duration associated with reduced variance in fatigue across the day. Consequently, illness duration was included as a covariate in all subsequent analyses.

7 The inclusion of illness duration as a possible confounder is discussed in Paper 3
Predicting Daily Mean Fatigue and Variability

Models examining the association between subjective and objective sleep variables and following-day fatigue mean and variance were calculated. Separate models were calculated for each predictor.

Subjective Sleep Variables as Predictors

Table 3 shows each of the subjective sleep predictors, coefficients of the predictors (C), confidence intervals (CI), standard error (SE), number of observations (n) and the significance level (p) for both mean fatigue and fatigue variance outcomes.

Table 3: Subjective sleep variables as predictors of next day fatigue mean and variance

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Fatigue outcome</th>
<th>C</th>
<th>95% CI</th>
<th>SE</th>
<th>p</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality</td>
<td>Mean</td>
<td>-4.613</td>
<td>-6.676, -2.586</td>
<td>1.052</td>
<td>&lt;0.001</td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.789</td>
<td>-0.313, 1.89</td>
<td>0.562</td>
<td>0.161</td>
<td>155</td>
</tr>
<tr>
<td>Feeling refreshed</td>
<td>Mean</td>
<td>-6.997</td>
<td>-9.416, -4.578</td>
<td>1.234</td>
<td>&lt;0.001</td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>1.992</td>
<td>0.700, 3.283</td>
<td>0.658</td>
<td>0.003</td>
<td>155</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>Mean</td>
<td>-0.204</td>
<td>-0.044, 0.003</td>
<td>0.012</td>
<td>0.089</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.009</td>
<td>-0.002, 0.021</td>
<td>0.006</td>
<td>0.102</td>
<td>144</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>Mean</td>
<td>-0.205</td>
<td>-0.358, -0.052</td>
<td>0.078</td>
<td>0.008</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.087</td>
<td>0.011, 0.162</td>
<td>0.039</td>
<td>0.025</td>
<td>144</td>
</tr>
</tbody>
</table>

Poorer subjective sleep quality, lower sleep efficiency, and feeling less refreshed on waking were all significantly associated with higher following day mean fatigue. Feeling less refreshed and lower sleep efficiency were both associated with reduced variance in next day fatigue.
Objective Sleep Variables as Predictors

Table 4 shows objective sleep variables as predictors of fatigue mean and variance, illustrating that fatigue (mean and variance) was not predicted by objective sleep variables.

Table 4: Objective sleep variables as predictors of next day fatigue mean and variance

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Fatigue outcome</th>
<th>C</th>
<th>95% CI</th>
<th>SE</th>
<th>P</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (mins)</td>
<td>Mean</td>
<td>-0.006</td>
<td>-0.030, 0.018</td>
<td>0.013</td>
<td>0.609</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.009</td>
<td>-0.021, 0.003</td>
<td>0.006</td>
<td>0.167</td>
<td>153</td>
</tr>
<tr>
<td>Sleep fragmentation</td>
<td>Mean</td>
<td>0.022</td>
<td>-0.179, 0.224</td>
<td>0.103</td>
<td>0.830</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>-0.005</td>
<td>-0.103, 0.94</td>
<td>0.050</td>
<td>0.922</td>
<td>153</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>Mean</td>
<td>-0.081</td>
<td>-0.374, 0.211</td>
<td>0.149</td>
<td>0.586</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.011</td>
<td>-0.129, 0.151</td>
<td>0.071</td>
<td>0.876</td>
<td>153</td>
</tr>
</tbody>
</table>

Negative mood as a mediator of the relationship between subjective sleep and fatigue

To examine the role of negative mood as a potential mediator of the association between subjective sleep variables and fatigue, subjective sleep variables were first examined as predictors of negative mood on waking. Negative mood on waking was associated with sleep quality (coefficient = -5.418, p< 0.001) feeling refreshed (coefficient = -6.701, p<0.001) and sleep efficiency (coefficient = -0.177, p= 0.039). Negative mood was not associated with total sleep time (coefficient = -0.021, p= 0.112).

Following this, subjective sleep variables that were significant predictors of fatigue mean and variability were examined, with and without negative mood as an additional predictor within the models, in order to examine the proportion of the total effect accounted for by negative mood. Table 5 shows these analyses for fatigue mean and variance outcomes.
In each of these models increased levels of negative mood on waking was related to increased mean fatigue across the day, and decreased variance in fatigue. The highest level of mediation (30.1%) was seen for the relationship between feeling refreshed and following day fatigue variance.
Predicting subjective sleep using pre-sleep variables

Pre-sleep cognitive and somatic arousal were next examined as predictors of sleep variables which were found to be associated with following day fatigue mean and variance, as shown in Table 6:

**Table 6: Pre-sleep cognitive and somatic arousal as predictors of subjective sleep variables**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predictor</th>
<th>C</th>
<th>95% CI</th>
<th>SE</th>
<th>p</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality</td>
<td>Cognitive arousal</td>
<td>-0.009</td>
<td>-0.014, -0.004</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>Somatic arousal</td>
<td>-0.012</td>
<td>-0.018, -0.006</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>161</td>
</tr>
<tr>
<td>Feeling refreshed</td>
<td>Cognitive arousal</td>
<td>-0.004</td>
<td>-0.009, 0.001</td>
<td>0.002</td>
<td>0.102</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>Somatic arousal</td>
<td>-0.006</td>
<td>-0.012, -0.001</td>
<td>0.002</td>
<td>0.015</td>
<td>161</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>Cognitive arousal</td>
<td>-0.151</td>
<td>-0.231, -0.070</td>
<td>0.041</td>
<td>&lt;0.001</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td>Somatic arousal</td>
<td>-0.119</td>
<td>-0.216, -0.022</td>
<td>0.049</td>
<td>0.015</td>
<td>147</td>
</tr>
</tbody>
</table>

Higher levels of cognitive and somatic arousal were associated with poorer sleep quality and sleep efficiency. Higher levels of somatic arousal, but not cognitive arousal, were associated with feeling less refreshed on waking.
Discussion

Although sleep difficulties are commonly reported in CFS, the relationship between sleep and subsequent fatigue in CFS has previously been unclear. The current research builds on the limited previous research by using a daily diary approach enabling a close examination of the link between sleep and fatigue over a six-day period, with comparisons made both between and within participants across study days. Importantly, this study demonstrated that perceived sleep quality, feeling refreshed on waking and perceived sleep efficiency were important predictors of following-day fatigue levels. In contrast, sleep variables estimated objectively using actigraphy did not show a similar relationship with fatigue. These findings illustrate the importance of sleep perception in the experience of fatigue in CFS.

Pre-sleep cognitive and somatic arousal were shown to predict perceived sleep quality and efficiency, and somatic arousal also predicted perceiving sleep to be unrefreshing, a commonly reported difficulty in CFS. To our knowledge, this is the first time these associations have been found in CFS and are key findings given the apparent importance of subjective sleep in the experience of fatigue. In line with this finding, previous research in non-clinical populations has found that both cognitive and somatic arousal can have a negative effect on perceptions of sleep efficiency and quality (Tang & Harvey, 2003). Although not measured in real time within the current study, it is possible that anxiety about sleep at bedtime contributed to high levels of pre-sleep arousal. This in turn could lead to poor perceived sleep, due to increased attention to cues indicating wakefulness during the night in line with processes hypothesised in insomnia populations (Harvey, 2002). In support of this proposition, all participants in our sample held unhelpful beliefs about sleep within the clinical range, including fears that poor sleep will have a negative impact on daytime functioning.
Perceiving sleep to be unrefreshing and inefficient was related to negative emotions on waking. In turn, negative mood on waking was shown to partially mediate the relationship between subjective sleep variables and next day fatigue levels. Negative emotions may have influenced the experience of symptoms through a number of mechanisms. Anxiety or sadness following poor sleep may result in a perceived need to limit activity, and subsequently increase attention to fatigue, due to a lack of distraction from symptoms. High levels of anxiety about symptoms may also result in hypervigilance to fatigue. Any symptoms subsequently noticed may then be attributed to poor sleep, in line with similar processes hypothesised within insomnia (Harvey, 2002).

The mediational role of negative mood could be viewed as being fairly low, with around 15 to 30% of the effect of perceived sleep on fatigue accounted for by negative mood. This is likely to be due to additional factors such as symptom focus or activity, influencing this relationship, and because ratings of negative mood within the current study were general in nature. A more specific measure of anxiety or hopelessness related to sleep, symptoms or functioning could have provided more information about the mediational role of these factors specifically. This is potentially an area for further research to explore.

Importantly, the current study is the first to demonstrate the impact of perceived sleep on variability in next-day fatigue in CFS, with unrefreshing sleep predicting reduced variability in fatigue across the following day. Negative mood again mediated this relationship. In addition to increasing attention to symptoms, negative mood following unrefreshing sleep may reduce variance in fatigue if individuals limit their activity levels due to feeling sad or hopeless, or because of anxiety about exacerbating symptoms. It has been found previously that some individuals with CFS can have particularly low levels of activity (Evering at al., 2011) and that this can be related to beliefs that activity will increase fatigue (Vercoulen et al., 1997; Nijs et al., 2013). Limiting activity therefore can be seen as a safety
behaviour which may prevent individuals from disconfirming unhelpful beliefs about the impact of activity following a night of unrefreshing sleep (Harvey, 2002). In addition, reduced activity is likely to further impact mood and fatigue levels, increase physical deconditioning, and decrease sleep quality (Singh et al., 1997) feeding into the maintenance of the condition (Deary et al., 2007; Clark & White, 2005).

Illness duration was also a significant predictor of variability in fatigue, with a longer duration related to fatigue being more fixed across the day. One potential explanation for this finding is that unhelpful illness-related beliefs may become strengthened over the course of the illness through attentional and attributional biases, and because safety behaviours may prevent disconfirmation of these beliefs (Deary et al., 2007). As a result, expectations about fatigue being unchangeable, hopelessness related to this, and decreased activity and increased attention to symptoms, may result in a more fixed perception of symptoms across the day.

Taken together, the results of the current study indicate that a number of psychological factors are relevant to the experience of both sleep and subsequent fatigue. These include pre-sleep cognitive and somatic arousal, perceptions of sleep quality and efficiency, and negative mood on waking. Moreover, although not examined directly within the current study, specific sleep-related anxiety, attentional and attributional biases, and safety behaviours such as decreasing activity following poor perceived sleep may also be relevant to sleep difficulties in this group. Further daily diary research could explore how these factors may contribute to the relationship between subjective sleep and fatigue in CFS. For example, by examining the impact of day to day variations in sleep-related anxiety on pre-sleep arousal. Our findings have important implications in that each of the identified factors can be targeted specifically within CBT for insomnia (CBT-I). CBT-I has previously been used to treat sleep difficulties in chronic pain conditions and can be effective in
improving perceived sleep quality and efficiency (e.g. Currie et al., 2000) and in reducing daytime fatigue (Martinez et al., 2014). This approach includes psycho-education about sleep, behavioural components including sleep restriction and stimulus control, relaxation strategies in order to target pre-sleep arousal, sleep hygiene and cognitive restructuring of unhelpful beliefs about sleep. Based on the findings of the current study, it seems likely that CBT-I would be helpful for those who are experiencing sleep difficulties in addition to existing interventions for CFS.

The current study has some limitations. Firstly, a limitation of the mediation analyses used is that the mediator, in this case negative mood on waking, was measured at the same time point as the subjective sleep variables. This allows for the possibility that negative mood impacted on subjective ratings of sleep, rather than being as a result of poor perceived sleep. Moreover, the mediation analyses used assumes that there are no unmeasured confounds between mediators and the outcomes, which could account for the relationship (Wearden & Emsley, 2013). This possibility was minimised by including illness duration as an additional covariate within the analyses in order to rule out this factor as a confounder. It is possible however, that other variables could act as confounders, although this may reflect a limitation of any research examining association between variables, given that for pragmatic reasons it may not be possible to measure all possible confounders. However, consequently the findings should be considered with these possibilities in mind.

A further limitation is that it well established that actigraphy can underestimate sleep onset latency and WASO, especially in quiet wakefulness, and can therefore overestimate sleep efficiency. This has been replicated in CFS samples (Creti et al., 2010). Actigraphy also does not provide measurement of sleep architecture and therefore we were not able to examine how this might relate to next day fatigue. Consequently although the use of actigraphy allowed participants’ sleep to be examined within their home setting, providing an
ecologically valid estimation of objective sleep variables, the findings should be viewed with an awareness of the limitations of this method.

As the research was sleep focused it is likely individuals who chose to participate were experiencing poorer sleep, or were more concerned by their sleep than other CFS patients, which is reflected by 100% of the sample meeting clinical cut offs on the Dysfunctional Beliefs and Attitudes about Sleep Scale (Morin et al., 2007). It is unclear whether similar associations between subjective sleep and fatigue would be seen in CFS patients less concerned about their sleep. However, it is clear that for a proportion of CFS patients at least, the association between subjective sleep and following day fatigue is important and an area in need of further research. Lastly, it was not possible to screen all participants with polysomnography in order to exclude the possibility of additional sleep disorders. However, all participants had been diagnosed with CFS within a specialist service and the possibility of the presence of additional sleep disorders was minimised by screening using the Brief Sleep Interview (Wilson et al., 2010) prior to participation.

In conclusion, this is the first study to examine the relationship between sleep and next-day fatigue in CFS using a daily diary approach. We found that subjective, and not objective sleep variables were associated with next-day fatigue and that negative mood partially mediated these relationships. We also showed that increased levels of pre-sleep arousal can be associated with poor perceived sleep in this group. These findings suggest that sleep specific interventions used within insomnia may be helpful in addition to existing interventions in CFS for those experiencing sleep difficulties. Further research should aim to examine the utility of such approaches in this patient group.
References


Introduction

Chronic Fatigue Syndrome (CFS) is a complex condition and a number of physical and psychological factors, including sleep difficulties, are currently understood to be involved in maintaining the condition (Deary et al., 2007). Within CFS however, there has previously been little focus on sleep and there is an absence of empirical evidence demonstrating that sleep difficulties can exacerbate CFS symptoms such as fatigue. In order to address this lack of evidence, the empirical research presented within this thesis aimed to examine how sleep might relate to the experience of fatigue in this group. The systematic review conducted aimed to explore whether the current evidence-based interventions for CFS can improve sleep, given the perceived importance of sleep in the maintenance of the condition.

The aim of this paper is to reflect on completing this empirical research and systematic review. This will include reflections on the process, the strengths and limitations of the review and empirical research, and the implications of the work completed.

Rationale for topic choice

Prior to beginning training the author had worked as an assistant psychologist within a CFS service. This involved facilitating group programmes for CFS patients during which it was often evident that sleep was a significant concern for patients and was viewed as exacerbating other symptoms. From this experience and through literature searching, the author was aware that there was very little empirical evidence for the role of sleep in CFS, or for how sleep could be treated in this condition. Therefore it was perceived that completing both an empirical piece of research and a systematic review in this area would fill in some gaps in the current evidence base.
Reflections on Paper 1: Systematic Review

Rationale for the review

There is substantial evidence for Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) for improving a number of different outcomes including fatigue and functioning in CFS. There has not however, previously been a focus on sleep as an outcome. As a result it was felt that identifying and synthesising CBT and GET studies that include sleep as an outcome would be useful for the CFS field, particularly as there has been an increasing interest in sleep in CFS in recent years (e.g. Mariman et al., 2012; Gotts et al., 2014).

Whilst conducting the review, a Cochrane Review of GET in CFS (Larun et al., 2015) was published and this had included sleep as an outcome in meta-analyses. Initially this felt challenging because it was thought this might mean that the focus of the review would have to be adapted. However, whilst reading the Cochrane Review it was clear that the focus of the reviews differed. Firstly the Cochrane review focused on a number of outcomes of which sleep was one, which meant that the discussion of issues related to the effectiveness of GET on sleep was limited. Secondly, the review classified some interventions, for example ‘Pragmatic Rehabilitation’ (PR) as being GET, when these interventions differed substantially from other GET interventions, both in terms of the content and delivery. Therefore, it was felt that a fuller description of these issues within a narrative synthesis would be helpful. Lastly, as the Cochrane review was focused on GET, it did not identify studies of CBT interventions, which was felt to be a strength of the current review as it allowed comparisons with GET interventions.
Search Strategy

It was decided that a systematic review would be appropriate for identifying articles for inclusion due to this method minimising the possibility of bias in the study selection process. It was felt that having fairly inclusive criteria and including non-randomised studies as well as randomised controlled trials (RCTs) would allow identification of all of the available literature.

Within searches, the term “sleep” and related search terms were not included because although our study aimed to identify studies including sleep outcomes, initial scoping searches had identified that in studies using sleep as an outcome, this was secondary to other outcomes and was not described within study titles or abstracts. As a result, searching for the term “sleep” was found not to be an effective way of identifying eligible studies within database searches. Consequently, as a way of identifying studies including sleep outcomes full text articles were obtained for all CBT and GET intervention studies in adults with CFS, and the methods sections of each of these were reviewed. Although this method was time consuming, limiting inclusion to studies with a sleep-related outcome meant that there was little uncertainty about whether to include or exclude articles.

Only published articles were included, and unpublished articles within the ‘grey literature’ were not. This allowed for bias as it is more likely that intervention studies with significant results will be published (Easterbrook et al., 1991), potentially leading to exaggerated estimates of intervention effectiveness (McAuley et al., 2000). However within the review, conclusions about the effects of CBT and GET on sleep could only usually be made based on the large, high quality randomised controlled trials (RCTs) included. This was due to smaller studies allowing for a greater possibility of bias due to less rigorous designs and having smaller sample sizes, limiting statistical power to detect effects particularly for sleep as a secondary outcome. It was thought that it would be unlikely that large high quality studies
would have remained unpublished. Therefore it was decided not to include unpublished studies as the conclusions that could be made based on any unpublished research may have been limited.

Studies including adolescents and children with CFS were not included, which meant that a number of studies that may have included sleep as an outcome were excluded. However, interventions used in this group may not have been directly comparable with CBT and GET in adults as they differed substantially in delivery and focus (for example, family focused CBT). Therefore it was felt that excluding studies of children and adolescents would mean that included articles (i.e. only adults) would be more comparable with one another, which felt important given the heterogeneity in delivery even in adult studies.

Quality Assessment

Quality of included articles was assessed in order to provide evidence on the risk of bias within each of the studies and to evaluate and discuss possible conclusions that could be made from each of the studies, based on their quality (Jüni et al., 2001; Popay et al., 2006). The Downs and Black (1998) Quality Assessment tool was selected for a number of reasons. Firstly, it had been highlighted as one of the ‘best’ tools for assessing quality in randomised and non randomised studies (Deeks et al., 2003), and has good reliability and validity. The checklist is relatively long and time consuming, which could be viewed as a limitation but for the purpose of the review this proved to be an advantage as using the tool required a very detailed inspection of included articles which was helpful in identifying potential sources of bias that were important to discuss within the narrative synthesis. Facilitating this critical approach within a narrative synthesis can increase the robustness of conclusions (Popay et al., 2006) and therefore using a comprehensive tool was felt to be a strength of the review. Each question within the checklist is very specific which is reflected in its length. It was thought that this would increase reliability particularly compared to
other checklists for which the items were thought to be more ambiguous and open to interpretation. This is reflected in the high level of inter-rater agreement achieved during quality assessment.

**Data Synthesis**

A narrative synthesis approach was used, which aimed to combine and synthesise the findings of included studies in line with guidance on using this approach (Popay et al., 2006). This included developing an understanding of how CBT and GET interventions might influence sleep, and how conditions related to the delivery of the intervention and the sample used might influence effectiveness (Popay et al., 2006). This also included evaluating possible conclusions based on the quality of included studies (Popay et al., 2006). Using this narrative synthesis approach allowed a full discussion of each of the relevant issues within the review. The possibility of completing a meta-analysis was considered, but because the review focused on two different interventions and because intervention delivery differed substantially across studies, it was not felt that combining the included studies within a meta-analysis would be meaningful or helpful. Such heterogeneity however, can be combined in a more meaningful way within a narrative synthesis (Popay et al., 2006). It also felt particularly important to provide a different focus to the recent Cochrane review of GET in CFS and to provide a fuller understanding of differences in sleep outcomes in GET studies.

There were however challenges in summarising information concisely in a narrative synthesis, given that there were often several factors that may have contributed to inconsistencies in findings between included studies. This reflects that in literature reviews it can be difficult to summarise information in a meaningful way whilst acknowledging potential limitations and disparities. As a way of addressing this limitation, tables and forest plots were presented as these allowed the reader to see information about confidence
intervals clearly and concisely. Evans (2002) highlighted that providing such descriptive information can be beneficial within a systematic review, but highlighted the importance of interpretation in addition to descriptive information within a narrative synthesis. It was felt that a strength of the review was that it included both of these elements.

The challenge of summarising heterogeneous studies and their findings concisely reflects a broader difficulty within clinical research, where the need for clear clinical guidelines means that limitations of and inconsistencies between studies cannot always be acknowledged fully (Ioannidis & Lau, 1999; Woolfe et al., 1999). However, despite the limitations in this methodology and the difficulty in summarising information concisely, from a pragmatic perspective, it is acknowledged that there is a need for conclusions to be made, based on the available evidence in order to move forward both in terms of research and clinical practice. Completing this review increased the author’s awareness of these issues substantially and highlighted the need to be mindful of the limitations of literature reviews and meta-analyses.

An aim of the review was to gain information on the effects of including sleep management techniques within interventions. This aim depended wholly on this information being reported accurately and in sufficient detail. Recent guidance has suggested that intervention studies should improve completeness of their reporting in order to allow accurate replication of interventions (Hoffman et al., 2014). Implementation of this guidance could potentially increase the robustness of reviews of intervention effectiveness. However, most of the studies included in the review did not provide sufficient detail, and therefore it was not possible to make robust conclusions about the importance of including sleep management techniques in interventions. However, the difficulties addressing this review aim highlighted that further research examining this issue would be beneficial.
The inclusion criteria used in the review were broad and allowed inclusion of a range of methodological designs including randomised controlled trials, non-randomised studies and a case study. These inclusive criteria aimed to identify all of the available evidence in an area of limited research. However, the inclusion of studies with low methodological quality meant that although these studies could be described, robust conclusions could not be drawn based on their findings. Therefore their inclusion could be viewed as having little utility, and may be a limitation of the inclusion criteria used. On reflection this has increased the author’s awareness of the need to carefully consider inclusion criteria during reviews, and in particular to consider the rationale for including lower quality studies.

**Conclusions**

CFS is a multi-factorial condition, and the measurement of outcome can therefore be complex (Hayward et al., 2012). This may be an important reason that sleep has not been widely used as an outcome in addition to the absence of empirical research demonstrating that sleep can maintain CFS. Another factor that may be related to the lack of focus on sleep is that within the current financial climate and health service provision, there has been an increased focus on using outcomes that reflect functioning, including ability to maintain employment. However, CFS can have a poor prognosis (Joyce et al., 1997) and ensuring that interventions are effective at treating potential maintenance factors, including sleep, is likely to be important in enabling individuals with CFS to maintain functioning and employment.

The process of completing the review was challenging as the author had little previous experience of completing systematic reviews and because it at times felt that possible conclusions based on the available evidence were limited due to disparities between studies. However, through completing the narrative synthesis and attempting to understand disparities it became clear that a number of conclusions and implications could
be drawn from this process, particularly in relation to implications for further research. Therefore overall, whilst at times the review felt challenging, it was viewed by the author as a useful contribution to the CFS literature. The review also provided a learning experience including increasing the author’s awareness of the need to critically evaluate evidence for intervention effectiveness. This is viewed as important whilst working within the scientist practitioner role of a clinical psychologist.

Reflections on Paper 2: Empirical Research

Rationale for the research

Prior to starting the review, a more general review of sleep in CFS had been published (Mariman et al., 2012). This proved helpful whilst considering the focus of the review and empirical paper as it highlighted that psychological factors may be involved in the experience of sleep difficulties in this group. As research within the CFS field is limited, the author, guided by supervisors considered how psychological factors known to be important in insomnia might be relevant in CFS. This included evaluating the relative importance of subjective and objective sleep in the experience of fatigue in CFS and examining the importance of pre-sleep arousal.

Methodology

Design

It was thought that the relationship between sleep and fatigue was likely to be a complex one, particularly given the fluctuating nature of CFS. Therefore it was felt that an Experience Sampling Methodology (ESM) might allow the research to capture this complexity, because these designs allow comparisons both between and within
participants across study days. ESM studies are also advantageous as data are collected in real time and are therefore less susceptible to memory biases (Santangelo et al., 2013), such as information consistent with current mood state being recalled more readily. A similar design had previously been used to test the relationship between sleep and next-day pain in a chronic pain sample, with some clinically very interesting findings (Tang et al., 2012). Therefore it was felt that using this design would be very informative given the lack of research in this area. However from the planning stage onwards it was acknowledged that it would be challenging to complete the project within the required timescales for ClinPsyD research.

Recruitment and Data Collection

Recruitment targets were based on other published ESM studies (e.g. Palmier-Claus et al., 2012) with the acknowledgement that using day level variables (fatigue mean and variability) as outcomes, rather than individual momentary data points would reduce statistical power to detect associations between sleep and fatigue. Therefore the recruitment target was based on the maximum that it was considered possible to achieve within the timescales of the ClinPsyD programme. Recruitment levels were around 10% of the total number of participant information sheets distributed which may reflect that some patients approached were not experiencing sleep problems or because study procedures, which involved a considerable participant burden, may have deterred some potential participants.

During recruitment there was a significant amount of travel involved, to participants’ homes across the North West region which was time consuming. This was particularly difficult as the researcher met with participants on two occasions; at the beginning and end of their participation. Data entry was also time consuming as it involved physically measuring visual analogue scales in addition to entering other questionnaire data. This
meant that achieving the recruitment and participation target was challenging and required careful planning of the available research time.

Whilst recruiting initial participants the researcher became aware that a large amount of information was provided during the initial session. This was an important consideration due to memory difficulties being frequently experienced in CFS (Fukuda et al., 1994). This led to the creation of a participant instruction sheet (Appendix 9) containing the information given in the initial session in written form. Although this was viewed as helpful for participants, using this during the study procedure required additional administration due to requiring approval from both University and NHS ethics committees (Appendix 10). This highlighted that despite careful planning of the research, potential difficulties cannot always be anticipated.

One participant was identified as requiring further assessment regarding possible restless legs syndrome whilst participating. This was identified through initial screening with the Wilson Sleep Interview (Wilson et al., 2010) and by actigraphy data which showed severely disrupted sleep rhythms on nights when the participant reported experiencing symptoms. This was discussed with academic and field supervisors and this individual was excluded from the research, and a letter was written to the participant’s medical consultant to highlight concerns and to suggest further investigations. This possibility had not been planned for, however whilst completing initial screening measures the researcher began to have concerns and informed the participant that any concerns resulting from the research would be shared with the medical team.

At times meeting with participants could feel challenging due to participants experiencing distress and because the researcher was aware that their current waiting times for psychological therapy within the CFS service could be considerable. As a result it was important for the researcher to maintain boundaries and work within their role as a
researcher, rather than to draw on therapeutic skills gained during clinical training and 

while working in CFS. This could feel personally and professionally very challenging at 
times.

Sample

Data on socio-demographic status were not collected, however the researcher was aware 
that the majority of participants were well educated and lived in fairly affluent areas which 
may reflect that individuals with a higher level of education may be more likely to 
participate in CFS research (Wessely et al., 1997). This may have been particularly 
important given the participant burden required by this research. It has been suggested 
that although the majority of those diagnosed with CFS are female and middle class, this 
may reflect that these groups are more likely to visit their GP, and subsequently gain a 
diagnosis, than men or those from lower socio-economic groups experiencing CFS 
symptoms (Lawrie & Pelosie, 1995). Other CFS research studies, including a large RCT have 
attempted to minimise this bias in medical recognition and referral patterns by educating 
GPs involved in recruitment (Wearden et al., 2010). This was not possible during ClinPsyD 
research; however reflecting on this limitation has increased the author’s awareness of 
issues related to sample representativeness.

A number of participants in the sample had been experiencing CFS symptoms for many 
years, which increased the mean duration of illness for the sample substantially. Including 
these individuals in the sample however may have been helpful in allowing identification of 
the association between length of illness and reduced variability in fatigue across the day, a 
finding which was not expected and has not, to the author’s knowledge been published 
elsewhere.
It was found that 85.2% of the sample fell within the clinical range for the Chalder Fatigue Scale (Chalder et al., 1993) although all had been diagnosed with CFS within a specialist service and met the Oxford criteria for CFS (Sharpe et al., 1991) during initial screening. There may be several explanations for this finding. Firstly, the scale items are rated based on how the individual has felt within the last month relative to how the individual usually feels based on whether fatigue levels are “less than usual”, “no more than usual”, “more than usual” or “much more than usual”. This allows for the possibility that some participants, who were perhaps feeling relatively well or experiencing a ‘good spell’, may not have reached caseness on this scale. Another consideration is that for those who have been experiencing fatigue for many years, this may be difficult to rate as feeling fatigued would be perceived as how they feel ‘usually’. This reflects the fluctuating nature of the condition, the limitations of ratings symptoms on a relative scale, and perhaps the limitations in validity and reliability of psychometric measures more generally.

As the research was sleep-focused it is likely individuals who chose to participate were experiencing poorer sleep, or were more concerned by their sleep than other CFS patients, which is reflected by 100% of the sample meeting clinical cut offs on the Dysfunctional Beliefs and Attitudes about Sleep Scale (Morin et al., 2007). It is unclear whether similar associations between subjective sleep and fatigue would be seen in CFS patients less concerned about their sleep. However, it is clear that for a proportion of CFS patients at least, the association between subjective sleep and following day fatigue is important and an area in need of further research.

Procedure

A possible limitation of the sleep diaries used is that perceived sleep may be susceptible to reporting bias, with the possibility of participants rounding up their estimates to the nearest quarter or half an hour, leading to loss of information (Tang et al., 2012). In line
with a previous study (Tang et al., 2012), this possibility was minimised by asking participants to complete the sleep diaries as soon as possible after waking and to complete estimates to the nearest minute.

Within the research, subjective ratings of sleep, mood and symptoms were given in paper booklets, rather than electronically due to pragmatic considerations and the lack of availability of electronic devices. Therefore, although participants were asked to record the time at which they completed their sleep ratings, it was not possible to verify the accuracy of these times. This allows for the possibility that symptom ratings could have been completed in retrospect, which has been found to occur commonly in ESM studies using paper diaries (Stone et al., 2002). The likelihood of retrospective reporting was minimised by emphasising to participants the importance of accurately recording time of completion, and that it was preferable that if entries that could not be completed within an hour of the requested time point that they be left incomplete. The use of paper ratings however did appear to be convenient to participants which is reflected in the high completion rate (95.7% for ESM items), which is a strength of the research.

Data analysis

Multi-level modelling was unfamiliar to the author prior to beginning this research. As a result it was important to gain advice from a statistician at each stage of the research process. This included helpful suggestions in designing the project which included using fatigue daily mean and variability, rather than single momentary data points, as primary outcomes in order to limit the complexity of the analysis and to produce clear findings in an area with little existing research to build on.

Within the design and statistical analyses, illness duration was included as a potential confounder. This was due to the understanding that having CFS for a longer period of time
could result in both increased sleep difficulties and greater fatigue levels due to a prolonged ‘viscious cycle’ of maintenance factors and increasing symptom levels, thus confounding any relationship between the sleep and fatigue. This did not appear to be the case for fatigue levels as illness duration did not predict mean fatigue. However, illness duration did predict variance in fatigue which provided an interesting finding that had not been demonstrated previously, and confirmed the justification for including illness duration as a potential confounder. As a result illness duration was included as an additional covariate in subsequent analyses.

Standard deviation was used as a measure of variability in contrast to using mean squared successive difference as recommended in ESM studies (Ebner-Priemer et al., 2009) due to the relatively small number of assessments per day compared with other ESM studies which have included up to 10 data collection points per day (e.g. Palmier-Claus et al., 2012). Calculating mean squared successive difference on a small number of data points would make the statistic less valid as an index of variability due to the small number of differences to calculate between data points.

Bootstrapping procedures (Mooney & Duval, 1993) are commonly used in ESM studies in order to correct non-normal data distribution (e.g. Palmier-Claus et al., 2012). However, they were not used within the analyses due to the fatigue mean and variance outcomes being broadly normally distributed following inspection of histograms. Moreover, previous ESM research has obtained similar findings with and without the inclusion of bootstrapping procedures (Palmier-Claus et al., 2012).

It has been suggested that within ESM studies, time should be included as an additional variable within models due to carryover effects that can occur from multiple daily data collection points (Bolger & Laurenceau, 2013). However, time was not included as an additional variable in the analyses because as the design includes substantially fewer data
collection points per day than other ESM studies, carryover effects related to participant burden were not expected.

A strength of ESM designs is that they can include simultaneous measurement of comparable objective and subjective variables (Santangelo et al., 2013). However, an important consideration within the research was that objective and subjective measures of sleep were not directly comparable. Actigraphy can provide an indication of sleep fragmentation but this is not an accurate indicator of subjective experiences of sleep quality. Similarly there are no objective indicators of how refreshing sleep might feel, due to this being inherently subjective. As direct comparisons between subjective and objective sleep variables were not made, it is not possible to conclude that a significant discrepancy between objective and subjective sleep existed within the sample based on the analyses presented. However, our conclusions that subjective sleep variables measured are more important than objective sleep variables measured in the experience of fatigue, can be made based on the available data.

The differences in coefficients approach (Bolger & Laurenceau, 2013) was used for the mediation analysis. This provided an estimate of the effects of the intervening variable, in this case negative mood on waking, by comparing the relationship between sleep and fatigue with and without negative mood as an additional covariate. However, limitations of this approach have been highlighted. This method provides only estimates of mediation, and is not as accurate as more formal tests of mediation such as the ‘products of coefficients’ approach (Mackinnon et al., 2002). As a result, although this method of analysis allowed a relatively straightforward estimation of possible mediation during the timescales of the research, the conclusions that can be drawn based on these analyses should be viewed with this limitation in mind.
A further limitation of the mediation analyses used is that it assumes that there are no unmeasured confounds between mediators and the outcomes, which could account for the relationship (Wearden & Emsley, 2013). This possibility was minimised by including illness duration as an additional covariate within the analyses in order to rule out this factor as a confounder. It is possible that other variables could act as confounders, although this may reflect a limitation of any research examining association between variables, given that for pragmatic reasons it may not be possible to measure all possible confounders. This reflects the need to have a theoretical rationale for measuring variables that could potentially confound associations (Macnamee, 2005).

**Reflections on Writing Up**

Writing up the empirical research was found to be challenging due to attempting to summarise a large amount of data in a concise and clear way. It also felt difficult to make strong conclusions given the lack of similar research in this area and because although the sample size was sufficient for an ESM study and appeared to be representative of those with CFS experiencing sleep difficulties, the sample was not large, due to the practical, financial and time constraints of completing research within a ClinPsyD programme. However, the ESM design which allowed analysis of a large amount of data, as well as the high completion rate are particular strengths of the research and enable the conclusions to be made.

On reflection on the research process overall it is possible to identify a number of possible additional variables that could have been measured and included within analyses. This is perhaps the case for all research studies and reflects the need to balance ethical, pragmatic and theoretical factors when designing studies.
An important factor that may be relevant to sleep difficulties in CFS and was not measured within the empirical research is attentional bias to sleep-related information. Within the cognitive model of insomnia (Harvey, 2002), increased attention to cues indicating wakefulness during the night and to cues indicating difficulties functioning during the day are understood to be important within the maintenance of insomnia. Similarly, the research did not measure anxiety related to sleep specifically although unhelpful beliefs about sleep which may contribute to such anxiety, were measured. However due to the lack of previous research, it was considered important to provide an initial exploration of the importance of subjective sleep in this condition. This enabled the research to provide clear initial findings without an overly complicated design, when there was little previous research providing a rationale for including variables such as attentional bias. It is felt that the findings of the empirical research have been presented clearly, in line within this aim. Furthermore, the recommendations suggest that examining additional factors specifically in further research will be beneficial to fully understand how subjective experiences of sleep may contribute to the maintenance of CFS.

Prior to beginning the research, a study suggested that CFS patients can be classified into subgroups according to differences in sleep variables (Gotts et al., 2013). Within the empirical research, there was no attempt to recruit or classify the sample based on these proposed subgroups for a number of reasons. Firstly, due to time and practical constraints, it would not be possible to obtain a large enough sample to allow such classification. Secondly, as the research aimed to examine the link between sleep and fatigue in CFS patients generally, it was not felt that including subgroups would be consistent with this aim. Lastly, because subgroups had only been suggested by one previous study, and these findings had not been replicated, it was not felt that these findings were sufficiently robust on which to base the research, particularly because the cluster analysis used may over-emphasise differences between subgroups (Kaufman & Rousseeuw, 2009).
A number of variables were measured and not included in the analyses. This includes activity data, measured by the actigraphy device, and momentary cognitive symptoms and positive mood. This reflects the large amount of data that was collected as part of the study and the need to be selective in including variables within analyses in order to present findings clearly to the reader. This at times felt challenging due to the desire to include additional information in analyses, particularly given the challenges in data collection and because participants had completed study procedures willingly and diligently. This highlights the need to have clear research aims and a detailed data analysis plan when planning research. In order to address the potential ethical issue of collecting data that might not be used, there are currently plans to utilise this additional data and to write up further articles in order to build on the empirical research presented as part of the thesis.

**Conclusions**

On reflection on the empirical research it is felt that the aims of the research project were fully met and that the research has provided some very interesting findings and a substantial contribution in an important area with little previous research. It is likely that these findings would not have been demonstrated without the use of an ESM design and therefore it is considered that although it was challenging to complete the research project within the required timescales, the efforts made by the author and research team are reflected in the quality of the research and the findings obtained.
Reflections on the Implications of Paper 1 and Paper 2

Conclusions based on the empirical research and review suggest that the effectiveness of sleep specific interventions, such as CBT for insomnia, should be examined within CFS. An important consideration related to this is how feasible such interventions might be in the current financial climate in the UK, particularly given that CFS service provision is currently considered inadequate and inconsistent (All-Party Parliamentary group on ME, 2010).

Another important issue related to the effectiveness of sleep-focused interventions in CFS would also be their acceptability to patients. There has been much debate between CFS patient groups and clinicians about the acceptability of CBT and GET interventions which have been viewed negatively by patient groups due to a number of factors. This includes the perception that research into CBT and GET diverts resources from possible research into biological factors involved in causing CFS symptoms and the development of interventions targeting these factors. However, from personal experience of working with this group it seems that patients would potentially be more accepting of additional sleep-focused interventions, perhaps more so than CBT interventions focused on managing the emotional impact of the condition. Further research may provide confirmation on whether this might be the case.
References


Appendix 1: Author guidance for submission to Sleep Medicine Reviews
INSTRUCTIONS FOR AUTHORS

Aims and scope
The aim of this journal is to review all aspects of sleep medicine. It will provide in-depth and up-to-date Clinical Reviews of sleep disorders, including their aetiology, diagnosis, treatment and implications for related conditions at an individual and a public health level, as well as Physiological Reviews, Theoretical Reviews and Historical Notes.

Clinical and (patho)physiological information about sleep disorders published in peer-reviewed journals devoted to the many disciplines involved in sleep medicine are reviewed. These disciplines include cardiology, dentistry, endocrinology, general medicine, geriatrics, neurology, ORL, paediatrics, pharmacology, physiology, psychiatry, psychology and pulmonology.

The journal intends to be an international forum for opinion within the field of sleep medicine, covering areas of controversy and debate as well as areas of future research. It publishes narrative reviews, systematic reviews and editorials primarily for the clinician. Submission of systematic or meta-analytic reviews following validated guidelines is encouraged.

Submission of papers
Articles are invited from recognised experts. Individuals who wish to submit an article should initially contact the Editor-in-Chief at the (e-mail) address above.

Manuscripts will only be accepted on the strict understanding that they are original publications that have not been published previously or are not under consideration for publication by other journals.

Please note that the readership of this journal comprises many different medical disciplines. Please ensure that your article will be accessible to all readers.

The final section of each article should highlight the important points raised in the article, summarise the current state of knowledge in the area and outline future avenues of research.
Presentation of papers
Submitted manuscripts must be written in Standard English. American or British usage is accepted, but not a mixture of these. If the authors are not native English speakers, it is strongly suggested that before submission they have their manuscript reviewed by a native English speaker or that they utilize a professional editing service.

The submitted manuscript should be typed double-spaced (i.e. a full line space between every typed line). Margins of at least 25 mm (1 inch) should be left on all sides.

Key Points for Authors

1. Unless otherwise directed, articles should be a maximum of 8000 words long including a maximum of 100 references.

2. Include a Summary and Keywords for each article.

3. Conflicts of interest should be noted in the Acknowledgements on the title page and should be set off by a specific subheading.

3. The final section of each article should highlight the important points raised in the article, summarise the current state of knowledge in the area and outline future avenues of research. This should be presented in boxed format as Practice Points and Research Agenda. However, wherever these summary points are necessarily extensive, the author may prefer to break them up and group them at the end of relevant sections within the text. It is very important that these items are included with all clinical, physiological and theoretical reviews.

4. References should be presented according to the Vancouver numbered style 3. A maximum of 100 references should be included; up to 10 key references are to be marked by an asterisk in front.

5. All Abbreviations must be explained in full when first used; a full alphabetically ordered list of abbreviations and definitions used in your review should be provided.

6. Text and tables should be double spaced and clearly laid out with suitable headings. Abbreviations used in tables and figures should be defined in their legend, even if they were defined elsewhere in the text.

7. Illustrations and tables should be used wherever appropriate. They should be clear and precise. All tables, figures including supplementary ones should be numbered and referred to in the body of text.

The title page of the article should include the title of the paper and full name (First Name, Middle initial (if any), Last Name) and affiliation of each author. Please indicate who is to be the corresponding author with a full address including with email address, telephone and fax numbers. A shortened version of the title should also be included for use in running heads.

Please avoid footnotes where possible.

Your article should include:

Summary The second page of your article should contain the abstract (which should not exceed 200 words). This should be comprehensible to readers before they have read the paper. References, illustrations and tables should not be mentioned; acronyms and abbreviations should be avoided in the abstract. Sleep Medicine Reviews does not publish research papers and therefore the summary should not be structured.

Keywords. Three to ten key words should be given below the abstract, to be used for indexing purposes.
Glossary of terms. Please include an explanatory list of uncommon or difficult terms used in the text following the Summary. This list should be clear and concise.

Capitalization. Capital letters should only be used for proper names and any references to things such as scores, indexes, syndromes etc. (e.g., Epworth sleepiness score, quality index, restless legs syndrome) should be set in all lowercase letters, even if those names are abbreviated.

Abbreviations. All abbreviations and acronyms used in a manuscript must be explained in full when first used in the Abstract, again when first used in the body of a manuscript or in a table. Authors should try to restrict the use of abbreviations/acronyms to the most commonly used terms. Abbreviated expressions should not be capitalized: It should be "restless legs syndrome (RLS)" and not "Restless Legs Syndrome (RLS)".

Units. Spell out all numbers under ten; numbers 10 and over should appear as digits. Please note, numbers should appear as numerics if part of a formula or as an expression of units (e.g. 2kg). The International System of Units (SI) should be applied (e.g. mm, kg etc.); use s for second, min for minute, d for day, wk for week, mo for month and y for year.

Drugs. Generic names should be used. Proprietary names may follow in parentheses (include both English and American names if different). Great care should be taken in describing the use of drugs and details of the regimen should be thoroughly checked.

Genetics. All genes should be underlined to indicate italicization. Proteins should be left as Roman.

Text. Underline only the words or letters that should appear in italics. Clearly identify unusual hand-written symbols and Greek letters. Differentiate between the letter “O” and zero and the letters I and L and the number 1. Lists of items may be numbered 1) ... 2) ... 3) ... but NOT (1) ... (2) ... (3) ... to avoid confusion with references.

Practice Points. Present the important points for readers to remember in clearly indicated box(es), e.g.:

<table>
<thead>
<tr>
<th>Practice Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep apnea clinical prediction rules may be useful to:</td>
</tr>
<tr>
<td>1. exclude the diagnosis when the probability is low and the patient has insignificant symptoms;</td>
</tr>
<tr>
<td>2. establish an a priori probability before considering the utilization of a non-PSG diagnostic method;</td>
</tr>
<tr>
<td>3. prioritize patients for polysomnography according to the probability that they will have a positive result.</td>
</tr>
</tbody>
</table>

Research Agenda. Please indicate points which you feel would repay further research in box(es), e.g.:

<table>
<thead>
<tr>
<th>Research Agenda</th>
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<tbody>
<tr>
<td>In the future we need to be able to not only predict those with sleep apnea, but also which patients:</td>
</tr>
<tr>
<td>1. are at highest risk of morbidity and mortality and whether this risk can be modified by treatment;</td>
</tr>
</tbody>
</table>
2. obtain the most significant improvement in their quality of life as a result of treatment;
3. are most likely to be compliant with therapy.

It is recommended not to use acronyms or abbreviations in the Research Agenda and the Practice Points.

Please note that Practice Points, Research Agenda and Asterisked Key References are standard features of reviews published in Sleep Medicine Reviews and we ask that authors to pay particular attention to incorporating these into their reviews before submitting the article.

Acknowledgements for personal and technical assistance should be indicated on the title page. Financial support and any conflict of interest are also to be stated in the acknowledgements (see above). The source of equipment and drugs may be included here as well.

Authors are actively encouraged to use tables and other forms of illustration where appropriate. Tables and Figures must however be fully self-explanatory; all abbreviations and acronyms used should be defined in their legends, even if defined elsewhere in the manuscript.

Tables should be quoted in the text (e.g. “See table 1”). Tables should be numbered consecutively using Arabic numerals in the order in which they are cited in the text. Each table should be typed in double spacing on a separate page and given a brief explanatory caption. Please us a simple lay out for tables, it is recommended not to use vertical lines or boxes.

Tables with a systematic overview of the included studies should be ordered either on the first author name, or on year of publication. With author names in the first column please use the same format as used in the text (author names if one or two authors, first author followed by et al. if more than 2 authors). In the latter case, the year of publication should be mentioned in the first column of the table, together with the first author name and reference number of the study.

Illustrations.
- Illustrations should be numbered according to their sequence in the text. Each illustration should be referred to in the text.
- Illustrations should be designed with the format of the page of the journal in mind. Illustrations should be of such a size as to allow a reduction of 50%.
- Lettering should be big enough to allow a reduction of 50% without becoming illegible. Any lettering should be in English. Use the same kind of lettering throughout and follow the style of the journal.
- If a scale should be given, use bar scales on all illustrations instead of numerical scales that must be changed with reduction.
- Each illustration should have a caption.
- Provide captions to illustrations separately.
- Explanations should be given in the figure legend(s). Drawn text in the illustrations should be kept to a minimum.
- Photographs are only acceptable if they have good contrast and intensity.
- Make sure you use uniform lettering and sizing of your original artwork.
- Save text in illustrations as “graphics” or enclose the font.
- Only use the following fonts in your illustrations: Arial, Courier, Helvetica, Times, Symbol.
- Use a logical naming convention for your artwork files.
- Provide all illustrations as separate files. The preferred formats are eps and tif; jpg, pdf or xls are also acceptable.

A detailed guide on electronic artwork is available on our website: [http://www.elsevier.com/artworkinstructions](http://www.elsevier.com/artworkinstructions)

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats: Regardless of the application used, when your electronic artwork is finalised,
please "save as" or convert the images to one of the following formats (Note the resolution requirements for line drawings, halftones, and line/halftone combinations given below.):

EPS: Vector drawings. Embed the font or save the text as "graphics".
TIFF: Colour or greyscale photographs (halftones): always use a minimum of 300 dpi.
TIFF: Bitmapped line drawings: use a minimum of 1000 dpi.
TIFF: Combinations bitmapped line/halftone (colour or greyscale): a minimum of 500 dpi is required.

DOC, XLS or PPT: If the electronic artwork is created in any of these Microsoft Office applications please supply "as is".

Please:
• do not supply embedded graphics in your word processor (spreadsheet or powerpoint) file
• do not supply files that are too low in resolution, like e.g. GIF, BMP, PICT or WPG
• do not submit graphics that are disproportionately large for the content

Preparation of supplementary data
Elsevier accepts electronic supplementary material to support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, movies, animation sequences, high-resolution images, background datasets, sound clips and more. Supplementary tables or figures must be indicated in text and legend as Video 1, Table S1, Table S2, etc. or as Figure S1, etc.

Supplementary files supplied will be published free of charge online alongside the electronic version of your article in Elsevier web products, including ScienceDirect: http://www.sciencedirect.com. In order to ensure that your submitted material is directly usable, please ensure that data are provided in one of our recommended file formats. Authors should submit the material in electronic format together with the article and supply a concise and descriptive caption for each supplementary table, figure or video.

References. The references should represent the most recent and pertinent literature available. It is essential that the references are thoroughly checked by the author as inaccuracies cannot be detected by the publisher. A maximum of 100 references should be included.

References should follow the Vancouver numerical style 3. Indicate references in the text by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given. Number the references (numbers in square brackets) in the list at the end of the paper in the order in which they appear in the text.

In the reference list supply all author names up to 6 author names, then use “et al.” In Endnote use style 3a like in: comp thera clin pract.ens (Complementary Therapies in Clinical Practice

Examples


Papers that have already been accepted but not yet published, should be indicated in the reference list followed by ("in press"). Papers in preparation, including those already submitted for publication, personal communications and unpublished observations should be referred to in the text only.

Please indicate with an asterisk, up to a maximum of ten, the most important references.

Advice on presentation of text
• Keep the layout as simple as possible; we will set your article according to house style. Do not try to “present” the document.
• Ensure that you use the correct characters – i.e. do not confuse lower case letter “l”s and the digit “1”, or capital “O” and zero.
• Do not justify your text
• Ensure that your files are not saved as read only

Peer review
Authors are encouraged to recommend peer reviewers for their paper. Peer reviewers must be experts in the given speciality, and be willing to provide a confidential and fair assessment of the review according to specified criteria and the aims of the journal. Reviewers must have no personal or financial competing interests or be involved in research or other collaborations with the author/s. Suggestions will be considered and selected by the Editors at their discretion. Final selection and responsibility for peer review rests with the Editors.

Change of Author Names
Requests to add or remove an author, or to rearrange the author names, must be sent to the Managing Editor from the corresponding author of the accepted manuscript and must include:

(a) The reasons why the name should be added, removed, or author names rearranged.
(b) Written confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.

Requests that are not sent by the corresponding author will be forwarded by the Managing Editor to the corresponding author, who must follow the procedure as described above. Note that the Managing Editor will inform the Journal Editors of any such requests. Publication of the accepted manuscript in an online issue is suspended until authorship has been agreed.

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*Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.
*If such consent has not been obtained, personal details of patients included in any part of the paper and in any illustration or supplementary materials (including videos) must be removed before submission

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**Summary**

1. Ensure that the article is clearly aimed at the intended readership.

2. Use clearly indicated headings throughout.

3. Use double line spacing throughout.

4. Leave margins of at least 25 mm (1 inch) all around the page.

5. Present the article in the following order: title page, summary, key words, glossary of terms, text, acknowledgements, references, (figure legends and captions), figures, tables.

6. Tables can be part of the Word document with the text or can be uploaded as a separate Word or as separate spreadsheet-files. Figures are to be uploaded in one or more separate files using the original format of the program that produced the figure. Preferred formats for figures are eps and tiff; jpg, ppt, xls and pdf are also acceptable for production purposes.

7. Include **Practice Points** and a **Research Agenda** in separate boxes.

8. Spelling should be English throughout; be consistent in American or British usage.

9. Provide no more than 100 references presented according to the Vancouver numbered system. Indicate the 10 key references with asterisks.

10. Sign the copyright assignment and conflict of interest disclosure forms at the end of this pack and submit them with your manuscript. They can be submitted on line with the submission or sent by fax or e-mail.

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12. You are encouraged to include recommendations for peer reviewers on submission of your manuscript.

13. The use of previously published material should be avoided where possible. If using material from published work, all necessary permissions (including the right to store and publish electronically) must be submitted with the article (please feel free to use the form provided below when requesting permissions).
Appendix 2: Downs and Black (1998) checklist for quality assessment
<table>
<thead>
<tr>
<th>ALL CRITERIA</th>
<th>DESCRIPTION OF CRITERIA (with additional explanation as required, determined by consensus of raters)</th>
<th>POSSIBLE ANSWERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Is the hypothesis/aim/objective of the study clearly described? Must be explicit</td>
<td>Yes/No</td>
</tr>
<tr>
<td>2</td>
<td>Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered no. ALL primary outcomes should be described for YES</td>
<td>Yes/No</td>
</tr>
<tr>
<td>3</td>
<td>Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given. Single case studies must state source of patient</td>
<td>Yes/No</td>
</tr>
<tr>
<td>4</td>
<td>Are the interventions of interest clearly described? Treatments and placebo (where relevant) that are to be compared should be clearly described.</td>
<td>Yes/No</td>
</tr>
<tr>
<td>5</td>
<td>Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided. YES = age, severity</td>
<td>Yes/No</td>
</tr>
<tr>
<td>6</td>
<td>Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.</td>
<td>Yes/No</td>
</tr>
<tr>
<td>7</td>
<td>Does the study provide estimates of the random variability in the data for the main outcomes? In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported</td>
<td>Yes/No</td>
</tr>
<tr>
<td>8</td>
<td>Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events</td>
<td>Yes/No</td>
</tr>
<tr>
<td>9</td>
<td>Have the characteristics of patients lost to follow-up been described? If not explicit = NO. RETROSPECTIVE – if not described = UTD; if not explicit re: numbers agreeing to participate = NO. Needs to be &gt;85%</td>
<td>Yes/No</td>
</tr>
<tr>
<td>10</td>
<td>Have actual probability values been reported (e.g. 0.035 rather than &lt;0.05) for the main outcomes except where the probability value is less than 0.001?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>11</td>
<td>Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected.</td>
<td>Yes/No/UTD</td>
</tr>
<tr>
<td>12</td>
<td>Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated.</td>
<td>Yes/No/UTD</td>
</tr>
<tr>
<td>13</td>
<td>Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. Must state type of hospital and country for YES.</td>
<td>Yes/No/UTD</td>
</tr>
<tr>
<td>14</td>
<td>Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered yes. Retrospective, single group = NO; UTD if &gt; 1 group and blinding not explicitly stated</td>
<td>Yes/No/UTD</td>
</tr>
<tr>
<td>15</td>
<td>Was an attempt made to blind those measuring the main outcomes of the intervention? Must be explicit</td>
<td>Yes/No/UTD</td>
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<tr>
<td>16</td>
<td>If any of the results of the study were based on &quot;data dredging&quot;, was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. Retrospective = NO. Prospective = YES</td>
<td>Yes/No/UTD</td>
</tr>
<tr>
<td>17</td>
<td>In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? Where follow-up was the same for all study patients the answer should be yes. Studies where differences in follow-up are ignored should be answered no. Acceptable range 1 yr follow up = 1 month each way; 2 years follow up = 2 months; 3 years follow up = 3 months.......10 years follow up = 10 months</td>
<td>Yes/No/UTD</td>
</tr>
<tr>
<td>18</td>
<td>Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. If no tests done, but would have been appropriate to do = NO</td>
<td>Yes/No/UTD</td>
</tr>
<tr>
<td>19</td>
<td>Was compliance with the intervention/s reliable? Where there was non compliance with the allocated treatment or where there was contamination of one group, the</td>
<td>Yes/No/UTD</td>
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<tr>
<td>Question</td>
<td>Yes/No/UTD</td>
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<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Were the main outcome measures used accurate (valid and reliable)? Where outcome measures are clearly described, which refer to other work or that demonstrates the outcome measures are accurate</td>
<td>Yes/No/UTD</td>
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<tr>
<td>Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Patients for all comparison groups should be selected from the same hospital. The question should be answered UTD for cohort and case control studies where there is no information concerning the source of patients</td>
<td>Yes/No/UTD</td>
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<tr>
<td>Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?</td>
<td>Yes/No/UTD</td>
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</tr>
<tr>
<td>Were study subjects randomised to intervention groups? Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation.</td>
<td>Yes/No/UTD</td>
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<tr>
<td>Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.</td>
<td>Yes/No/UTD</td>
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<tr>
<td>Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? In nonrandomised studies if the effect of the main confounders was not investigated or no adjustment was made in the final analyses the question should be answered as no. If no significant difference between groups shown then YES</td>
<td>Yes/No/UTD</td>
<td></td>
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<tr>
<td>Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported = unable to determine.</td>
<td>Yes/No/UTD</td>
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<tr>
<td>Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance &lt;5% Sample sizes have been calculated to detect a difference of x% and y%</td>
<td>1-5</td>
<td></td>
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Appendix 3: Ratings of study quality
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</thead>
<tbody>
<tr>
<td>1. Hypothesis/aim clear?</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<td>2. Main outcomes clearly described?</td>
<td>1</td>
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<td>3. Participants clearly described?</td>
<td>1</td>
<td>1</td>
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<td>4. Interventions clearly described?</td>
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<td>1</td>
<td>0</td>
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<td>5. Distribution of principal confounders clearly described? Age, severity (0,1,2)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<td>6. Main findings clearly described?</td>
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<td>7. Estimates of random variability provided?</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<td>8. Adverse events reported?</td>
<td>0</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>9. Characteristics of participants lost to follow up reported?</td>
<td>0</td>
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<td>10. Actual probability values reported?</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>11. Sample approached representative?</td>
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<td>0</td>
<td>1</td>
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<td>12. Participants representative?</td>
<td>0</td>
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<td>13. Treatments representative?</td>
<td>1</td>
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<td>14. Attempted blinding – participants?</td>
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<td>15. Attempted blinding – assessors?</td>
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<td>16. Unplanned analyses?</td>
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<td>17. Time period same for cases and controls?</td>
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<td>18. Statistical tests appropriate?</td>
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<td>19. Was compliance with the intervention reliable?</td>
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<td>20. Main outcomes valid &amp; reliable?</td>
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<td>21. Intervention and control from same population?</td>
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<td>22. Recruited over same time period?</td>
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<td>23. Randomisation?</td>
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<td>24. Randomisation concealed?</td>
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<td>25. Adequate adjustment for confounding?</td>
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<td>26. Numbers lost to follow up accounted for?</td>
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<td>27. Sufficient power?</td>
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<tr>
<td><strong>Total Score</strong></td>
<td>19</td>
<td>18</td>
<td>8</td>
<td>20</td>
<td>18</td>
<td>11</td>
<td>25</td>
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</tr>
</tbody>
</table>
Appendix 4: Author guidance for submission to The Journal of Consulting and Clinical Psychology
Prior to submission, please carefully read and follow the submission guidelines detailed below. Manuscripts that do not conform to the submission guidelines may be returned without review.

Submission

Please submit manuscripts electronically, either using Microsoft Word (.doc) or Rich Text Format (.rtf) via the Manuscript Submission Portal.

If you encounter difficulties with submission, please email Allie Robertson or call 202-336-5611.

General correspondence may be directed to the Editorial Office via email.

Masked Review

This journal uses a masked reviewing system for all submissions. The first page of the manuscript should omit the authors' names and affiliations but should include the title of the manuscript and the date it is submitted.

Footnotes containing information pertaining to the authors' identities or affiliations should not be included in the manuscript, but may be provided after a manuscript is accepted.

Make every effort to see that the manuscript itself contains no clues to the authors' identities.

Please ensure that the final version for production includes a byline and full author note for typesetting.

Keep a copy of the manuscript to guard against loss.

Cover Letter

The cover letter accompanying the manuscript submission must include all authors' names and affiliations to avoid potential conflicts of interest in the review process. Addresses and phone numbers, as well as electronic mail addresses and fax numbers, if available, should be provided for all authors for possible use by the editorial office and later by the production office.

Length and Style of Manuscripts

Full-length manuscripts should not exceed 35 pages total (including cover page, abstract, text, references, tables, and figures), with margins of at least 1 inch on all sides and a standard font (e.g., Times New Roman) of 12 points (no smaller). The entire paper (text, references, tables, etc.) must be double spaced.

Instructions on preparing tables, figures, references, metrics, and abstracts appear in the Publication Manual of the American Psychological Association (6th edition). Authors submitting manuscripts that
report new data collection, especially randomized clinical trials (RCTs), should comply with the newly developed APA Journal Article Reporting Standards (PDF, 98KB) (JARS; see American Psychologist, 2008, 63, 839–851 or Appendix in the APA Publication Manual).

For papers that exceed 35 pages, authors must justify the extended length in their cover letter (e.g., reporting of multiple studies), and in no case should the paper exceed 45 pages total. Papers that do not conform to these guidelines may be returned without review.

The References section should immediately follow a page break.

**Brief Reports**

In addition to full-length manuscripts, the JCCP will consider Brief Reports of research studies in clinical psychology. The Brief Report format may be appropriate for empirically sound studies that are limited in scope, contain novel or provocative findings that need further replication, or represent replications and extensions of prior published work.

Brief Reports are intended to permit the publication of soundly designed studies of specialized interest that cannot be accepted as regular articles because of lack of space.

Brief Reports must be prepared according to the following specifications: Use 12-point Times New Roman type and 1-inch (2.54-cm) margins, and do not exceed 265 lines of text including references. These limits do not include the title page, abstract, author note, footnotes, tables, or figures.

An author who submits a Brief Report must agree not to submit the full report to another journal of general circulation. The Brief Report should give a clear, condensed summary of the procedure of the study and as full an account of the results as space permits.

**Commentaries**

JCCP now publishes papers that are commentaries of previously published articles in this journal. Two types of commentaries will be considered:

**Brief Comment**

A Brief Comment would be written in response to a single article previously published in JCCP. The primary purpose would be to provide a meaningful insight, concern, alternative interpretation, clarification, or critical analysis. It is not intended to be pedestrian in nature (e.g., simply highlighting that a given study is statistically underpowered). Rather, its publication would provide for a richer and more comprehensive understanding of a methodological, conceptual, or professional issue that significantly adds to the literature.

Similar to a Brief Report, Brief Comments should not exceed 265 lines of text including references. This limit does not include the title page, abstract, or author notes. The title of a Brief Comment should include a subtitle reflecting the actual title and year of publication of the article that engendered the comment. For example — “The Importance of Focusing on External Validity: A Brief Comment on Testing the Efficacy of Two Differing Types of Stress Management Interventions for the Treatment of Essential Hypertension (Jones & Smith, 2012).” Brief Comments should be submitted in a timely
manner, no later than 9 months after publication of the original article. Upon acceptance of a Brief Comment, the author(s) of the original paper would be invited to submit a response, whereupon, if acceptable, both the Brief Comment and Response would be published together. Such Responses to a Brief Comment should also not exceed 265 lines of text including references.

Extended Comment

The purpose of this type of article is essentially similar to that of a Brief Comment (i.e., to provide a meaningful insight, concern, alternative interpretation, clarification, or critical analysis), but would be written in response to a series of articles previously published in *JCCP* or that involves a more extensive and far-reaching conceptual or methodological issue. An example might include describing and analyzing the limitations of a particular statistical or methodological procedure used in several studies previously published in *JCCP*, provided along with meaningful recommendations.

This type of article should not exceed approximately one half the length of the original paper (note that 1 journal page equals approximately 3–3.5 manuscript pages). Unless permission from the editor is received, no Extended Comment should exceed 20 manuscript pages inclusive of all references, tables, and figures.

Similar to a Brief Comment, where and when appropriate, if such a paper is accepted, the author(s) of the original article(s) will be contacted to write a response, whereupon, if acceptable, both the Extended Comment and Response would be published together. This Invited Response should not exceed approximately one half the length of the Extended Comment.

The title of this type of article need not include a subtitle representing the original article(s). One important review criteria involves the timeliness of the topic and its potential contribution to the scientific literature base relevant to the scope of *JCCP* content.

Conceptual/Theoretical Papers

Whereas the majority of papers published in *JCCP* will involve descriptions of quantitatively-based investigations, this journal also considers conceptual articles on topics of broad theoretical, methodological, or practical interest that advance the field of clinical psychology. Examples might include describing a new methodological or statistical procedure, delineating methods of enhancing dissemination of research findings from the lab to real-world settings, or advocating the need to increase the profession's research efforts regarding a traditionally underserved population.

Similar formatting guidelines for submitting a full length research article would apply for these types of papers.

Title of Manuscript

The title of a manuscript should be accurate, fully explanatory, and preferably no longer then 12 words. The title should reflect the content and population studied (e.g., “treatment of generalized anxiety disorders in adults”). If the paper reports a randomized clinical trial (RCT), this should be indicated in the title. Note that JARS criteria must be used for reporting purposes.
Abstract

All manuscripts must include an abstract containing a maximum of 250 words typed on a separate page. After the abstract, please supply up to five keywords or brief phrases.

Manuscripts published in the Journal of Consulting and Clinical Psychology will include a structured abstract of up to 250 words.

For studies that report randomized clinical trials or meta-analyses, the abstract also must be consistent with the guidelines set forth by JARS or MARS (Meta-Analysis Reporting Standards) guidelines, respectively. Thus, in preparing a manuscript, please ensure that it is consistent with the guidelines stated below.

Please include an Abstract of up to 250 words, presented in paragraph form. The Abstract should be typed on a separate page (page 2 of the manuscript), and must include each of the following sections:

Objective: A brief statement of the purpose of the study
Method: A detailed summary of the participants (N, age, gender, ethnicity) as well as descriptions of the study design, measures (including names of measures), and procedures
Results: A detailed summary of the primary findings that clearly articulate comparison groups (if relevant), and that indicate significance or confidence intervals for the main findings
Conclusions: A description of the research and clinical implications of the findings

Public Health Significance Statements

Authors submitting manuscripts to the Journal of Consulting and Clinical Psychology are required to provide 2–3 brief sentences regarding the public health significance of the study or meta-analysis described in their paper. It should be written in language that is easily understood by both professionals and members of the lay public.

Examples are included below. This description should be included within the manuscript on the abstract/keywords page. When an accepted paper is published, these sentences will be boxed beneath the abstract for easy accessibility. All such descriptions will also be published in the back of each issue, as well as on the journal’s web page. This new policy is in keeping with efforts to increase dissemination and usage by larger and diverse audiences.

Examples of these 2–3 sentences include the following:

“This study strongly suggests that (description of a given psychosocial treatment) is an effective treatment for anxiety, but only if it is of mild to moderate severity. For persons with severe anxiety, additional treatments may be necessary.”

“When treating individuals of (name of a particular ethnic minority group) who are experiencing PTSD, this study demonstrated the importance of taking into account cultural factors, especially those that involve one’s spiritual beliefs.”
“This study highlights the importance of directly including one’s family in treatment when helping adults diagnosed with cancer overcome their depression.”

Keywords
Please supply up to five keywords or short phrases.

Participants: Description and Informed Consent

The Method section of each empirical report must contain a detailed description of the study participants, including (but not limited to) the following: age, gender, ethnicity, SES, clinical diagnoses and comorbidities (as appropriate), and any other relevant demographics.

In the Discussion section of the manuscript, authors should discuss the diversity of their study samples and the generalizability of their findings.

The Method section also must include a statement describing how informed consent was obtained from the participants (or their parents/guardians) and indicate that the study was conducted in compliance with an appropriate Internal Review Board.

Measures

The Method section of empirical reports must contain a sufficiently detailed description of the measures used so that the reader understands the item content, scoring procedures, and total scores or subscales. Evidence of reliability and validity with similar populations should be provided.

Statistical Reporting of Clinical Significance

_JCCP requires the statistical reporting of measures that convey clinical significance. Authors should report means and standard deviations for all continuous study variables and the effect sizes for the primary study findings. (If effect sizes are not available for a particular test, authors should convey this in their cover letter at the time of submission.)_ 


In addition, when reporting the results of interventions, authors should include indicators of clinically significant change. Authors may use one of several approaches that have been recommended for capturing clinical significance, including (but not limited to) the reliable change index (i.e., whether the amount of change displayed by a treated individual is large enough to be meaningful; see Jacobson et al., Journal of Consulting and Clinical Psychology, 1999), the extent to which dysfunctional individuals show movement into the functional distribution (see Jacobson & Truax, Journal of Consulting and Clinical Psychology, 1991), or other normative comparisons (see Kendall et al., Journal of Consulting and Clinical Psychology, 1999).
Discussion of Clinical Implications

Articles must include a discussion of the clinical implications of the study findings or analytic review. The Discussion section should contain a clear statement of the extent of clinical application of the current assessment, prevention, or treatment methods. The extent of application to clinical practice may range from suggestions that the data are too preliminary to support widespread dissemination to descriptions of existing manuals available from the authors or archived materials that would allow full implementation at present.

Randomized Clinical Trials: Use of JARS Guidelines

*JCCP* requires the use of JARS guidelines for randomized clinical trials, consistent with the recommendations and policies established by the Publications and Communications Board of the American Psychological Association. JARS offers a standard way to improve the quality of such reports, and to ensure that readers have the information necessary to evaluate the quality of a clinical trial.

Manuscripts that report randomized clinical trials are required to include a flow diagram of the progress through the phases of the trial. When a study is not fully consistent with JARS guidelines, the limitations should be acknowledged and discussed in the text of the manuscript.

For follow-up studies of previously published clinical trials, authors should submit a flow diagram of the progress through the phases of the trial and follow-up. The above checklist information should be completed to the extent possible, especially for the Results and Discussion sections of the manuscript.

Authors of RCTs should also describe procedures to assess for treatment fidelity (also known as treatment integrity), including both therapist adherence and competence. Where possible, results should be reported regarding the relationship between fidelity and outcome found in the investigation.

Manuscript Preparation

Prepare manuscripts according to the *Publication Manual of the American Psychological Association* (6th edition). Manuscripts may be copyedited for bias-free language (see Chapter 3 of the *Publication Manual*).

Review APA's Checklist for Manuscript Submission before submitting your article. Double-space all copy. Other formatting instructions, as well as instructions on preparing tables, figures, references, metrics, and abstracts, appear in the *Manual*. Below are additional instructions regarding the preparation of display equations, computer code, and tables.

We strongly encourage you to use MathType (third-party software) or Equation Editor 3.0 (built into pre-2007 versions of Word) to construct your equations, rather than the equation support that is built
into Word 2007 and Word 2010. Equations composed with the built-in Word 2007/Word 2010 equation support are converted to low-resolution graphics when they enter the production process and must be rekeyed by the typesetter, which may introduce errors. To construct your equations with MathType or Equation Editor 3.0:

Go to the Text section of the Insert tab and select Object.
Select MathType or Equation Editor 3.0 in the drop-down menu.

If you have an equation that has already been produced using Microsoft Word 2007 or 2010 and you have access to the full version of MathType 6.5 or later, you can convert this equation to MathType by clicking on MathType Insert Equation. Copy the equation from Microsoft Word and paste it into the MathType box. Verify that your equation is correct, click File, and then click Update. Your equation has now been inserted into your Word file as a MathType Equation.

Use Equation Editor 3.0 or MathType only for equations or for formulas that cannot be produced as Word text using the Times or Symbol font.

Computer Code

Because altering computer code in any way (e.g., indents, line spacing, line breaks, page breaks) during the typesetting process could alter its meaning, we treat computer code differently from the rest of your article in our production process. To that end, we request separate files for computer code.

In Online Supplemental Material
We request that runnable source code be included as supplemental material to the article. For more information, visit Supplementing Your Article With Online Material.

In the Text of the Article
If you would like to include code in the text of your published manuscript, please submit a separate file with your code exactly as you want it to appear, using Courier New font with a type size of 8 points. We will make an image of each segment of code in your article that exceeds 40 characters in length. (Shorter snippets of code that appear in text will be typeset in Courier New and run in with the rest of the text.) If an appendix contains a mix of code and explanatory text, please submit a file that contains the entire appendix, with the code keyed in 8-point Courier New.

Tables

Use Word's Insert Table function when you create tables. Using spaces or tabs in your table will create problems when the table is typeset and may result in errors.

Submitting Supplemental Materials
APA can place supplemental materials online, available via the published article in the PsycARTICLES® database. Please see Supplementing Your Article With Online Material for more details.

References
List references in alphabetical order. Each listed reference should be cited in text, and each text citation should be listed in the References section. Examples of basic reference formats:

- **Journal Article:**

- **Authored Book:**

- **Chapter in an Edited Book:**

**Figures**

Graphics files are welcome if supplied as Tiff or EPS files. Multipanel figures (i.e., figures with parts labeled a, b, c, d, etc.) should be assembled into one file.

The minimum line weight for line art is 0.5 point for optimal printing.

For more information about acceptable resolutions, fonts, sizing, and other figure issues, please see the general guidelines.

When possible, please place symbol legends below the figure instead of to the side.

APA offers authors the option to publish their figures online in color without the costs associated with print publication of color figures.

The same caption will appear on both the online (color) and print (black and white) versions. To ensure that the figure can be understood in both formats, authors should add alternative wording (e.g., “the red (dark gray) bars represent”) as needed.

For authors who prefer their figures to be published in color both in print and online, original color figures can be printed in color at the editor's and publisher's discretion provided the author agrees to pay:

- $900 for one figure
- An additional $600 for the second figure
- An additional $450 for each subsequent figure

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See also APA Journals® Internet Posting Guidelines.

APA requires authors to reveal any possible conflict of interest in the conduct and reporting of research (e.g., financial interests in a test or procedure, funding by pharmaceutical companies for drug research).

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  Publication Rights (Copyright Transfer) Form (PDF, 83KB)
- For manuscripts funded by the Wellcome Trust or the Research Councils UK
  Wellcome Trust or Research Councils UK Publication Rights Form (PDF, 34KB)

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It is a violation of APA Ethical Principles to publish “as original data, data that have been previously published” (Standard 8.13).

In addition, APA Ethical Principles specify that “after research results are published, psychologists do not withhold the data on which their conclusions are based from other competent professionals who seek to verify the substantive claims through reanalysis and who intend to use such data only for that purpose, provided that the confidentiality of the participants can be protected and unless legal rights concerning proprietary data preclude their release” (Standard 8.14).

APA expects authors to adhere to these standards. Specifically, APA expects authors to have their data available throughout the editorial review process and for at least 5 years after the date of publication.
Authors are required to state in writing that they have complied with APA ethical standards in the treatment of their sample, human or animal, or to describe the details of treatment.

- Download Certification of Compliance With APA Ethical Principles Form (PDF, 26KB)

Appendix 5: NHS research ethics committee study approval letter
16 May 2014

Mrs Charlotte Russell
Trainee Clinical Psychologist
Manchester Mental Health & Social Care Trust
Doctoral Programme in Clinical Psychology
Zochonis Building
Brunswick Street, Manchester
M13 9PL

Dear Mrs Russell

Study Title: An investigation into the relationship between sleep and day to day fatigue in patients with chronic fatigue syndrome

REC reference: 14/NW/0258
IRAS project ID: 149719

Thank you for your letter of 12 May 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 09 May 2014

Documents received

The documents received were as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of insurance or indemnity</td>
<td>Public/Product Liability</td>
<td>04 June 2013</td>
</tr>
<tr>
<td>Evidence of insurance or indemnity</td>
<td>Employers Liability</td>
<td>01 June 2013</td>
</tr>
<tr>
<td>Evidence of insurance or indemnity</td>
<td>Professional Indemnity</td>
<td>30 May 2013</td>
</tr>
<tr>
<td>Participant Information Sheet</td>
<td>5</td>
<td>12 May 2014</td>
</tr>
<tr>
<td>Questionnaire: Demographic</td>
<td>3</td>
<td>12 May 2014</td>
</tr>
<tr>
<td>Questionnaire: Daily Sleep, Symptom and Mood Diary</td>
<td>2</td>
<td>12 May 2014</td>
</tr>
</tbody>
</table>
Approved documents

The final list of approved documentation for the study is therefore as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering Letter</td>
<td>11</td>
<td>11-Apr-14</td>
</tr>
<tr>
<td>Evidence of insurance or indemnity</td>
<td>04</td>
<td>04-Apr-14</td>
</tr>
<tr>
<td>Evidence of insurance or indemnity</td>
<td>Public/Product Liability</td>
<td>04 June 2013</td>
</tr>
<tr>
<td>Evidence of insurance or indemnity</td>
<td>Employers’ Liability</td>
<td>01-Jun-13</td>
</tr>
<tr>
<td>Evidence of insurance or indemnity</td>
<td>Professional Indemnity</td>
<td>30-May-13</td>
</tr>
<tr>
<td>GP/Consultant Information Sheets</td>
<td>4</td>
<td>07-Apr-14</td>
</tr>
<tr>
<td>Investigator CV</td>
<td>Kyle</td>
<td>24-Feb-14</td>
</tr>
<tr>
<td>Investigator CV</td>
<td>Wearden</td>
<td>17-Feb-14</td>
</tr>
<tr>
<td>Investigator CV</td>
<td>Russell</td>
<td></td>
</tr>
<tr>
<td>Participant Consent Form</td>
<td>2</td>
<td>07-Apr-14</td>
</tr>
<tr>
<td>Participant Information Sheet</td>
<td>5</td>
<td>12-May-14</td>
</tr>
<tr>
<td>Protocol</td>
<td>2</td>
<td>07-Apr-14</td>
</tr>
<tr>
<td>Questionnaire: Questionnaire Pack</td>
<td>1</td>
<td>11-Apr-14</td>
</tr>
<tr>
<td>Questionnaire: Wilson Sleep Interview</td>
<td>1</td>
<td>11-Apr-14</td>
</tr>
<tr>
<td>Questionnaire: Demographic</td>
<td>3</td>
<td>12-May-14</td>
</tr>
<tr>
<td>Questionnaire: Daily Sleep, Symptom and Mood Diary</td>
<td>2</td>
<td>12-May-14</td>
</tr>
<tr>
<td>REC application</td>
<td>3.5</td>
<td>08-Apr-14</td>
</tr>
</tbody>
</table>

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor’s responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

14/NW/0258: Please quote this number on all correspondence

Yours sincerely

Anna Bannister
REC Manager

E-mail: nrescommittee.northwest-gmwest@nhs.net

Copy to: Ms Lynne Macrae

Maureen Daniels, Associate R&D Manager, Salford Royal Foundation Trust
Appendix 6: Clinician letter
Dear

I am writing to invite you to participate in a research study that is being conducted in conjunction with the University of Manchester. The title of the research is as follows:

**An investigation into the relationship between sleep and day to day fatigue in patients with chronic fatigue syndrome (CFS/ME)**

The study is investigating how sleep is related to next day fatigue in CFS/ME. The researchers will be looking at several aspects of sleep as well as other factors such as mood and mental arousal before bed, and how these might affect sleep quality and fatigue.

Taking part in the study will involve completing a number of questionnaires and completing a 7 day assessment of your sleep and fatigue levels. This will include wearing a watch-like device called an actigraph that will monitor your sleep and you will be asked to complete a sleep diary each morning and rate your fatigue levels and mood four times daily.

Taking part in the study does not involve any extra treatment, follow up or investigations. Taking part is also completely voluntary and if you do decide to take part, you can change your mind at any time. Please be reassured choosing not to take part at all, or withdrawing at any stage will not affect the standard of care you receive at any time, now or in the future.

Please find the attached study information sheet, which provides full details of what is involved in taking part in the study. This letter has been sent on behalf of the research team and the research team do not have access to your personal information or health records. If you are interested in taking part or have any questions about the research, please contact the researcher Charlotte Russell by email at charlotte.russell-2@postgrad.manchester.ac.uk or by telephone on 07434661413.

Yours Sincerely,

Clinicin’s name
Title
Appendix 7: Participant information sheet
An investigation into the relationship between
sleep and day to day fatigue in chronic fatigue syndrome (CFS/ME)

We would like to invite you to take part in a research study. Before you decide you
need to understand why this research is being done and what it would involve for
you. Please take the time to read the following information carefully and discuss
this with others if you wish. Please ask us if there is anything that is unclear or that
you would like more information about.

What is the aim of the study?
This study aims to investigate how sleep is related to next day fatigue in chronic
fatigue syndrome/ myalgic encephalomyelitis (CFS/ME). We will be looking at
several aspects of sleep, including total sleep time and number of awakenings
during the night. We will also be looking at how participants perceive their sleep
quality and how this is related to their fatigue levels the following day. In addition,
we will also investigate how mood and levels of mental arousal before bedtime
might affect sleep quality.

Why have I been invited?
We are inviting you to take part in this study if you have a diagnosis of CFS/ME and
you identify yourself as having difficulties with sleep. This can include having
difficulty falling asleep, staying asleep and/or if you feel that your sleep is un-
refreshing.

Do I have to take part?
No you do not have to take part. It is completely up to you to decide, but if you do
we will then ask you to sign a consent form to show that you have read the
information sheet and have agreed to take part. If you do decide to take part but
change your mind later you are free to withdraw at any time and you do not need to
give us a reason for this. Choosing not to take part or withdrawing at any stage will
not affect the standard of care you receive at any time, now or in the future.

What will participation involve?
After you first contact the researcher, they will discuss the study with you over the
telephone or by email. If you are eligible and agree to participate then the study will
be split into 2 parts:

• The researcher will arrange to meet with you at a time and a place that is
  convenient for you. During this initial meeting you will be given a set of
  questions to fill in about your CFS/ME and about your sleep. These
  questions will be left with you and can be filled in at your own pace. The
  procedure for studying your sleep and fatigue will be fully explained to you,
  and you will also be given study equipment and materials to fill in. This
  meeting will last up to 40 minutes and you will have the opportunity to ask
  any outstanding questions or to change your mind about taking part if you
  wish.

Version 5 12/05/2014
Part 2 of the study will last for seven days and will start the day after your initial meeting. During the seven day study period you will be asked to:

- Wear a small watch like device called an actigraph. This will measure your movement and will provide information on your sleep quality.
- Fill in a brief sleep diary each morning. This will ask you to estimate how long it took to fall asleep and the number of times you awoke. It will also ask about your levels of mental arousal before sleep.
- Rate your fatigue levels and mood at four time points during each day (when you wake up, 12pm, 6pm and before bedtime).

At the end of the seven days, the researcher will visit you again to collect all equipment and to ask you about your experience of the study.

**What are the possible risks of the study?**

All of the questions that you will be asked as part of the study will be related to your sleep, your fatigue levels and your mood. If you were to find any of these questions upsetting or uncomfortable you would be free to leave any of these questions unanswered and would be free to end your participation any time.

**What will be done to ensure confidentiality?**

All personal information which is collected about you will be kept confidential, and information collected for the study will have your name and address removed so that you cannot be recognised. No information collected as part of the study will be shared with your GP unless the research team have concerns about your safety or the safety of others. Completed questionnaires, and study data will all be kept in secured filing cabinets, or password protected electronic storage at the University of Manchester. This information will only be seen by the members of the research team and in some cases individuals from regulatory authorities from the University or the Trust will need to look at this information to ensure that the study is being carried out properly. All questionnaires and study data will be destroyed 5 years after the end of the study.

**What are the benefits of this study?**

There may be no direct benefit to you as a result of participating within this study. However, it is hoped that the research will result in a greater understanding of how sleep is related to fatigue in CFS/ME. We also hope that having this greater understanding will allow more effective treatments to be developed in the future.

**What will happen if I don’t want to carry on with the study?**

You can withdraw from the study completely at any time and this will not affect your current or future treatment or any dealing with the CFS/ME service. You would not need to give reasons for your withdrawal.

**Who is organising the study?**

This study is being carried out as part of a doctorate in clinical psychology at the University of Manchester. The study has been reviewed by the University of Manchester, by Greater Manchester West NHS Research Ethics Committee (Ref: 14/NW/0258), and by the Research and Development Department at Salford Royal Foundation Trust.

Version 5 12/05/2014
What if I have any questions?
If you have any questions about any aspect of this study, you should speak to the researcher who will do their best to answer your questions. You can contact the researcher by telephone on [redacted] or by email at Charlotte.Russell-2@postgrad.manchester.ac.uk. You may also want to talk to your healthcare team or family about the study. If you would like to gain general advice about taking part in research you can contact the Salford Patient Advice and Liaison Service (PALS) by telephone on 0161 206 2003 or by email on PALS@srft.nhs.uk.

What if there is a problem or I want to complain about this study?
If there is a problem, you may contact the researcher in the first instance. All concerns will be dealt with promptly, and information will be provided by telephone or in writing to inform you of how the problem has been addressed. If the researcher is unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email to Research.Complaints@manchester.ac.uk. In the event that you may wish to make a formal complaint, you may wish to contact the Salford NHS Patient Advice and Liaison service (PALS) by telephone on 0161 206 2003 or by email on PALS@srft.nhs.uk.

Will I be able to find out about what this study has found?
It is hoped that this research will be published in a scientific journal when it is completed. A short summary of the results will also be sent to everyone who takes part following completion of the study.

What do I do if I want to take part?
If you are interested in taking part or have any questions about the research, please contact the researcher Charlotte Russell via email at charlotte.russell-2@postgrad.manchester.ac.uk or by telephone on [redacted]. Please leave an answering machine message or send a text message if the researcher is unavailable and they will telephone you back.

Thank you very much for reading this. If you would like any further information or have any questions, please contact the chief investigator of this project:

Charlotte Russell, Trainee Clinical Psychologist
The University of Manchester
Email: Charlotte.Russell-2@postgrad.manchester.ac.uk
Telephone: [redacted]

Version 5 12/05/2014
Appendix 8: Consent form
CONSENT FORM

An investigation into the relationship between sleep and day to day fatigue in CFS/ME

REC ref: 14/NW/0258

Participant Number

Consent for participation in the above study:

<table>
<thead>
<tr>
<th>Consent for participation in the above study:</th>
<th>Please delete as necessary and initial</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I confirm that I have read and understand the participant information sheet (Version 5, 12/05/2014) for the above study and have had the opportunity to ask questions.</td>
<td>YES/NO Initials:...........</td>
</tr>
<tr>
<td>2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.</td>
<td>YES/NO Initials:...........</td>
</tr>
<tr>
<td>3. I understand that data collected during the study may be looked at by individuals from the University of Manchester, where it is relevant to my taking part in this research. I understand that my personal details will be kept confidential.</td>
<td>YES/NO Initials:...........</td>
</tr>
<tr>
<td>4. I would like to be informed of the results. Declining to do so will not affect my participation in the study in any way.</td>
<td>YES/NO Initials:...........</td>
</tr>
<tr>
<td>5. I agree to take part in the above study.</td>
<td>YES/NO Initials:...........</td>
</tr>
</tbody>
</table>

Name or participant: ..............................................................................................................................
Signed: .................................................................................................................................
Date: .................................................................................................................................

Name of researcher: ..............................................................................................................................
Signed: .................................................................................................................................
Date: .................................................................................................................................

Version 2 07/04/14
Appendix 9: Participant instruction sheet
An investigation into the relationship between sleep and day to day fatigue in chronic fatigue syndrome

Study Instructions

Questionnaire Pack:
This contains four questionnaires that we would like you to complete as part of the study. It is ok to complete these in small chunks over the week if this feels more manageable to you.

Actiwatch
This will measure movement and light, and will give us information on your sleep pattern and quality. As part of the study we would like you to do the following:

- Start wearing the watch from **6pm this evening**
- Please wear this 24 hours a day except when you have a bath or shower
- Press the button on the front of the watch **when you get into bed at night and when you get out of bed in the morning.**
- If you nap during the day, or if you take the watch off for a period of time, please record this on the notes page back of the Daily Sleep, Symptom and Mood Diary.

Daily Sleep, Symptom and Mood Diary
Please complete one booklet per day. We would like you to fill this in at four time points during the day. You will need to complete the following ratings at each time point:

- **When you wake in the morning:** Sleep diary and Symptom and Mood ratings
- **12pm, 6pm and bedtime:** Symptom and Mood ratings only.

Please complete the sleep diary as accurately as possible to the nearest minute. There is an example of a completed sleep diary overleaf.

For the mood and symptom ratings, please complete the ratings as close as possible to the requested time and record the actual time of completion. Place a mark along the line to indicate your response. We are interested in your spontaneous responses on each of these, so try not to think for ‘too long’ about your responses.

The notes pages at the back of the diary can be used to provide any further information that you feel might be relevant. Please also record if you have napped during the day, or if you have taken the watch off for a length of time, and also if you have taken any medications to help you sleep.

Version 1 18.7.14
An example of a completed Sleep Diary is shown below:

### Sleep Diary: To be completed when you wake

<table>
<thead>
<tr>
<th>What time did you get into bed?</th>
<th>10.15pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>What time did you try to go to sleep?</td>
<td>10.45pm</td>
</tr>
<tr>
<td>How long did it take you to fall asleep?</td>
<td>55 min</td>
</tr>
<tr>
<td>How many times did you wake up, not counting your final awakening?</td>
<td>3 times</td>
</tr>
<tr>
<td>In total, how long did these awakenings last?</td>
<td>1 hour 10 min</td>
</tr>
<tr>
<td>What time was your final awakening?</td>
<td>6.35am</td>
</tr>
<tr>
<td>What time did you get out of bed for the day?</td>
<td>7.20am</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How would you rate the quality of your sleep?</th>
<th>Very poor</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td>How rested or refreshed did you feel when you woke up for the day?</td>
<td>Not at all rested</td>
<td>Slightly rested</td>
<td>Somewhat rested</td>
<td>Well rested</td>
<td>Very well rested</td>
</tr>
</tbody>
</table>

As you were trying to go to sleep last night, how much did thoughts keep running through your mind? *(Please place a mark along the line)*

Very little ___________________________ Very much

As you were going to sleep last night, how much did you experience a jittery, nervous feeling in your body? *(Please place a mark along the line)*

Very little ___________________________ Very much
Appendix 10: NHS research ethics committee amendment approval letter
30 July 2014

Mrs Charlotte Russell
Trainee Clinical Psychologist
Manchester Mental Health & Social Care Trust
Doctoral Programme in Clinical Psychology
Zochonis Building
Brunswick Street, Manchester
M13 9PL

Dear Mrs Russell

Study Title: An investigation into the relationship between sleep and day to day fatigue in patients with chronic fatigue syndrome

REC reference: 14/NW/0258
Amendment number: 1
Amendment date: 18 July 2014
IRAS project ID: 149719

- Include support verbal information given by researcher in the initial briefing.

The above amendment was reviewed the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notice of Substantial Amendment (non-CTIMP)</td>
<td>1</td>
<td>18 July 2014</td>
</tr>
<tr>
<td>Other [Study Instructions]</td>
<td>1</td>
<td>18 July 2014</td>
</tr>
</tbody>
</table>
Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/NW/0258: Please quote this number on all correspondence

Yours sincerely

Dr Lorraine Lighton (Chair)
Chair

E-mail: nrescommittee.northwest-gmwest@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Maureen Daniels, Associate R&D Manager, Salford Royal Foundation Trust
Ms Lynne Macrae
## NRES Committee North West - Greater Manchester West

### Attendance at Sub-Committee by correspondence

#### Committee Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Present</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Lorraine Lighton (Chair)</td>
<td>Consultant in Communicable Diseases</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Dr Gideon Smith</td>
<td>Consultant in Public Health</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

#### Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miss Lorraine Bannister</td>
<td>REC Manager</td>
</tr>
</tbody>
</table>