THE ROLE OF SLEEP IN CHRONIC FATIGUE SYNDROME

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IN CHRONIC FATIGUE SYNDROME

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ABSTRACT

Poor quality and unrefreshing sleep is one of the most common symptom complaints in Chronic Fatigue Syndrome (CFS). Despite this, the links between sleep dysfunction and CFS are not well understood, and there has been an absence of good quality research into the nature of sleep problems in CFS, which also lack consistency in the data reported. However, it remains plausible that sleep problems may help to maintain and exacerbate other existing symptoms. Given the dispute in models ranging from the biological to the psychological, competing to explain symptomology, it is a critical time by which we try to understand the relationship between poor sleep, fatigue, endocrine activity and CFS, in an attempt to short-circuit this debate.

With an aim to redress this, this thesis intended to examine the role of sleep from several angles, utilizing a range of assessment methods;

Study 1 addressed the lack of in depth qualitative interview studies, to understand the extent to which sleep, its management and problems, are linked to the lived experience of CFS, and how it interacts with other symptoms (chapter 3). Patient narratives demonstrated that sleep disturbances experienced were highly unpredictable and variable over time, but played a key role in symptom maintenance;

Study 2 examined self-reported sleep (via sleep diaries) in CFS patients, exploring whether sleep quality and daytime napping had an impact on daytime fatigue, sleepiness and cognitive functioning (key dimensions of the illness experience) (chapter 4). The results were highly variable but indicated that afternoon-evening napping was associated with greater impairment in daytime cognitive functioning in CFS patients. It was also evident that CFS patients with longer wake time and a shorter diagnosis had more severe fatigue;

Study 3 explored the possibility that sleep problems in this population are not homogeneous and revealed four sleep-specific phenotypes to exist, which are amenable to different treatment approaches. The initial cross-sectional examination of single-night polysomnography (PSG) data identified 30% of the sample had a primary sleep disorder (PSD), which underscores the need to assess for PSDs in CFS populations (chapter 5);

Study 4 was conducted to address the principle aim of this thesis; to determine the feasibility of a detailed, 3-night sleep assessment protocol in a small cohort of CFS patients. By utilising

a range of methods including ambulatory PSG and a gold-standard protocol for sampling of diurnal salivary cortisol, the study piloted the most comprehensive assessment of sleep ever attempted in a CFS population. The findings established a successful protocol that was acceptable to patients (chapter 6), a key advancement in this field where effective and thorough sleep assessment is needed. Preliminary sleep data confirmed a notable variability of sleep problems to exist. Further, the temporal stability of sleep variables was established; sleep continuity (sleep duration, wake duration, sleep efficiency) and main architectural (sleep stages) parameters were consistent across two nights of assessment (chapter 7).

The results presented in this thesis indicate that disturbed sleep is a major problem for patients with CFS, albeit highly variable between and within individuals. The identification of sleep phenotypes also confirms the heterogeneity of sleep in CFS. Interestingly, light sleep and arousability was a recurring sleep characteristic in patients that was mirrored by the studies presented throughout the thesis, highlighting a potential autonomic component. This should be a consideration for forthcoming work, along with the possibility that sleep disturbances may mediate the maintenance and exacerbation of symptoms, fuelling a reciprocal cycle that keeps the condition going.

The preliminary findings presented throughout this trajectory of research will help to form the systematic development of a sleep characterisation and intervention programme. With this field moving towards more patient-centred medicine and tailored treatments, by combining data from the objective and subjective sleep measures, we aim to design a definitive multi-centre study, using sleep-specific interventions, amenable to the four phenotypes identified. The long-term goal is to improve treatments that will enhance symptom management, which is crucial in this condition, at least until the CFS research understands the pathogenesis of this debilitating disease.

Key words: sleep, chronic fatigue syndrome, phenotypes, polysomnography, feasibility

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LIST OF ABBREVIATIONS

The following abbreviations and acronyms have been used in this thesis and have been defined upon first appearance in the text used throughout the thesis.

Abbreviation	Meaning
AASM	American Academy of Sleep Medicine
AUC_G	integrated area under the curve
AHI	apnea / hypopnea index
BMI	body mass index
CAR	cortisol awakening response
CBT	cognitive behavioural therapy
CBT-I	cognitive behavioural therapy for insomnia
CDC	Centers for Disease Control and Prevention
CFQ	Chalder fatigue questionnaire
DSQ	DePaul symptom questionnaire
ECG	electrocardiography
EEG	electroencephalography
EMG	electromyography
EOG	electrooculography
ESS	Epworth sleepiness scale
FFT	fast fourier transformation
FMS	fibromyalgia syndrome
GET	graded exercise therapy
GHQ	general health questionnaire
HADS	hospital anxiety and depression scale
HPA	hypothalamic-pituitary-adrenal (axis)
IPQ	illness perception questionnaire
ME	myalgic encephalomyelitis
MSLT	multiple sleep latency test
MWT	Maintenance of wakefulness test
N1	stage 1 sleep

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N2	stage 2 sleep
N3	slow wave sleep
NICE	National Institute for Health and Clinical Excellence
NREM	non-rapid eye movement sleep
NWAK	number of awakenings
OSAS	obstructive sleep apnea syndrome
PLMD	periodic limb movement disorder
PSA	power spectral analysis
PSG	polysomnography
PSD	primary sleep disorder
PSS	perceived stress scale
REM	rapid eye movement
REML	rapid eye movement latency
RLS	restless legs syndrome
SAQ	sleep assessment questionnaire
SE	sleep efficiency
SEI	sleep efficiency index
SL	sleep latency
SOL	sleep onset latency
SSM	sleep state misperception
SWS	slow wave sleep
TMT	trail making test
TST	total sleep time
WASO	wake after sleep onset
WSAS	work and social adjustment scale

GLOSSARY OF TERMS

The following table describes various sleep-related terms used throughout the thesis.

Term	Description
integrated area under the curve ($AUC_{G)}$	formula provides a measure of total cortisol secretion over the CAR period, and places less emphasis on the 1st and last CAR samples
apnea / hypopnea index (AHI)	number of apnea/hyponea events per hour of sleep
number of arousals (NoA)	number of arousals over the entire sleep period
number of awakenings (NWAK)	number of wake bouts following first episode of stage 2 sleep
rapid eye movement latency	length of time to first REM stage
percentage of wake (of TST)	percentage of recorded wake over the total sleep period (ie, how long they were awake following first episode of stage 2 sleep)
percentage of N1 (of TST)	percentage of recorded stage 1 sleep over the total time asleep
percentage of N2 (of TST)	percentage of recorded stage 2 sleep over the total time asleep
percentage of N3 (of TST)	percentage of recorded slow wave sleep over the total time asleep
percentage of REM (of TST)	percentage of recorded REM sleep over the total time asleep
Sleep architecture	the structure and pattern of sleep
Sleep macrostructure	the temporal organisation of sleep
Sleep microstructure	phenomena such as arousals, k-complexes and sleep spindles, as measured by EEG

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sleep onset latency (SOL)	length of time from lights out to first episode of stage 2 sleep
slow wave sleep (SWS)	often referred to as deep sleep, consists of stage N3 (non-rapid eye movement sleep)
total sleep time (TST)	total time asleep
wake after sleep onset (min)	number of minutes of recorded wake following first episode of stage 2 sleep

PREFACE

Peer-reviewed publications that have arisen from this thesis

Gotts, Z. M., Deary, V., Newton, J., Van der Dussen, D., De Roy, P., & Ellis, J. G. (2013). Are there sleep-specific phenotypes in patients with chronic fatigue syndrome? A cross-sectional polysomnography analysis. *BMJ open*, *3*(6).

Conference proceedings that have arisen from this thesis

Gotts, Z. M., Ellis, J. G., Brannan, K., Newton, J. L., & Deary, V. (2013). Daytime Napping Impairs Cognitive Functioning in Chronic Fatigue Syndrome (CFS). *UK Society for Behavioural Medicine (UKSBM) 9th Annual Scientific Meeting, 9-10 December 2013, Oxford, p.76*

Non-refereed publications that have arisen from this thesis

Gotts, Z. M., Deary, V., & Ellis, J.G. *Sleep Studies* - International Association for CFS/ME (IACFS/ME) Newsletter. April 2013, attachment 6. Reviewed by Professor Julia Newton.

This thesis is dedicated in loving memory to my Nanna.

Without her encouragement throughout my education,

I would never have got here.

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There have been many people, too many to name individually, that have provided much-valued guidance and support throughout this PhD. I can only hope you all know how grateful I am.

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More personally, I would like to thank my family for their love and endless support in all aspects of my life. Tawfik, for his constant support and ensuring I maintain a firm perspective on life. Without his love, patience, and sunny optimism I would be lost. I am also grateful to my Mum, Grandad and Mike, who have also seen me through the ups and downs of this PhD over these past three years. They have always been on the other end of the phone, at all hours of the day, with their encouragement and reassurance. Thank you for putting up with me. I love you all very much.

One person cannot go unnamed, my Nanna, who sadly passed during my PhD. She was my most enthusiastic cheerleader and my rock. Without her endless encouragement throughout my education, none of this would have happened and it only seems right that I dedicate this thesis to her.

Finally, a special thank you to Professor Trudie Chalder and Dr Nicola Barclay for a truly enjoyable and memorable viva.

Zoe Marie Gotts, Northumbria University, April 2014

AUTHOR'S DECLARATION

This work has not been submitted for any other award. In all experimental chapters of this thesis the author had sole responsibility for the data collection, analysis, and interpretation. The writing of this thesis is the sole work of the author. The work was done in collaboration with Newcastle University & Newcastle Hospitals NHS Foundation Trust.

Any ethical clearance for the work presented in this thesis has been approved. Approval has been sought and granted by the faculty of Health & Life Sciences Ethics Committee at Northumbria University, and the Newcastle and North Tyneside Local Research Ethics Committee, on 3rd August 2012. The Newcastle Hospitals NHS Foundation Trust sponsored the study.

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Signature:

Date:

"If sleep doesn't serve an absolutely vital function, then it is the greatest mistake the evolutionary process ever made"

Professor Allan Rechtschaffen,
University of Chicago Sleep Laboratory, 1978

CHAPTER ONE
CHRONIC FATIGUE SYNDROME (CFS): CLASSIFICATION, MODELS AND SYMPTOM MANAGEMENT

1.1 Introduction

What is CFS?

Most people feel overly tired at some time or another and in 10% of people who see their GP, fatigue presents as the principle symptom. However, 1-2% of the population experience severely disabling and ongoing fatigue. It is this significant minority of patients enduring the profound and unexplained fatigue that has been the topic of debate for the past 30 years. Naming the illness has been a topic of controversy dating back to the early 1980's where patients were considered to be having a reaction to stressors from modern society, otherwise labelled as "yuppie flu" (Wessely, 1997). Conflicting arguments advocating an organic cause of the illness advanced a series of names to reflect this, such as postviral fatigue syndrome and myalgic encephalomyelitis (ME).

In response to the debates surrounding the use of terminology with the condition, and in an attempt to define a homogenous patient group for the purpose of research, a renaming of the condition to chronic fatigue syndrome (CFS) was coined by the Centre for Disease Control in Atlanta, who also published the first standardised diagnostic criteria for the condition (Holmes et al., 1988). Following this, a number of related definitions were published from the UK, Australia and Canada (Oxford, 1991; Fukuda et al., 1994; Carruthers et al., 2003; Reeves et al., 2005; NICE, 2007), and these case definitions are discussed further later in the chapter.

Fukuda and colleagues endeavoured to standardise the diagnosis of CFS across countries, in their publication of a consensus definition for the illness (Fukuda et al., 1994). The definition specified that fatigue is the primary symptom, which should be of definite onset and cause significant disruption to the person's life. In addition to fatigue, at least four other key symptoms are required to fulfil these diagnostic criteria, including muscle and joint pain, headache, cognitive dysfunction and unrefreshing

sleep. The NHS estimated that 250,000 people in the UK have CFS (Choices, NHS, 2011). Sleep disturbances are frequently reported in CFS, and these complaints have been shown to persist throughout the course of the illness (Nisenbaum et al., 2003). The symptom presentation and issues with the diagnostic criteria are discussed further in the following sections.

1.2 CFS and its clinical presentation

CFS is a severely disabling condition, and with no consistently identifiable biomarkers, diagnosis relies upon symptom report criteria. Patients with CFS experience a multitude of symptoms. These range from those of a physical nature (i.e. severe malaise and fatigue following physical activity, muscle and joint pain/myalgia) to those that suggest ongoing abnormalities in immune system function (i.e. sore throat, swollen/painful glands, headaches, temperature control, intermittent flu-like feelings), to brain and central nervous system symptoms (i.e. dizziness, mental fatigue, cognitive dysfunction, palpitations and symptoms associated with low blood pressure/postural hypotension, fainting). Other symptoms include sleep disturbances (often increased requirements for sleep at illness onset followed by problems with sleep maintenance or onset and waking unrested) and irritable bowel symptomology. Over time, patients can also develop emotional lability and mood disturbances. Not all symptoms are experienced by all patients, and besides the widespread symptoms described, there are also a myriad of "minor" ones. Fluctuation in symptom severity is common and patients often report as having "good" and "bad" days. Nonetheless, individuals experience marked functional disability (Tiersky et al., 2001) and face significant reductions in their quality of life (Anderson & Ferrans, 1997).

1.3 Diagnostic challenges

In order to accurately diagnose an illness or disease, it is important to have a reliable set of criteria for researchers and clinicians. That said, diagnosing CFS can be complicated by a number of factors. There is no generally accepted diagnostic test to reliably diagnose or exclude CFS (i.e. no lab test or biomarker for CFS), and fatigue and other symptoms of CFS are common to many illnesses. Further, the illness has a

pattern of remission and relapse, and symptoms vary from person to person in type, number and severity.

Whilst CFS affects at least 250,000 people in the UK (Choices, NHS, 2011), the variance in the rates reported from epidemiological studies (0.23% to 2.6%, Jason et al., 2009; Reyes et al., 2003), are a likely result of the differing published criteria and the guidance they set out. A meta-analysis to examine variability among prevalence estimates for CFS suggested observed heterogeneity in CFS prevalence may also be due to differences in the method of assessment used (Johnston et al., 2013). The following section will discuss the difficulties that surround classification of CFS, based on the differing case definitions that there are to describe CFS clinically.

1.3.1 Case Definitions

There are many aspects to CFS that are controversial, from its etiology through to pathophysiology, treatments and even to the naming of the condition. The classification including the case definitions and problems surrounding varied clinical descriptions of CFS are the key issue when it comes to agreement on naming the condition, and this disagreement occurs among researchers, medical practitioners and patients. This is problematic for a field of research that is attempting to redress the uncertainty. Despite there being some overlap of symptoms between the clinical descriptions, the definitions differ (see table 1.1 for CFS definitions, chronologically).

The Fukuda Case Definition (CDC 1994 Criteria) is the international consensus definition that is most widely used. It specifies that in addition to being present for at least six months, fatigue must have a definite onset, cause substantial disruption to the individual's day to day activities, and should not be caused by continual exertion. At least four additional key symptoms, such as muscle and joint pain, headaches, unrefreshing sleep and cognitive dysfunction need to be reported. There is also a final requirement that other known causes of chronic fatigue must have been ruled out, specifically clinical depression, side effects of medication, eating disorders and substance abuse.

Case definitions (chronologically)	Developed from other criteria or definitions?	Institution & country of first author
CDC-1988/Holmes *et al*		Centers for Disease Control, Atlanta, USA
Oxford-1991/ Sharpe *et al*		University of Oxford, Oxford, UK
CDC-1994/Fukuda *et al*	CDC-1988	Centers for Disease Control, Atlanta, USA
Working case definition-1996/Komaroff *et al*	CDC-1988	Brigham and Women's Hospital Massachusetts, USA
CFS-1998/Hartz *et al*	CDC-1994	Medical College of Wisconsin, USA
Canadian-2003/ Carruthers *et al*		Royal College of Physicians and Surgeons of Canada, Canada
Empirical CDC-2005/ Reeves *et al*	CDC-1994	Centers for Disease Control and Prevention, Atlanta, USA
Empirical-2007/ Jason *et al*		DePaul University, Chicago, USA
NICE-2007 Guidelines		National Institute for Health and Clinical Excellence, London, UK
Revised Canadian-2010/ Jason *et al*	CDC-1994, Empirical CDC-2005, Canadian-2003	DePaul University, Illinois, USA
ICC-2011/ Carruthers *et al*	Canadian-2003	Independent, Canada

Notes: ICC, international consensus criteria

Table 1.1: Case definitions for CFS, (adapted from Brurberg et al., 2014)

The Holmes Definition (CDC 1988 Criteria) differs from the 1994 CDC criteria in that it excludes patients with psychiatric diagnoses and requires the presence of eight secondary symptoms, not just four. The Oxford Criteria, published in 1991, include both CFS of unknown etiology and a subtype of CFS called post-infectious fatigue syndrome which "either follows an infection or is associated with a current infection." (Sharpe et al., 1991). An important difference is that the presence of mental fatigue is necessary to fulfil the criteria. It is also worth noting the London Criteria (1994) and the 2011 'international consensus criteria for ME' (Carruthers, 2011). These definitions refer to the condition as 'M.E.', however they are also considered as definitions of CFS, further highlighting the contentious nature in the naming of this condition. The Canadian Criteria, published in 2003 indicates that for diagnosis, there is a requirement for "two or more neurological/cognitive manifestations" and one or more symptoms from at least two of the categories of autonomic, neuroendocrine and immune manifestations, in addition to multiple major criteria of fatigue, post exertional malaise and/or fatigue, chronic pain and sleep dysfunction (Carruthers, et al., 2003).

With the Canadian clinical case definition (Carruthers, et al., 2003), there is the requirement for specific CFS/ME symptoms (i.e. post-exertional malaise and memory/concentration problems) to be present and the definition tends to be more complex to apply, it is thus rarely used for research and clinical diagnosis purposes, compared with the more widely used Fukuda definition. This creates methodological problems for research that is carried out in different settings, where investigators recruit samples of patients with different levels of each of the core symptoms. This in turn generates problems when comparing research studies on patients, as study groups are potentially heterogeneous.

	HOLMES	FUKUDA	REEVES 2005	OXFORD	ICC
Minimum duration of illness	6 Months	6 Months	NA	6 Months	NA
Onset type	Distinct	New or definite	NA	Distinct	Infectious or gradual.
Lab tests used	Minimum battery of standard laboratory screening tests looking for known cause of fatigue.	Minimum battery of standard laboratory screening tests looking for known cause of fatigue.	Routine analysis of blood and urine	None	None listed.
Exclusions	Clinical conditions that would produce similar symptoms	Unless clinically indicated no additional tests are required to exclude other diagnosis. Findings, lab or imaging test suggesting the presence of a condition that may explain chronic fatigue must be resolved (meaning is not clear) before further classification.	A list of permanent medical and psychiatric exclusions is given, as well as possible exclusions.	Medical conditions that cause chronic fatigue. Range of mental health disorders. Organic brain disease	Unless clinically indicated no additional tests are required to exclude other diagnosis. Primary psychiatric disorders, somatoform disorder and substance use are excluded.
Depression and anxiety	Not excluded	Not excluded, only major depressive disorder WITH psychotic OR melancholic feature is excluded.	Not excluded, only major depressive disorder WITH psychotic OR melancholic feature is excluded for 5 years before onset of illness.	Not excluded	Not excluded, reactive depression is.
PEM	Increased symptoms of fatigue as a result of exercise (previously tolerated). Recovery 24 hours or longer.	PEM not required for this diagnosis, but can be included as a minor symptom. Increased symptom of malaise after exertion. Recovery 24 hours or longer.	Increased symptoms of fatigue a result of any activity that is not a demanding schedule.	No version of PEM included in the criteria.	Increased symptoms of fatigue a result of any level of activity. No duration of recovery required.
Fatigue	Debilitating fatigue or fatiguability	Persistent or relapsing chronic fatigue that is not the result of ongoing exertion, not substantially alleviated by rest that substantially reduces activity level.	Fatigue is incorporated into the 3 self-report scales.	Fatigue of psychiatric or idiopathic origin.	Fatigue is included under the term PENE: a pathological inability to produce sufficient energy on demand.

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Minor symptoms	6 or more of the 11 symptom criteria and 2 or more of the 3 physical criteria; or 8 or more of the 11 symptoms listed. Minimum of 6 to 8 symptoms)	4 or more of 8 symptoms listed	NA	May be present	1 symptom from each of the 3 symptom categories of pain, sleep disturbance and cognitive symptoms. 3 symptoms from a mix of immune and neuroendocrine/autonomic symptoms. 1 symptom from autonomic symptoms (minimum of 7 symptoms).
Pain	New headaches, muscle discomfort or myalgia. Migratory arthralgia without joint swelling or redness.	New headaches. Muscle pain. Multi joint pain without swelling or redness.	NA	NA	Headaches. Non inflammatory muscle pain or joint pain. Abdomen or chest pain.
Sleep disturbance symptoms	Sleep disturbance	Unrefreshing sleep	NA	NA	Sleep disturbance. Unrefreshing sleep.
Cognitive/ Neurological symptoms	Neuropsychological complaints. Muscle weakness.	Symptoms related to cognitive impairment.	NA	NA	Symptoms related to cognitive impairment. Perceptual and sensory disturbances. Ataxia. Muscle weakness. Fasciculations. Sensory overload.
Autonomic symptoms	Fever (temp 37.5°C to 38.6) or chills.		NA	NA	Symptoms related to blood pressure, gastric and urinary systems, cardiac involvement.
Neuroendocrine symptoms	NA	NA	NA	NA	Symptoms related to temperature. Genitourinary symptoms.
Immune symptoms	Painful lymph nodes, sore throat.	Painful lymph nodes, sore throat.	NA	NA	Symptoms such as painful lymph nodes, sore throat, flu like symptoms, sensitivities to food, medicine and/or chemicals.

Notes: NE, not applicable; ICC, international consensus criteria for ME; PEM, post-exertional malaise; PEN, Post-Exertional Neuroimmune Exhaustion

Table 1.2: Overview of the different case definitions for CFS (adapted from Morris and Maes, 2013)

These issues with classification only add to the contentious nature of the illness (see table 1.2 for an overview of case definitions). With disagreements already existing between patients, clinicians and researchers over its etiology, treatment and name, classification of this condition is an area that warrants further work. That said, the 1994 CDC case definition (Fukuda) appears to be the most reliable clinical assessment tool available at the current time (Johnston et al., 2013) and has been recommended for use in the UK clinical services (NICE, 2007). However, improving clinical case definitions and their adoption internationally will enable better comparisons of findings and inform health-care systems about the true burden of CFS.

The etiology and pathophysiology of CFS remains as disputed as the nosology, with several theories proposed ranging from viral infections (Wessely & Powell, 1989), immunological and neurobiological factors (Cho et al., 2006; Cleare, 2004), to psychological stress (Van Houdenhove et al., 2002). Given that CFS is not likely to be explained by one single etiological mechanism, it has been proposed that it is the interaction of multiple factors that serves to precipitate and/or maintain CFS. This more generic bio-psychosocial model has been proposed by various authors (Deary, Chalder & Sharpe, 2007; Harvey & Wessely, 2009). This model proposes that illness onset and maintenance is the result of the interaction of multiple factors in different domains, as described in the following section.

1.4 A Biopsychosocial Model

Part of the confusion with CFS is due to competing models of the condition. A general biopsychosocial model has been applied to explain CFS from a multi-factorial perspective. It is one which incorporates predisposing, precipitating and perpetuating factors that ultimately seeks to explain the phenomenology of the condition as arising through the interaction of biological, affective, behavioural and cognitive factors (Deary, Chalder & Sharpe, 2007; Moss-Morris, Deary & Castell, 2013). In a recent review of explanatory models of functional somatic symptoms (Van Ravenzwaaij et al., 2010), this multi-factorial model was distinguished from other single modality models (which propose that symptoms are the result of one pathogenic mechanism), as being a meta-model that provides a coherent theoretical framework for describing how the interaction of such physiological, behavioural, cognitive and affective factors can

cause and/or exacerbate physical symptoms. The categories of this model will be used to describe what is known in terms of predisposing, precipitating and perpetuating biopsychosocial factors in CFS (a 3-P Model).

1.4.1 Predisposing Factors

Who is affected, what makes the person vulnerable to these symptoms?

There have been some prospective studies investigating vulnerability to developing CFS. Longitudinally, experience of distress, anxiety and depression makes people more likely to subsequently develop CFS (Moss-Morris & Spence, 2006; Wessely et al., 1995; White et al., 2001). This may be partly genetically mediated with there being evidence from a large prospective twin study (Kato et al., 2006) that there appears to be a genetic vulnerability to both emotional and physical markers of distress (such as fatigue). That said, retrospective studies highlight the importance of early life experiences, with people suffering from CFS being more likely to report histories of abuse than normal or illness controls (Borsini et al., 2014). Increased physiological arousal in individuals, perhaps associated with stress could therefore be contributing early on in this condition, to predispose the individual to illness onset. Other predisposing factors, although largely from cross sectional and retrospective studies, include being physically active, persisting with physical activity when ill and the self-critical aspects of perfectionism (Deary & Chalder, 2010; Moss-Morris et al., 2011).

1.4.2 Precipitating Factors

Viral infections (White et al., 1998) and stress (Kato, et al., 2006) are the most frequently self-identified triggers for fatigue onset. One prospective study has shown that the combination of these factors may be important; people who had glandular fever were more likely to go on to develop CFS if they had experienced more stressful life events prior to the onset of their glandular fever (Buchwald et al., 2000). These findings have been confirmed in both cross sectional and retrospective studies (Chalder, 1998; Salit, 1997).

1.4.3 Perpetuating Factors

The multi-factorial model proposes that the interaction of physical processes, illness behaviours and illness related cognitions and social factors can serve to perpetuate physical symptoms (Deary, Chalder & Sharpe, 2007; Moss-Morris, Deary & Castell, 2013) (Figure 1.1). This has been demonstrated in two prospective studies (Candy et al., 2004; Moss-Morris, et al., 2011). Individuals with more generalised and more negative illness and symptom attributions, and those who responded to symptoms with more 'all-or-nothing' behavioural patterns, were more likely to develop CFS six months after a glandular fever infection.

1.4.3.1 Perpetuating Factors – Physical

The hypothalamic-pituitary-adrenal (HPA) axis serves to regulate the body's response to acute and chronic stress. It has effects on energy metabolism and mood, and also influences immune functioning. Biological research has focussed on the HPA axis and its dysfunction in patients with CFS (Tomas, Newton and Watson, 2013). In particular, there is evidence for a reduced cortisol output in patients (Roberts et al., 2004; Cleare, 2003), which may be a result of prolonged stress leading to a down-regulation of the HPA axis; hypocortisolism is a marker of symptoms such as pain, fatigue and enhanced stress sensitivity as observed in CFS.

Research by Heim et al (2009) has also highlighted the role of cortisol in CFS. Their study found that low levels of cortisol, a hallmark biological feature of CFS, are associated with early life stress such as childhood trauma. The study indicates that low cortisol levels may actually reflect a marker for the risk of developing CFS rather than being a sign of the syndrome itself. Such findings indicate that neuroendocrine dysfunction in patients may reflect a biological correlate of *vulnerability.*

Further, lowered levels of cortisol may also lead to the increased release of inflammatory cytokines and that are important determinants of the "illness response" marked by non-specific symptoms such as fatigue, increased pain sensitivity, depressed activity and concentration difficulties that accompany the response to infection (Fries et al., 2005). Hypocortisolism is also considered an adaptive response by the body, characterised by a decrease in energy consumption during periods of

sickness or injury (i.e. a state of chronic fatigue) to promote subsequent recuperation (Van Hoof et al., 2003).

Issues with existing cortisol studies

Although this mild hypocortisolism has been shown in CFS patients, other work has been unable to replicate these low baseline cortisol levels, finding no links between reduced secretion of cortisol and the symptom of fatigue (Wood et al., 1998). The variability between studies may be a result of the differential methods of assessment method used for sampling cortisol, and also the heterogeneity of patient samples (Nijof et al., 2014; Papadopoulos & Cleare, 2012; Cleare, 2003). Ideally, sampling of cortisol should occur over a several consecutive days, and at several time points per day to overcome the potential for state influences upon levels of cortisol. This affords the opportunity to obtain a more stable variable (Hellhammer et al., 2007).

It is also possible (and beneficial) to obtain a number of indices of HPA function in patients; The cortisol awakening response (CAR), describes a surge in cortisol levels upon awakening and has two components; the total cortisol output within this period and; the dynamic response, usually referring to the change in cortisol output from waking to peak levels. Total cortisol output is estimated by computing the area under the curve from baseline (AUC_G), and the dynamic response by the area under the curve from a baseline defined as cortisol level at waking (AUC_I) (Pruessner et al., 2003). The diurnal cortisol slope can also be calculated, this models the declining pattern of cortisol secretory activity throughout the rest of the day, following the CAR. Also an estimation of total cortisol output may also be calculated for the complete circadian rhythm (or profile) using AUC_G or mean cortisol levels. These indices afford more robust cortisol assessment in patients, yet a recent review of cortisol studies in CFS highlights how existing protocols have been limited in the number of indices obtained, and often utilise 1-2 day sampling protocols (Powell et al., 2013).

HPA axis function is also affected by inactivity, sleep disturbance, medication, ongoing stress and psychiatric comorbidity, all frequently experienced by CFS patients. Deterioration in the patients' physical condition (a result of decreased activity due to fatigue and pain that in turn results in loss of muscle strength) perpetuates symptoms, making daily functioning even more problematic (Van

Houdenhove et al., 2007). Persistent sleep problems also serve to worsen symptoms and functional limitations in CFS patients as they mimic the body's neuroendocrine response to stressful circumstances. The neuroendocrine-mediated disturbances that have been identified in the sleep-wake cycle of CFS patients (i.e. altered temperature and melatonin circadian rhythms) (Fossey et al, 2004), have reciprocal effects on the release of the stress hormone cortisol (i.e. concentration and timing of cortisol released does not follow a circadian pattern), that in turn produces symptoms of daytime fatigue, nonrestorative sleep, depression, anxiety and memory and concentration problems, such as are seen in CFS (Fossey et al, 2004). Despite the undeniable effects of desynchronisation in these cycles, the precise role of disturbed sleep in the perpetuation of CFS remains unclear (Armitage et al., 2007; Majer et al., 2007). There are also suggestions that such endocrine changes may be secondary to the CFS; given the dysregulation is more pronounced in patients who have had the illness for a longer period (Cleare, 2004). Nevertheless, these endocrine disturbances are likely to perpetuate existing symptoms in patients (Van Houdenhove & Luyten, 2008).

1.4.3.2 Perpetuating Factors – Illness Behaviours & Cognitions

Patient's illness beliefs and coping strategies are key (unintentional) perpetuating factors in CFS. For instance, symptom-focus and perceived loss of control over symptoms has been associated with fatigue severity (Vercoulen et al., 1998). Further, patients who have difficulty in making sense of the situation, or a lack of acceptance for their CFS diagnosis has been linked to lower quality of life and more associated psychiatric symptoms (Van Damme et al., 2006). Patients with CFS are also more likely to make fixed physical attributions for their physical symptoms (Moss-Morris, et al., 2012), and a common response to physical illness is rest; patients may exacerbate their illness by putting their already disturbed stress mechanisms under pressure by trying to press on and keep going (Moss-Morris, Deary & Castell, 2013). Those with a history of a particularly overactive lifestyle are prone to this "boom-and-bust" activity pattern (Van Houdenhove et al., 2001), and these periodic bursts of activity in an attempt to meet expectations, inevitably amplify symptoms (particularly disability and fatigue severity (Harvey et al., 2009)), resulting in beliefs in failure.

There is consistent evidence for complaints about disturbed sleep in CFS. As with reduced activity and excessive rest, sleep disturbance may be both a cause and a consequence of the fatigue and other physical symptoms associated with CFS (Morriss, Wearden & Battersby, 1997). Sleep dysfunction is considered a hallmark symptom of CFS, and features as a key component of the criteria outlined above. This disturbance can take various presentations, from problems initiating sleep, waking frequently and for long periods during the sleep cycle, through to early awakenings, and prolonged sleep duration. However, the specific role of sleep in this condition is not fully understood. Given the importance of sleep to human health and wellbeing is undeniable (i.e. recuperative, restorative and learning properties (Van Cauter et al., 2000; Stickgold, 2005), there is a need to broaden our understanding of its precise role in CFS. Chapter 2 will examine and review the current literature regarding sleep and its implication in CFS in further detail.

1.4.3.4 Perpetuating Factors - Social

Social and environmental factors in CFS cannot be overestimated. A lack of recognition, stigma and disbelief from both family members and healthcare professionals, are reactions that create extra stress for the patient and thus negatively impact on their quality of life, also encouraging illness behaviour (in the words of Hadler (1996): “when you have to prove you are ill, you cannot get well”). With a lack of explanation for symptoms and conflicting advice, paired with a dissatisfaction with healthcare professionals, there is the suggestion that such lifestyle factors (adjunct with worry and rumination) can contribute to a prolonged activation of the stress response over time (Brosschot, Pieper & Thayer, 2005), which leads to physiological changes (described earlier), that in turn maintain CFS and its symptoms.

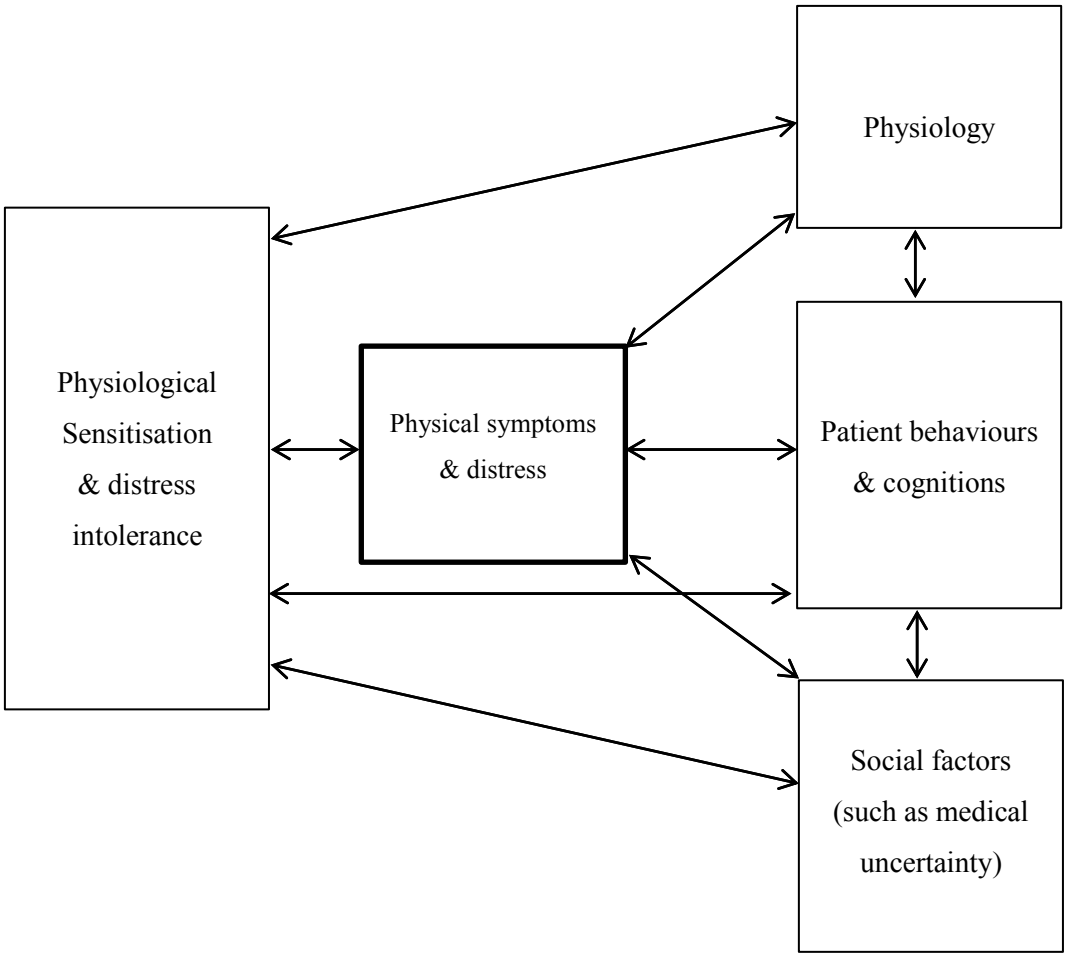

Figure 1.1: Explanatory model for CFS; a focus on the perpetuating factors and maintenance of the condition (adapted from Deary, Chalder & Sharpe, 2007)

In summary, the multifactorial biopsychosocial model of CFS proposes that susceptible individuals, for example those prone to distress, high achievers, and overactive individuals, experience an onset of symptoms precipitated by a viral illness and/or stressful life event(s). Symptoms may then become maintained through interactions between several processes. For instance reduced and inconsistent physical

activity may lead to physiological changes, such as deconditioning and increased physical symptoms of fatigue. Management of these factors may be further impeded by medical uncertainty and unhelpful illness beliefs and behaviours. There is indirect evidence for this model through treatment trials for CFS. Cognitive Behavioural Therapy (CBT) is currently the evidence based treatment for CFS, and is based on tackling the interaction between the aforementioned factors. Studies have shown, for instance, that improvement in CFS, following CBT, is partly mediated by changes in symptom focus (Deale et al., 1997).

1.5 From perpetuating factors to therapy: current CFS treatment practices

Diagnosis of CFS depends upon self-reported symptoms, and its clinical management is therefore challenging for the physician but equally so for the patient. There is no "cure" for CFS, rather the best evidence is for symptom management, however there remains disagreement with regards to treatment options and their efficacy. That said a combination of graded exercise and cognitive behavioural therapy (CBT) is considered the best evidence therapeutic approach (White et al., 2011). The rationale for these interventions stems from tackling illness-perpetuating factors. It should be noted however, that the use of pharmacological therapies (e.g. antidepressants, analgesics and other medications with a CNS site of action) alongside these approaches is common, however, currently there is little evidence for these, including treatments targeting the proposed underlying pathophysiology of CFS, such as hypocortisolism (Van Houdenhove & Luyten, 2008).

The cognitive changes that occur during CBT for CFS are important; increased perceived activity, physical functioning and sense of control over fatigue, together with a decrease in focusing on symptoms does appear to result in lower levels of fatigue in patients (Heins et al., 2013). Burgess, Andiappan & Chalder (2012) even demonstrate mild to moderate improvements in physical functioning and fatigue following treatment utilising telephone-based CBT.

Interventions that gradually increase physical activity (i.e. Graded Exercise Therapy (GET) and pacing) and CBT may work not only in the reversal of deconditioning, but also in working towards desensitising the fear of activity in patients, fear that may

have derived from their experience of avoiding exposure to sensations (i.e. pain and fatigue) (Deary, 2008). Further, Deary (2008) emphasises how a self-regulating cycle of 'unhelpful' illness cognitions and behaviours serves to maintain medically unexplained conditions such as CFS. By incorporating treatment approaches that address this self-dysregulation (i.e. 'third wave' behavioural therapies such as acceptance and commitment therapies), may help individuals switch from avoidance to mindfulness and acceptance of symptoms and distress, however, as yet there is no evidence for 3rd wave therapies in CFS.

CBT and graded exercise approaches to treatment offer an opportunity to shift patient perceptions from symptom avoidance to general wellbeing, or life enhancement (Deary, 2008). They work by encouraging patients, despite their symptoms, to switch their focus of themselves and the progress being made during treatment, to what they feel and are able to do. Further, CBT studies have also demonstrated efficacy in increasing cortisol levels (Papadopoulos & Cleare, 2012; Roberts et al., 2004); the therapy works to reverse the effects brought on by reduced activity levels, stress and depression. In addition to CBT, graded exercise also works to modify patient's illness perception, which in turn encourages patients to make adjustments that optimise their energy expenditure (Van Houdenhove & Luyten, 2008; Moss-Morris et al., 2005). Further there is evidence for the favourable therapeutic effects of CBT and exercise on increasing the resilience of the HPA axis (Gaab et al., 2006). Such studies highlight the multidirectional relationship between cognitive, behavioural and biological processes in CFS (Tomas, Newton and Watson, 2013).

1.5.1 Management of sleep disturbance

Part of the perpetuating cycle concerns disturbed sleep as a maintaining factor in CFS. Likewise, one therapeutic goal in CFS management is to improve sleep in patients. The current best evidence treatments (GET and CBT) all involve a sleep management component (i.e., establishment of a regular sleep pattern, cessation of daytime sleeping, establishing a set wake-up time every morning, and a general reduction of total time spent in bed), and these evidence-based treatments have observed improvements in patients' sleep disturbances (White et al., 2011) and reductions in severity ratings for unrefreshing sleep (Jason et al., 2007), at both post-treatment and

follow-up, however it is not yet clear how significant the sleep component may be on its own i.e. how the treating sleep alone contributes to the efficacy of the overall treatment. Improved sleep would serve to affect the perception of other symptoms and the ability of individuals with CFS to carry out daytime activities. On the other hand, pharmacological therapies are often prescribed alongside other therapies to manage disturbed sleep; low dose antidepressants (i.e. selective serotonin reuptake inhibitors) are often prescribed to patients with CFS to be taken at bedtime for enhancing sleep. This is despite the adverse effects of such pharmacological treatments on sleep documented in non-CFS populations (Menefee, at al., 2000). Given that disturbed sleep is a common symptom of CFS, careful assessment is necessary, to distinguish a primary sleep disorder (PSD) from a potential comorbid condition than may require specific treatment (i.e. hypothyroidism, psychiatric disorder, or other PSD).

Disturbed sleep is likely to be an important factor in CFS. It is unquestionable that sleep is vital for human health, and the implication of poor sleep in the perpetuating cycle of CFS has been shown (described in section 1.4.3). This, together with sleep management being a component of evidence based CFS therapies, highlights the importance of more thorough exploration of the nature and extent of the role of sleep in CFS. However, the current evidence-base for sleep and its specific role in CFS is fragmented. The next chapter will therefore examine the existing research and techniques that have attempted to explain these connections.

CHAPTER TWO
LITERATURE REVIEW: SLEEP IN CHRONIC FATIGUE SYNDROME

2.1 Introduction

2.1.1 The regulation and structure of normal adult sleep

Sleep is an anabolic state which means it is a time when most rejuvenation, repair and growth occur. Specifically, it is during sleep that the immune system becomes fully active and where we fight off disease, counteract allergies and build up new resistances. First of all, it is important to understand the 'normal' characteristics of human sleep, as it provides a context for understanding the role of sleep in CFS, in which 'normal characteristics may be altered.

The sleep-wake cycle is controlled by two separate but interacting processes (Borbély, 1982); the circadian process and the homeostatic or recovery process. The circadian process is that which regulates the daily rhythms of the body and brain. This main circadian pace-maker is found in a group of cells in the suprachiasmatic nucleus (SCN) of the hypothalamus, providing a pattern of activity that drives all bodily rhythms including sleep-wake activity, hormone release and liver function. The biological phase markers responsible for measuring the timing of an individual's circadian rhythm are melatonin, cortisol and temperature. The drive to sleep from the circadian clock starts slowly around 11pm, increases to peak around 4am and tails of during the morning. The clock provides a sleep-promoting process which continues into mid-morning and then provides a wakefulness-promoting process during the day.

The homeostatic or recovery drive to sleep (process S) is wake-dependent; increasing in proportion to the amount of time a person has been awake since their last sleep. Process S reaches a maximum after around 16 hours of being awake and rapidly declines during sleep. When sleep has been shorter than usual, there is a 'sleep debt' which leads to an increase in this process, working to ensure the debt is made up at the next sleep period. These two processes interact to promote the onset of sleep when

both are high (at the usual bedtime), and maintain sleep when the circadian process is high and the S process in declining.

Sleep comprises two states; rapid eye movement (REM) and non–REM (NREM) sleep that alternate cyclically across a sleep episode. The natural pattern of sleep in adults begins in non-REM (stage 1) and progresses through deeper non-REM stages (2 & 3), before the first episode of REM that occurs 90-110 minutes later. (Carskadon & Dement, 2011) Stage 1 (N1) is the light stage of sleep, occurring at the beginning of the sleep cycle and considered a transition period between wakefulness. In Stage 1 (N1), the brain produces high amplitude theta waves, which are very slow brain waves. Stage 2 (N2) sleep is a light stage of sleep, characterised by increasingly slower brain wave activity with occasional spikes (sleep spindles), which are thought to be part of the sensory-gating system (reducing our responsiveness to external noise or internal sensations). Stage 3 (N3) was previously divided into stages 3 and 4 (Rechtschaffen & Kales, 1968) which have since been combined to form stage 3 (N3) (Iber, et al., 2007). Progressing from light sleep to deeper or slow wave (stage 3 (N3) sleep, brain waves become even slower and this is when the body begins the repair and rejuvenation process.

After slow wave sleep the brain enters a shorter period of lighter sleep before starting the first rapid eye movement (REM) sleep. Here brainwaves resemble those of being awake but there is no muscle tension. Heart rate and breathing increase and this is when the majority of dreams occur. This is also the time that it is believed that learning and memory consolidation occur (Stickgold, 2005). Just as slow wave sleep replenishes the body, REM replenishes the mind. A night of normal adult sleep usually consists of four to six sleep cycles lasting approximately 90 to 110 minutes, (Edinger et al., 2004). As the night progresses, the amounts of deep non-REM sleep decreases and the amount of REM sleep increases (See Table 2.1 for a summary of the sleep stages and normal architectural parameters).

Recording the Electroencephalogram (EEG) and other physiological variables such as muscle activity and eye movements during sleep (a technique called Polysomnography, PSG) can provide information about the different stages of sleep

and their pattern of occurrence (also considered the 'macrostructure' of sleep), and the presence of EEG phenomena during sleep (i.e. arousals, k-complexes, sleep spindles, also known as sleep 'microstructure') (see Table 2.3 for a summary of sleep stages and patterns of the EEG). Likewise, other PSG-derived sleep variables offer a basis for clinical decision-making and research analyses. Quantitative criteria for 'normal' sleep, set out by Edinger et al (2004) suggests sleep onset (SOL) should occur within 30 minutes, and the amount of time spent awake during the sleep period should not exceed 30 minutes, beyond which is considered problematic. Furthermore, a total sleep time of less than 6 hours and sleep efficiency (SE) less than 85% are also considered problematic (See table 2.2 for a description of these sleep variables).

	Sleep Stage	Activity	Normal Architectural Parameters
	Wake	Eyes open, responsive to external stimuli, can hold intelligible conversation	<5%
NREM Sleep	**N1**	Transition between wakefulness and sleep. Eyes closed, breathing slows, muscles relax, brain starts to produce alpha waves. Many people notice the falling sensation during this stage of sleep, which may cause a sudden muscle contraction (called hypnagogic Jerk).	2-5%
	N2	Onset of sleep, heart rate slows and the body temperature drops. The brain produces bursts of rapid, rhythmic brain wave activity known as sleep spindles.	45-55%
	N3 (SWS)	Deep sleep or Slow-wave sleep (SWS), delta brain waves occur. Deepest most restorative sleep, muscles relaxed, blood pressure drops, breathing slows. Blood supply to muscles increases, tissue growth & repair occurs.	13-23%
REM Sleep	**REM**	Body becomes immobile, muscles relax. Energy provided to brain and body. Heart rate & breathing become more variable. Rapid eye movement & dreaming (dreaming can also occur in other stages of sleep).	20-25%

Notes: NREM, non-rapid eye movement; REM, rapid eye movement; N1, stage 1; N2, stage 2; N3, stage 3; SWS, slow wave sleep.

Table 2.1: Summary of sleep stages and normal architectural parameters (Carskadon & Dement, 2011).

As mentioned previously, poor sleep is a consistent complaint of those suffering from CFS. 87-95% of CFS patients identified in community-based surveys report awakening unrefreshed, (Hamaguchi et al., 2011; Jason et al., 1999; Nisenbaum, et al., 2003; Nisenbaum et al., 2004), making it one of the most commonly reported of the Fukuda symptom criteria. Patients also commonly report disrupted and fragmented sleep and difficulties in getting to sleep or staying asleep, despite feeling tired (Anderson & Ferrans, 1997), which may, in some part explain the overall reports of unrefreshing sleep. Given the implication of disturbed sleep in the maintenance of CFS considered above, and sleep management being componential to CBT and GET approaches, it is clearly an important element of CFS. Despite this, the understanding of sleep and its role in this condition is limited. Similarly, the reported results from studies of sleep in CFS have been fragmented and tenuous (Mariman et al., 2013; Jackson & Bruck, 2012; Spitzer & Broadman, 2010).

The following narrative review will examine the current evidence from subjective- and objectively-based studies of sleep in CFS. It will also consider the difficulties that exist in establishing the relationship between sleep, behaviour, cognition, physiology and the physical symptoms of CFS. Searches were made of Medline from 1960 to the present, for the terms "CFS", "chronic fatigue syndrome" AND "sleep" to identify articles concerning sleep and CFS. We then cross-referenced the above terms with qualitative; self-report and objective assessment. Abstracts identified from the searches were reviewed and this material was used to conduct the narrative review.

2.2 Sleep Assessment in CFS

2.2.1 Subjective assessment

2.2.1.1 Qualitative findings

The qualitative literature in CFS typically describes themes from both patients and physicians outlining their perspectives of the illness and identifying the struggle to understand and manage CFS (Anderson & Ferrans, 1997; Clarke, 1999; Lovell, 1999; Schoofs et al., 2004; Soderlund et al., 2000). These studies utilise interview-based techniques with relatively small samples of patients (See Appendix A for summary of

study characteristics), and differ in their use of case definitions of CFS (i.e. Fukuda, Oxford, Holmes – see Appendix A). Although they discuss quality of life and social factors in CFS - with extreme fatigue, pain, cognitive dysfunction and unrefreshing sleep being described as key patients' illness experiences - the studies rarely explore below the surface of these symptoms (Clarke, 1999; Schoofs, et al., 2004). The main focus of these studies is rather on themes of gender differences in the illness experience, illness beliefs regarding development and potential causes. A recent comprehensive review of the qualitative literature on CFS highlighted that a large proportion of the qualitative studies in CFS and Fibromyalgia describe perspectives from healthcare professionals regarding medical practice (Anderson et al., 2012), rather than focussing on patients' experience. As such there is no real in-depth data in these qualitative accounts on the role of sleep in CFS. This is an area of research that needs to be addressed, as qualitative work can, amongst other things, indicate the direction to move forward with hypothesis-driven studies, larger cohort studies, objective measures, and intervention development. In sum, a potentially rich source of data on sleep, and how sleep related disturbances may play a role in maintaining other symptoms experienced in CFS is being overlooked.

2.2.1.2 Self-report diaries and questionnaires

Self-report techniques have been employed to determine the perceptual role of sleep in CFS and include the use of sleep diaries and sleep questionnaires, such as the Pittsburgh Sleep Quality Index (PSQI: Buysse et al., 1989) and the Epworth Sleepiness Scale (ESS: Johns, 1991). Studies assessing sleep through self-report methods show higher than normal ESS scores (Decker et al., 2010; Mariman et al., 2012) and PSQI scores (Mariman, et al., 2012). Mariman and colleagues (2012) reported ESS and PSQI scores in 415 Fukuda defined CFS patients. Excessive sleepiness was observed in 53% (ESS scores greater than 10) and poor sleep quality (global PSQI scores above 5) in 86% of CFS patients. Further, when patients were divided into groups based on ESS results, these scores corresponded to a clinical profile of insomnia (complaints of sleep disturbance associated with increased alertness) or hypersomnia (excessive daytime sleepiness persists despite normal nocturnal sleep) (Mariman, et al., 2012). This provides an indication that sleep problems may be heterogeneous in this population. Conversely, in a study of 339 CFS patients from the Wichita population (Unger et al.,

2004), ESS scores and factors from the Sleep Assessment Questionnaire (SAQ), showed that while fatigued, CFS subjects tended not to report excessive sleepiness. This study also showed that most (81.4%) CFS patients had an abnormal score in at least one of the five possible SAQ sleep factors (sleep apnoea, restlessness, non-restorative sleep, insomnia, excessive daytime somnolence). Interestingly, those with sleep abnormalities also had significantly lower wellness scores but unchanged fatigue severity scores compared to those with no abnormalities (Unger et al., 2004).

Morriss et al (1997) included 69 Oxford diagnosed CFS patients without psychiatric disorder (Sharpe, 1991), 58 CFS patients with a psychiatric disorder, 45 controls, and 38 psychiatric out-patients with chronic depressive disorders. A specially designed sleep questionnaire was constructed to measure self-rated sleep complaints according to the International Classification of Sleep Disorders (Thorpy, 1990), over four weeks (Morriss, et al., 1997). The study found a higher prevalence of sleepiness and daytime naps in CFS patients compared to healthy controls and depressed subjects, and CFS patients were also significantly more likely to wake up because of temperature problems and pain than healthy controls or depressed patients. Further, restless legs were more frequently reported by CFS (41%) and depressed patients (40%) than by controls (4%). This study suggests that difficulty in maintaining sleep is the principle sleep complaint in CFS patients with or without psychiatric disorder, and showed the nocturnal waking and restless legs to be significantly associated with global disability in CFS patients, as assessed by the Medical Outcomes Survey (MOS: Stewart et al., 1988).

Krupp et al (1993) assessed 68 CFS patients diagnosed according to Holmes criteria and 20 non-illness controls, using a modified version of the St. Mary's Sleep Questionnaire (Ellis et al., 1981). They showed patient's sleep to be more disrupted than healthy controls; 37% CFS patients reported sleeping lightly compared to 20% of controls, and upon awakening, 76% of CFS patients reported feeling drowsy compared to 48% of controls (Krupp et al., 1993). Additionally, patient sleep diaries have shown that compared to controls, those with CFS report a significantly longer time in bed at night, take longer to fall asleep and wake more frequently during the night, whilst also feeling less refreshed on waking (Fossey et al., 2004; Morriss et al., 1993).

There are methodological issues with these studies. There is a lack of standardized assessment for sleep disorders and subjective self-report is not corroborated by any objective indicators such as actigraphy or polysomnographic assessment. In addition there are a range of self-report scales utilised to assess the degree to which sleep disturbances occur in this patient group. This lack of consistency is further compounded by inconsistent criteria for patient selection and atypical CFS patient groups (Krupp, et al., 1993; Vercoulen et al., 1994), small patient samples (Krupp, et al., 1993; Moldofsky, 1989; Morriss, et al., 1993) and the examination of only a limited number of sleep complaints (Krupp, et al., 1993; Morriss, et al., 1993; Vercoulen, et al., 1994). Given these caveats probably the most robust conclusion that can be drawn from the self-report data is that sleep disturbances are commonly reported and they appear analagous to a range of sleep disorders including hypersomnia, and both sleep onset and sleep maintenance insomnia; in short, we can say that despite methodological issues, sleep problems are variable but significant in this population. There are also indications of how this might fit into the multi-factorial model outlined above. Duncan (1993) highlighted the possible interaction of daytime behavioural and lifestyle factors driving the sleep disturbance in CFS. He has suggested that a sedentary lifestyle and daytime sleep (napping) may serve to maintain disturbed night time sleep, thus establishing a vicious circle of poor night time sleep and compensatory day time sleep.

2.2.2 Objective Assessment

2.2.2.1 Actigraphy

Actigraphy offers a method of characterising gross objective measures of sleep continuity (the quantity and timing of sleep episodes), without interfering with sleep or daytime functioning. Actigraphy is usually measured by an unobtrusive device on the subjects body (often placed like a wrist-watch), and allows for 24-hour recording of wake and sleep activity in a person's natural environment. A combination of actigraphy and symptom measurement offers real-time prospective activity-symptom relationships to be examined (Yoshiuchi et al., 2007).

Actigraphy studies in CFS differ in sample selection and their reporting practices. One assessment was carried out with children (Ohinata et al., 2008), another with a small group of CFS patients (Rahman, 2011) and a third study with no comparative control group (Creti et al., 2010). With regard to the findings, an assessment of 12 children with CFS showed longer sleep durations and lower levels of daytime physical activity compared to age-matched controls. The actigraph also identified an interaction between disrupted sleep-wake and daytime napping (Ohinata, et al., 2008). Conversely, a more recent sleep study of 15 CFS patients and 15 controls found no significant actigraphy differences between CFS patients and healthy controls in daytime activity levels, fragmentation during sleep, sleep efficiency or duration of sleep, or duration of napping. Interestingly in this study CFS patients still reported poorer sleep quality than healthy control subjects (Rahman, 2011). The Rahman (2011) sample, however, is particularly small and perhaps unrepresentative of the general CFS population, given these were patients undergoing an intervention program of graded-activity oriented cognitive-behavioural therapy at a tertiary referral clinic. As such they were treatment motivated patients who were also likely to be well-informed in terms of behavioural strategies for sleep and symptom management. Of note, Creti et al. (2010) identified difficulties with actigraphy as an objective measurement modality in this population, showing that it underestimated sleep onset latency (SOL: how long it took to get to sleep following retiring to bed) in patients, and was also not able to accurately or consistently identify nocturnal wakefulness.

Further, it is difficult to elucidate actual sleep versus inactivity (lying still in bed, but awake) in actigraphy and the actigraph alone cannot provide specific information on sleep architecture (i.e. the progression and timing of sleep/wake stage transitions). As a sole method for examining sleep actigraphy is considered problematic (Sadeh, 2011). Creti (2010) concludes however, that when combined with other objective measurement modalities, actigraphy can help differentiate CFS individuals who have chronic insomnia from those without insomnia.

2.2.2.2 Multiple Sleep Latency (MSLT) Tests

CFS patients often use the terms tired, sleepy and fatigued interchangeably, which is why it is important, albeit difficult, to separate the symptoms of fatigue and daytime

sleepiness (Neu et al., 2008). It is also important as the two complaints have different implications for diagnosis and treatment. Whereas fatigue relates to lack of available energy and loss of ability to exert mental and physical effort, sleepiness is a tendency to fall asleep, and only becomes problematic if it occurs at an inappropriate time or situation (Shen et al., 2006). The Multiple Sleep Latency Test (MSLT; Carskadon & Dement, 1977) objectively measures daytime sleepiness, by measuring the amount of time it takes people to fall asleep during the day, given the opportunity. In the case of an MSLT four daytime sleep opportunities are offered, separated by 2 hours each time. The results from MSLTs carried out in CFS have generally been inconsistent. Several studies show CFS patients do not differ from healthy controls on MSLT values (Bailes et al., 2006; Buchwald et al., 1994; Majer et al., 2007; Reeves et al., 2006). A twin study has shown that CFS twins, despite reporting significantly more subjective sleepiness than their healthy co-twins, did not differ in their mean sleep latencies (Watson et al., 2004). This indicates that CFS and biological sleepiness is not associated, and also points towards a heightened sense of sleepiness among CFS twins.

Where clinically significant MSLT latencies (<10 min) have been identified in CFS patients, these again are not consistent; one study revealed 41% of CFS patients had an abnormal MSLT yet scores did not differ significantly from those of non-fatigued controls (Buchwald, et al., 1994). Another study showed a quarter of their CFS sample had an abnormal MSLT (Krupp, et al., 1993). In a recent study of CFS patients from the Wichita population (n=225), 59.5% of patients had an abnormal MSLT. Interestingly in the same sample 61.7% had an Epworth Sleepiness Score (ESS) within the normal range (Decker, et al., 2010). Moreover, in a study assessing CFS patients, apnoea patients, and healthy controls, the CFS group showed significantly smaller MSLT scores than controls during 2 of the 4 sleep opportunities provided, however these still fell within a normal range. Overall comparisons of scores on the MSLT showed CFS patients presented with intermediate values between apnoea patients (demonstrating the most excessive sleepiness) and healthy controls (Neu et al., 2008).

The key shortcoming of the reported results of MSLTs carried out with CFS patients is that they are based on tests usually following a single night of Polysomnography (PSG, see section 2.2.2.3 for a description). As such, MSLTs after a single night of PSG, may not be an accurate indication of a patient's daytime somnolence, given that the first

night of PSG (usually conducted in an unfamiliar environment) is commonly associated with a phenomenon known as the "first-night effect". The first-night effect is the set of differences in sleep parameters observed on the first night of recording in comparison to consecutive ones. The main characteristics of the first-night effect include; a reduction in sleep time, more time awake during the night and reduced sleep efficiency (SE) parameters (Agnew et al., 1966; Rechtschaffen & Verdone, 1964). Moreover, polysomnography studies are often criticised for their artificial sleep laboratory conditions that do not reflect normal sleep at home and do not allow for habituation to cumbersome equipment (Newell et al., 2012). As such, patients are likely to be sleepy the next day. The functional impact of the PSG study night may also explain the lack of relationship between MSLT scores, sleepiness scores and fatigue scales.

Examinations of individuals deprived of or restricted from sleep consistently demonstrate deteriorations in mood, cognition and performance (Turner et al., 2007). The purpose of each different sleep stage is also unclear, although it is generally agreed that the lighter stages of sleep (stage 1 sleep and stage 2 sleep) afford transitions between wakefulness and sleep and then between slow wave sleep (SWS) and Rapid Eye Movement sleep (REM). SWS and REM are believed to confer recuperative, restorative and learning properties for the individual (e.g. the secretion of growth hormone, consolidation of memory) (Van Cauter, Leproult & Plat, 2000). Therefore, the proportion of each sleep stage and timing of entry into each sleep stage, SWS and REM in particular, are important for the long-term maintenance of human physical and mental health. PSG studies allow us to measure these sleep parameters, and the next section will review the PSG studies that have been carried out in CFS.

2.2.2.3 Polysomnography (PSG) studies

Overnight Polysomnography (PSG) is an all-night recording of sleep physiology, including both sleep continuity and sleep architecture (the progression and timing of sleep/wake stage transitions) and involves attaching electrodes to the scalp, forehead, and chin to record electroencephalogram (EEG) eye movements or electro-oculogram (EOG) and muscle activity from the submental muscle (electromyogram, EMG). In addition, variables such as electrocardiogram (ECG), EMG from leg muscles, a range

of respiratory variables and body movements may be measured at the same time. Overall, PSG sleep findings have not shown any clear pattern of sleep abnormality in this population. One characteristic of the PSG research in CFS may account for this: there is a high degree of variability in terms of the sleep continuity and sleep architecture features that are reported in research studies (see Appendix A). This makes comparisons between PSG studies of sleep in CFS difficult, and meta-analyses virtually impossible. There is also a fair degree of variability in the protocols, adding to the complexity. PSG Studies have mostly been carried out over one night (Buchwald, et al., 1994; Creti, et al., 2010; Fossey, et al., 2004; Guilleminault et al., 2006; Kishi et al., 2008; Krupp, et al., 1993; Morriss, et al., 1993; Sharpley et al., 1997; Stores et al., 1998; Togo et al., 2008) or two (Ball et al., 2004; Decker et al., 2009; Fischler et al., 1997; Le Bon et al., 2003; Le Bon, Majer, et al., 2007; Neu et al., 2009; Neu, et al., 2008; Neu et al., 2007; Reeves, et al., 2006; Van Hoof et al., 2007; Watson, et al., 2004), which may present with potential 'first night effect'.

Does the 'first-night effect' exist in CFS?

A great deal of the assumptions regarding the variability and lack of consistency in the objective sleep patterns of patients with CFS rests on the idea that people with CFS experience a first-night-effect. In a seminal study (Le Bon, et al., 2003) this phenomenon was studied in 83 CFS patients without an objectively verifiable sleep disorder. Le Bon and colleagues observed clear differences between the first and second night sleep parameters. On night one there was less Total Sleep Time and REM sleep, a longer REM latency, more intermittent Wake Time and a reduced number of sleep cycles (Le Bon, et al., 2003), all indicating poorer first night sleep, in comparison to night two. That said, and rather complicating the issue, a quarter of Le Bon at al's (2003) sample demonstrated an 'inverse first-night-effect' with patients experiencing better sleep on night one than night two. These issues may highlight the need for at least a 3-night assessment for PSG research.

Continuity

There is large variation between PSG studies on reported sleep continuity variables (See Table 2.2 for descriptors of sleep variables), for example, in one single-night PSG assessment study, Sharpley and colleagues showed a mean Sleep Onset Latency (SOL) of 69 minutes (Sharpley, et al., 1997), whereas Togo and colleagues showed a SOL of

31 minutes (Togo, et al., 2008). Further, Morris et al (1993) report mean SOL of 12.2 minutes in their CFS patient cohort. Given that a SOL longer than 30 minutes is considered as a presence of potential "sleep initiation difficulty" (Edinger et al., 2004), these findings are highly variable and relate to both problematic and non-problematic sleep values. A two-night PSG assessment, arguably a more representative indication of 'typical' sleep, identified a significantly longer SOL (39.9 minutes) on night two in CFS patients compared to healthy controls (21.5 minutes) (Fischler, et al., 1997).

Abbreviated Variable	Sleep Variable (measure)	Description
AHI	Apnea /Hypopnea Index	Number of Apnea or Hypopnea events during sleep
TST	Total Sleep Time (minutes)	Amount of time asleep
SOL	Sleep Onset Latency (minutes)	Length of time from lights out to first episode of stage 2 sleep
WASO	Wake After Sleep Onset (minutes)	Number of minutes of recorded wake following first episode of stage 2 sleep
NWAK	Number of Awakenings (over TSP)	Number of wake bouts following first episode of stage 2 sleep
NoA	Number of Arousals	Number of arousals over the entire sleep period
REML	REM Latency	Length of time to first REM stage
SE (%)	Sleep Efficiency	Percentage of time spent asleep from the amount of time spent in bed (TST/TIB*100)
%N1	Percentage of Stage 1 (of TST)	Percentage of recorded stage 1 sleep over the total time asleep
%N2	Percentage of Stage 2 (of TST)	Percentage of recorded stage 2 sleep over the total time asleep
%SWS	Percentage of SWS (of TST)	Percentage of recorded slow wave sleep over the total time asleep
%REM	Percentage of REM (of TST)	Percentage of recorded Rapid Eye Movement sleep over the total time asleep
%WAKE	Percentage of WAKE (of TSP)	Percentage of recorded wake over the whole sleep period (from lights out to lights on)

Notes: Arousal defined as an abrupt shift in EEG frequency (alpha, theta waves and/or frequencies greater than 16 Hz, but not sleep spindles), lasting at least 3s, after at least 10 continuous seconds of sleep, and is associated with sleep fragmentation (Iber et al., 2007). REM, rapid eye movement; TSP, total sleep period; TST, total sleep time.

Table 2.2: Description of sleep variables

Further single-night PSG assessments have shown other types of sleep disruption in CFS. After exclusion for medical illness, psychiatric disorders, apnoea, hypersomnia and Periodic Limb Movement Disorder, 26 CFS patients - with co-existing fibromyalgia - had significantly reduced total sleep time and reduced sleep efficiency than controls (Togo, et al., 2008). Home-based PSG studies have also shown CFS patients to sleep less efficiently than controls, with patients spending more time in bed and significantly more time awake during the night (Morriss, et al., 1993; Sharpley, et al., 1997). However, results of percentage time awake during the night are also highly variable between studies, with ranges from 11.7% (Majer, et al., 2007; Reeves, et al., 2006) to 31.9% (Morriss, et al., 1993) and even as much as 46.28% (Van Hoof, et al., 2007).

Architecture

Architectural findings of PSG studies in CFS are equally equivocal. Discrepancies between studies in their reporting of sleep stages and abbreviations used, may account for this, based on the advancements that have been made in the visual scoring of sleep stages. Since 2007, the AASM manual (Iber, et al., 2007), replaced Rechtschaffen and Kales' (R&K; 1968) rules that had originally divided the sleep stages into; wakefulness, stage 1-4 (non-REM), or REM. Sleep stages were now defined as, N1-N3 (non-REM) and stage R (REM), the key difference being stage 3 and stage 4 in the old R&K rules being abbreviated to stage N3 (SWS) in the new rules (Iber, et al., 2007) as it is considered that no physiological basis exists for a difference between stages 3 and 4. This creates discrepancies with regard to some studies reporting stage 3 and 4 with others referring to SWS. Adding to this, few studies report a full characterization of sleep architectural variables (amount of each sleep or wake stage and the timing of transitions to each sleep stage), making any conclusive statements about sleep abnormalities in this patient population difficult. (See table 2.1 for a summary of sleep stages). The first report, from a group of 49 CFS patients compared to 20 matched healthy controls, found a significantly lower percentage of NREM N3 (formerly considered S3 & S4 sleep) in CFS (Fischler, et al., 1997). Conversely, Le Bon (2007) showed significantly increased NREM N3 in the sleep of CFS patients (free of medical illness, psychiatric or primary sleep disorders),, compared to apnoea patients and healthy controls, thus drawing the conclusion that there is an increase in the amount of

deep sleep over light sleep in CFS. This latter finding was corroborated in 2009 by Neu and colleagues, who reported architectural differences from the second night of PSG assessment with CFS patients exhibiting less light (N1 and N2) sleep and more deep (Slow Wave) sleep than healthy controls or apnea patients (Neu, et al., 2009).

Sleep Stage		EEG Features	Waveform Type	EEG Size (Amplitude)
Awake		Low-amplitude, mixed, and sometimes alpha rhythm.	Alpha 8-13 Hz; Beta >13 Hz	Low
NREM Sleep	**N1**	Low amplitude, mainly irregular theta activity, and triangular vertex waves.	Theta 4-7Hz	Low
	N2	Sleep spindles, K complexes, some low amplitude theta and delta activity.	Spindles 12-15Hz	Medium
	N3 (SWS)	High-amplitude delta activity, spindles less prominent, K complexes longer, and less discrete.	Delta or SWA <4.5 Hz	High
	REM	Low-amplitude, frequency EEG, and sometimes saw-toothed waves.	Theta 4-7 Hz	Low

Notes: NREM, non-rapid eye movement; REM, rapid eye movement; N1, stage 1; N2, stage 2; N3, stage 3; SWS, slow wave sleep; Spindles, short bursts of rhythmic activity (occur during light and deep non-REM sleep) to keep the cortex from processing during sleep; K complexes, manifestations of a downward signal (from cortex to thalamus and brain stem) to stay asleep (evoked readily in light sleep by auditory stimulation); SWA, slow wave activity.

Table 2.3: Sleep stages and patterns of the EEG (Carskadon & Dement, 2011).

Large variations also exist between studies in terms of reported percentage of REM sleep in CFS cohorts. Normal adults spend approximately 20-25% of their total sleep time in REM (Kryger, Roth & Dement, 2011). Some CFS studies have shown reduced REM; 7.6% (Kishi, et al., 2008), normal range; 22.3% (Reeves, et al., 2006) and others have observed increased REM; 27.7% (Ball, et al., 2004). Moreover, reported REM latencies (length of time to the first REM cycle), which in normal adult sleep is around 90 minutes (Kryger, Roth & Dement, 2011), are equally varied in individuals with CFS. Some report latencies as short as 63.5 minutes (Ball, et al., 2004) and others much longer, for example 149 minutes, (Togo, et al., 2008).

These results relating to the proportion of REM are based on either a single night (Kishi, et al., 2008; Togo, et al., 2008) or a second night (Ball, et al., 2004; Reeves, et al., 2006) of recording, so perhaps, again, the first-night effect explains this variance. Indeed, much of the variance in the reported structural and architectural sleep variables in these studies of CFS patient's sleep may well be explained by the number of study assessment nights. Very few studies have conducted a three-night protocol of PSG assessment (Armitage et al., 2007; Fischler, et al., 1997; Whelton et al., 1992). This protocol inconsistency is further complicated by the fact that reporting practices differ, making interpretation and comparisons difficult. Some studies report the percentage of each sleep and wake stage as an index of Sleep Period Time (amount of the whole sleep period), Total Sleep Time (amount of time once sleep has been initiated) or even amount of Time in Bed (Armitage et al., 2007; Ball et al., 2004; Fischler et al., 1997; Majer et al., 2007; Manu, et al., 1994; Reeves et al., 2006; Stores et al., 1998; Van Hoof et al., 2007; Watson et al., 2003; Whelton, et al., 1992), whilst others report minutes of each stage (Le Bon et al., 2003; Le Bon, et al., 2007; Morriss et al., 1993; Sharpley et al., 1997; Togo et al., 2008). However, collectively these studies do not demonstrate any consistent architectural differences in sleep of patients and healthy controls/co-twins. Consequently, results should be treated carefully. The variability in measures of sleep parameters could be the result of either the heterogeneity of sleep problems within the CFS populations, a variability in measurement protocols, and/or the result of still often neglected primary sleep disorders (PSD) in these studies (i.e. mild OSAS or PLM).

There have also been indications of alteration in the transition pattern of sleep stages in CFS - particularly, significantly fewer transitions from REM to non-REM sleep over the night in CFS patients than in controls (Kishi, et al., 2011; Kishi, et al., 2008). This suggests a potential disruption in the normal circadian regulation of sleep-wake patterns, abnormalities that could lead to unrefreshing sleep.

Power Spectral Analysis (PSA)

EEG brain wave activity can be categorised in frequency bands and they can to some extent provide a gross indication of a particular sleep/wake state. For example, alpha activity (8 to 12 Hz) is the dominant rhythm in relaxed wake state (eyes closed) in posterior regions of the scalp. That said, alpha waves can also be observed (although they do not predominate) during the various stages of sleep. When these alpha waves intrude into deep sleep it is suggested the brain is not resting like it should (also known as alpha-delta intrusion), indicating a wakeful period during sleep and high levels of alpha-intrusion into sleep is often associated with complaints of non-refreshing sleep. PSA deconstructs the amount, and density, of each frequency band over each phase of wake and sleep. PSA integrates the amount of energy (power) and respective density in each frequency band and potential overlap or 'intrusion'. In some cases, these intrusions can result in a change of stage shift (e.g. going from one sleep stage to another, including wake). In terms of the PSA evidence, Armitage and colleagues (Armitage et al, 2007) assessed 13 twin-pairs (from the University of Washington CFS Twin Registry) of the 22 who originally underwent PSG assessments. Having applied PSA, using Fast Fourier Transformation (FFT: a widely applied linear modelling method to obtain EEG power spectra), delta power was observed to be slightly elevated overall in the CFS-twins, although this was not enough to significantly differentiate them from their healthy co-twins (Armitage, et al., 2009). Moreover, there have been new perspectives in what the homeostatic impairment in slow wave sleep (SWS) in CFS might be. Le Bon and colleagues looked at delta activity in the very slow end of the frequency band, which had mainly been overlooked in studies. They showed lower ultra-slow delta power in the sleep of 10 young females with CFS in comparison with healthy controls (Le Bon et al., 2012). This underlines the importance of looking beyond the conventional gross EEG.

Decker and colleagues (Decker, et al., 2009), also used FFT, and analysed the PSG recordings of 35 CFS patients from the Wichita population study, comparing these to 40 non-fatigued controls. Overall there was significantly reduced spectral power of alpha activity in CFS subjects during stage 2 sleep, SWS, and with the greatest reduction observed during REM sleep. CFS patients also showed significantly reduced delta power activity in SWS, which would concur with the common symptoms found in CFS, as reduced delta power is associated with reported fatigue and the perception of pain (Lentz et al., 1999). However, this delta power was increased during stage 1 and REM sleep. This latter finding has been corroborated elsewhere (Guilleminault, et al., 2006; Neu, et al., 2009). This rebound might reflect an impairment of sleep related homeostatic functions in CFS.

However, alpha-delta sleep, or alpha intrusions are not entirely specific to CFS. Other disorders, such as rheumatoid arthritis, fibromyalgia and lupus erythematosus also feature differences in alpha range EEG frequencies compared to control subjects (Macfarlane & Moldofsky, 2011). Additionally, there are reports of this alpha-delta sleep in stages 2, 3 and non-REM sleep in fibromyalgia patients who present with excessive daytime somnolence and chronic fatigue (Branco et al., 1994; Drewes et al., 1995; Moldofsky et al., 1975; Roizenblatt et al., 2001). Furthermore, changes in alpha can also be found in several primary sleep disorders (PLMD, sleep apnoea, and narcolepsy) and occasionally in patients with no complaints of fatigue (MacFarlane et al., 1996). The role of alpha-delta sleep in the development of CFS remains questionable, with some studies of CFS patients observing alpha intrusions in SWS (Manu et al., 1994; Whelton, et al., 1992) and others failing to support this (Armitage et al., 2009; Flanigan et al., 1995; Mariman et al., 2012).

Co-twin control methodology

Despite offering a powerful method by which to control for genetic factors (Hrubec & Robinette, 1984), PSG twin studies have not provided strong evidence for sleep abnormalities in CFS. In one 2-night PSG assessment study, and following exclusion of psychiatric and medical disorders, CFS twins did not appear to differ from their healthy co-twin on any sleep parameter (Armitage, et al., 2009; Ball, et al., 2004; Watson, et al., 2004). However, delaying sleep onset by 4-hours resulted in CFS twins

showing less slow wave activity than their healthy co-twins (Armitage, et al., 2007). This finding may be indicative of a potential impairment in homeostatic sleep pressure in CFS and supports that the daytime complaints observed in people with CFS may be associated to potential issues in sleep regulation.

Summary of PSG

Overall, the PSG studies report that CFS patients have abnormal sleep, however such disturbances are variable and not found across all patients. There is also no standardisation in protocol, selection criteria, or reporting practices, making interpretation and comparisons between studies difficult. Moreover, different studies exclude different groups, and, whilst most exclude medical illness, psychiatric disorders, and some sleep disorders (primary hypersomnias, sleep aponea and PLMD), they tend not to exclude insomnia (Creti, et al., 2010; Le Bon, et al., 2003; Sharpley, et al., 1997). This is highly problematic in terms of reporting sleep findings in CFS where patients are likely to encounter symptoms similar to those experienced in Insomnia such as problems getting off to sleep or staying asleep. Further, given the considerable overlap in the existing diagnostic criteria (used in the reported studies), between CFS and insomnia (namely non-restorative sleep), it is highly important to tease these conditions apart to be able to understand CFS exclusively.

2.2.3 A combination of methods

There have been several studies, mentioned earlier, that have used a combination of objective sleep assessment with subjective measures of patient's sleep (Creti, et al., 2010; Majer, et al., 2007; Sharpley, et al., 1997; Watson, et al., 2004; Watson et al., 2003). These triangulation studies demonstrate interesting discrepancies between what emerges in subjective and objective measures. Overall, CFS patients report poorer sleep quality and more non-restorative sleep than healthy and non-fatigued controls, but objectively they appear to have close to normal sleep architecture (structure and pattern of sleep) or macrostructure (temporal organisation of sleep). Similarly, CFS patients report more subjective sleepiness, yet objective measures (MSLTs) of sleepiness do not tend to differ between CFS twins and their healthy co-twins (Watson, et al., 2004). These discrepancies between subjective daytime complaints and objectively measured sleep are also common in individuals with insomnia, often

described as sleep-state misperception (SSM; i.e. perceiving sleep as wakefulness/overestimating sleep). Such sleep misperception has been explained by the neurocognitive model of insomnia, emphasising that brain cortical arousal is a central component whereby both physiological and cognitive arousal arises from increased cortical arousal around the sleep onset period (Perlis et al., 1997).

Neu et al (2007) specifically demonstrated this difference between subjective and objective sleep. After exclusion of psychiatric disorders and certain sleep disorders (aponea, PLMD and hypersomnia), their 28 'pure' CFS patients reported significantly poorer subjective sleep quality - as demonstrated by PSQI scores - compared to healthy age and gender matched controls but there was no evidence of structural PSG abnormalities. This might suggest that CFS patients negatively perceive their sleep quality even though they may sleep well. One suggestion is that they may over-monitor their sleep and this perhaps contributes to perceived sleep problems, a phenomenon which has also been observed in insomnia (Harvey & Payne, 2002). Also, in CFS, the lack of explanation and guidance surrounding the condition may increase patient anxiety, symptom experience and consequently, symptom focus (Deary, Chalder & Sharpe, 2007). This in turn could cause an increased monitoring of sleep duration and quality. Again this emphasises the importance of considering the interaction between cognitions, behaviours, physiology and symptoms in this condition and also the importance of combining assessment techniques.

2.3 Issues, conclusions and recommendations.

2.3.1 Minor case definition criteria – the pitfalls

The lack of regularity in working case definitions and guidelines for CFS creates uncertainty regarding the role of sleep in CFS. Specifically, complication exists as to where sleep complaints fit within the available case definitions of CFS. For example the Holmes (CDC) definition includes sleep disturbances such as hypersomnia or insomnia in its minor criteria (Holmes et al., 1988), whereas the Fukuda (CDC) definition considers sleep disorders such as sleep apnea and narcolepsy as exclusionary and regards unrefreshing sleep as minor criteria (Fukuda, et al., 1994). Given that some available criteria regard sleep problems as minor - whilst sleep complaints are

consistently reported in CFS - together with the considerable variation in the use of terminology, there is scope to investigate sleep disturbances in CFS in much more detail, and certainly, the need to establish more definitive criteria with regard to sleep. This raises the issue of the overlap/confusion between sleep disorders and CFS.

2.3.2 Sleep disorders

The presence of sleep disorders has been highlighted in sleep studies with CFS patients. In a single night PSG and self-report observational study (Fossey, et al., 2004), it was found, that of the 37 CFS patients, 58% fulfilled the criteria for a diagnosable sleep disorder (Diagnostic Classification Steering Committee, 1990); 11 (42%) had apnea and 4 (16%) had restless legs syndrome/ periodic limb movement disorder (RLS/PLMD). High rates of self-reported insomnia (86%) were also evident in the CFS group. In another study that combined PSG, actigraphy and self-reports, 42 (86%) of the 49 CFS patients had a diagnosable sleep disorder, with 32 (65%) meeting DSM-IV criteria for chronic insomnia and 10 (20%) with aponea (Creti, et al., 2010). In a recent large-scale study of 205 patients (n=410, combined data over 2 recorded nights), one third of the sample had suspected apnoea, based on their respiratory disturbance index (RDI: average number of episodes of apnoea, hypopnea, and respiratory event-related arousal per hour of sleep) (Decker, et al., 2010). In a recent survey of a specialist CFS service in London, (Devasahayam et al., 2012) it was reported that of the 377 patients referred to the CFS service – almost half (49%) had alternative diagnoses made, based on an assessment that included a detailed history, physical and mental state examination. Of those assessed (n = 250), a sleep disorder was the most common (28%), which suggests an alternative diagnosis may be warranted.

These findings highlight the fact that sleep disorders (i.e. insomnia, apnea, RLS, PLMD) may well be comorbid, overlooked or misdiagnosed in CFS. Further some authors have suggested that CFS is a primary sleep disorder in itself. However this questions the nature of causal relationships between physiology, symptoms, and behaviour in this population (indeed in any chronic condition) and how the appellation "primary" must be used with caution. Hypersomnia and insomnia are common features of CFS and are as likely to be effects as they are causes of fatigue. To date no

treatment studies have sought to exclusively target sleep to ascertain how this impacts on other symptoms. Only experimental designs would afford causality. Given the lack of consistency in findings from studies of sleep architecture and multiple sleep latency times, it could also be considered that symptoms such as unrefreshing sleep and unremitting fatigue may not reflect a sleep disorder per se but rather an impaired sleep homeostasis (Armitage, et al., 2007; Le Bon et al., 2012), the body's natural ability to regulate the sleep/wake cycle (Borbely & Achermann, 1999), but again this would have to be experimentally tested. Practically, what this work highlights is the necessity to perform thorough sleep assessments in this population.

2.3.3 Future research

Sleep studies in CFS have shown very mixed results, particularly with regard to polysomnography. Not only do these studies significantly differ in their results, but their protocol and exclusion criteria are equally inconsistent. As a result no consistent picture of sleep disturbance emerges from the data. The most consistent findings are in the subjective reports of sleep quantity and quality. However, rather than dismissing this inconsistency as an artefact of inconsistent methodologies, we would suggest that a more plausible conclusion is that there is significant heterogeneity of sleep phenotypes in the CFS population. This needs to be further investigated.

There is a need for more qualitative accounts from patients about their experience of sleep. This could highlight the proposed heterogeneity and also guide or complement subsequent objective studies to further investigate which specific components of sleep are disturbed, and how they might play a role in maintaining symptoms such as fatigue. There is a need for more mixed method studies, combining and comparing objective and subjective data. This would afford an examination of sleep state misperception (SSM), as a principle problem in this population. Moreover, it is important that research moves forward in measuring sleep according to more stringent protocols, avoiding single-night recordings, selecting well-matched control subjects and accounting for sleep disorders such as apnoea.

More research is also needed to tease apart the causative and consequential role of sleep in CFS and to explore whether the daytime fatigue that is attributed to the CFS is

related to a sleep disturbance or something else (i.e. autonomic dysregulation, activity patterns, homeostatic dysregulation). Changes have now been made in the DSM-5 and International Classification of Sleep Disorders - Third Edition, where non-restorative sleep is removed from the criteria for Insomnia Disorder and may afford a greater differentiation between CFS and Insomnia. In clinical practice, it is important that CFS patients are screened for the presence of a sleep disorder to identify any incorrect or co-morbid diagnoses, as currently, complete sleep testing is not part of routine CFS evaluation (Carruthers et al., 2011; Fukuda, et al., 1994; Holmes, et al., 1988).

Ultimately, sleep comprises specific brain activities and physiological systemic adaptations, which are implicated in various functions of brain and body restoration, learning processes, memory consolidation and mood regulation (Kryger et al., 2011). Investigating sleep is thus highly relevant to this population given the overlap of these features with symptom presentation in CFS patients (loss of physical functioning, impairments in memory, attention and concentration) (Afari & Buchwald, 2003). Currently though there is no standardised method to measure sleep in this patient cohort. Practically there is a need to address and standardise the technical aspects of assessing sleep efficiently by employing a standardised 3-night protocol to observe sleep continuity, architecture and microstructure in CFS patients. This would help to determine 1) sleep disorders in this patient group, 2) the overlap between sleep disorders and CFS and 3) the distinct sleep characteristics of CFS patients. It may then be possible to clarify the precise relationship between sleep, behaviour, cognition, physiology and the physical symptoms of CFS.

2.4 Summary of thesis aims

This thesis intends to examine the specific *role* of sleep in CFS from a number of perspectives; from the personal through to the biological, using a range of sleep assessment methods. This biopsychosocial research programme aims to;

- Explore CFS patients' lived experience of sleep, through *qualitative* interviews;
- Evaluate *subjective* sleep quality in CFS patients and its association with key dimensions of the illness experience;
- Examine sleep *objectively* via a single-night of PSG and explore the possibility of heterogeneity of sleep problems in patients with CFS;
- Determine the feasibility of a comprehensive (mixed-methods) protocol for the assessment of sleep and cortisol, in an ambulatory setting, with CFS patients.

More far-reaching aims;

- Focussing in depth on one aspect of this condition, sleep, will lead to a greater understanding of CFS; helping to characterise CFS at every level from the biological through to the social and understand how these mechanisms interact.

- Establishing a feasible protocol for standardised assessment of sleep and cortisol in CFS, will inform future research practice and also lead to enhanced therapeutic delivery with more focus on the central role of sleep in CFS.

CHAPTER THREE
THE EXPERIENCE OF SLEEP IN CHRONIC FATIGUE SYNDROME: A QUALITATIVE INTERVIEW STUDY (STUDY 1)

3.1 Introduction

CFS affects between 0.23% and 2.6% of the adult population (Wessely et al., 1997; Jason et al., 1999; Reyes et al., 2003) and previous research has shown that there is a relationship between disrupted sleep patterns and CFS (Morriss, Wearden et al. 1997; Boneva, Decker et al. 2007; Togo, Natelson et al. 2008). Sleep is a consistent complaint of those suffering from CFS, with 87-95% of CFS patients report awakening unrefreshed following sleep (Jason, Richman et al. 1999; Nisenbaum, Jones et al. 2003; Nisenbaum, Reyes et al. 2004; Hamaguchi, Kawahito et al. 2011). Patients also report experiencing disrupted and fragmented sleep and difficulties in getting to sleep despite feeling tired (Anderson and Ferrans 1997). The effect of sleep is important to consider in CFS because disrupted sleep can cause fatigue, myalgia and poor concentration in healthy volunteers and therefore sleep disruption may result in a worsening of the effects of fatigue and other symptoms (Morriss, Sharpe et al. 1993).

Qualitative studies provide a potential for a richer understanding of the specific experiences patients have of their condition. A review by Anderson et al (2012) summarised thirty five qualitative studies in CFS. The key areas and themes they identified related to patient's experiences of living with the condition and physician understanding of the condition. However as yet, no qualitative studies in CFS have looked specifically at the sleep experience of patients in depth. Instead they have explored coping experiences, illness identity, social impact and physician-specific perspectives (Hart & Grace, 2000; Larun & Malterud, 2007; Whitehead, 2006).

The aim of the present study then was to explore the experience of sleep in CFS from the patients' perspective. This qualitative work will inform the systematic development of a sleep characterisation and intervention development programme. However what is missing from this and from the existing literature on sleep is the person with CFS's perspective and voice. This is a voice that is often obscured in the ideological battles

which occur in the definition and aetiology of CFS. It is an illness which is often poorly understood, where a crude dualism pits biological against psychological models and the complex experience of living with it is often lost. By utilising qualitative methods, particularly a critical realist approach, there is the potential to short circuit this debate by making the patients' lived experience of the condition, and their own understanding of it, the focus of research.

This method potentially offers a deeper understanding of the processes that may be involved in maintaining this chronic condition. Given the lack of extant qualitative accounts of sleep then, this study seeks to elicit in detail CFS patient's accounts of this key aspect of their illness experience. It will seek to build a picture of their complete sleep experience over a typical 24-hour period, from their own individual point of view. Further, we will attempt to see how sleep has an impact on patient's daytime functioning and quality of life in a way that could have implications for clinical practice.

3.2 Methods

3.2.1 Participants

A consecutive sample of participants were recruited and considered eligible if they fulfilled the Fukuda diagnostic criteria for CFS (Fukuda et al., 1994), and referred to the Newcastle-upon-Tyne Royal Victoria Infirmary. Patients were excluded if they met caseness on the Hospital Anxiety and Depression Scale (HADS), or were taking Thyroxine or sleep medications. Eleven patients (2 male and 9 female) participated in the research in response to an invitation letter, with ages ranging from 22-68 (mean = 48.2 years), and length of illness ranging from 4-33 years, (mean =10.2 years).

The research was given approval by the Newcastle and North Tyneside Local Research Ethics Committee, all subjects provided written informed consent and the Newcastle Hospitals NHS Foundation Trust sponsored the study.

3.2.2 Procedures and Data Collection

Data was collected through individual semi-structured interviews. All interviews were conducted privately, by the same researcher and participants had the option of being interviewed at home or in the University. Two participants chose to be interviewed at home, one via telephone, one via Skype video call and seven at the Northumbria Centre for Sleep Research (NCSR). Interview length ranged from 0.5-1.5 hours and all sessions (including the telephone and Skype interview) were audio-recorded. To maintain the anonymity of the participants, transcripts were labelled simply as the Participant numbered 1 to 11 (e.g. P1). All participants were asked "Can you please tell me a bit about your experience of having CFS" from the outset, and further interview prompts were used to follow up responses as necessary. Nevertheless, all interviews followed the same interview schedule (see Appendix C). The interview typically elicited a narrative of the patients' experience of their condition, with particular attention to their sleep and any particular disturbances. They were able to describe a 'typical' 24 hour period, including any symptoms, what made these better or worse, and their impact on daily functioning. Interviews were carried out until a point of data saturation. It was following the 11th patient interview, that it was considered saturation had been reached; at this stage in the study, no new themes were emerging in the data.

3.2.2.1 Data Analysis

A critical realist approach was taken to data analysis, making the patients' lived experience of the condition, and their own understanding of it, the focus of research. This is particularly important for this population, given that in the medical field the ontology of CFS is a matter of dispute. Braun and Clarke's (2006) thematic approach was chosen to address the focus of this research because as a realist methodology, it explores individual experiences and the meanings they attach to them without looking for hidden connotations or imposing the researcher's biases.

We transcribed the digital recordings verbatim, and analysed the transcripts thematically. During the analytical process initial thoughts and ideas were noted down, this is considered an essential stage in analysis (Riessman, 1993). The transcribed data were then read several times, and the recordings were also listened to several times to

ensure the accuracy of the transcription. This process of 'repeated reading' (Braun & Clarke, 2006) and the use of the recordings to listen to the data, results in "data immersion", a sense of closeness with the data. Following on from this initial stage and having become immersed in the data, we next developed codes which identified key features, for instance "broken", "pain" and "temperature". The codes identified features of the data that were considered pertinent to the research, and also ensured the whole data set was given equal consideration when repeated patterns in the data were seen to emerge.

In the third stage, we searched for themes that were able to explain larger sections of the data by combining different codes that were very similar. For example, if a participant talked about an aspect of experience, such as utilisation of alternative treatment approaches, we then allocated that part of their interview to the broad theme 'attempts at coping/sleep management'. We then refined and considered the themes in stage four, and this refinement of the themes took place on two levels; firstly ensuring the coded data formed a coherent pattern, and next, once a coherent pattern had been established, the themes were considered in relation to the data set as a whole, which in turn ensured the themes accurately reflected what was evident in the data.

The fifth stage involved defining and naming the themes. In addition, we felt it was important to develop short but informative names that conveyed an immediate sense of what the theme was concerned with. The final stage involved choosing examples of each transcript to illustrate elements of the themes. These extracts were selected on the basis that they clearly identified the issues within the theme and presented a clear example of the point being made. Such examples, illustrated as patient quotes from the transcriptions and the themes they fit into are shown in Table 3.1

3.3 Results

After characterising a full sleep-wake profile for each patient based on their individual narratives, and exploring in detail, their sleep-related experiences and the meanings they attach to them, the thematic analysis that was applied to the transcripts elicited three overarching themes; 1. Sleep Disturbances; 2. Effect of sleep on daytime functioning; and 3. Attempts at coping and sleep management. These are set out in

Table 3.1 which displays each main theme with their associated sub-themes and illustrative quotes from patients. It is important to note that the integrated sub-themes should not be considered mutually exclusive or independent of one another. For example, one patient describes how over the course of the year, her sleep patterns have become more irregular, describing how some periods are different to others and the unpredictability is a problem for maintaining a schedule. This illustrates the time-course variability of her sleep (Theme 1 subtheme 2) but also that has an impact upon her day-to-day living (Theme 2). Thus one theme may also contribute to others. Overall, sleep emerged as a key aspect of the experience of CFS, and its management and the effect on daytime functioning was a central preoccupation for all 11 participants; all of them saw sleep as playing a critical role in either maintaining or exacerbating existing symptoms. The themes and incorporated sub-themes are set out in the following sections, and a schematic of the cyclic nature of these themes can be seen in Figure 3.1. The nature of sleep problems and their *frequency* in the patient group are also illustrated in Table 3.2.

Main Theme	Associated Sub-themes	Illustrative quotes
Sleep Disturbances	*Variation between individuals** **[See Table 3.2 for the nature and frequency of sleep problems across the sample]*	"I have a lot of problems getting to sleep but it comes in phases" (P5) "99% of the time I go to bed and I'm out... I'm out like a light" (P8) "Being in bed wide awake and there is no chance of going to sleep, it's just awful. Hours and hours and hours of it... at least one night a week I have no sleep at all" (P7) "I'm quite good at going to sleep, but I have a lot of other problems.." (P1) "I feel I'm sleeping quite a lot but it's not good sleep if that makes sense" (P5) "It's not consistent.. feel like I haven't had enough sleep and broken sleep.." (P1) "I can't get to sleep and I just have to wait until I get tired.. it's a nightmare" (P11) "For me, it's waking up very very early..waking varies, sometimes it could be an hour, others it's a question of waking up stretching and going back to sleep again.. it does vary quite a lot" (P2) "I tend to wake up and then just keep going back to sleep for an hour or so" (P5) "sometimes I will have very distinct, quite vivid dreams" (P11)
	Variability of sleep over illness course	"It's just different on different nights… it varies" (P1) "for the last months, perhaps a year my sleep patterns have become more and more interrupted and irregular" (P2) "When it [CFS] started, I just couldn't get out of bed any day" (P9) "not sleeping when I want to sleep is a thing that's hit me at the moment…I have periods where sleeping is all I can do" (P7) "It's not like in the past. It used to be one night a week that wasn't constantly disturbed, now I'm having only one night a week where I'm awake most of the night, I think I've improved" (P7) "It was very much in the beginning, as though I had gone to sleep and my body had forgotten how to wake up, there was one point at that time where I slept for 6 days solid" (P8)
	Disturbers of sleep	"…these temperature fluctuations are quite a problem.. hot flushes every two hours or so but at night much worse, this is what wakes me up" (P1) "..my body temperature can change rapidly. I can be really hot one moment, really cold the next..I can't sleep if I am cold" (P10) "I wake up and I realise that I am frozen.. because I've thrown the bedclothes off so I must be feeling hot and that's difficult to regulate especially in the winter" (P11) "I wake up in a lot of pain during the night, in my body and it's the pain that actually wakes me up" (P3) "I'm always in a lot of pain, I get terrible neck and shoulder pain which gets worse through the night" (P4) "It's not great, I wake up at like any noise, I'm always waking up... like I'll say to my fiancé "Did you hear that?" during the night, he's like "Uh?" whereas I seem to wake up at everything" (P9) "..my mind's quite active as well..I can't get back to sleep ..I never get up when I'm awake at night, because there would be no advantage, the only thing that seems to be able to help me, to distract me from it, is to just read"(P1)

Continued on next page

Effect of Sleep on Daytime Functioning	*Maintenance/ exacerbation of Symptoms*	"Sleep is such a big part of the effect on me… sleep is a big factor in how I am" (P1) "If I haven't slept well I'm aching before I get up..physically it's more difficult for me..I feel unrefreshed.. very tired, my body is very tired if I haven't slept well" (P1) "combination of stress and lack of sleep creates an element of stress in me that consequently will cause me to become more confused" (P11) "I find I can't pull my thoughts together, my thinking..muddled and my thoughts fuzzy" (P3) "I get word salad really badly when I'm tired, I use wrong words or can't think of a word to use" (P11) "I feel quite unwell when I wake up, extremely...very, very tired on a morning even when I've slept ok... my body is very painful and I have nausea" (P3)
	Impact on quality of life and living	"When I was asleep all the time I hardly spent any time with my husband and there was no sense of achievement from the day." (P7) "I was spending 2 or 3 months in bed to get myself back on track to be able to take on work again" (P7) "having patches of sleep, with lots of awake time in between is a dominant part of my life, it's boring" (P7) "When it [CFS] started I couldn't get out of bed, I stopped going to school, my brother had to carry me to the bathroom.." (P9) "I haven't got any energy, I can be bed ridden for days" (P8) "the unpredictability of the onset of symptoms, I went on holiday and then had to spend a considerable percentage of the holiday in bed" (P11) " Because there's no kind of set pattern, some days I'm just so tired, at the minute, the last 4 weeks, I haven't even picked a book up. I can't even function so I am just like a vegetable. I'll go to the supermarket and I don't even know what I am putting in the…. Just do the shopping and come out and talk about rubbish with the school" (P6)
	Beliefs about impact on daytime functioning	"I would say eight hours, it really affects me if I don't…If I've had five or six, I can definitely feel that. I probably get between six and seven, but it's the fact that it's so broken, it's also a factor. "(P1) "In an ideal world I would like to go back to having around 8 hours sleep, I functioned well on that, and providing that pattern wasn't interrupted. Now, I am not getting as much...Erm, I function now within what I do, with the sleep that I get, erm... just spend a lot more time feeling very tired." (P2) "I feel like no matter how much sleep... I never function like a normal person would..Like I always, I always wake up tired no matter how much I sleep I have. Some nights, if I just have 2 or 3 hours obviously I will be a lot worse, but there's no difference between having like 6 hours and 12 hours sleep, I still feel just as bad." (P9) "For me, I would say I need 8 hours solid sleep… And I haven't had that for years. I'm in bed for about 10 hours, erm... but my actual sleep is probably about 6 hours." (P10)
Attempts at Coping and Sleep Management	*Balancing activity*	"I wake up at my own rate, very slowly, I could never burst out of bed and run round, that couldn't happen so it's a very slow pace and it dictates to me whether or not I'm going to be able to shower or dress myself" (P8) "I will nap between lectures because I am just so exhausted from uni" (P9)

Continued on next page

	"I find the more active I am, the more chance I have of having a better sleep, because if I'm not using the energy the mind is not going to switch off" (P10) "I stringently pace myself. If I eat the right food, get the right amount of exercise, get the right amount of sleep and do this to a fairly constant regime, it seems to improve my condition. You must not flatten the battery, and it took me a long time to learn that" (P11) "You can improve and maximise the situation by management, that's what I've done and that's what my life now consists of, it's an optimised condition" (P11) "Everyday, as soon as I come home I have a nap, because I am just exhausted" (P7) "I try to avoid any form of sleep throughout the day to try to keep that night time sleep pattern.. if you can call it that" (P10)
Adaptation & accepting disturbed sleep	"You just don't get a decent night's sleep, so I wake up most mornings feeling fairly lousy, but I've gotten used to it, you adapt." (P2) "I spent 8 months sleeping on the couch, It's really hard sharing your living space with someone who has to get up on a morning, and it's a big factor. I also now have a stair lift, so there's the practical aspects of being able to go to bed" (P7) "I've adapted my lifestyle and my thinking and I live within my limits" (P11) "It's how I cope with the erm... it doesn't matter what the day before was like..you don't tend to plan things too much or anything you just..... kind of go with it" (P8) "[as a family] we've learned how to handle and cope with the sleeping" (P8) "it's [not sleeping well] always bothered me, but I've put up with it for 8 years so it's just a part of my life now, I'm not going to sleep" (P9) "It's accepting it and being willing to try" (P10)
Alternative treatment approaches	"I empty my head before going to bed, if I have worries or stress on my mind – I tend to write it down" (P10) "I have learned some techniques, like to use positive thinking, like my bed is really comfortable…" (P1) "when I wake up, sometimes if I read it helps" (P1) "I've got a homeopathic kit.. I use the Bach Flower Olive remedy for sleep" (P6) "I've actually almost been prescribing myself sleep.. feeling recovered after sleeping" (P7) "I use lavender spray on my wrists and pillows, it works for me. I've got CD's with nature sounds and whale sounds, I try counting backwards [sighs]. I throw the whole lot at it [sleep]" (P7) "I do a lot of meditation, to switch [my] mind off. When lying in bed it's time to switch everything off. I use relaxation exercises and shut my body down and relax" (P11)

Table 3.1: Sleep-related themes (and associated sub-themes), developed from the qualitative analysis

	Frequency in group *N* (%)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Sleep Continuity Problems												
SOL problem	4 **(36.4%)**	✓				✓		✓		✓		
Frequent Awakenings/Broken Sleep	9 **(82%)**	✓	✓	✓	✓	✓		✓		✓	✓	✓
WASO (long duration)	3 **(27.3%)**					✓		✓		✓		
Extended sleep duration	3 **(27.3%)**					✓	✓		✓			
Short sleep duration	6 **(54.5%)**	✓	✓	✓	✓			✓			✓	
Waking too early	6 **(54.5%)**	✓	✓		✓		✓	✓		✓		✓
Napping	6 **(54.5%)**				✓	✓		✓	✓	✓		✓
Sleep Disturbers												
Vivid dreaming	4 **(36.4%)**				✓	✓			✓	✓		✓
Mentally Alert (during sleep)	5 **(45.5%)**	✓		✓	✓					✓	✓	
Temperature	5 **(45.5%)**	✓	✓	✓							✓	✓
Pain During Sleep	5 **(45.5%)**		✓	✓	✓				✓		✓	
Changes over course of illness	10 **(90.9%)**	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓

SOL, sleep onset latency; WASO, wake after sleep onset

Table 3.2: Nature and frequency of sleep problems and factors that disturb sleep in the sample of patients (N = 11)

Theme 1: Sleep Disturbances

"I feel as though I sleep deeply but feel dreadful the next morning, as if I've never been to bed." (P3)

A key overarching theme that was developed from the interviews was 'Sleep Disturbances'. This theme has three sub-themes that emerged across the sample of patients: 1.Whilst sleep was universally disturbed, for each person the nature of this disturbance was different. We have called this theme "variation of sleep between individuals". 2. For every patient sleep was not a stable phenomenon, rather the pattern of sleep disturbance had changed over the illness time course. We have called this theme "variability of sleep over the illness course". 3. Finally, the factors that disturbed sleep were a recurring theme - "the disturbers of sleep". These themes are summarised in Table 3.2 where we can see the unique "Sleep fingerprint" for each individual, the nature and frequency of sleep disturbers by patients, and the number of patients reporting change over time. We will now explore these themes in more detail.

Variation between individuals

Evident through the differing narratives, each patient had their own unique experience of sleep. This emerged through the different kinds of sleep problems being described by each patient. Despite this variability *between* patients in the types of problems identified, there were also complaints that were more common than others (see Table 3.2 for the nature and frequency of sleep complaints experienced by patients). Each patient however, considered their sleep-related problems to have a significant bearing on their lived experience of CFS and overall quality of life (discussed in a later theme). Examples of the nature of sleep continuity problems observed across the patient group are described below.

Difficulties getting to sleep (Sleep Onset Latency (SOL) problem) (4/11; 36.4%);

"it usually takes about 1 hour to an hour and a half when I first go to bed" (P9)

"I have a lot of problems getting to sleep but it comes in phases" (P5)

"Being in bed wide awake and there is no chance of going to sleep, it's just awful. Hours and hours and hours of it... at least one night a week I have no sleep at all" (P7)

For other patients, there were no latency-related issues:

"99% of the time I go to bed and I'm out... I'm out like a light" (P8)

"I'm quite good at going to sleep, but I have a lot of other problems.." (P1)

Frequent awakenings/broken sleep (9/11; 82%);
Most patients interviewed also regarded their sleep as broken, with the experience of frequent awakenings:

"I get it so rarely all in one go.. having broken sleep affects the quality of it, you don't hit the full sleep cycle" (P7)

"I never get through a night without waking up…it's at least six times.. because I don't get into a deep sleep" (P10)

"It's not consistent.. feel like I haven't had enough sleep and broken sleep.." (P1)

"A good night - where I have actually been in bed for 10 hours - depends on how many times I have been awake in-between those 10 hours" (P10)

"I don't think I sleep longer than two hours at a time, ever"(P1)

Wake after sleep onset (WASO) (3/11; 27.3%)

A long duration of wake time throughout the sleep period was problematic for three patients:

> *"I can be awake from an hour to up to 4 hours 5 hours"* (P4)

> *"I spend most of the night awake… it does hit me maybe one night a week, one night of sleep that wasn't constantly disturbed through exhaustion and now I'm having one night of being wake most of the night"* (P7)

Short sleep duration (6/11; 54.5%)

Six patients considered their sleep duration to be too short:

> *"I think I need about 8-9 hours and I only get probably on average about 5 hours, so it is quite a bit less than I think I need"* (P4)

> *"I was just sleeping a couple hours here and a couple of hours there. That's more of the pattern, sleeping for a couple of hours, an hour and a half, two hours; awake for a few hours, asleep for a few hours 24 hours a day"* (P10)

Extended sleep duration (3/11; 27.3%)

Three patients recounted how their sleep was long or had extended periods of sleep:

> *"Sleep is a thing that's hit me at the moment and I tend to have periods when sleeping is all I can do. When I'm sleeping all of the time it doesn't matter how much I sleep, I just want to sleep more"* (P7)

> *"I can continue that for a good 12 -14 hours, that's the norm. It has been longer and it can go on for days. Erm... when I haven't got any energy I can be bed ridden... like say this week for example, I was in bed on Monday afternoon and I got out yesterday [Wednesday] afternoon more or less"* (P8)

"At the minute I feel like I do need 12 hours a night. I feel I really do, or my body will suffer" (P6)

Waking too early (6/11; 54.5%)

More than half of patients considered themselves to be waking up too early:

"For me, it's waking up very very early..waking varies, sometimes it could be an hour, others it's a question of waking up stretching and going back to sleep again.. it does vary quite a lot" (P2)

"…for the past few months it has been the same thing…waking up very early, well early for me, so waking up at 5.30 or 4am in the morning, it is rarely that I would be asleep after that". (P2)

"Recently the last like couple of months I've been waking up about half an hour before my alarm" (P9)

"Wake up time varies, it varies between sometimes I wake up between 4-5am in the morning" (P11)

The variability of sleep problems between the patients is significant, In short, it highlights the heterogeneous nature of sleep in CFS and how for each patient, there is the experience of a different manifestation of sleep-related problems. What also emerged was that the nature of the sleep disturbance pattern changed over time for most patients. We explore this theme next.

Variability of sleep over the illness course

> *"It was very much in the beginning, as though I had gone to sleep and my body had forgotten how to wake up, there was one point at that time where I slept for 6 days solid"* (P8)

This was the single most consistent theme across the data, the fact that sleep changed over the illness course. 'Time course changes' was identified by all but one patient in this sample (10/11; 90.9%).

For each individual patient, they felt that throughout the entire course of their illness (i.e. prior to CFS, illness onset, over the illness course, up to the present time point), their experience of sleep-related problems, including the severity and the extent to which they impact upon other symptoms, has been highly variable and unpredictable. Many patients reflected upon "the beginning" or the early stages of their illness, a point at which they felt their sleep was highly disturbed. Patients on the whole considered their sleep to be different to how it had been before their CFS:

> *"It's [sleep] totally different. Before this started every morning I was up at 5 o'clock, out into the fields walking my dog. You know prepare for work, go to work. I probably had around 6 hours sleep and felt absolutely fine* (P3)

> *"It used to be [before CFS] 6 hours, 7 hours sleep, no bother...no bother at all. Now, I'm in bed 10 hours, erm, but actual sleep is probably about 6 hours because of all the disturbances and that's just my mind and my body. I don't get solid sleep like I used to, I think getting by on such little sleep has had that, you know, effect of running on empty and me having no fuel…it's led to the complete mental and physical breakdown of exhaustion"* (P10)

> *"My daughter had a sleep over and I wanted to try to stay awake for the simple reason... well... I couldn't believe it because I even fell asleep within the first 10 minutes of that going on downstairs.. which you know, wouldn't happen to me. So there is an abnormality definitely formed in my sleeping, whatever it is, I do not know"* (P8)

Interestingly, the sleep-related problems being experienced by patients were changeable across the illness trajectory (longer term), but also highly variable from one day to the next:

> *"It was very much in the beginning, as though I had gone to sleep and my body had forgotten how to wake up, there was one point at that time where I slept for 6 days solid"* (P8)

> *"When it [CFS] started, I just couldn't get out of bed any day"* (P9)

> *"It's not like in the past. It used to be one night a week that wasn't constantly disturbed, now I'm having only one night a week where I'm awake most of the night, I think I've improved"* (P7)

> *"I must be sleeping now, differently if I'm remembering my dreams"* (P7)

> *"it's just different on different nights.. it varies"* (P1)

> *"waking varies, sometimes it can be an hour, others it's a question of waking up, stretching and going back to sleep"* (P11).

Disturbers of sleep

Having identified and described the nature of the sleep-related complaints experienced by patients, there are specific problems described that patients consider highly contributory to the actual disturbance of their sleep. The key sleep 'disturbers' to emerge from the interviews were; bodily pain, mental alertness/arousals, vivid dreaming and temperature problems:

Bodily pain

The experience of bodily pain during their sleep was a problem for nearly half of the sample (5/11; 45.5%):

"I wake up in a lot of pain during the night, in my body and it's the pain that actually wakes me up again…I feel very very uncomfortable with the pain in my body" (P3)

"Pain…yes, because if I am in one position for more than an hour that's what wakes me up. I do take er... 60 mg of codeine at night; not for the sleep but to try to stay on top of the pain. Erm, to see if that can get me into a more settled sleep, just to take the edge off the pain or the discomfort in order to be able to settle" (P10)

"Sleep is a nightmare; I am in so much pain during the night. I sleep, I feel as if I sleep in a little ball, tensed up, I don't relax when I'm asleep and I don't sleep... I go to sleep easily but I wake frequently" (P4)

"I'll wake up... "Oh God, that really hurts!" I've got to move, find a different position. Every time I change position I wake up" (P10)

Mental alertness/arousals

Arousability during the sleep period was a factor recounted by many patients (5/11; 45.5%). They described that during sleep, they experienced mental alertness, and this contributed to a sense of light and unrefreshing sleep:

"It's like my brain won't stop. So whether it's been hungry or being awake or erm, yeah it just seems "Right, that's what I'm doing right now" it doesn't know what the off switch is" (P7)

".. You feel as though you've been awake which you haven't ... it's just the sleep is probably not as deep as I would normally have" (P3)

"I would say I wake at least every two hours, but sometimes for a long time can be for an hour, or even up to two hours, and then my minds quite active as well, I can't get back to sleep so I might read. I never get up, I never get up when

I'm awake at night, because there would be no advantage, the only thing that seems to be able to help me, to distract me from it, is to just read" (P1)

"I wake up at like any noise, I'm always waking up... like I'll say to my fiancé "Did you hear that?" during the night, he's like "Uh?" whereas I seem to wake up at everything" (P9).

"I'm disturbed, easily woken, like noise, So I must sleep fairly lightly" (P4)

*"Every time I change position I wake up, unfortunately I don't seem to be... you know... one of those who can have a restless sleep but not even seem to be aware of it. I am!" (*P10)

Vivid dreaming

Although fewer patients (4/11; 36.4%) reported experiencing vivid dreaming as part of their CFS, they emerged as being a significant problem for these particular patients; they regarded them as *"horrendous" and "disturbing"* (P4) with *"difficulty distinguishing dream from reality"* (P5) and highly significant to their negative sleep experience:

"I have horrendously vivid dreams.. the more I sleep, the more it happens, troublesome, vivid dreams...the doctor put me on medication to try and get rid of these quite disturbing nightmares" (P4)

"Sometimes I have very distinct dreams and what was worrying me about this episode … I was getting dreams because I had slept in the afternoon and I was getting my dream mixed up with reality" (P11)

"When I wake up it is really hard to distinguish the dream from reality, it actually feels as if it has really happened and I can feel the emotions from it" (P4)

"I get a lot of really messed up dreams that I can't really remember, but I get a lot of weird dreams, you know, when they are with you when you first wake up and you get a bit groggy, I have trouble when waking up constantly like every few minutes whatever it is telling the difference between what has happened when I'm asleep and when I'm awake" (P5)

Temperature problems

Nearly half of patients (5/11; 45.5%) highlighted temperature problems, typical of autonomic dysfunction, as a key contributor to their disturbed sleep:

"I wake up and I realise that I am frozen.. because I've thrown the bedclothes off so I must be feeling hot and that's difficult to regulate especially in the winter" (P11)

"I think what wake me up is the temperature, the heat, and the sweating; I wear a cotton nightdress which I try to mop myself with… these temperature fluctuations are quite a problem, hot flushes every two hours or so but at night much worse, this is what wakes me up" (P1)

"Temperature is another factor...my body temperature can change rapidly. I can be really hot one moment, really cold the next. During the night I am exactly the same. Again, I can't get to sleep if I am cold" (P10)

Daytime Sleep (napping)

Patients who avoided sleeping during the day described how they were aware of the impact such napping on their night-time experience of sleep, and thus considered it to be a 'disturber' (5/11; 45.45%). This is also discussed as part of Theme 3, under sleep management strategies.

"Whenever I have done [nap], because I have been particularly tired, which is a rare occurrence.. I always feel dreadful when I wake up" (P2)

"My priority is sleeping at night.. so I never nap during the day… it doesn't help what is already a problem for me [sleep]." (P3)

"If I sleep at all during the day…my [sleep] pattern gets worse" (P10)

Theme 2: Effect of sleep on daytime functioning

Maintenance/Exacerbation of Symptoms

Patients expressed how the poor quality of their sleep had a significant bearing on their daytime symptoms the following day. Bodily pain, confusion and concentration problems were shown to be the key symptoms exacerbated by poor sleep. It is clear from these patient narratives that sleep quality, symptoms and daytime functioning are highly inter-related.

Confusion/concentration problems

Most patients (73%; 8/11) considered the consequences of their disturbed sleep as impacting upon their memory, creating feelings of confusion and affecting their ability to concentrate during the day;

"I find depending on how tired I am.. I get word salad really badly when I'm tired. I use wrong words or I can't think of a word to use… I just don't have the energy, the focus and the concentration to you know.." (P11)

"The combination of stress and lack of sleep creates an element of stress in me that consequently will cause me to become more confused" (P11)

"Sometimes I get quite tired and for the last few weeks, I might have been eating dinner or watching the television and I actually go blank for a few moments which is quite an odd experience. I really need to go and get that checked out, but sort of blank or dizzy for a few seconds, just a short while" (P2)

"With exhaustion all of the time, I have with it like this mental fuzziness, this is quite difficult because my brain doesn't work very well so it is quite hard just to get my brain to work properly" (P4)

"I find I can't pull my thoughts together, my thinking...muddled and my thoughts fuzzy" (P3)

"...there's a difference in the fatigue of the syndrome and to feeling very tired due to a lack of sleep, there is a subtle difference between the two I think. You know when you're tired and you know when you're deeply fatigued. When you are deeply fatigued everything is a big effort and when you are tired you are a bit dozy obviously and it is a bit harder to concentrate on doing things or reading a book or whatever, that's quite hard work. Concentrating on a book for example, or listening to someone talking, trying to explain something to you" (P2)

Bodily pain/discomfort

Nearly half of patients (5/11; 45.5%) considered their poor quality sleep to have an impact physically in the form of bodily pain:

"If I haven't slept well I'm aching before I get up...physically it's more difficult for me…I feel unrefreshed… very tired, my body is very tired if I haven't slept well" (P1)

"I wouldn't say that I have any good days... but at the moment on my better days when I can get out, I still don't feel well, I don't wake up and think, oh, you know 'I feel fine this morning', I feel quite unwell when I wake up, extremely... very, very tired on a morning even when I've slept ok... my body is very painful and I have nausea" (P3)

"If I do sleep... it's not... I don't ever feel rested from it. I always just feel in so much pain when I wake up, so I don't know what it would be like to have a restful night's sleep [laughs] I can't remember what that's like"(P4)

Impact on Quality of Life and Living

> *"When I was asleep all the time I hardly spent any time with my husband and there was no sense of achievement from the day."* (P7)

All patients interviewed emphasised the negative impact of sleep-related complaints on their lived experience of CFS, which ultimately affected their quality of life. Patients found that their irregular sleep schedules affected their capacity to socialise with friends, and by spending long periods of time in bed, not necessarily asleep, this took away time spent with family members and the ability to maintain employment status or school attendance. These consequences in turn impact upon the illness, with patients struggling to address and overcome the social consequences of their condition when they barely have the energy to function.

> *"When sleeping all of the time, it's as if those days and weeks and months never happened. And sometimes I can't remember what year it is or how old I am because I just feel like I've lost so much time, you know?"* (P7)

> *"I was spending 2 or 3 months in bed to get myself back on track to be able to take on work again"* (P7)

> *" ..because there's no kind of set pattern, some days I'm just so tired, at the minute, the last 4 weeks, I haven't even picked a book up. I can't even function so I am just like a vegetable. I'll go to the supermarket and I don't even know what I am putting in the…. Just do the shopping and come out and then go and talk about rubbish with the school"* (P6)

Beliefs about impact on daytime functioning

Patients also held beliefs about their sleep and the impact it had on their daytime functioning. They highlighted that in order to 'function' the following day they required a certain amount of sleep; the consensus across this patient group was for 8 or more hours. However, it is important to note that patients did *not* feel they obtained

this amount each night, and that it was highly disturbed. They also emphasised how their sleep amount varied and was inconsistent and even if they did reach this level of sleep duration, they still felt as though they had not slept. It did not matter how much sleep was being obtained, the quality was not there and that it was the quality of the sleep that affected their functioning capacity the following day:

> *"There's no difference between having 6 hours and 12 hours of sleep, I still just feel as bad, I never function like a normal person would"* (P9).

> *"I feel I'm sleeping quite a lot but it's not good sleep if that makes sense"* (P5)

> *"I don't feel like the length of sleep makes much difference makes any difference, it doesn't matter how much sleep I have time wise, because it doesn't mean the quality is there"* (P5)

> *"In an ideal world I would like to go back to having around 8 hours sleep, I functioned well on that, having more sleep would make life better, more enjoyable... tolerable, and probably easier to cope with this underlying fatigue problem because it must compound upon itself"* (P2)

Theme 3: Attempts at coping and sleep management

> *"You can improve and maximise the situation by management, that's what I've done and that's what my life now consists of, it's an optimised condition"* (P11)

Balancing Activity

All patients (11/11) described the need to balance their activity as a means of managing their energy levels. This formed an integral part of their day-to-day lives, and was the focus for all patients. The key to maintaining some quality of life for patients was being able to integrate some form of activity or social interaction into each day, albeit different levels for different individuals.

Over half of patients in the sample described that they also slept during the daytime (Napping) (6/11; 54.5%). Patients found by utilising frequent naps during the day, they were able to better cope with the demands of that day in terms of physical activities and mental demands. Others also felt improvements in mental symptoms such as confusion in thoughts and concentration difficulties:

> *"I will nap between lectures because I am just so exhausted from uni"* (P9)

> *"I sleep during the day, whereas the majority of people I would imagine if they had slept that bit during the day, it would keep them awake during the night. It doesn't happen like that with me it is a constant sleeping.. I just need to do it.. to cope.. and do a little more in the day."* (P8)

> *"I sleep in the afternoon, usually my sleep varies between 20 minutes and 2 hours and I don't have a cut off on it…it helps me in my thinking in general…"* (P11)

> *"Every day as soon as I come home.. I have a nap, because I am just exhausted"* (P7)

On the other hand, five patients were very aware that daytime napping was a disturber of their sleep at night (described previously under Theme 1) and made a conscious effort to avoid doing it, a strategy for sleep management. These differences between patients demonstrate the heterogeneity in the group; some using the napping as a strategy to help with their energy levels, whilst others avoiding doing so – aware that it was a key disturber of their sleep at night:

> *"I do not nap during the day, I've always hated that... that may well be because whenever I have done, because I have been particularly tired, which is a rare occurrence.. I always feel dreadful when I wake up"* (P2)

> *"I try to avoid any form of sleep throughout the day to try to keep that night time sleep pattern... if you can call it that"* (P10)

"I never want to get into a habit where I nap during the day I would rather... my priority is sleeping at night really" (P3)

One patient considered their night-time sleep to be improved if they increased the activity levels in the day, stating *"if I am not using the energy then the mind is not going to switch off"* (P10). Patients also described the need for a "dozing" period after waking, and once awake the slow and paced routine that would help them to get through the day ahead. Through attempts at coping and overall lifestyle management, patients describe how "you can improve and maximise the situation by management:

"I stringently pace myself. If I eat the right food, get the right amount of exercise, get the right amount of sleep and do this to a fairly constant regime, it seems to improve my condition. You must not flatten the battery, and it took me a long time to learn that" (P11)

"I know I've got to find a balance again and get the juicing back… 3 times a week and the food right, that keeps my health right and my brain works better" (P6).

"I wake up at my own rate, very slowly, I could never burst out of bed and run round, that couldn't happen so it's a very slow pace and it dictates to me whether or not I'm going to be able to shower or dress myself" (P8)

These examples demonstrate how patients consider the balance of activity for regulation of both physical and mental energy as vital in their day-to-day living, with the utilisation of sleep-specific means to deal with anticipated lifestyle demands.

Adaptation & Accepting Disturbed Sleep

> *"You just don't get a decent night's sleep, so I wake up most mornings feeling lousy, but I've gotten used to it, you adapt"* (P2).

A key element to emerge from the interviews with patients was that over the course of their illness they had learned, to varying extents, to adapt their lifestyle and accept their limitations, and this acceptance and adaptation also occurred around sleep problems.

Patients described how they "*live within* [my] *limits"* and *"have adapted* [my] *thinking"* (P11), as a way of coping with the condition. Others have adapted their homes, for example one patient described how she *"spent 8 months sleeping on the couch and now has a stair lift, so there are the practical aspects of being able to get to bed"*(P7). Patients also made attempts at modifying their diet, for example P6 expressed how she had cut dairy from her diet completely, which had beneficial effects on energy levels and also resulted in helping sleep initiation difficulties she was experiencing.

As a means of coping, an integrative theme that was evident across the patient group was a sense of acceptance, and this was particularly true with regard to the sleep problems they were experiencing as part of their CFS. *"I've put up with it* [not sleeping well] *for 8 years, so it's just part of my life now, I'm not going to sleep"* (P9). Acceptance was even expressed on a family level "[as a family] *we've learned how to handle and cope with the* [problems] *sleeping"* (P8). This depicts how perhaps over time, patients adjust to the symptoms they experience, sleep problems being the example here, and as a consequence, accept that they play a part of their illness experience, so learn to live with it.

Alternative Treatment Approaches

> *"I've actually almost been prescribing myself sleep… feeling recovered after sleeping. I use lavender spray on my wrists and pillows, I've got CD's with whale and nature sounds and I try counting backwards – I throw the whole lot at it [sleep]"* (P7)

The use of alternative treatments was a common integral theme for sleep-management strategies utilised among many participants in the study. Patients identified how they resort to approaches such as homeopathic remedies (e.g. *"I've got a homeopathic kit.. I use the Bach Flower Olive remedy for sleep"* (P6)), methods of relaxation (e.g. *"I do a lot of meditation and use relaxation exercises to shut my body down and relax"* (P11)), and practice general sleep hygiene, techniques to promote better sleep (e.g. *"I empty my head before going to bed, if I have worries or stress on my mind – I write it down"* [P10]). It is evident from the interviews that patients have a good awareness of sleep hygiene and many put into practice the appropriate measures to maximise the potential for good sleep opportunity.

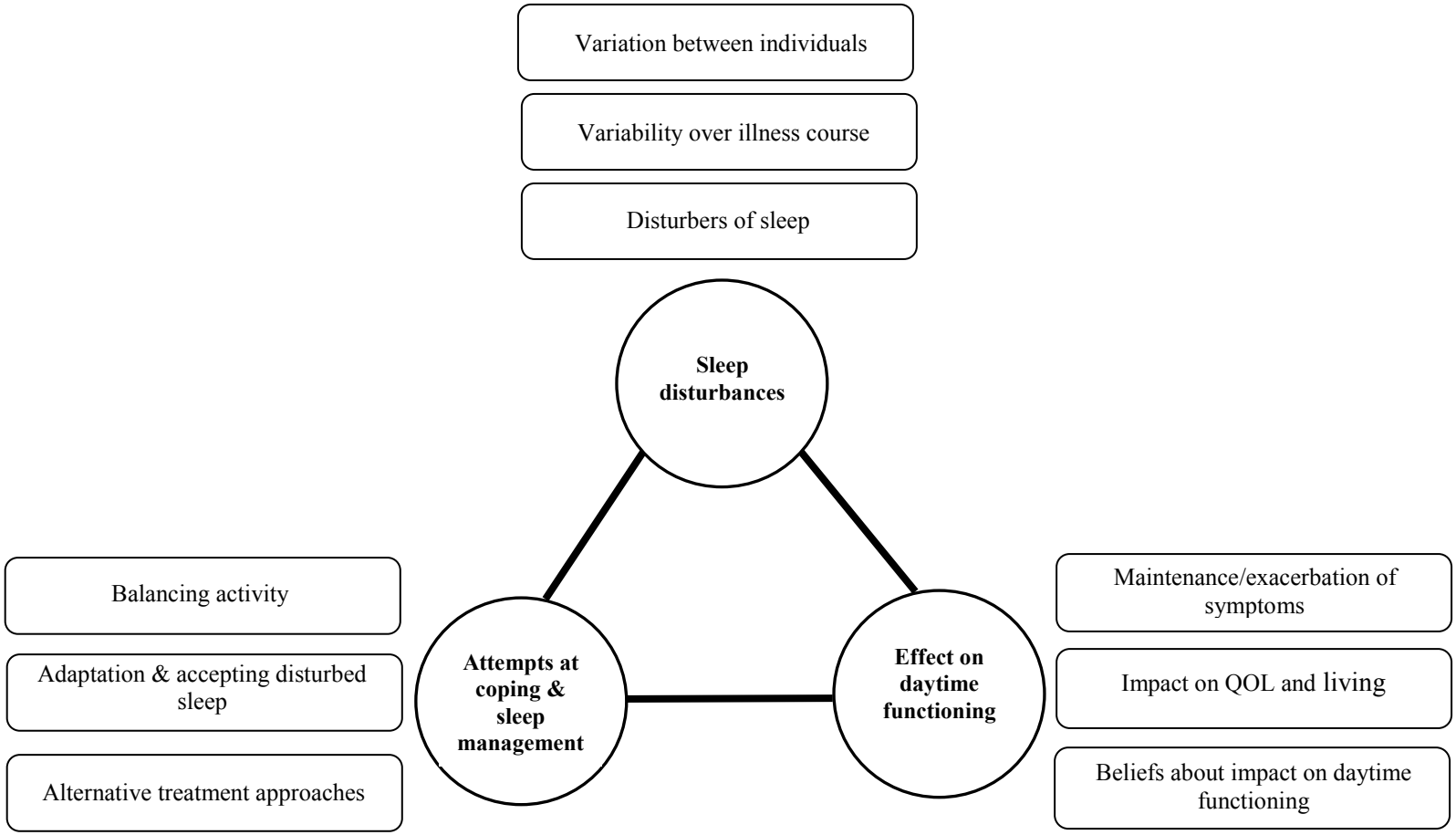

Figure 3.1: Cycle of themes and associated sub-themes, developed from the qualitative analysis

3.4 Discussion

The study aimed to understand the nature and severity of sleep disturbances experienced by patients with CFS by examining a sample of patients with the condition using qualitative methods, in particular a critical realist approach which ensured that patients experience and understanding was at the centre of the results rather than pre-existing coding frames or any analytic preconceptions.

Overall, there were three key findings. Whilst sleep was disturbed in all patients, the nature of the disturbance was highly individual, changed over the course of time and was caused by a cycle of multiple factors. Secondly, sleep was universally seen as impacting on daytime functioning and symptoms. Finally, the attempts to manage sleep formed a considerable part of the emotional and physical "work" of coping with CFS.

The variability of sleep patterns within and between individuals mirrors a recent exploratory study that highlighted the changeable nature and progression of CFS over the illness trajectory (Anderson et al., 2012). This provides qualitative corroboration of what was observed in the literature review – that sleep problems might be highly heterogeneous in CFS. Further qualitative work with CFS patients when focussing on their sleep may wish to identify the different sub-groups of sleep-related complaints prior to the study. This could offer a deeper and more representative insight into specific types of sleep complaints presenting in this population. Future research should also consider illness length when examining the role of disturbed sleep in patients, particularly in light of the variability in length of illness in the current sample. The length of illness may not necessarily reflect illness severity, but it should be highlighted nevertheless. We will further explore the heterogeneity of sleep in CFS in Chapter 5.

The ‘sleep disturbers’ that emerged from the patient accounts mirror the causes of waking (temperature fluctuations, pain and vivid dreams) identified by a study that an examined self-reported sleep, fatigue and disability in CFS patients (Morriss, Wearden & Battersby, 1997). Interestingly, such disturbances appear related to the psychophysiological processes (HPA/physiological arousal, cortical arousal,

emotional/autonomic arousal), and the dysregulation of these self-regulatory biological systems that has been postulated as being important in the maintenance of CFS (see Tomas, Newton & Watson, 2013 for a review). As such temperature dysregulation, pain sensitivity and nocturnal mental alertness and vivid dreams may be reflections of underlying dysregulation of homeostatic mechanisms. This could be reflecting the interaction between the sleep homeostat and circadian phase marker regulation. These dysregulations disturb sleep, causing more daytime symptoms and further attempts at self-regulation. Such a vicious cycle may be involved in the perpetuation of the condition.

The thematic findings build upon previous qualitative work that describe coping experiences and the social impact of CFS (Hart & Grace, 2000; Larun & Malterud, 2007; Whitehead, 2006), and illness course and progression (Anderson et al., 2012). However, this study offers a deeper insight into sleep-specific issues faced by patients, one of the key symptoms experienced as part of the illness (Anderson et al., 2012), and how sleep relates to the overall experience of their condition. Importantly, not only did this study highlight that sleep problems were evident in these patients, but more precisely that they contributed substantially to the weight of the illness burden. Chronic illness can be seen as a biographical disruption and part of that disruption is the new workload of managing the illness and the responsibility of being a patient that the illness entails (Bury, 1982). Sleep-management was "work" for these patients, part of the more general work of energy management and pacing, and formed a central part of the daily coping strategies that ultimately helped them live with their condition.

3.4.1 Clinical implications & future directions

Disturbed sleep is common in CFS and like other symptoms experienced in this condition, the way in which the sleep disturbances present and their intensity is highly variable between patients, and also within the same patient across their illness path. Despite the differing narratives regarding the role of sleep in CFS, all patients held the belief that sleep was central to their wellbeing and had a direct bearing on the course and progression of their CFS. The sleep-related themes identified above should not be viewed as individual categories, but rather as factors that reinforce one another, and thus may serve to maintain other symptoms of the condition, even the CFS itself.

Working out the "sleep fingerprint" of each patient through detailed assessment can then lead to tailored therapies, individualised for each patient. This indicates a potential way forward for implementing genuinely stratified medicine, an avenue that is becoming increasingly favoured in the CFS research domain.

In terms of research, utilising qualitative methodology in CFS sleep research affords the exploration of sleep-specific patient insights and experiences in greater depth. The patient insights and experiences that emerged from this study highlight the importance of drilling down into parts of the CFS experience, and a similar approach could be used around other specific parts of the illness experience. This in turn could help inform and guide clinicians and researchers working with CFS patient groups. Certainly it seems to be that further investigation, both objective and subjective, of the role of sleep disturbances on maintaining and/or exacerbating existing symptoms in CFS is warranted.

3.4.2 Conclusion

All patients in this study made attempts to implement ways of managing their sleep problems, yet all patients still regarded their sleep as in some way "broken" and in need of management/repair. The impact of broken sleep contributes to the cycle of biopsychosocial interaction that may serve to maintain this illness. The study highlights a need to go into more depth with the sleep difficulties faced by this patient group, and work with patients at an individual level during treatment. In terms of the current research programme, this study has informed the systematic development of a detailed sleep characterisation and intervention study, and in the coming chapters we will describe how we utilised a range of quantitative and self-report assessment methods to address the inconsistencies in existing sleep studies with CFS patients, and work towards developing a tailored sleep-treatment intervention. However, all of this work would not have been possible without first listening to what the patients had to say about sleep.

CHAPTER FOUR
AN EXAMINATION OF SELF-REPORTED SLEEP IN CHRONIC FATIGUE SYNDROME: THE ASSOCIATION BETWEEN SLEEP QUALITY AND DAYTIME PHYSICAL AND MENTAL FUNCTIONING (STUDY 2)

This chapter was presented at the UK Society for Behavioural Medicine (UKSBM) Annual Scientific Meeting, 2013, Oxford:

Gotts, Z. M., Ellis, J. G., Brannan, K., Newton, J. L., & Deary, V. (2013). Daytime Napping Impairs Cognitive Functioning in Chronic Fatigue Syndrome (CFS), 76.

4.1 Introduction

CFS, characterised by intense fatigue which affects both physical and cognitive functioning (Fernandez, Martin et al. 2009), is also associated with cognitive and affective symptoms including: poor memory and concentration, anxiety, depression, sleep disturbances and mood swings (Afari and Buchwald 2003). Whilst fatigue is the principal complaint of this complex illness, this is closely followed by sleep disturbance which is also a cardinal feature of CFS. A study by Togo and colleagues found that patients with CFS felt more sleepy and fatigued after a night's sleep compared to controls. This was shown to be primarily due to a decrease in the length of periods of uninterrupted sleep in patients with CFS compared to healthy controls (Togo et al., 2008). More specifically, patients tend to report fragmented sleep and sleep onset difficulties despite feeling tired (Anderson & Ferrans, 1997), and one study found that 61% of patients reported sleep continuity complaints which were independent of cognitive functioning, fatigue and psychological wellbeing (Vercoulen et al., 1994). Disrupted sleep has been shown to cause fatigue, myalgia and poor concentration in healthy volunteers and therefore sleep disruption may be not just a consequence but also a cause of the other symptoms in patients with CFS (Morriss et al., 1993).

Daytime sleep, or napping, has been shown to have a negative impact on nocturnal sleep in non CFS populations. For example a long nap or a nap taken later in the day or early evening has been shown to have a detrimental effect on the length and quality of

sleep during the subsequent night, by decreasing homeostatic pressure (Karacan et al., 1970; Feinberg et al., 1985; Dijk et al., 1989; Werth et al., 1996).

Disrupted sleep may serve to complicate the course of CFS by worsening existing symptoms. Even if sleep complaints are common in CFS, existing studies of self-rated sleep and its association with daytime functioning and disability are limited. Findings show sleep complaints are associated with greater global disability and that sleep continuity complaints become worse when the underlying condition and fatigue worsen (Morin & Barlow, 1993). Sleep disturbances form a key dimension of CFS (alongside others such as social functioning, psychological wellbeing and functional impairment) (Vercoulen et al., 1994), and CFS patients report more naps and restless legs than healthy controls (Morin & Barlow, 1993). However, studies have not directly examined self-reported sleep and its impact on daytime physical and mental functioning in CFS, nor have they looked at the impact of daytime napping in this population.

Importantly, there are methodological limitations in existing studies. These include taking measures of sleep disturbance based on self-rated presence or absence of sleep problems (Morin & Barlow, 1993); not defining the duration of sleep complaints (Vercoulen et al., 1994); having a limited range of complaints (Vercoulen et al., 1994; Morriss, Wearden & Battersby, 1997); or examining sleep related complaints lasting only one night (Morriss, Wearden & Battersby, 1997). These limitations make the generalizability of this research problematic, and none of these studies meet the standard for sleep assessment - 14-day consecutive sleep diaries – which is needed to afford appropriate characterisation of patient's sleep patterns. The present study therefore aims to utilise this standard sleep assessment to examine self-reported sleep in CFS, and to establish whether disrupted sleep continuity and daytime napping predict markers of daytime functioning, specifically fatigue severity, sleepiness and cognitive dysfunction.

4.2 Methods

4.2.1 Subjects

A power calculation (significance level of 0.05 and statistical power of 80%) was performed to estimate participant numbers. In order to detect the smallest change of clinical relevance, a sample size of 87 subjects was required. A consecutive sample of one hundred and eighteen patients (allowed for a 10% drop out rate), referred to the Newcastle-upon-Tyne Royal Victoria Infirmary who fulfilled the Fukuda diagnostic criteria for CFS (Fukuda et al, 1994), and had been screened by a specialist physician for any medical and mental illness which could explain their fatigue, as per the UK NICE (British National Institute for Health and Clinical Excellence) Guidelines for CFS (NICE, 2007). The study was approved by the Newcastle and North Tyneside Local Research Ethics Committee, all subjects provided written informed consent and the Newcastle Hospitals NHS Foundation Trust sponsored the study.

4.2.2 Procedure

Subjective assessments

Subjective sleep was assessed using a 14-day sleep diary (Krupp et al., 1991) (Appendix D). Patients were required to complete the diary on waking each morning. Patients recorded the times at which they retired to bed, identified time of lights out, the number of nocturnal awakenings, time of morning awakening, the number, duration and timing of daytime naps, alcohol and caffeine consumption, and medication use. Patients returned the completed diaries and data were averaged across the number of days completed (Mean completion 14 ± 0 days) for each participant. The following sleep continuity variables were calculated; Time in Bed (TIB), Total Sleep Time (TST), Sleep Onset Latency (SOL), Wake After Sleep Onset (WASO), Number of Awakenings (NWAK), and Sleep Efficiency (SE). To characterise patient's napping behaviour, an overall duration of daytime napping was calculated in minutes, including duration of napping that occurred in the morning (AM napping) and afternoon-evening (PM napping) period, on average across the 14 days. (Descriptions of sleep variables are detailed in table 4.1).

Functional and symptom assessment tools

On commencing the study, patients completed a series of assessments, each of these were completed once. Levels of daytime sleepiness were determined by the Epworth Sleepiness Scale (ESS) (Appendix E). Patients self-report their chance of dozing or sleeping based on 8 given situations. The responses are made on a Likert-type scale ranging from 0 (would *never* doze/sleep) to 3 (*high* chance of dozing/sleeping) Total possible scores derived from the 8 questions range from 0-24, with a score of 10 or more being indicative of significant daytime sleepiness (Johns, 1991).

The 11-item Chalder Fatigue Questionnaire (CFQ) evaluated fatigue severity. It is one of the most widely used measures for assessing physical and mental symptomatic fatigue experienced by CFS/ME patients. Four response options are available, ranging from ‘‘less than usual’’ to ‘‘much more than usual’ The Likert system for scoring was used (0, 1, 2, 3), with a total possible score ranging from 0-33. A higher score indicates more fatigue. The test has been shown by its authors to have good reliability (r =.86 for physical fatigue, and r =.85 for mental fatigue) and has high internal consistency as measured by Cronbach’s alpha (.89) (Chalder et al., 1993) (Appendix F).

Cognitive functioning was assessed using the Trail Making Test (TMT) (Appendix G). The TMT is a task designed to measure visual attention and task switching and requires participants to connect-the-dots between 25 consecutive targets on a sheet of paper. In version A of the test all of the targets are numbers. In version B, targets alternate between numbers and letters (1, A, 2, B). The time it takes to complete the task is the measure of performance, with longer time indicating poorer cognitive performance (Reitan, 1958).

Patients completed the 25-item Cognitive Failures Questionnaire (CFQ) (Appendix H, a tool developed by Broadbent (Broadbent et al, 1982) to assess self-reported deficits in attention, perception, memory and motor functioning. The questionnaire measures the frequency of everyday cognitive failures or lapses by asking participants to rate how often they make mistakes on a 5-point Likert scale, from 0 (never) to 4 (very often). The total possible CFQ score ranges from 0-100, with higher scores indicating more cognitive failures.

To control for the impact of anxiety and depression on daytime functioning, patients completed the 14-item Hospital Anxiety and Depression Scale (HADS) (Appendix I), 7 items provide a measure of anxiety and 7 a measure of depression (Zigmund & Snaith, 1983). For both Anxiety and Depression scales, raw scores between 8 and 10 identify mild cases, 11-15 moderate cases and 16 or above, severe cases.

4.2.3 Statistical analysis

The data were analysed with SPSS (IBM 19.0). First, descriptive statistics for CFS patients' self-reported sleep variables and napping were calculated. HADS variables were also compared with published data of a reference sample (Crawford et al., 2001). Second, Multiple Regression analyses examined the extent to which self-reported sleep and napping predicted patient's daytime physical and mental functioning, fatigue severity and sleepiness. Step one of each model incorporated patient characteristics (age, gender, length of disease), step two consisted of the mood variables of anxiety and depression (from HADS), and step three contained the subjective sleep parameters (SE, NWAK, WASO, SOL, napping duration), TIB and TST were not included in the models as together these variables make up SE. Daytime symptoms measured by fatigue severity (Chalder Fatigue Scale), daytime sleepiness (ESS) and objective and subjective cognitive functioning (Trail Making Test, Cognitive Failures Questionnaire) were included as dependent variables in each analysis, respectively, and checks for multicollinearity were carried out.

Abbreviated Variable	Sleep Variable (measure)	Description
TST	Total Sleep Time (minutes)	Amount of time asleep
SOL	Sleep Onset Latency (minutes)	Length of time from lights out to first onset of sleep
WASO	Wake After Sleep Onset (minutes)	Number of minutes of recorded wake following first onset of sleep
NWAK	Number of Awakenings (over TSP)	Number of wake bouts following first onset of sleep
SE (%)	Sleep Efficiency	Percentage of time spent asleep from the amount of time spent in bed (TST/TIB*100)

Notes: REM, rapid eye movement; TSP, total sleep period; TST, total sleep time

Table 4.1: Description of sleep variables included in study 2

4.3 Results

Of the 118 diaries returned by patients, 17 had missing data so 101 were used in the analysis. The final sample therefore consisted of 101 patients with an average length since diagnosis of 7.8 years (±7.34). The mean age of the sample was 42.05 (±12.99), range 16 - 68 years, and 81.2% were female.

21 (20.8%) patients in the sample did not report any daytime napping throughout the 14-day period. Of the 80 (79.2%) that did nap, on average napping duration was 39.55 (±55.35) minutes. Patients spent on average 7.80 (±16.03) minutes napping in the morning period (AM), and 31.74 (±43.94) minutes napping in the afternoon-evening period (PM). (The mean values for all sleep and functioning variables of the study, including demographic characteristics are shown in Table 4.2).

The sleep diary data show patients had on average TST of 426.69 (±80.30) minutes, SOL of 37.60 (±41.67) minutes, WASO of 50.81 (±43.75) minutes and sleep efficiency at 75.74 (±13.64) %, demonstrating values in the abnormal range (Edinger et al., 2004).

	N	Mean (SD)
Patient Characteristics		
Gender M, F [N (%)]	101	M: 19 (18.8%), F: 82 (81.2%)
Age	101	42.05 (12.99)
Length of Illness [Months]	101	93.69 (88.12)
Sleep Continuity Parameters		
Sleep Onset Latency (SOL) [Minutes]	101	37.60 (41.67)
Time In Bed (TIB) Sleep Period [Minutes]	101	569.50 (83.18)
Total Sleep Time (TST) Sleep Period [Minutes]	101	426.69 (80.30)
Number of Awakenings (NWAK)	101	1.48 (1.14)
Wake After Sleep Onset (WASO)[Minutes]	101	50.81 (43.75)
Sleep Efficiency (%)	101	75.74 (13.64)
Daytime Sleep (napping)		
Total Napping Duration [Minutes]	80	39.55 (55.35)
Duration AM Napping [Minutes]	80	7.80 (16.03)
Duration PM Napping [Minutes]	80	31.74 (43.94)
Functional and Symptom Measures		
HADS Anxiety	101	8.31 (4.62)
HADS Depression	101	8.42 (4.10)
Chalder Fatigue Questionnaire	101	25.19 (6.31)
Epworth Sleepiness Scale	101	9.87 (5.07)
TRAIL Making Test [Minutes]	96	135.31 (74.03)
Cognitive Failures Questionnaire	89	58.45 (21.14)

Notes: *N* differs on different measures. Data *presented as means and standard deviations (SD).*
HADS, hospital anxiety and depression scale

Table 4.2: Self-reported sleep, functional & symptom assessment data for CFS patients

4.3.1 Fatigue Severity

For fatigue severity (based on Chalder Fatigue Questionnaire scores), three predictors (length of disease, depression, WASO) accounted for 23.7% of the variance. Examination of the beta weights in the third model showed that length of disease significantly predicted Chalder Fatigue scores, with people who had been diagnosed for less time being more fatigued. Having higher depression scores and more WASO were the other significant factors (see Table 4.3).

4.3.2 Daytime Sleepiness

Anxiety was the single determinant of daytime sleepiness and explained 14% of the variance in scores on the Epworth Sleepiness Scale. Higher anxiety significantly predicted higher scores on the ESS, based on the third model (see Table 4.3).

4.3.3 Cognitive Functioning

With regards to subjective cognitive functioning, three predictors (gender, anxiety and depression) explained 30% of the variance in scores on the Cognitive Failures Questionnaire (CFQ). Examination of the beta weights in the third model showed that gender significantly predicted subjective cognitive dysfunction, with women reporting more cognitive failures than men. Higher scores on anxiety and depression were also significant predictors (see table 4.3).

Patients' Trail Making Test performance (objective cognitive functioning) was within the normal range for both TMT part A (mean = 43.79 ± 30.02 seconds) and part B (mean 92.83 ± 49.85 seconds) (completion time >78 seconds (TMT A) and > 273 seconds (TMT B) are indicative of cognitive impairment [Reitan, 1958]). For the regression, Total Trail time was used. Two predictors (depression scores and napping duration) explained 14% of the variance on TMT performance, based on the third model that incorporated the self-reported sleep variables. Examination of the beta weights in the third model showed that having a higher depression score and a longer duration of *overall* daytime napping significantly predicted poorer TMT performance (longer completion time on the test) (see Table 4.3).

	Dependent Variable							
	Chalder Fatigue Scale (*N=101)*		**Epworth Sleepiness Scale** *(N=101)*		**Cognitive Failures Questionnaire** (*N=89)*		**Trail Making Task** (*N=96)*	
Variables in the model	β	*t*	β	*t*	β	*t*	β	*t*
Step 1								
Constant		10.11		3.54		5.07		5.03
Length of Disease	-0.41**	-3.27	0.00	0.01	0.13	1.17	-0.03	-0.28
Age	0.23*	2.22	0.15	1.36	0.08	0.75	0.11	0.99
Gender	-0.09	-0.96	0.03	0.33	0.09	0.82	-0.24*	-2.36
***Adj*. R^2**	0.08		-0.01		0.00		0.03	
F	4.05**		0.75		1.05		2.12	
Step 2								
Constant		8.04		1.68		2.90		3.32
Length of Disease	-0.31**	-3.20	0.00	0.03	0.12	1.30	-0.01	-0.05
Age	0.11	1.06	0.10	0.93	-0.08	-0.84	0.01	0.10
Gender	-0.00	-0.04	0.09	0.89	0.24*	2.48	-0.17	-1.67
Anxiety	-0.02	-0.17	0.27*	2.41	0.33**	3.10	0.04	0.31
Depression	0.42***	3.77	0.11	2.41	0.34**	3.02	0.33**	2.70
***Adj*. R^2**	0.22		0.09	0.96	0.30		0.13	
F	6.61***		3.05*		8.41***		3.73**	
Step 3								
Constant		3.38		-0.79		2.40		2.24
Length of Disease	-0.41***	-3.94	0.07	0.59	0.10	0.96	-0.02	-0.20
Age	0.07	0.62	0.11	1.03	-0.12	-1.17	-0.03	-0.31
Gender	-0.01	-0.09	0.11	1.16	0.23*	2.37	-0.16	-1.64
Anxiety	-0.08	-0.68	0.29*	2.48	0.32**	2.86	-0.02	-0.20
Depression	0.45***	4.02	0.12	1.04	0.30*	2.55	0.35**	2.81
SE (%)	0.05	0.39	0.20	1.66	-0.17	-1.43	-0.10	-0.80
NWAK	-0.18	-1.52	0.07	0.54	0.11	0.88	-0.11	-0.85
WASO (min)	0.34**	2.47	-0.09	-0.58	-0.02	-0.11	0.01	0.08
SOL (min)	-0.03	-0.28	0.02	0.18	0.01	0.08	-0.05	-0.46
Total Napping (min)	-0.05	-0.55	0.17	1.76	0.06	0.62	0.22*	2.19
***Adj*. R^2**	0.24		0.14		0.30		0.14	
F	4.10***		2.57**		4.76***		2.49*	

Notes: *$p < .05$, **$p < .01$, ***$p < .001$; Entries represent standardized beta coefficients.
SE, sleep efficiency; NWAK, number of awakenings; WASO, wake after sleep onset; SOL, sleep onset latency

Table 4.3: Hierarchical regressions for the dependent variables; Chalder Fatigue Scale, Cognitive Failures Questionnaire, Trail Making Task and Epworth Sleepiness Scale.

To explore the specific time of day at which napping occurred and determine whether this made a difference to performance on the TMT task, a further Multiple Regression analysis was carried out. Step three of the model which incorporated the subjective sleep parameters was modified to include total AM (morning) napping duration and total PM (afternoon-evening) napping duration, in place of total napping duration.

Three predictors (depression scores, AM napping duration and PM napping duration) explained 19% of the variance in time taken to complete the TMT. Examination of the beta weights in this revised third model indicated that having a higher depression score, a longer duration of afternoon napping (β = .49) and less morning napping (β = -.30) were determinates of poorer objective cognitive functioning (see table 4.4).

	Trail Making Task	
Variables in the model	β	*t*
Step 1		
Constant		5.03
Length of Disease	-0.03	-0.28
Age	0.11	0.99
Gender	-0.24*	-2.36
***Adj.* R^2**	0.03	
F	2.12	
Step 2		
Constant		3.32
Length of Disease	-0.01	-0.05
Age	0.01	0.10
Gender	-0.17	-1.67
Anxiety	0.04	0.31
Depression	0.33**	2.70
***Adj.* R^2**	0.13	
F	3.73**	
Step 3		
Constant		2.30
Length of Disease	-0.02	-0.17
Age	-0.06	-0.54
Gender	-0.14	-1.39
Anxiety	0.00	0.03
Depression	0.29*	2.36
SE (%)	-0.11	-0.89
NWAK	-0.13	-1.01
WASO (min)	0.13	0.81
SOL (min)	-0.07	-0.63
Napping AM (min)	-0.30*	-2.15
Napping PM (min)	0.49**	3.41
***Adj.* R^2**	0.19	
F	3.03**	

Notes: $N = 96$ *$p < .05$, **$p < .01$, ***$p < .001$; Entries represent standardized beta coefficients
SE, sleep efficiency; NWAK, number of awakenings; WASO, wake after sleep onset; SOL, sleep onset latency

Table 4.4: Hierarchical regression for the dependent variable; Trail Making Task (replacing total napping duration with AM and PM napping duration in the model).

4.4 Discussion

This study sought to characterize the sleep and daytime napping of patients presenting with CFS and the extent to which their self-reported sleep and napping behaviour impacted upon the daytime symptoms. The major findings of this study are: (i) CFS patient's self-reported WASO, SOL and Sleep Efficiency are in the abnormal range, but also highly variable, (ii) higher self-reported depression, more WASO and a shorter time since diagnosis together explained 24% of patient variance in fatigue severity on the Chalder Fatigue Scale, (iii) scoring more highly on depression and longer duration of PM napping, with shorter amounts of AM napping explained 14% of variance on objectively assessed cognitive functioning (TMT). Being female and scoring more highly on anxiety and depression predicted 30% of the variance in self-reported daily cognitive failures (CFQ); (iv) Patients with higher scores of self-rated sleepiness (ESS) were characterised by those who self-reported higher levels of anxiety on the HADS, explaining 14% of the variance on the ESS.

4.4.1 The role of sleep in daytime functioning

The variability in reported sleep may be a reflection of sleep phenotypes in CFS. For instance, the mean sleep onset latency was 37.6 minutes but the standard deviation was 41.67 minutes. As such, whilst the present results are suggestive of the role of disturbed sleep in the CFS population as a whole, future work should be mindful that the nature of CFS patients' sleep problems may differ but may fit the characteristics for a sleep-specific phenotype.

Given this caveat, sleep still emerges as a significant predictor of impaired daytime functioning. Disturbed sleep at night, specifically longer amounts of wake time during the sleep period, is significantly associated with daytime fatigue, and longer duration of napping during the afternoon-evening period is associated with objective measures of daytime cognitive impairment. This would suggest that rather than being "primary symptoms" of CFS, daytime fatigue and cognitive dysfunction may in part be mediated by disturbed sleep and daytime napping. This in turn would suggest that interventions, such as the sleep management strategies that form part of cognitive behavioural therapy for CFS, may impact on these symptoms by way of improving sleep. Daytime napping is a common target of CFS management interventions. In

particular, Cognitive Behavioural Therapy for Insomnia (CBT-I) discourages napping during the course of treatment; excessive napping and extended time in bed are considered factors that can amplify existing disturbances in night-time sleep by weakening the homeostatic sleep drive (Manber et al., 2012). The present study would add that daytime napping impairs cognitive function and may lead to a vicious circle where such napping causes daytime sleepiness which in turn leads to daytime napping.

4.4.2 The role of other factors

Overall this study suggests that sleep is only one of the factors that affects daytime functioning in CFS as WASO was the only sleep parameter to influence fatigue. The other key predictors were scoring higher on the depression scale of the HADS and having a more recent diagnosis. The latter is interesting in that it would suggest that there is an "acute" phase to CFS, whereby fatigue is higher. This would fit with the qualitative study described in the previous chapter, and reports of patients in clinic, who frequently mention having learned to adjust to the disease and to pace themselves the longer they have it. This has particular implications for early stage treatment strategies, which should involve helping people adjust to and manage their condition. The depression finding is less easy to interpret. Patients are rightly wary of being diagnosed as depressed and the overall means of this group are at the very low end of caseness. Overall the most parsimonious interpretation of these results would be that fatigue is influenced by multiple factors, and that this study has highlighted that sleep, adjustment to illness, and mood may be pieces in the complex biopsychosocial fatigue jigsaw. Again this would also suggest that helping people to adjust and adapt to illness, sleep management strategies, and mood management may impact positively on daytime fatigue.

Scores on the depression scale, and scores on the anxiety scale, also emerged, along with daytime napping, as significant contributors to objective and subjective measures of cognitive functioning. Anxiety also emerged as a single predictor of levels of daytime sleepiness. Any explanation of this is speculative, but it could be that higher anxiety, marked by higher autonomic arousal, may produce more sleepiness.

Overall these results suggest the determinates of daytime fatigue severity, sleepiness and cognitive functioning in CFS are multi-factorial. Whilst sleep is an important determinant, particularly disturbed sleep and daytime napping, other factors are also important. As such, any intervention probably needs to consider each factor on an individual basis. Whilst one person may benefit from straight forward sleep management, another person relatively early post-diagnosis may also need help adjusting to the illness, whilst others still may need help with the emotional impact of being ill. As there is no one sleep phenotype, there is no one typical CFS patient. It is therefore recommended that at the minimum patients receive an individualised sleep assessment by an experienced clinician and a sleep and napping diary.

There are several limitations to this study. The main methodological problems were that we largely relied on self-report data. Further, the time of day at which functional measures are taken should be considered for future studies, particularly where daytime napping occurs, as sleep inertia following a nap may have implications for cognitive performance (Groeger et al., 2011). As for objective measures, there was no clinical screening, by way of standardised interview for sleep disorders, no multiple sleep latency testing (MSLT) to objectively measure daytime sleepiness, and no polysomnography (PSG) to objectively measure sleep parameters. Nevertheless, subjective reports are a good way to identify the parameters of interest for future studies, and they are also what is routinely used in the clinic with CFS patients to assess treatment outcomes. Future work should consider a triangulation of subjective and objective reports of sleep, fatigue, sleepiness, and daytime functioning, both in the lab and in intervention studies. In terms of the latter, the present works suggests that sleep interventions merit further study in this population.

In conclusion, disturbances in sleep continuity may serve as a mediator of daytime mental and physical dysfunction in CFS. Whilst they need to be considered in the context of other factors, it would seem that targeting disturbed sleep and napping may improve daytime fatigue and cognitive functioning. Most current interventions in CFS are multi-factorial, and so involve sleep management strategies. However to date there has been no trial of sleep interventions on their own. The present study would suggest that this is an avenue worth exploring.

CHAPTER FIVE
A CROSS-SECTIONAL POLYSOMNOGRAPHY ANALYSIS TO DETERMINE SLEEP-SPECIFIC PHENOTYPES IN A SAMPLE OF CFS PATIENTS (STUDY 3)

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(For the full manuscript see Appendix CC)

5.1 Introduction

Despite 87–95% of CFS patients reporting sleep difficulties (Hamaguchi et al., 2011; Jason et al., 1999; Nisenbaum, et al., 2003; Nisenbaum et al., 2004), previous research has been unable to reliably identify specific irregularities in objectively measured sleep. Over 30 PSG studies on individuals with CFS exist, however, conclusive statements about the type of sleep abnormalities in this population are difficult. Few studies report a full characterisation of both sleep continuity (the timing, efficiency and amount of sleep obtained) and sleep architecture (amount of each sleep or wake stage and the timing of transitions to each sleep stage), with some studies providing no PSG data at all (Buchwald, et al., 1994; Creti, et al., 2010; Decker et al., 2009; Fossey et al., 2004; Kishi et al., 2010; Watson, et al., 2004). Moreover, reporting practices differ widely, making interpretation and comparisons difficult (e.g. studies report the percentage of each sleep and wake stage as an index of Sleep Period Time, Total Sleep Time (TST) or even Time in Bed) (Manu et al., 1994; Whelton, Salit & Moldofsky, 1992; Armitage et al., 2007; Ball et al., 2004; Fischler et al., 1997; Majer et al., 2007; Reeves, et al., 2006; Stores, Fry & Crawford, 1998; Van Hoof et al., 2007; Watson et al., 2003), while others report the number of minutes spent in each stage (Le Bon et al., 2003; Le Bon et al., 2007; Morriss et al., 1993; Sharpley et al., 1997; Togo, et al., 2008).

What can be concluded from previous PSG studies is that, in each study, deviations from 'normal sleep' exist, but there is no consistent pattern. For example, where two

studies (Le Bon et al., 2003; Le Bon et al., 2007) report poor sleep efficiencies and 'normal range' REM latencies, others (Armitage et al., 2007; Ball, et al., 2004; Le Bon et al., 2007) found 'normal range' sleep efficiencies and short REM latencies and yet others still report a normal sleep efficiency and a long-REM latency (REML) (Stores, Fry & Crawford, 1998) or poor sleep efficiency and long-REM latencies (Togo, et al., 2008). Moreover, the picture remains unclear after controlling for the severity of patients' self-reported sleep complaints (Guilleminault et al., 2006; Rahman et al., 2011). Although differences in protocol, definitional criteria and reporting criteria may, to some extent, explain these differences, an alternative explanation is that sleep difficulties in individuals with CFS are not homogeneous and various sleep phenotypes exist in this population.

Symptoms such as unrefreshing sleep may not only be markers of CFS; they may also serve to maintain it. For instance, there may be reciprocal links between sleep quality, sleep-wake regulation and fatigue. There is evidence of this. For instance, studies have shown that adopting activity and sleep management strategies improves HPA axis functioning as measured by cortisol levels (Roberts et al., 2004). This suggests that further investigation of sleep disturbance of CFS is of more than academic importance but may highlight new avenues for intervention. From a clinical perspective, it is also important to study sleep more thoroughly in CFS as it may highlight some areas of diagnostic ambiguity. For instance, previous studies have shown that sleep disorders (notably obstructive-sleep apnoea) are occasionally identified during polysomnographic (PSG) assessments with CFS patient cohorts (Buchwald, et al., 1994; Krupp, et al., 1993; Manu, et al., 1994; Whelton, Salit & Moldofsky, 1992).

To explore the possibility that sleep problems in this population are not homogeneous and clarify the specific characterisation of sleep in CFS objectively, the current study examined PSG data for a single night of sleep in a large group of CFS patients. The aim was to determine whether specific sleep disturbances exist in this group, and if so, whether they are consistent across all patients.

5.2 Method

A cross-sectional, single-site observational study was undertaken on a consecutive series of 343 patients (mean age 37.21±12.42 years; 72 men and 271 women) referred for a single-night PSG study at a fatigue clinic in the Netherlands. The referral criteria for PSG investigation were that the patient (1) met diagnostic criteria for CFS according to the Fukuda definition, (2) they were drug-free for at least 2 weeks prior to the overnight study and (3) their symptoms could not be explained by a physical or psychological illness (e.g. anxiety or depression). Patients were interviewed and medically screened for the referral criteria by a registered physician and a registered psychiatrist. The collection of the PSG data was part of patients' routine clinical care under the management of Pierre de Roy (director, Vermoeidheidcentrum, NL). The Ethics Committee for the School of Life Sciences at Northumbria University approved the secondary data analyses.

Patients arrived at the clinic 2 hours before normal bedtime for electrode placement and biocalibration. The PSG montage comprised a standard 10/20 (i.e. F4-M1, C4-M1, O2-M1 and Cz with backups at F3-M2, C3-M2, O1-M2 and Fpz). Additional channels were used for electro-oculography (EOG; E1 and E2 referenced to M2), electromyography (chin and anterior tibialis placements), ECG, and airflow, effort, body position and oximetry (via a pulse oximeter). Filter settings were set to the American Academy of Sleep Medicine (AASM, 2007) guidelines (e.g. low 0.3 Hz/high 35 Hz for EEG and EOG) with a sampling rate of 500 Hz. Impedances were maintained below 5 kΩ. Participants slept in the laboratory overnight and were allowed to retire to bed when they wished and left to naturally wake in the morning. Scoring was conducted manually by a registered BRPT-certified technician at 30 s epochs, according to the AASM guidelines. The scorer was blind to the aims of the study. The mean recording period was just over 8 h (508.5±63.11 min). Descriptions of all sleep variables are detailed in table 5.1.

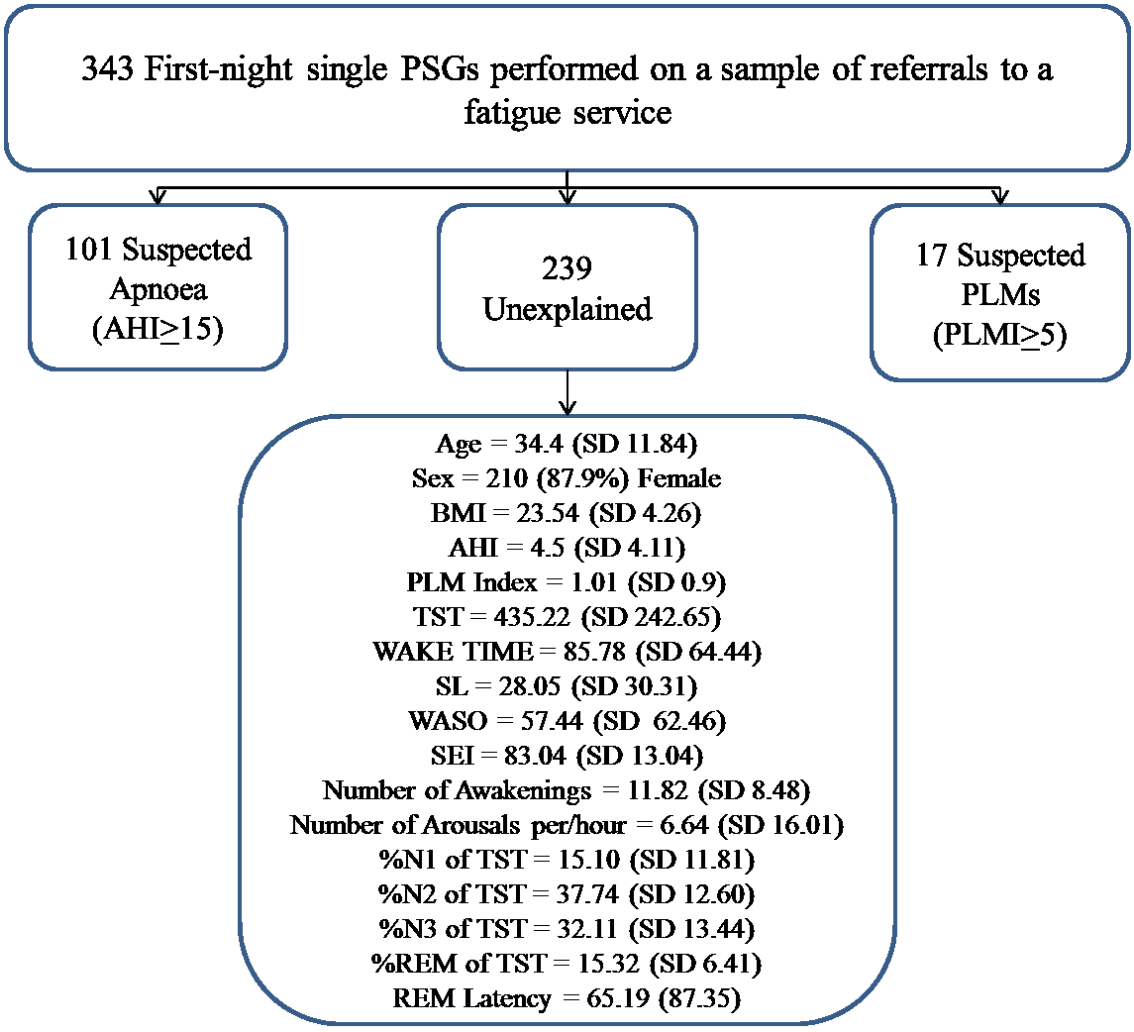
Sleep Variable	Description
Total Sleep Time (min)	Amount of time asleep
Sleep Onset Latency (min)	Length of time from lights out to first episode of stage 2 sleep
Wake After Sleep Onset (min)	Number of minutes of recorded wake following first episode of stage 2 sleep
Number of Awakenings (over TSP)	Number of wake bouts following first episode of stage 2 sleep
Number of Arousals	Number of arousals over the entire sleep period
REM Latency	Length of time to first REM stage
AHI Index	Number of apnea or hypopnea events per hour of sleep
% N1 (of TST)	Percentage of recorded stage 1 sleep over the total time asleep
% N2 (of TST)	Percentage of recorded stage 2 sleep over the total time asleep
% N3 (of TST)	Percentage of recorded slow wave sleep over the total time asleep
% REM (of TST)	Percentage of recorded Rapid Eye Movement sleep over the total time asleep
% WAKE (of TSP)	Percentage of recorded wake over the whole sleep period (from lights out to lights on)

Notes: REM, rapid eye movement; TSP, total sleep period; TST, total sleep time.

Table 5.1: Description of sleep variables included in study 3

5.2.1 Analytic strategy

A hierarchical cluster analysis was used to determine the number of phenotypes within the present sample after excluding those with Sleep Apnoea or Periodic Limb Movement (PLM) Disorder. Cluster analysis is a data-reduction technique that examines patterns among a set of variables to form homogeneous groups. The Euclidean squared distance measure of similarity method was chosen for the cluster analysis as it uses the progressive distance between variables to form the groups and does not rely upon standardised data. As cluster analysis can be affected by multicollinearity, a correlation matrix was used to exclude variables that were highly correlated with one another. A one-way analysis of variance (ANOVA) was used to examine which of the sleep variables differentiated the phenotypes.



BMI, body mass index; AHI, apnoea/hypopnea index; TST, total sleep time; SL, sleep latency; WASO, wake after sleep onset; SEI, sleep efficiency index; %N1, percentage of stage 1 sleep; %N2, percentage of stage 2 sleep; %N3, percentage of slow wave sleep; %REM, percentage of rapid eye movement sleep.

Figure 5.1 Study Overview.

5.3 Results

An initial examination of the Apnoea Hypopnoea Index (AHI) and PLM indices indicated that 104 (43 men and 61 women) of the original 343 referrals (30.3%) met the AASM criteria for either sleep apnoea (AHI≥15; n = 101) or a PLM disorder (PLM ≥5; n = 17) (14 participants met the criteria for both disorders). The overall sleep profile of the remaining 239 patients (mean age 34.4±11.84; 210 women and 29 men) was highly variable, indicating the presence of phenotypes (Figure 5.1).

A hierarchical cluster analysis, using Ward's method, was undertaken to determine the number of groups (clusters) within the remaining 239 patients. Prior to the cluster analysis, a correlation matrix was examined to avoid multicollinearity influencing the cluster model. On this basis, four variables were excluded (height, weight, sleep efficiency and number of spontaneous arousals per hour) for having correlation coefficients with one or more variables above r = 0.8. The final grouping variables included in the cluster analysis were: age, sex, body mass index (BMI), AHI's, PLM index, Number of Awakenings, Number of Arousals per hour, TST, Sleep Latency (SL), Wake After Sleep Onset (WASO), percentage of %N1 (stage 1 sleep) of TST, %N2 (stage 2 sleep) of TST, %N3 (SWS) of TST, %WAKE of TST, %REM of TST and REML. The Euclidean squared distance measure of similarity was used to group patients according to the included variables.

There were six clustering iterations overall (going from 8 to 2 clusters). The fourth iteration was chosen as the saturation point as it was the point where the agglomeration schedule and dendrogram had the highest reduction in the number of groupings (from six groups to four groups) while retaining at least 5% of the total sample size in each group (i.e. n ≥11). This latter rule was chosen to afford sufficient power for inferential data analysis to occur. A one-way ANOVA was undertaken on the four groups to determine which sleep variables significantly differentiated the groups. There were no overall differences between the groups on age (p = 0.12) or BMI (p = 0.48). On inspection of the sex frequencies in each group, there was a higher ratio of men to women in the first group compared with the other three groups. However, as two groups contained less than five men, this could not be tested statistically. In relation to the polysomnography variables, there were no group differences in the number of

arousals per hour or AHI index scores (PLMs were not included as less than 10% of the total sample had a PLM index), but significant differences were observed on all the other sleep variables (table 5.1).

5.3.1 First phenotype

The first phenotype comprised 14 patients with the longest Sleep Onset and REMLs and the highest percentage of SWS. Moreover, this group had the lowest percentages of both stage 2 sleep and REM sleep. Statistically; this phenotype differed from the other three groups in terms of longer Sleep Onset and REMLs and a lower percentage of REM.

5.3.2 Second phenotype

The second phenotype comprised 55 patients with the highest percentage of stage 2 sleep and the highest number of arousals per hour, although neither of these variables statistically separated them from the other three phenotypes.

5.3.3 Third phenotype

The third phenotype comprised 146 patients with the highest TST and percentage of REM. Additionally, this group demonstrated the shortest Sleep Onset and REMLs, lowest WASO and percentages of wake time and stage 1 sleep, and the lowest number of awakenings. Statistically, TST, percentage wake and WASO differentiated this phenotype from each of the others.

5.3.4 Fourth phenotype

The fourth phenotype comprised 24 patients who demonstrated the highest WASO, percentages of wake and stage 1 sleep, and the highest number of awakenings. This group was also the lowest in terms of TST, number of arousals per hour and percentage of SWS. Statistically, only WASO and percentage of wake differentiated this group from each of the other groups.

Grouped Variable Clusters	Group 1 (N = 14)	Group 2 (N = 55)	Group 3 (N = 146)	Group 4 (N = 24)	F	P Value
Demographics						
Age	35.79 (12.39)	37.29 (12.72)	32.99 (10.82)	35.54 (14.49)	1.95	n.s.
Sex	5 Males (35.71%)	10 Males (17.65%)	14 Males (9.59%)	1 Male (4.17%)	*	*
BMI	24.86 (5.68)	23.85 (4.63)	23.41 (4.03)	22.81 (3.86)	0.82	n.s.
Sleep Variables						
Total Sleep Time (min)	$270.95\ (41.85)_{ab}$	$387.03\ (46.1)_{acd}$	$473.21\ (45.82)_{bce}$	$264.15\ (74.43)_{de}$	188.07	p<.001
Sleep Onset Latency (min)	$107.79\ (42.09)_{abc}$	$30.97\ (29.13)_{ad}$	$19.17\ (14.71)_{bd}$	$28.94\ (27.54)_{c}$	67.26	p<.001
Wake After Sleep Onset (min)	$75.79\ (39.35)_{ab}$	$82.12\ (45.25)_{cd}$	$35.45\ (25.39)_{ace}$	$180.2\ (58.48)_{bde}$	119.74	p<.001
Number of Awakenings (over TSP)	15.21 (8.06)	$14.75\ (11.62)_{ab}$	$9.54\ (5.85)_{a}$	$16.96\ (9.26)_{b}$	10.52	p<.001
Number of Arousals	3.57 (9.21)	10.91 (23.01)	6.2 (15.26)	1.38 (4.13)	2.24	n.s.
REM Latency	$173.22\ (55.03)_{abc}$	$57.71\ (34.31)_{ad}$	$47.01\ (28.22)_{be}$	$84.46\ (48.21)_{cde}$	63	p<.001
AHI Index	3.43 (3.46)	4.58 (4.39)	4.73 (4.04)	3.54 (4.19)	0.92	n.s.
% N1 (of TST)	$21.84\ (13.36)_{a}$	$14.35\ (9.14)_{b}$	$12.55\ (7.37)_{ac}$	$24.22\ (14.82)_{bc}$	14.15	p<.001
% N2 (of TST)	$27.57\ (13.15)_{ab}$	$38.82\ (12.36)_{a}$	$38.44\ (12.14)_{b}$	36.95 (13.66)	3.46	p<.02
% N3 (of TST)	$44.46\ (20.45)_{abc}$	$31.07\ (11.05)_{a}$	$31.78\ (12.41)_{b}$	$29.28\ (16.42)_{c}$	4.64	p<.004
% REM (of TST)	$6.11\ (4.58)_{abc}$	$15.16\ (5.47)_{ad}$	$17.19\ (5.57)_{be}$	$9.65\ (6.35)_{cde}$	26.46	p<.001
% WAKE (of TSP)	$60.32\ (21.09)_{abc}$	$25.75\ (11.61)_{ade}$	$11.03\ (6.16)_{bdf}$	$75.26\ (22.92)_{cef}$	271.62	p<.001

Notes: Letters sharing the same subscript are significantly different.
*Statistical tests of between-group sex differences could not be performed due to the small number of men in each group.
AHI, Apnoea Hypopnoea Index; BMI, body mass index; CFS, chronic fatigue syndrome; TSP, total sleep period; TST, total sleep time; REM, rapid eye movement.

Table 5.2: Characteristics of sample of individuals with CFS

5.4 Discussion

The aim of the study was to determine whether specific sleep phenotypes existed in patients with CFS. A large consecutive series of patients, meeting the criteria for CFS, underwent a single night of polysomnography to determine the presence or absence of distinct sleep phenotypes. The first finding, over 30% of individuals meeting diagnostic criteria for CFS, also demonstrated that a Primary Sleep Disorder (PSD; sleep apnoea or PLMD) is important and underscores the need to assess for PSDs in CFS populations. As the recommended treatment strategies for some PSDs differ considerably from those for CFS (e.g. Continuous Positive Airway Pressure for apnoea vs sleep management strategies in CFS), it is important to direct the individual to, or adjunct, appropriate care pathways as soon as possible. This finding also questions the ability to differentiate fatigue associated with sleep apnoea or PLMD from that associated with CFS. Here, family members and/or carers may be helpful for diagnosis sensitivity as they are likely to be aware of nocturnal breathing disturbances (i.e. heavy snoring, gasping or pauses in breathing).

The overall PSG results (after excluding sleep apnoea and PLMD) confirm objective sleep difficulties in patients with CFS. When the percentages of each sleep stage in 'normal' adult sleepers (i.e. <5% wake, between 2% and 5% stage 1, between 45% and 55% stage 2, between 13% and 23% SWS and between 20% and 25% REM (Carskadon & Dement, 2011) are compared with those in the present sample, it is seen that this group falls outside the range for all these variables. The present sample is spending more time awake and in the lighter stages of sleep (stages 1 and 2 sleep), and less time in the deeper sleep stages of sleep (i.e. stage 2 sleep and SWS) and in REM. Further, using the quantitative benchmarks of sleep disturbance outlined by Edinger et al. (2004), it can be seen that where sleep efficiency and SLs appear to be on the cusp of 'normal' sleep in the present sample (85% sleep efficiency is considered normal and SL of >30 denotes a sleep problem), WASO appears to be almost twice as long as is considered problematic (>30 min tends to denote a sleep problem). Together, these findings indicate that sleep is an objectively verifiable problem for patients with CFS that should be addressed clinically.

The cluster analysis identified, at saturation, four sleep phenotypes. The dendrogram identified two groups partially related (i.e. groups 1 and 4) and two that were largely independent (i.e. groups 2 and 3). This configuration was confirmed by ANOVA showing statistically significant differences in sleep continuity and architecture variables between the groups. That said, where statistical significance and relative characterisation (e.g. group 1 highest in the variables SL and REML and lowest in AHI Index) are important in understanding between-group differences, the more salient question is whether these four groups are clinically relevant in terms of specific sleep treatments in patients with CFS. The use of different pharmacological agents (benzodiazepines, z-hypnotics or stimulants) or therapeutic interventions (i.e. Cognitive Behavioural Therapy for Insomnia or behavioural modification strategies) has been shown to have differential effects on specific aspects of sleep continuity and architecture. For example, zolpidem appears to have a better impact on the number of awakenings and perceived quality of sleep compared with nitrazepam, and lormetazapam appears to be better in reducing SLs than zoplicone (Dündar et al., 2004). As such, tailoring treatment options to the sleep problems presenting in this population is likely to be more effective (table 5.3).

Sleep Phenotype	**Central Differential Features**	**Associated Diagnostic Features**	**How this may present subjectively**
1	Long Sleep Onset Latency Long REM Latency High amounts of Slow Wave Sleep Low amounts of REM	Low amounts of Stage 2 Sleep	Problems in getting off to sleep but when asleep few awakenings. The Sleep that is obtained is of normal quality.
2		High number of arousals per hour High amounts of Stage 2 Sleep	No difficulties in getting off to sleep and few awakenings but feelings or evidence of a 'restless' night sleep.
3	High Total Sleep Time Low amounts of time awake during the night Low number of wake periods during the night	High amounts of REM Sleep Short Sleep Onset Latency Low number of Awakenings Short REM Latencies Low amounts of Stage 1 Sleep	No difficulties in getting off to sleep and few awakenings but feelings of being unrefreshed on waking despite a significant amount of time in bed asleep.
4	Highest number of wake periods during the night Highest amounts of time awake during the night	Low Total Sleep Time Low number of arousals per hour during the night Low amounts of Slow Wave Sleep	Short sleep duration and although no difficulties getting off to sleep lots of awakenings for significant periods of time. Also increased feelings of daytime sleepiness.

Notes: CFS, chronic fatigue syndrome; REM, rapid eye movement

Table 5.3: Characteristics (statistical and phenomenological) of patients with CFS

Another consideration, albeit related, is the presence within the final sample of PSDs for which PSG is either not routinely recommended or where, as stand-alone, it is insufficient for a definitive diagnosis (AASM, 2007). Most relevant to the present sample are insomnia disorder and hypersomnolence disorders. Interestingly, groups 1 and 4 appear to be characterised by insomnia-like symptoms (i.e. difficulties initiating sleep or maintaining sleep), whereas groups 2 and 3 appear to share overlapping characteristics with disorders characterised by poor sleep quality (table 5.1). In relation to group 3, there is some overlap with hypersomnolence disorders (the term hypersomnolence will replace hypersomnia under the DSM-5) as 14 patients (9.59%) slept for 9 hours or longer and eight patients (5.48%) demonstrated the main polysomnographically defined symptom of narcolepsy (i.e. an REML of less than 15 min). For group 2, there is no obvious overlap with a specific DSM-5-defined sleep disorder, although as stage 2 sleep has been associated with hormonal and autonomic regulation (Brandenberger et al., 2005), increased amounts are likely to relate to both higher levels of autonomic and cortical arousal inhibiting deep sleep. As such, a PSG study with adjunct sleep history interviews, sleep diaries, actigraphy and/or a Multiple Sleep Latency Test or Maintenance of Wakefulness test would be valuable tools in determining whether these groups share all the diagnostic features of each PSD.

The findings from the present study should be viewed with the limitations in mind. There was no control group to determine the extent to which the four phenotypes exist in the general population. That said, with 6–10% of the population meeting the diagnostic criteria for insomnia (Dauvilliers, 2006) and 5% meeting the diagnostic criteria for hypersomnia (Ohayon, 2002), the present data do not reflect this with 213 of the 239 (89.1%) participants, without apnoea or PLMS, meeting at least one quantitative criterion for insomnia or hypersomnia. It could also be argued that a single night of polysomnography may not be enough to capture the sleep of patients with CFS due to the first-night-effect (Le Bon et al., 2003). The first-night-effect is a commonly observed response to the first night of sleeping in an unusual environment, such as a sleep laboratory, whereby aspects of sleep can be affected. That said, where Le Bon and colleagues demonstrated significant differences between nights 1 and 2 in a cohort of individuals with CFS, these differences were not largely evident in the sleep architecture and many differences in the sleep continuity variables disappeared

after those with psychiatric illnesses were excluded from the analysis. Interestingly, over 25% of Le Bon et al's (2003) sample also demonstrated an 'inverse first-night-effect' whereby they slept better on the first night compared with the second night. This issue of the first-night-effect in CFS is further complicated by other studies which have shown no such effect in this population (Whelton, Salit & Moldofsky, 1992). It is very likely that inconsistencies in the first-night-effect reflect typical night-to-night variability (Buysse et al., 2010; Perlis et al., 2010; Vallieres et al., 2011) in addition to situation-specific factors, such as acclimating to a new environment, relating to PSG on the first and second nights. What would be ideal, albeit expensive, is a PSG study over several nights (e.g. at least 14 continuous nights are suggested for insomnia (Wohlgemuth et al., 1999)) to ensure that these issues are accounted for. That said, what may be more practical is to determine how information from the present study can inform, in conjunction with other assessments, actual clinical practice. One suggestion is that, ideally after ruling out PSDs, individuals should be interviewed about their sleep (usually over the last month) and provided a sleep diary. This information would provide a subjective account that could be matched to the four phenotypes (as in table 5.3) to inform treatment.

Overall, the results suggest a significant overlap between CFS and a variety of symptoms of sleep disturbance. One night of PSG is sufficient to tease apart, and exclude, those with apnoea and PLM disorders from four other distinct sleep phenotypes in patients with CFS. Interestingly, these four phenotypes tend to mirror symptoms related to sleep quality and quantity that are amenable to different treatment strategies. As such, clinicians tailoring sleep-based interventions for patients with CFS should be mindful of these phenotypes.

CHAPTER SIX
THE FEASIBILITY AND ACCEPTABILITY OF A 3-NIGHT AMBULATORY PSG SLEEP ASSESSMENT IN PATIENTS WITH CFS (STUDY 4)

This chapter presents the feasibility and acceptability findings of a comprehensive sleep assessment study with a small group of patients with CFS. Whilst presented in accordance with CONSORT guidelines, the chapter is expanded upon to emphasise the feasibility rather than effectiveness, through assessment of recruitment, attrition, protocol acceptability and fidelity. The results are considered with a view to inform the design of future sleep studies in CFS, and will help inform practice in a clinical setting when applied to the assessment process of this illness.

6.1 Introduction

It is clear that sleep needs to be examined in depth in this patient population, given the findings from the qualitative interviews, and the subjective (diaries) and objective (PSG cluster analysis) exploration of sleep in CFS. These results show that not only does disturbed sleep play a critical role in the maintenance and exacerbation of symptoms, but that there also appear to be specific sleep phenotypes in CFS patients as assessed through nocturnal PSG. Developing a detailed, high quality sleep protocol assessment that is acceptable to patients is therefore crucial in order to explore these findings further.

As discussed in the introductory chapter, PSG studies on individuals with CFS have not been uniform in their data reporting or methodological practices, and so determining the nature and extent of sleep difficulties in CFS patients remains difficult. It is fundamental that the sleep of patients with CFS should be looked at in as much detail as possible, given the probable reciprocal effects of disturbed sleep on existing CFS symptoms. Equally, it is important to consider how we measure the function of the HPA axis. As discussed earlier hypoactivity in this axis has been postulated as one of the underlying pathophysiological processes in CFS (Demitrack et al., 1991) and reviews confirm this dysregulation as indicated by attenuation in cortisol levels and Cortisol Awakening Response (CAR), albeit with variable results

(for recent reviews of this literature see Tomas et al., 2013; Papadopoulos & Cleare, 2012). However as with the PSG studies, the protocol with respect to HPA axis measurement has been highly variable. With respect to saliva sampling for cortisol, existing studies have utilised at most a protocol of one to two days of assessment with samples ranging from 3-9 time points per day (Powell, 2013). It is recommended that to obtain a stable variable for the CAR and overcome state influences, 4 samples should be taken on a given day and over the course of 2/3 days (Hellhammer et al., 2007).

To redress this, the present study utilised a range of methods, combining sleep and comprehensive cortisol assessment over a 3-day period, a protocol that has never been endeavoured in this patient population. The cortisol sample collection in this study was for the purpose of protocol feasibility. As such, procedural findings are described and analysis of cortisol is not included as part of this study. The study combines 3-night home-based PSG and a gold-standard protocol for salivary cortisol sampling (7 assessments per day), alongside self-reported sleep diaries, functional and symptom assessment questionnaires and Actigraphy. Given this is the most comprehensive assessment of sleep and cortisol ever attempted in a CFS population, the primary aim of the study was to establish its *feasibility* in a small group of CFS patients, with particular emphasis on the extent to which patients were able to adhere to this comprehensive protocol. The demands of such protocol for a CFS patient group, already experiencing a host of debilitating symptoms had the potential to impact on their sleeping patterns, consequently affecting the assessed sleep parameters of interest. Continuous monitoring throughout the study was therefore of utmost importance. The outcome of this study will then inform whether it is possible to move forward and utilise this protocol, or a modified version (based on how well tolerated it is found to be) in larger more definitive sleep and cortisol studies (and in clinical screening), thus affording a more definitive answer to the question of the role of sleep and cortisol in CFS.

6.2 Methods

6.2.1 Design

The study was a cross-sectional feasibility study of sleep and cortisol assessment in CFS patients. The objectives of this study were as follows:

6.2.1.1 Acceptability and feasibility objectives

- To assess the feasibility and acceptability of the methods and procedures of a 3-night ambulatory sleep assessment, and 3-day gold-standard saliva sampling protocol for cortisol in CFS patients;
- To take measures of compliance to the protocol, and the assessment of barriers and facilitators to participation with the full protocol.

The objectives were measured through patient retention to the study and completion rates (acceptability of the procedures and assessment methods included in the protocol), and through monitoring patients' experience of the protocol via an observational process made by the researcher taking field notes throughout the entire study process.

6.2.1.2 Outcomes

The primary outcomes for the study were the estimates of feasibility and acceptability in CFS patients, assessed as described above, through retention to the study process and by participant adherence to protocol. Participant adherence was assessed through both the sleep and cortisol components of the assessment via completion of specific measures (sleep diary completion, saliva sampling correctly wearing monitoring equipment) and fidelity to timing protocol (sample time-log completion, marker press for lights out/lights on during PSG).

Given the small sample size, and the primary feasibility aims of this study, definitive comments on the nature of sleep and cortisol would not be appropriate. We will however attempt a preliminary, primarily descriptive characterisation of this study sample based on the measures deployed in the feasibility study. These symptom and

functional assessments, subjective and objectively-derived sleep variables and the preliminary characterisation of sleep can be found in Chapter 7.

6.2.1.3 Sample size

A pragmatic approach was used to determine the sample size. The primary determinant was the number of patients to be assessed through the study period whilst also factoring in estimates of patient ineligibility, rescheduling and attrition. It was anticipated to be approximately 25 patients (and 25 normal sleepers) entered into the study over 12 months.

6.2.2 Participants and setting

6.2.2.1 Inclusion

Study participants were CFS patients recruited from the local CFS clinical service based at the Newcastle upon Tyne Hospitals NHS Foundation Trust. All participants fulfilled the CDC 1994 (Fukuda) diagnostic criteria for CFS (Fukuda et al., 1994), they shared the same referral and assessment path and were identified and approached by their clinician (who was seeing patients as part of routine clinical practice). Potentially eligible patients were identified on the basis of their age and clinical demographics, and participants who expressed an interest were subsequently contacted regarding their participation in the study. Non-illness control participants were recruited from a bank of participants held by the Northumbria Centre for Sleep Research (NCSR) and consented using the same process as indicated for patient participants.

Participants were considered eligible for the study if they were between 18-65 years of age, and met the criteria for CFS, according to the Fukuda definition (patients). Participants were excluded from the study if they were taking sleep medication, seeing a sleep medicine specialist, had travelled beyond one time zone within three months of study participation, and if they had a diagnosis of Obstructive Sleep Apnoea (OSA).

Ethical approval was sought and approved by the Newcastle and North Tyneside Local Ethics Committee, the sponsor was Newcastle upon Tyne Hospitals NHS Foundation Trust, and the study was registered with the UKCRN Portfolio database, under the

title: A case controlled study exploring the roles of sleep architecture, and diurnal patterns of salivary cortisol in CFS/ME (Short title: CFS Sleep), Identifier: 12889. All participants provided written informed consent prior to the study.

6.2.2.2 Assessment

The study was carried out at participant's homes. Prior to the 3-day assessment, participants were required to wear an Actiwatch and complete a sleep diary over a 14-day pre-assessment period. During this time, participants were also required to complete a series of functional and symptom assessment questionnaires. The following section will detail the included measures that were used to measure sleep, cortisol and assess functioning and symptoms in participants.

6.2.3 Measures

6.2.3.1 Functional and symptom measures

A range of measures were incorporated into a questionnaire booklet that patients were required to complete during their 14-day pre-assessment period which was considered to represent less burden than all at once in one session.

DePaul Symptom Questionnaire (DSQ: Jason et al., 2010)

The DePaul Symptom Questionnaire (DSQ: Appendix N), is a self-report measure that assesses the presence of core CFS symptoms, originally developed to provide a structured way to gather standardized information that can be used to aid in the diagnosis of CFS. It is important to consider the contentious nature in attempting to operationalize the assessment criteria in CFS, as currently, the Fukuda and the Canadian criteria have yet to be formally operationalized. This issue creates methodological problems where studies in different settings recruit samples of patients with different amounts of each of the core symptoms. It is evident there is need for a new approach, and Jason et al. (2010) suggests the DSQ assesses the core symptoms of CFS in a consistent way across settings, affording investigators in different settings to identify more homogenous samples of patients, and this more standardized approach to patient identification will increase the likelihood of reliable detection of biomarkers across samples, that will ultimately aid diagnosis. Using the DSQ in this study will add to such developments and it is the first use of it in the United Kingdom. The format of

the DSQ integrates scores of symptoms and functional health status data (see below for SF-36 and symptom measures), through which an algorithm produces a "diagnosis" based on several of the more common definitions of ME and CFS. If found to be sufficiently sensitive, the instrument could aid patient diagnosis, saving time through home/clinic completion, and improving overall confidence in the diagnosis process.

The DSQ captures critical symptoms and their frequency/severity. The 54-item scale of symptoms loads onto 3 factors; 1) Neuroendocrine, Autonomic and Immune Dysfunction; 2) Neurological/Cognitive Dysfunction; and 3) Post-Exertional Malaise (PEM). A 'total' score can be obtained to represent overall illness burden. Participants are required to rate on a Likert scale (0-4) as to how often they have experienced each symptom and how much each symptom has bothered them over the last 6 months. Brown and Jason (under review) demonstrate that the threshold criteria that seems the most able to differentiate CFS patients from controls is a score of 2 or more on Frequency of symptoms (2 = about half the time) and Severity of symptoms (2 = moderate).

Integrated into the DSQ is the Short Form-36 Health Survey (SF-36: Appendix O), a 36-item questionnaire constructed to collect data on health status, functioning, and well-being for the Medical Outcomes Study (Ware & Sharebourne, 1992). It measures Quality of Life (QoL) across eight domains, which are both physically and emotionally based. The multi-item scales assess functional impairment in eight areas: limits in physical activities (physical functioning), limits in one's usual role activities due to physical health (role physical), limits in one's usual role activities due to emotional health (role emotional), bodily pain (pain), general health perceptions (general health), vitality (energy and fatigue), social functioning (social), and general mental health (Ware et al., 2000). Scores in each area reflect ability to function and higher values indicate better functioning (QoL). Reliability and validity studies have demonstrated high reliability and validity in a wide variety of patient populations for this instrument (Stewart et al., 1989). Based on the CDC empiric case definition (Reeves et al., 2005), the SF-36 was used to assess disability. Significant reductions in occupational, educational, social, or recreational activities have been defined as scores lower than the 25^{th} percentile on physical functioning (≤70), *or* role physical functioning (≤50), *or* social functioning (≤75), *or* role emotional (≤66.7). A person would meet the disability

criterion for the empiric CFS case definition by only showing impairment in one or more of these four areas (Reeves et al., 2005). Measures of caffeine consumption, alcohol intake, smoking status and amount of exercise per week were also taken (Appendix P).

General Health Questionnaire (GHQ-28; Goldberg, 1978)

The 28-item General Health Questionnaire (Appendix Q) is an assessment comprising four 7-item subscales: somatic symptoms (items 1-7), anxiety/insomnia (items 8-14), social dysfunction (items 15-21) and severe depression (items 22-28). Patients are asked to assess changes in their mood, feelings and behaviours based on the previous four weeks, evaluating their occurrence on a 4-point response scale ("less than usual", "no more than usual", "rather more than usual", "much more than usual").The total possible score on the GHQ-28 ranges from 0 to 84.

Chalder Fatigue Questionnaire (CFQ; Chalder et al., 1993)

One of the most widely used measures for assessing fatigue in research with CFS patients, the Chalder Fatigue Questionnaire (Appendix R) was used as a measure of symptomatic fatigue experienced by patients. The Likert system for scoring was used (0, 1, 2, 3), with a total possible score ranging from 0-33. A higher score indicates more fatigue. A score of 18 or less (based on Likert system) out of a total 33 is considered as within the normal range of fatigue (White et al., 2013).

Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983)

The Hospital Anxiety and Depression Scale (Appendix S) measured symptoms of depression and anxiety in patients. Its seven depression items and seven anxiety items were rated on a four-point Likert scale (0-3), with scores ranging from 0-21 on each subscale. Scores of 11 or more are indicative of a 'case' of depression and/or anxiety in a general population sample.

Work and Social Adjustment Scale (WSAS Mundt et al., 2002)

The Work and Social Adjustment Scale (Appendix T) is a simple, valid and reliable 5-item patient self-report measure of impairment in functioning. It assesses the impact of the patient's illness on their ability to function in terms of work, home management, social leisure, private leisure and personal and family relationships. Scale responses for

each item range from 0-8 and the maximum total score on the WSAS is 40, higher scores indicate worse functional impairment.

Perceived Stress Scale (PSS; Cohen et al., 1983)

The Perceived Stress Scale (Appendix U) is a 14-item measure of individuals' appraisal of levels of stress over the past month. Evaluating the degree to which individuals believe their life has been unpredictable, uncontrollable and overloaded during that time. Responses to each item are scored on a five-point Likert scale (0-4) and total scores range between 0-56 with higher scores indicating higher levels of perceived stress.

Illness Perception Questionnaire (IPQ; Broadbent, et al., 2006)

The brief Illness Perception Questionnaire (Appendix V) was used to assess patient's cognitive representation of their illness. With an overall possible score ranging from 0 to 80, higher scores reflect a more severe illness perception.

6.2.3.2 Self-report measures of sleep

A standard sleep diary was used to derive core measures of subjective sleep continuity (Time in Bed [TIB], Sleep Onset Latency [SOL], Wake After Sleep Onset [WASO], Number of Awakenings [NWAK], Total Sleep Time [TST], and to calculate Sleep Efficiency [SE] (TST/TIBx100)) over a period of 14 continuous days, during the baseline pre-assessment period. A 3-day version of the sleep diary was used in the sleep assessment stage of the study. Participants were required to complete the diary upon waking each day. Mean values were derived for each variable based on the number of nights completed. The pre-assessment phase of the study was an opportunity for the participant to become familiarised with the format of the diary and address any uncertainty with regard to completion prior to the 3-night assessment.

Incorporated into the Questionnaire booklet were a range of retrospective sleep measures;

The Pittsburgh Sleep Quality Index (PSQI: Buysse et al., 1989)

The Pittsburgh Sleep Quality Index (Appendix W) is a 19-item questionnaire evaluating sleep quality and disturbances over the previous month. The 19 self-rated items (5 questions rated by the bed partner or roommate (if available)) are combined to form 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction), responses are rated on 4-point Likert scale (0=no difficulty, 3=severe difficulty). The PSQI has good internal consistency and a reliability coefficient (Cronbach α) of 0.83 for its seven components (Buysse et al., 1989). The seven component scores are then added to yield one global score that has a possible range of 0-21 (0=no difficulty, 21=severe difficulties in all areas). A global PSQI score >5 suggests poor quality sleep.

The Insomnia Severity Index (ISI: Morin et al., 2011)

The Insomnia Severity Index (Appendix X) is a reliable and valid tool for detecting cases of insomnia in a population. It's' 7-items evaluate the severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties, over the previous month. Each item is rated on a 5-point Likert scale (0 = no problem; 4 = very severe problem) that yields a total score ranging from 0 to 28. It has good internal consistency (Cronbach's α of 0.90), and convergent validity is supported by high ISI scores being significantly correlated with QoL and fatigue. Interpretation of total ISI scores are able to determine; an absence of insomnia (0-7), subthreshold insomnia (8-14) or 'caseness' for clinical insomnia (15-21), a cut-off of 10 is considered optimal for detecting insomnia cases (Morin et al., 2011).

Ford Insomnia Response to Stress Test (FIRST: Drake et al., 2004)

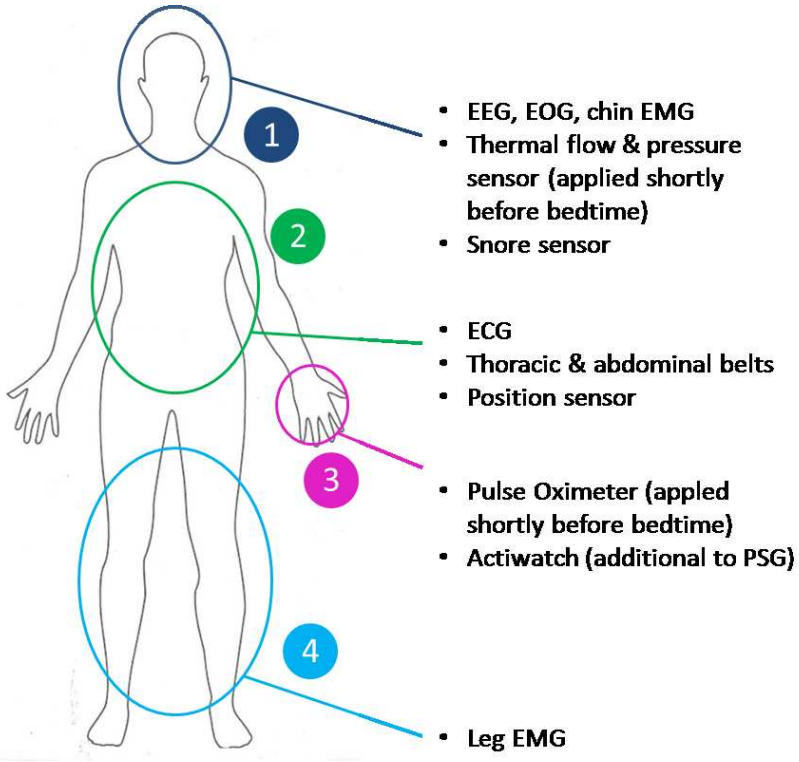
The Ford Insomnia Response to Stress Test (Appendix Y) is a measure to identify individuals who have an increased risk of developing a sleep difficulty when confronted with a stressor. The 9-item questionnaire asks respondents to rate the

likelihood that various stressful events would disturb their sleep. Responses are rated from 1 (not likely) to 4 (very likely) with a total possible score ranging from 9-36. The scale has high reliability (Cronbach's α = .83) and factor analytic techniques identified a single 9-item factor that was representative of the construct of "stress-related" vulnerability to sleep disturbance. It has also been established that higher scores on the FIRST is a significant risk factor for the development of insomnia in normal sleepers over 13-month period (Drake et al., 2004[b]).

6.2.3.3 Objective measures of Sleep

Polysomnography

Polysomnography (PSG) was carried out over three consecutive nights, in participants' homes. The researcher arrived at the participant's home 2 hours before normal bedtime for electrode placement and biocalibration. The first night of assessment served as a screening night and opportunity for participant adaptation. This first night of assessment included an extended EEG montage, with placement of electrodes at; FP1, FP2, F3, F4, C3, C4, P3, P4, O1, O2, A1, A2 and Cz, in accordance with the International 10/20 system (Harner & sannit, 1974), additional channels were used for electro-oculography (EOG; left and right eyes), electromyography (EMG; chin and anterior tibialis placements), ECG, thermal flow and effort sensor, body position and oximetry (via pulse oximeter) and snore microphone. The second and third nights of assessment used a reduced montage, but utilised the same EEGs, EMG (chin placement only), EOG and heart rate measurements (See Figure 6.1 for a schematic of the polysomnogram hook-up). Participants slept in their own home and could retire to bed when they wished and left to naturally wake in the morning. The PSG was recorded on 33-channel SOMNOscreen plus, using DOMINO software (SOMNOmedics GmbH, Randersacker, Germany), at a sampling rate of 128 Hz for EEG channels, and 256 Hz for EMG and ECG channels. Impedances were maintained below 5kΩ during the recording period. PSG data was scored manually by an independent registered technician blind to the aims of the study, at 30s epochs in accordance with American Academy of Sleep Medicine criteria (Iber, et al., 2007). The mean recording period was 8.5 h (513.5±90 min). Descriptions of all sleep variables are detailed earlier in Table 4.1 (chapter four).



Notes: EEG, electroencephalography; EOG, electrooculography, EMG, electromyography; ECG, electrocardiography PSG, polysomnography

Figure 6.1: The Polysomnogram

Actigraphy

Actiwatches were worn by patients on their non-dominant wrist during the 14-day pre-assessment period and also throughout the 3-day sleep assessment, to monitor sleep/wake activity. Using a piezo-electric accelerometer, Actiwatches measure and record the amount, duration and intensity of movement in all directions, storing this activity in the memory of the Actiwatch. Actigraphy was used to complement the sleep diary and to aid the researcher in confirming the relative circadian stability of participants prior to the start of the study. It was not used in any further analyses. Wearing the Actiwatch throughout the entire study period affords the ability to determine its feasibility in conjunction with the PSG and saliva sampling procedures and equipment.

6.2.3.4 Salivary Cortisol Sampling Protocol

There have been difficulties in the interpretation of previous studies that measure levels of cortisol in CFS patients, partly due to the stressful procedures entailed by sampling (i.e. hospital admission, cannulation, blood sampling and drug administration). Alternatively, markers of basal HPA axis function in a CFS patient group, can be assessed through the measurement of cortisol in saliva, across a diurnal period in an ambulatory setting (Saxbe, 2008).With this in mind, a comprehensive procedure of 7 samples per day allows for a stable assessment of cortisol across the diurnal period. If adhered to, the protocol provides the opportunity to characterise patients on the basis of a number of indices of HPA function, specifically; a) overall cortisol secretion across the entire day, through the calculation of the area under the curve with respect to ground (AUC_G^1) (Pruessner et al., 2003); b) the cortisol awakening response (CAR) as measured by taking the individual's peak cortisol value (the highest value of the CAR, observed between the sample taken at 15 minutes post-wake and the sample obtained at 60 minutes post-wake), and total secretion during the CAR period as measured by AUC_G^1.

To overcome the potential for state influences upon levels of cortisol, a 3-day protocol for sampling was employed to obtain a more stable variable (Hellhammer et al., 2007). The sample timings were immediately at wake, 15, 30, 45 and 60 minutes post-wake, for a measure of the CAR, and subsequent samples were at a mid-afternoon point (between 2-4pm) and immediately preceding bedtime to provide further measures of diurnal secretion and evening nadir.

Participants provided their samples using Salivettes (Sarstedt, Leicester, UK), this required chewing on an absorbent piece of cotton until saturated, before depositing into a protective plastic storage tube. Samples were then stored in a refrigerator until collected by the researcher, and then frozen at -20°C at the earliest opportunity until assaying (samples centrifuged at 3000 rpm for 15 minutes and assays performed in-house using luminescence immunoassay methods in accordance with manufacturer's instructions (Salimetrics, Newmarket, UK).

Given this was a home-based protocol, adherence was crucial. Participants were given a demonstration of how to use the Salivette device and the importance of the timing of samples and avoidance of behaviours known to affect concentrations of saliva (Kudielka et al., 2003) were emphasised. Participants were additionally required to complete the sample log provided (integrated into 3-day sleep diary: see appendix AA) indicating time of waking and specific sample times as well as state mood rating on a Likert scale. The log enabled the researcher to undertake a retrospective adherence check against the sleep diary (wake timings) for the first sample time.

6.2.4 Data analysis

Data analysis was carried out via a number of stages; the primary outcomes of feasibility and acceptability were assessed by recording a tally of recruitment, attrition and exclusion of patients in the study. Monitoring compliance to the procedures and fidelity to timing protocols included in the study was determined by making a tally of rates of completion and by taking a record of timed activities required by the protocol. Finally, to gain a comprehensive account of the study's acceptability by patients, keeping detailed field notes throughout the course of the study made it possible to evaluate the entire study process, based on patient's experiences of the protocol. Statistical methods were employed for analysis of secondary outcome measures of the study (Chapter 7).

6.3 Results

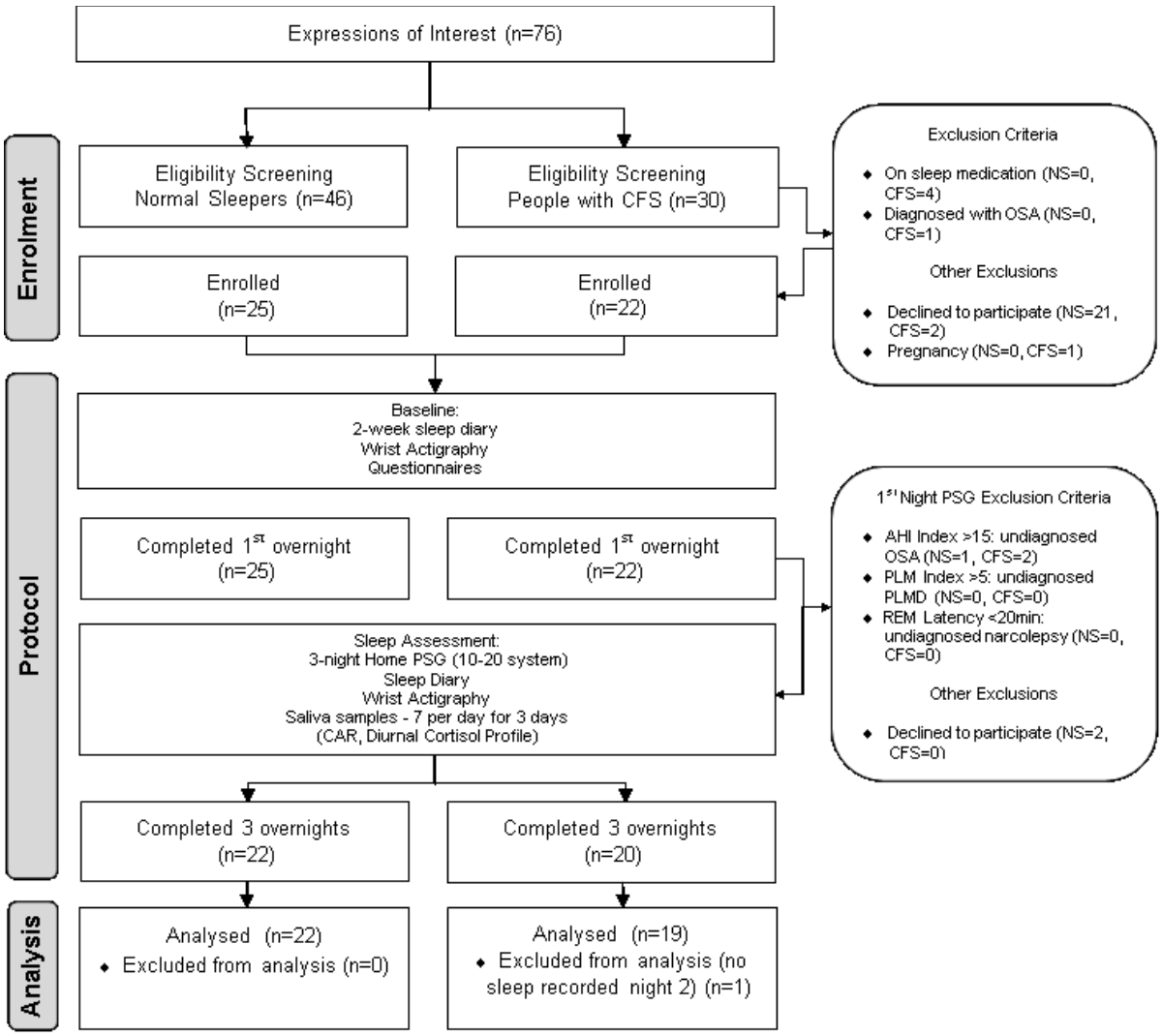
6.3.1 Feasibility and acceptability in patients

As the feasibility of the protocol for normal sleepers was not the focus of this part of the study, in the following sections, data are considered from a standpoint of feasibility and acceptability to CFS patients. Based on the guidelines set out by Thabane and colleagues (2010), the results are reported in line with the CONSORT format, with a greater emphasis on the feasibility objectives and outcomes.

6.3.2.1 Participant Flow and Recruitment

30 patients with CFS (Fukuda defined) undergoing routine care at the Newcastle CFS clinical service, expressed an interest to participate in the sleep study. Of the 30 that expressed an interest, five (16.6%) met at least one of the exclusion criteria for the study: one patient (3.3%) had a current diagnosis of OSA, and a further four patients (13.3%) were taking sleep medication. The rate of eligibility of those assessed to participate was therefore 83.3% (25/30). Of those who were eligible, a further three (12%; 3/25) did not consent to the study. Of these, two declined to participate towards the enrolment stage due to poor health, and one patient was no longer able to participate due to pregnancy. 22 patients (73.3%; 22/30) were enrolled onto the study and underwent a 2-week pre-assessment including: wrist actigraphy, sleep diary and questionnaires. Following this phase of the protocol all patients continued to participate in the study process, and so a 0% rate of attrition provided a preliminary indication that the pre-assessment phase of the study was acceptable to this CFS patient group (see study flow diagram presented in Figure 6.2).

Over the 12-month study period, it was also feasible to recruit 25 normal sleepers (Figure 6.2). Of note, exclusion of normal sleeper controls throughout the study process (n =2) was based on their declining to participate, not due to having an existing primary sleep disorder.



Notes: AHI, Apnea/Hypopnea Index. AHI combines apneas (pauses in breathing of 10 seconds or more) and hypopneas to provide an overall sleep apnea severity score, evaluating both number of sleep disruptions and degree of oxygen desaturation (low blood oxygen).(AHI values are typically categorized as 5–15/hr = mild; 15–30/hr = moderate; and > 30/h = severe.) (AASM criteria, Ruehland et al., 2009)

Figure 6.2: Flow Diagram of Study (recruitment, protocol and analytical) Process

All 22 patients continued onto complete night one (habituation) of home-based Polysomnographic assessment. Following the first study night, and based on an examination of the Apnoea Hypopnoea Index (AHI) and PLM indices, two (1 male and 1 female) of the original 22 patients who underwent night 1 (9.1%), met the AASM criteria for sleep apnoea (i.e. considered moderate; AASM criteria for Sleep Apnoea, AHI ≥15, Ruehland et al., 2009), and therefore did not meet the inclusion criteria to continue the study beyond night 1.

Of those eligible to partake in the study, all patients completed the three overnights of home-based polysomnographic assessment and all three study days (wrist actigraphy, sleep diary, saliva sampling). This 0% rate of attrition for patients who took part in the 3 day sleep and cortisol assessment, indicates that the protocol is acceptable to this CFS patient group.

By considering participant dropouts from the study as a measure of protocol feasibility/acceptability, on reflection of the study flow process (Figure 6.1), the pattern and rates of attrition indicate that this protocol was both feasible and acceptable to patients who were eligible to take part in this study.

At the analysis stage of the study, one patient (5%; 1/20) had incomplete PSG data, in that no actual 'sleep' was recorded on night two, during the allotted 15 hour recording period the battery affords for. Having gone to bed at 10pm, the patient only commenced sleep at 9am (the morning following recording commenced) waking at 12:40pm with a sleep duration of 03:45min (225 mins), so the recording did not pick up any actual 'sleep'.

A key aspect of determining the feasibility of the comprehensive sleep and cortisol assessment is the extent to which patients were able to successfully adhere to the protocol. The following sections will report on patient's fidelity to the procedures and techniques, including their experience of the 3-day sleep and cortisol assessment.

6.3.2.2 Adherence to Sleep Assessment Protocol

Given the study met the feasibility/acceptability criteria based on a 0% patient drop out of those eligible to take part (as described above), the following section will discuss the level of adherence to procedural elements of the study, including fidelity to timing protocol.

Both protocol adherence and fidelity to timing protocol were monitored on an on-going basis by taking field notes throughout the study process and keeping a record of deviations from protocol via a tally. Timing references required for accuracy in sleep

analysis were based on self-reported times from sleep diaries and by a marker press on the head box device, which was required by the participant to indicate the times at which they turned the 'lights off' to retire to bed and again to indicate 'lights on' upon wake.

With regard to completion of the 2-week sleep diary and wearing the actiwatch throughout the pre-assessment phase, all patients adhered to this protocol successfully, only removing the wrist device for showering and other water immersion activity as required. In addition, all patients were able to fully complete the questionnaire booklet provided (functional and symptom assessments) throughout this period. This 100% adherence indicated that the techniques included in the study were acceptable to patients.

With regards to patient's fidelity to timing protocol by pressing markers on the PSG box (important for determining lights out and lights on timings when researcher is not present), 18/20 (90%) were consistent in doing so on all three nights, and all 20 (100%) patients did so on nights two and three. This demonstrates how the first habituation night is also a useful opportunity for 'learning' a detailed protocol that would not interfere with the subsequent assessment nights. Furthermore, after a retrospective check across the reported timings provided by patients on their sleep diary and the recorded times for the marker press on the PSG head box, it was evident that all patients were accurately reporting their timings for 'lights out' and 'wake' based on the times at which they pressed their marker on the PSG head box to indicate 'lights off' and 'lights on' respectively, over the 3-day period.

6.3.2.3 Adherence to Saliva Sampling Protocol

For accurate timing of sample points across the day and to enable potential to compare patients based on specific time-points, it is critical that samples were taken according to the protocol guidelines (wake, +15, +30, +45, +60, mid-afternoon, pre-bed). Any deviations from this protocol had the potential to off-set the projected diurnal profile and make such profile incomparable between patients. By on-going monitoring of fidelity to the saliva sampling timing protocol via keeping records of patient's wake and bed times (sleep diary) and saliva sampling time-logs, it was possible to determine the level of adherence to the saliva sampling protocol.

The adherence checklist for saliva sampling (Table 6.1) demonstrated a 95% adherence to sampling protocol, with all but one patient being able to take their 7 samples per day over all 3 days. Only one patient (5%; 1/20) did not complete the saliva sample at one time point (wake+60 sample), from the 21 required during the 3-day period. This was due to sickness: the patient felt too poorly at that time point in the morning. Overall, of 420 total possible saliva samples across the study, 419 (99.8%) were provided by patients.

The fidelity to saliva sampling table (table 6.2) provides a calculation of the discrepancy in time between wake and first saliva sample (which should be provided at participant's wake time), based on values of wake timing (taken from sleep diaries) alongside first-sample times (taken from sample log) for each patient. This is important in that such a discrepancy could have implications for the saliva profile for the patient that could potentially result in a blunted CAR, and off-set the cortisol awakening response profile/slope for the day. Timing discrepancies between wake time and time of first sample ranged from 0 (being taken on actual time of waking) to 45 minutes (first sample not provided until 45 minutes post-wake). Across the 3 days, timing discrepancy was on average 5.1 (±6.9 minutes) (day one ~2.3 minutes, day two ~7.8 minutes, day three ~5.2 minutes).

Patients	Sample Time Points Across 3-Day Period																					% Complete
	Day 1							Day 2							Day 3							
	T1 Wake	T2 +15	T3 +30	T4 +45	T5 +60	T6 a/n	T7 Bed	T1 Wake	T2 +15	T3 +30	T4 +45	T5 +60	T6 a/n	T7 Bed	T1 Wake	T2 +15	T3 +30	T4 +45	T5 +60	T6 a/n	T7 Bed	
Patient 1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 4	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 5 excl																						
Patient 6	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 8	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 9 excl																						
Patient 10	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 11	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 13	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 14	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 15	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 17	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 18	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	95.24
Patient 19	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 20	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 21	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100
Patient 22	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100

Notes: $N = 20$. T, time point; a/n, afternoon sample (between 2-4pm).

Table 6.1: Patients' adherence to saliva sampling protocol across 3-day period.

	Day 1			Day 2			Day 3			
	Wake (hh:mm)	Sample (hh:mm)	Diff (min)	Wake (hh:mm)	Sample (hh:mm)	Diff (min)	Wake (hh:mm)	Sample (hh:mm)	Diff (min)	**Average (min)**
P1	08:35	08:35	0	08:50	08:50	0	08:54	08:54	0	**0**
P2	06:30	06:30	0	06:45	06:45	0	06:45	06:45	0	**0**
P3	07:12	07:13	+1	07:32	07:33	+1	07:55	07:56	+1	**1**
P4	05:55	05:55	0	05:20	05:20	0	05:35	05:38	+3	**1**
P5excl										
P6	07:40	07:40	0	07:34	07:38	+4	07:30	07:39	+9	**4.3**
P7	08:30	08:30	0	08:30	08:32	+2	08:25	08:27	+2	**1.3**
P8	10:30	10:33	+3	10:30	10:55	+25	11:30	11:45	+15	**14.3**
P9excl										
P10	09:00	09:00	0	10:30	10:30	0	08:00	08:00	0	**0**
P11	06:55	06:55	0	06:00	06:05	+5	06:05	06:10	+5	**3.3**
P12	09:20	09:20	0	09:30	09:35	+5	09:30	09:30	0	**1.7**
P13	06:15	06:16	+1	06:29	06:30	+1	06:15	06:22	+7	**3**
P14	06:30	06:30	0	07:30	07:33	+3	06:55	06:55	0	**1**
P15	07:30	07:35	+5	06:50	07:30	+40	07:30	07:30	0	**15**
P16	08:00	08:15	+15	07:00	07:45	+45	06:40	06:50	+10	**23.3**
P17	10:30	10:35	+5	12:45	12:49	+4	12:40	12:40	0	**3**
P18	08:00	08:00	0	08:20	08:20	0	07:45	08:00	+15	**5**
P19	07:30	07:45	+15	07:30	07:40	+10	07:30	08:00	+30	**18.3**
P20	07:30	07:30	0	07:25	07:26	+1	07:20	07:20	0	**0.3**
P21	10:55	10:55	0	11:00	11:10	+10	08:40	08:45	+5	**5**
P22	10:38	10:39	+1	11:11	11:11	0	10:53	10:54	+1	**0.7**
Average (min)			**2.3**			**7.8**			**5.2**	**5.1**

Table 6.2: Fidelity to saliva sampling timing protocol. (N=20).

6.3.2.4 Patient-specific experience of the protocol – field observations.

An important aspect in determining the feasibility of the protocol is to identify parts that may not be well tolerated or perhaps problematic for patients. Monitoring the patient experience of the study process, through taking field notes over the course of the study, it was possible to identify any problems with equipment or procedures in this patient group. The table below details the experience of the procedures for each patient throughout the study process;

Patient	**Observations**
Patient 1	Patient stated on the morning following night 1 of the PSG – exhausted – will need to change her sleep pattern as a result of the procedure (PSG), said will sleep during day. It is noteworthy that the daytime sleep will in turn have an effect and disturb her sleep in night 2 of PSG study. Finger clip (night 1) irritating fingertips, nerve endings sensitive (Hyperesthesia). Paste on scalp - temporary tingling sensation (almost burning) subsides after several minutes. Overall, found the procedures ok with only minor sensations from some of the equipment.
Patient 2	Washing hair daily (to remove paste) is very difficult and demanding on energy levels. Patient stated she wouldn't have come into a sleep lab - too much, tiring, felt that it is better that it is carried out at her own home. Lightweight feel, expected the electrodes and wires to be much heavier on head. By Night 3 patient felt "absolutely worn out" couldn't do another night (it's washing hair each morning) activities that are usually paced are made compulsory in this protocol - wash hair every morning arms aching. In the days during study period, patient experienced the "bad symptoms" that are usually caused through "over doing it".

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Patient 3	Wake nearly every night; usually wake for a while early morning then back to bed. By ensuring patient pressed the marker for 'lights off' and 'lights on' this was technically not a problem, and combined with the self-reported timings provided on the sleep diary, it was possible to identify the actual start and end of the sleep period.
Patient 4	Rescheduled study dates after patient's ENT specialist gave an 8-week treatment of steroid drops and sprays for facial pain and sinus problems. It was logical to wait until this treatment had finished before commencing the sleep study, which involves applying electrodes to the facial area. Early to bed so arrived early each evening to set up equipment and allow patient to relax prior to retiring to bed. Initially, concerns over nasal thermistor (night 1) and facial electrodes due to facial pain she experiences, but overall found the equipment ok and non-intrusive.
Patient 5	excl after night 1 ; AHI Index > 15
Patient 6	No problems regarding technical aspects or equipment. Patient felt that planning for the timings of procedural elements (saliva sampling, researcher picking up equipment) of the study was beneficial, to help with maintain the daytime schedule she had set in place for university work.
Patient 7	No issues with procedural aspects or equipment, but felt that her sleep must have been affected somewhat on first night due to feeling terrible throughout the following day. Overall, at the end of the three days patient felt very "drained" but otherwise, managed the study ok with no real issues.
Patient 8	Long sleep duration realised after night 1. Re-configured the recording box to record for longer duration and also went to patient's home later to set up to ensure enough battery power for recording. No issues with PSG, patient felt it was difficult and unpleasant taking the saliva samples soon after waking. *continued over page*

Patient 9	excl after night 1; AHI Index > 15
Patient 10	Patient noted their legs are always a problem, with achy muscles that can be painful and so was initially worried about wearing the extra equipment on night one (leg wires), but overall found it did not exacerbate any existing pain.
Patient 11	Legs a problem and fidget a lot in bed because uncomfortable, so was concerned about leg wires (night 1) initially, but overall found it ok and not problematic.
Patient 12	Patient stated she usually spends lots of time in bed and lays awake for hours, sometimes until 5/6am, poor sleep efficiency (baseline mean 41.8% from 2-week diary) average 5 hrs sleep. During the study she found all aspects (procedural and equipment) ok, but where usually she would spend more time in bed in the morning after a restless night, found it a struggle to ensure she was awake on time for the researcher to collect equipment.
Patient 13	Legs a problem usually, often in pain and uncomfortable but felt the leg wires (night one) were not problematic.
Patient 14	PSG equipment and procedures all ok. Due to work commitments, patient had to plan for the morning saliva sampling and adjust their wake time, also taking the lunchtime sample to work and refrigerating before returning home.
Patient 15	Due to work commitments, patient had to consciously plan ahead for the morning procedures (sampling timings and researcher collecting equipment), to ensure sufficient time available to prepare for the day ahead. Patient felt the first night of the study was difficult and affected their sleep quality and how they felt throughout the following day, but noted that this improved during the study.

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Patient 16	Poorly during night 1 - sickness meant missing one of the CAR (wake+60) saliva samples on the first day of saliva sampling protocol. The scalp was slightly sensitive and so it was necessary to be extra gentle with marking reference points on the head. Otherwise, felt the procedures were ok and not intrusive to usual sleeping.
Patient 17	Patient had an irregular sleeping pattern and so pre-planned times were arranged for the setting up and collection of equipment each day. Following night one, the timings had to be adjusted to be better suited to the patient's needs. It was noticeable that sleep duration was longer than anticipated and so the recording box was reconfigured to ensure the monitoring sleep for a corresponding period on nights two and three. Also, the researcher adjusted the time they went to patient's home to set up equipment to be later on nights two and three to ensure complete recording for battery power available. Patient also noted they sleep during daytime and this is their usual sleep pattern. This should be noted for future assessment (PSG for daytime sleep)
Patient 18	Wore equipment on bare skin as too hot at night. Patient also noted that he regularly slept during the day and made note of the times he had done so.
Patient 19	Due to commitment to voluntary work in the morning, procedural aspects had to be considered with regards to planning timing of saliva sampling and the researcher collecting the equipment. Otherwise no problems with the equipment.
Patient 20	Equipment placed on skin under bed wear due to experiencing hot flushes during the night. Patients found the first night difficult in terms of gaining quality sleep, but felt this improved throughout the course of the study.

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Patient 21	Patient felt more comfortable adjusting placement of shoulder strap each night, to prevent discomfort. No problems with other procedural aspects, but felt sleep quality was affected on night one after feeling unwell during the following day, but felt his sleep gradually improved over the three nights.
Patient 22	Housebound, application of equipment done whilst patient remained in the bed. Carer aided in washing hair each day (to remove paste), changed the shoulder strap each night (different shoulder each night) for comfort. Equipment ok except nasal thermistor felt uncomfortable, and Actiwatch noticeable during sleep i.e. hitting self in face. Patient found the study only manageable because researcher came to her home each evening and morning.

6.4 Discussion

This is the first study to systematically assess and report on the feasibility and acceptability of a comprehensive 3-night and 3-day sleep and cortisol assessment in a group of patients with CFS. The data indicates that the 3-night ambulatory Polysomnographic assessment and gold-standard protocol for saliva sampling to assess cortisol was possible in this patient group, and further that the patients tolerated the protocol successfully.

6.4.1 Feasibility and Acceptability

6.4.1.1 As indicated by recruitment and attrition

There was a very low refusal rate in the study. Of those patients considered eligible for enrolment, only three did not consent to take part in the study; their reasons being health-related and not associated to the study. This suggests that the idea of the study and its procedures was acceptable to all patients. The acceptability of the study was further confirmed by the 0% drop out rate. All patients who were eligible to continue on with the assessment beyond night one (screening), did so. Those that did not

continue (N =2) were those who met the exclusionary criteria based on AHI Index >15, making them ineligible. In general, patients were all highly motivated to take part in the study.

6.4.1.2 As indicated by adherence to the assessment protocol

The protocol was possible in all eligible patients that took part, which emphasises the feasibility of incorporating all the included procedures of a detailed 3-night PSG sleep assessment with a gold-standard measure for saliva sampling. Overall, the protocol was well tolerated, with only minor issues relating to individuals and their experience of the equipment (sensitivity, planning, energy depletion), also it is worth emphasising how several patients brought to light of the issue of daytime sleep, and this also posed a problem with regard to analyses, where a night of PSG data for one patient had to be excluded due to no nocturnal sleep having been recorded. With regard to fidelity to procedures; all patients were consistent in pressing the marker on the PSG box (important for determining lights out and lights on timings when researcher is not present) on nights two and three, and accurate in reporting their retrospective sleep and wake times on the sleep diary as affirmed by the marker press. Patients were also consistent in their saliva sampling, with only one individual sample not taken, and this being for health-related issues. Whilst patients adhered to the study procedures, after an evaluation of timing discrepancies between self-reported wake time and the time of first saliva sample, there was an average discrepancy of 5.1 (± 6.9) minutes. It should be noted that the accuracy in patients reporting their wake and sample timings was the key outcome for fidelity here and, despite two (P16, P19) patients delaying the provision of their first sample, their honesty in reporting the discrepancy between these timings is what was most important.

From the viewpoint of feasibility, these findings indicate that the sleep and cortisol protocol was indeed acceptable to these patients. This is ideal from the clinical viewpoint of conducting quality procedures for sleep and cortisol assessments with CFS patients, where thorough screening and measures are warranted, and one night of assessment is inadequate (Le Bon, et al., 2003). The feasible nature of this protocol is also of value to the research domain, where prospective sleep studies can utilise a detailed sleep protocol effectively with CFS patients, without a need for less than gold-standard measures, thus affording for more quality research.

6.4.2 Limitations and future directions

It is important to note that this study was an assessment of protocol feasibility and did not intend to infer definitive judgements with regard to patients' sleep and cortisol profiles. The preliminary characterisation of sleep in these patients (see chapter 7) was in itself an outcome of feasibility success, and adds support for the heterogeneity of sleep in CFS as a topic for further exploration.

As identified throughout the monitoring process, several patients were sleeping during the daytime and did this on a regular basis as part of their usual sleeping pattern. This was problematic for the procedural aspects of the nocturnal assessment, where recording ambulatory PSG relies somewhat on battery life, it was not possible in these circumstances to record beyond the nocturnal sleeping period. This should be made a consideration for future ambulatory sleep assessments with patients who may be likely to spend a notable amount of their sleep schedule outside of the nocturnal period. Thus, to ensure complete feasibility of this protocol in CFS patients, it should allow for the daytime monitoring of sleep to account for these irregular patterns, through sufficient planning and by ensuring equipment is able to tolerate the timings.

In addition to the alpha activity/arousability association (Perlis, et al., 1997), beta EEG activity in insomnia has been linked with central nervous system hyperarousal (Perlis et al., 2001). Beta activity, like alpha, is also high frequency and occurs in the lighter stages of sleep. This appears to be relevant in light of the findings of the present study. Patients may present as having normal amounts of stage 2 sleep (45-55%) but, this sleep may be more high frequency. Future work may want to consider utilising techniques that enable the assessment of these frequencies, such as the Q- EEG (quantitative electroencephalography), where electrical patterns can be measured and for example, alpha and beta waves could be identified according to their frequency.

Physiologically, the study has developed a standardised protocol for the assessment of salivary cortisol in an ambulatory setting with CFS patients. This demonstrates how we have the ability to measure basal HPA functioning in a naturalistic setting with this patient group, an environment that is not stressful or medicalised. The feasibility of this protocol in conjunction with the detailed assessment of sleep warrants moving

forward with more mixed methods study designs. This is important for research that looks to explore the interaction between sleep processes (circadian rhythm, melatonin) and HPA axis functioning within the same patient. It echoes the holistic view of CFS and its' pathogenesis, where it is the reciprocal interaction of processes that serves to keep the condition going (Moss-Morris, Deary & Castell, 2013).

In consideration of sleep interventions, outcomes for CBT-I (cognitive behavioural therapy for insomnia) and its efficacy in somatoform disorders such as fibromyalgia has been demonstrated (Sánchez, et al., 2012), however, it is yet to be trialled in a CFS population. Using PSG to measure its efficacy, CBT-I has been shown to be effective in significantly improving objective sleep parameters, specifically in reducing the amount of light sleep (stages 1 & 2) and awakenings in patients, and increasing deep sleep (stages 3 & 4) (Sánchez, et al., 2012). Furthermore, sleep restriction, a componential aspect of CBT-I has been shown to reduce cortical processing (Vallieres et al., 2013). The findings from these studies may also have therapeutic potential for a CFS population, and, if such interventions are shown to be effective, they offer the potential to be useful in the multidisciplinary management of CFS.

6.4.3 Conclusion

This study was a process of determining feasibility and acceptability of the 3-night sleep and cortisol assessment in a small group of CFS patients. As previously mentioned, there are no sleep studies with CFS patients that utilise such detailed protocol. It is proposed that the protocol described in this study (integrating the methods and procedures as shown to be well tolerated), is a valuable means of sleep and cortisol assessment. It affords more detailed exploration of sleep parameters than what is currently being used in practice with CFS patients, and is able to identify (and exclude on this basis) primary sleep disorders after one single PSG assessment night. Importantly though, it is the acceptability of this protocol to patients which highlights how methodologically, the procedures and equipment are not intrusive or detrimental to their existing experience of their CFS. This protocol has the potential to be utilised in future sleep studies and could be used for clinical screening of sleep-related disturbances in CFS.

CHAPTER SEVEN
PRELIMINARY SLEEP RESULTS FROM A 3-NIGHT AMBULATORY PSG SLEEP ASSESSMENT IN PATIENTS WITH CFS (STUDY 4)

In this chapter, the preliminary findings from the sleep assessment feasibility study (Chapter 6) are described. This chapter is not intended to present effectiveness data, but instead offer a preliminary characterisation of sleep and cortisol profiles in these patients. Finally, the stability of the polysomnograpic measures of patient's nocturnal sleep are discussed with a view to informing future studies.

7.1 Introduction

The 3-night sleep protocol (fully described in chapter 6) was considered both feasible and acceptable by the group of CFS patients. This is important for future studies pursuing sleep-based research with this patient-group, where a detailed, thorough assessment of sleep is key, particularly with regard to methodological uniformity and upholding standardised means of reporting results. The current chapter intends to describe the preliminary sleep characteristic results of the study. These results will provide an insight into the sleep complaints presenting in this patient group, and the extent to which they differ from normal sleep parameters.

7.2 Methods

7.2.1 Objectives (secondary) of Study 4

- To clinically characterise patients on symptom severity and functional status;
- To preliminary characterise sleep (subjective and objective) in patients with CFS, based on measures derived from the methods utilised in the 3-night ambulatory sleep assessment (Chapter 6).

These objectives were measured through scores derived from symptom and functional assessments, retrospective reports of patient's sleep, and the objectively-derived PSG measures taken from night two and three of assessment.

7.2.2 Outcomes (secondary)

The secondary outcomes of study 4 were the descriptive measures taken to clinically characterise patients based on their symptom and functional assessments; subjective and objectively-derived sleep variables. These outcomes were assessed with regard to their variability across the patient sample. Outcomes for sleep characteristics were also assessed with regard to; 1) their variability across nights two and three (evaluated by comparing mean sleep variables measured by nocturnal polysomnography on night two and the same sleep variables for night 3, to determine temporal stability of the continuity and main architectural sleep variables); 2) a comparison of subjectively (diary) reported sleep and objectively (PSG) measured sleep parameters (SOL, WASO, TST, SE), and their level of concordance, based on average across nights two and three of the assessment; and 3) outcomes for sleep characteristics were further evaluated in relation to comparative quantitative benchmarks of sleep disturbance (Edinger. et al., 2004), and criteria for normal architectural parameters (Carskadon & Dement, 2011). (Refer to table 4.1 for description of abbreviated sleep variables).

7.2.3 Statistical methods

To analyse the secondary outcomes of the study, 1) paired samples *t*-tests were used to compare sleep variables (see table 7.2 for included sleep variables on t-test), as measured by nocturnal Polysomnography on night two, and the same mean sleep variables, as measured by nocturnal Polysomnography on night three, as a determinant of temporal stability; 2) a correlational analysis was used to determine the level of concordance between objective and subjectively derived measures of sleep by comparing SOL, WASO, TST and SE as measured by nocturnal Polysomnography with SOL, WASO, TST and SE as measured by the Sleep Diary respectively; 3) additionally, descriptive statistics, including frequencies and percentages, were used to describe the sample in terms of their objectively measured sleep variables, comparing these sleep characteristics to quantitative benchmarks of sleep disturbance (Edinger. et al, 2004), and the criteria for normal architectural parameters (Carskadon & Dement, 2011).

7.3 Preliminary Results

7.3.1 Baseline data

7.3.1.1 Patient characteristics

The descriptive measures taken to clinically characterise patients were based on their symptom and functional assessments, including self-reported retrospective sleep assessment. (Table 7.1 shows the baseline demographic and clinical characteristics of patients in the study, including the mean scores obtained on each of the functional and symptom assessments; Table 7.2 shows the subjective sleep characteristics based on self-report measures of sleep).

Demographically, there were a smaller proportion of men to women (25%; 5/20 and 75%; 15/20 respectively), with a mean age of 43.9 (±10.1) years at the time of study. The mean time since diagnosis (length of illness at time of study) was 131 (±100) months, but highly variable across the group, ranging from 7 to 312 months. Most patients were not in employment (80%; 16/20), with 9 (56.3%; 9/16) on disability. Of those who were in employment at the time of the study (25%; 5/20), only one patient was working on a full-time basis, with 80% (4/5) working part-time hours. All but two patients took some form of medication, mostly pain relief and herbal remedies, with nine patients taking a form of anti-depressant (45%; 9/20). All patients were non-smokers and only four (20%; 4/20) patients consuming alcohol on a daily basis. The mean Body Mass Index (BMI) of patients in the study was 25.83 (±3.97), only slightly above what is classified the healthy range (18.5-24.9) for adults. 60% (12/20) of patients were able to integrate a form of exercise into their lifestyle, on at least one day per week, with a quarter of these patients (25%; 3/12) factoring in exercise every day.

Characteristics of sample		**Caseness** N (%)
Demographics		
Gender (M:F)	M: 5/20(25%) F: 15/20(75%)	-
Age (years)	43.85 (10.11)	-
Time since diagnosis (months)	131.05 (100.01)	-
BMI	25.83 (3.97)	-
Functional & symptom assessment		
GHQ-28	29.95 (10.02)	15 (75%)
DSQ (frequency)	117.55 (33.63)	11 (55%)
DSQ (severity)	110.70 (28.18)	11 (55%)
SF-36 (general health perceptions)	29.50 (17.91)	16 (80%)
SF-36 (physical functioning)	25.00 (14.42)	19 (95%)
SF-36 (role physical)	6.25 (13.75)	19 (95%)
SF-36 (energy/fatigue)	19.00 (15.78)	19 (95%)
SF-36 (social functioning)	35.13 (22.23)	12 (60%)
SF-36 (pain)	36.75 (17.86)	15 (75%)
CFQ (physical)	15.55 (4.95)	*npv*
CFQ (mental)	8.85 (3.31)	*npv*
CFQ (total)	24.40 (7.78)	19 (95%)
HADS anxiety	7.80 (3.68)	11 (55%)
HADS depression	8.55 (3.09)	12 (60%)
IPQ	51.40 (8.60)	*npv*
WSAS	28.45 (6.46)	19 (95%)
PSS	29.50 (7.15)	*npv*

Notes: data presented as mean (SD), *N*=20. *npv*, no published values for caseness score cut-offs on scale/measurement. BMI, body mass index; GHQ-28, general health questionnaire; DSQ, DePaul symptom questionnaire; SF-36, short form 36-item health survey; CFQ, Chalder fatigue questionnaire; HADS, hospital anxiety and depression scale; IPQ, illness perception questionnaire; WSAS, work and social adjustment scale; PSS, perceived stress scale.

Table 7.1: Clinical and demographic characteristics of patients with CFS.

Patient's mean General Health Questionnaire scores exceeded the caseness threshold of 22 (Goldberg & Williams, 1988), with 75% of patients scores equalling or exceeding the threshold based on their total GHQ-28 scores.

As a representation of illness burden, mean total DSQ scores for frequency and severity of symptoms (117.55 ± 33.63, and 110.70 ± 28.18, respectively), exceeded the recommended threshold criteria (total frequency score ≥108, total severity score ≥108, based on individual item scores ≥2) that differentiates controls from CFS (Brown and Jason, under review); more than half of patients exceeded the threshold for frequency and this was comparable for severity.

Patients' quality of life scores were lower than the general population norm on all QoL domains measured by the SF-36 (Ware & Sharebourne, 1992); over half had scores representing impaired social functioning. The majority of patients had lower than normal functional scores on general health perceptions and bodily pain, and 95% of patients had functional impairment on their limits in physical activities, limits in usual role activities due to physical health, and on vitality (energy/fatigue).

In consideration of the CFS case definition recommendation for meeting disability criteria (Reeves et al., 2005) and representing significant reductions in occupational, educational, social, or recreational activities, all patients (20/20) met the defined scores on physical functioning (≤70) and on social functioning (≤75). 95% of patients (19/20) met the criteria on role physical functioning (≤50).

Based on the CFQ, a measure of the severity of symptomatic fatigue, patients' mean fatigue levels (24.40 ± 7.78) were higher than what is considered within the normal range for fatigue, based on the Likert-based scoring threshold (<18) (White et al., 2013), with 95% of patients having scores equalling to or greater than 18 on the questionnaire.

On HADS (Zigmond and Snaith, 1983), where the caseness cut off for anxiety and depression is 8 on both subscales (Crawford et al., 2001), average depression (8.55 ± 3.09) and anxiety (7.80 ± 3.68) scores, showed patients met caseness for depression,

and were approaching caseness on anxiety. In consideration of individual patient characteristics, over half of the sample met caseness for depression and for anxiety.

In assessing illness perception in patients, i.e. the degree to which they perceived their illness as threatening (IPQ), there are no published indicators of "caseness" for the scale, but higher scores represent a more threatening view of the illness, thus on average mean illness perception scores were moderate (51.40 ± 8.60) and ranged from 33-68 out of a possible 80.

Average WSAS scores exceeded the clinical threshold for severe functional impairment (>20) (Mundt et al., 2002), with all but one patient's scores exceeding 20 on the scale. One patient scored in the range (10-20) that is still associated with significant functional impairment but less severe clinical symptomology.

On the PSS, mean scores (29.50 ± 7.15) indicated a high degree of perceived stress among patients. Scores ranged from 14-44 out of a possible 80.

7.3.2 Preliminary characterisation of sleep variables

7.3.2.1 Patient sleep profiles; self-reports

The table below (table 7.2) displays the sleep characteristics of CFS patients in the study, based on retrospective sleep questionnaires (PSQI, FIRST, ISI) completed during the pre-assessment phase of the study. It also shows the included continuity and main architectural sleep variables from the PSG-derived measures, taken from night 2 and night 3 of the sleep assessment. As detailed in the study flow section, complete sleep measures (night 2 and night 3) were not available for one participant, thus all objective sleep-related analyses were carried out on the sleep data of the remaining 19 patients (note *N* varies in Table 7.2 below).

Sleep Characteristics	Mean (SD)		
Self-report (*N* = 20)			
PSQI (subjective sleep quality)	1.55 (0.69)		
PSQI (sleep latency)	0.85 (0.93)		
PSQI (sleep duration)	0.65 (0.93)		
PSQI (habitual sleep efficiency)	0.80 (1.06)		
PSQI (sleep disturbances)	1.75 (0.44)		
PSQI (use of sleep medication)	0.60 (1.14)		
PSQI (daytime dysfunction)	1.55 (0.94)		
PSQI (global)	8.75 (3.45)		
FIRST	25.6 (6.73)		
ISI	13.75 (4.68)		
PSG Variables (*N* = 19)	**(n2)**	**(n3)**	**(average n2 & n3)**
TST (min)	465.42 (97.43)	442.39 (85.85)	453.91 (73.74)
SOL (min)	16.00 (16.38)	28.95 (29.55)	22.47 (20.49)
WASO (min)	32.11 (17.45)	42.16 (42.26)	37.13 (24.32)
SEI (%)	93.42 (3.53)	91.64 (7.35)	92.53 (4.18)
%N1 (of TST)	4.81 (2.93)	4.33 (2.11)	4.57 (2.26)
%N2 (of TST)	54.47 (11.59)	53.15 (11.58)	53.81 (10.57)
%N3 (of TST)	18.40 (10.64)	17.07 (10.38)	17.74 (9.74)
%REM (of TST)	22.33 (5.72)	25.45 (8.11)	23.89 (5.80)
REM Latency (min)	142.39 (80.87)	140.00 (84.33)	141.20 (70.60)
NWAK (over TSP)	17.58 (8.36)	18.37 (10.34)	17.97 (7.90)
% wake (over TSP)	9.54 (4.70)	13.01 (9.39)	11.27 (5.74)
Subjective Sleep Diary (*N* = 19)	**(n2)**	**(n3)**	**(average n2 & n3)**
TST (min)	452.79 (111.26)	446.47 (113.34)	448.68 (101.31)
SOL (min)	34.47 (31.53)	33.16 (22.62)	33.95 (21.67)
WASO (min)	46.05 (56.34)	46.05 (56.34)	41.58 (56.48)
SEI (%)	77.83 (14.95)	77.83 (14.95)	78.89 (13.51)

Notes: PSQI, Pittsburgh sleep quality index; FIRST, ford insomnia response to stress test; ISI, insomnia severity index; PSG, polysomnography; SOL, sleep onset latency; WASO, wake after sleep onset; TST, total sleep time; %N1, percentage of stage 1 sleep; %N2, percentage of stage 2 sleep; %N3, percentage of slow wave sleep; %REM, percentage of rapid eye movement sleep; NWAK. number of awakenings; SEI, sleep efficiency index; TSP, total sleep period

Table 7.2: Sleep characteristics of patients derived from retrospective and objectively - (PSG) derived measures.

Data were also collected for 22 normal sleepers. However, because these were considered in the normal range and the study was not intending to make between-groups comparisons, the data for normal sleeper participants can be found in (Appendix BB)

All patients had PSQI global scores of 5 or more, exceeding the threshold that is indicative of poor quality sleep (≥5). Scores ranged from 5 to 17 points, with a group mean of 8.75 (± 3.45). For individual components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction), each with a possible range of 0-3, the observed ranges were 0-3.

In considering the severity of patients' self-reported sleep difficulties, mean ISI scores (13.75 ± 4.68) indicated the sleep difficulties reported by this patient group were 'subthreshold insomnia', with 50% (10/20) of patients reporting as having sleep difficulties meeting criteria for this category (8-14). 40% of patients (8/20) met 'caseness' for clinical insomnia (ISI score 15-21)), and one patient's sleep difficulties were classified as 'severe'. 10% of patients (2/20) were not considered as having clinically significant insomnia (total ISI score ≤ 7) (Morin et al., 2011).

In light of Stress-related vulnerability to sleep disturbance, patients were considered as 'high scorers' (total FIRST score > 20) (Drake et al., 2004), (mean 25.6 ± 6.73), with patient's scores in the range of 12-36: 85% (17/20) of patients in this group were considered high scorers.

7.3.2.2 Patient sleep profiles; Polysomnography

When characterising patient's sleep based on the objectively derived PSG measures, sleep continuity parameters were considered within the 'normal' range, using quantitative benchmarks of sleep disturbance outlined by Edinger et al (2004). On average, total sleep duration was 7.6 hours (453.91 minutes) (± 1.2 hours (73.74 minutes)), with all but one patient (94.7%; 18/19) exceeding the minimum threshold for 'normal sleep' (< 6 hours is considered problematic). It can also be seen that patients fall in the 'normal' range for sleep latency (SOL ≥ 30 minutes denotes a sleep

problem), taking on average 22.47 (± 20.49) minutes to reach their first episode of stage 2 sleep from lights out. Of note is the *variability* in the sample, SOL ranged from 1.75-64.25 minutes, and 36% (7/19) did exceed the 30 minute threshold. Patient's sleep efficiency index (92.53 ± 4.18%), met the criteria for what is considered 'normal sleep' (≥85% sleep efficiency is considered normal), with 94.7% (18/19) patients showing a sleep efficiency index greater than 85%. 11 patients exceeded the threshold for what is considered a problematic duration of wake (WASO ≥ 30 minutes denotes a sleep problem), with an average 37.13 (±24.32) minutes of recorded wake time following the first episode of stage 2 sleep, 57.9% (11/19) of patients were spending longer than 30 minutes awake during the sleep period. It should be noted that WASO was also highly variable across the sample, and ranged from 8.75 minutes to as much as 110.50 minutes wake during the night. Patients on average had longer REM latencies (mean 141.20 ± 70.60 minutes) than what is usual for 'normal sleep' (90 minutes is considered the 'normal' length of time to get to first REM stage). 63.2% (12/19) of patients had REM latencies greater than 90 minutes. It was also highly variable; a range of 65.5 minutes to as long as 291.8 minutes was observed in the sample.

Further, when comparing the percentages of each sleep stage in 'normal' adult sleepers (i.e., <5% wake, between 2% and 5% stage 1, between 45% and 55% stage 2, between 13% and 23% SWS and between 20% and 25% REM (Carskadon & Dement, 2011)) to those observed in the present sample, patients on average fell within the 'normal' parameters for time spent in each of the sleep stages (see Table 7.2 for mean and SD of architectural sleep variables). They do however, exceed the threshold for the amount of wakefulness during the sleep period; with a mean of 11.27 (±5.74) % wake time, with a range from 5.05% to 26.75%, all patients spent more than 5% of their sleep awake. Architecturally, the sample does not present objective sleep difficulties with regard to time spent in the sleep stages. They are however, spending a marked amount of time awake. Of note though, is the architectural variability in the sample. With this in mind, it is of particular interest to highlight that stage 2 sleep ranged from 28.1% to as much as 72.9% of the night, with more than half of patients spending over 55% of the night in this lighter stage of sleep (52.6%; 10/19).

7.3.3 Stability of sleep variables across night 2 and night 3

After building a sleep profile of patients from the sleep parameters identified, it is of interest to establish whether these sleep characteristics are stable across different nights. By assessing the temporal stability of Polysomnographic variables across different nights of assessment, it adds to the evaluation of protocol feasibility in terms of what might be considered a sufficient number of study nights to gain the most accurate characterisation of patients' sleep. It should be noted that the first night of PSG data was discarded. This is typical of multi-night PSG sleep assessments due to the novelty of the procedure to patients.

To assess the temporal stability of the sleep variables, a paired samples *t*-test was carried out to compare the selected sleep variables (continuity and main architectural variables) on the two assessment nights (2 and 3). The paired comparisons showed that sleep onset latency (SOL) was the only variable to be statistically different from night 2 to night 3. SOL was significantly longer on night 3 (28.95 ± 29.55 minutes), than on night 2 (16.00 ±16.38 minutes) (refer to table 7.2 for means and SDs for individual study nights), $t(18) = -2.30$, (95% CI 1.10 - 24.79 minutes) (see table 7.3 for mean differences from the paired comparisons). However, after conducting statistical corrections for multiple comparisons (.05/11), an adjusted Bonferroni alpha level of .005 resulted in no statistically significant differences observed from night 2 to night 3 on all sleep variables. This demonstrates that a third study night may not be needed, for the purposes of research constraints.

		Paired Differences					*t*-test	
		Mean Dif.	Std. Deviation	Std. Error Mean	95% confidence interval of the difference			
					Lower	Upper	*t*	*p* (2-tailed)
Pair 1	SOL(night 2) / SOL(night 3) (min)	-12.95	24.57	5.64	-24.79	-1.10	-2.30	**.034***
Pair 2	WASO(night 2) / WASO(night 3) (min)	-10.05	42.61	9.78	-30.59	10.48	-1.03	.317
Pair 3	TST(night 2) / TST(night 3) (min)	23.03	109.43	25.10	-29.72	75.77	0.92	.371
Pair 4	Percentage N1(night 2) / Percentage N1(night 3) (of TST)	0.48	2.37	0.54	-.66	1.62	0.88	.391
Pair 5	Percentage N2(night 1) / Percentage N2(night 3) (of TST)	1.33	9.49	2.18	-3.25	5.90	0.61	.550
Pair 6	Percentage SWS(night 2) / Percentage SWS(night 3) (of TST)	1.33	7.94	1.82	-2.50	5.15	0.73	.476
Pair 7	Percentage REM(night 2) / Percentage REM(night 3) (of TST)	-3.12	7.89	1.81	-6.92	.68	-1.73	.102
Pair 8	Percentage WAKE(night 2) / Percentage WAKE(night 3) (of TSP)	-3.47	9.43	2.16	-8.01	1.08	-1.60	.126
Pair 9	REM latency(night 2) / REM latency(night 3) (min)	2.39	85.80	19.68	-38.96	43.75	0.12	.910
Pair 10	SEI(night 2) / SEI(night 3) (%)	1.78	7.94	1.82	-2.05	5.61	0.98	.342
Pair 11	NWAK(night 2) / NWAK(night 3) (over TSP)	-.79	10.19	2.34	-5.70	4.12	-0.34	.739

Notes: $N = 19$, *p < .05. SOL, sleep onset latency; WASO, wake after sleep onset; TST, total sleep time; N1, stage 1 sleep; N2, stage 2 sleep; SWS, slow wave sleep; REM, rapid eye movement sleep; SEI, sleep efficiency index; TSP, total sleep period; NWAK, number of awakenings

Table 7.3.: Mean differences following the second assessment night on equivalent sleep variables (t-test: paired samples).

This finding demonstrates the temporal stability of variables across study nights. Those variables that were identified as being outside of the 'normal' sleep parameters (WASO, REML, %WAKE) when profiling patients, remained abnormal over both nights; REML, as previously identified as being abnormally long, was shown to be consistently so across both nights. WASO as previously identified as longer than what is seen in normal sleep, was also consistently abnormal across both nights. The remaining sleep variables (TST, SEI, NWAK, % stage 1, % stage 2, % SWS, % REM,), remained within the parameters for 'normal' sleep (as identified previously in the profile), consistently across both nights. This stability of the sleep variables across study nights is a good indication that two nights are sufficient to determine objective sleep profiles in CFS patients, and move forward with this protocol for future studies with larger samples.

7.3.4 Subjective vs Polysomnographic assessment of sleep

Interestingly, based on the retrospective measures of sleep (PSQI, ISI, FIRST), patients scored highly across all assessments for reporting sleep difficulties and poor quality sleep. On the other hand, the objectively-derived PSG measures shed a different light; patients' sleep profiles on the whole appeared to reflect 'normal sleep' parameters, presenting abnormalities on only one continuity variable (WASO), and in the architectural variables of %WAKE and REM latency.

It is therefore of interest to explore this discrepancy further. To evaluate the level of concordance between the two assessment modalities; self-reported measures of sleep based on the sleep diary; and the objectively derived Polysomnographic variables (PSG), a Pearson product-moment correlation was carried out to determine the level of agreement between corresponding sleep variables (TST, SOL, WASO and SE) derived from the two assessment modalities (based on an average of night 2 and night 3).

TST as measured by the PSG (453.91 ± 73.74 minutes) and TST self-reported on the sleep diary (448.68 ± 101.31 minutes) were significantly correlated, $r = .65$, $p < .01$, indicating a strong positive relationship between objectively derived (PSG) measures of total sleep time and total sleep time as self-reported (sleep diary) by patients (See table 7.4). Patients were therefore accurately estimating their sleep duration. However,

there was a nonsignificant correlation of .21 (p = n.s) between SOL measured by the PSG and SOL self-reported on the sleep diary. There was also a nonsignificant correlation of .32 (p = n.s) between WASO measured by the PSG and WASO self-reported on the sleep diary, and a further nonsignificant correlation of .37 (p = n.s) between SE measured by PSG and SE derived from sleep diaries. This indicates that patients were overestimating the amount of time it took them to get to sleep and the amount of time they were spending awake during the night.

	Means[a]		**Correlation**	
Sleep Parameters	**PSG**	**Diary**	Pearson *r*	*p* (2-tailed)
TST (min)	453.91 (73.74)	448.68 (101.31)	.65	**.003**[*]
SOL (min)	22.47 (20.49)	33.95 (21.67)	.21	.379
WASO (min)	37.13 (24.32)	41.58 (56.48)	.32	.179
SE (%)	78.89 (13.51)	92.53 (4.18)	.37	.123

Notes: N =19 [a]Values are means; values in parentheses are standard deviations.*p < .01
TST, total sleep time; SOL, sleep onset latency; WASO, wake after sleep onset; SE, sleep efficiency; PSG, polysomnography

Table 7.4: Comparison of Sleep Parameters: PSG vs. Sleep Diary: Pearson Product-Moment Correlation Coefficients.

Patients appear to be misestimating their wake duration, sleep latency and overall sleep efficiency. This highlights the importance of accurate measurement of sleep to evaluate the severity of patients' sleep complaints, which is critical in being able to adequately *manage* sleep disturbances that are commonly reported by CFS patients.

7.4 Discussion

As previously mentioned, study 4 was carried out to determine the feasibility and acceptability of a comprehensive 3-night and 3-day sleep and cortisol assessment in CFS. In addition to determining feasibility, the study protocol also enabled the preliminary characterisation of sleep profiles in patients with CFS; including the assessment of sleep variables' temporal stability, and the level of concordance between the subjective and objective measures of sleep.

7.4.1 Sleep findings

Prior to the sleep assessment, patients self-reported their sleep as disturbed and of poor quality, as demonstrated by the retrospective measures. However, on initial examination of patients' sleep profiles, based on the objectively derived measures (PSG), on average they fell into the parameters of 'normal' sleep. However, the variability in values derived on each of the sleep parameters is of relevance; it highlights how a significant minority of the sample fell outside of the 'normal' parameters, a reflection of the heterogeneity of sleep, and is also characteristic of patient's sleep profiles as identified in the previous studies. For example, increased amounts of stage 2 sleep mirrors what has been shown in patients characterised by the second phenotype identified in the cluster analysis of CFS patients from study 3, (as described in Chapter 5), and its association with information processing, arousability and the perception of sleep in fibromyalgia patients has also been demonstrated (Perlis, et al., 1997). Alpha activity (a shallow form of sleep), has been associated with an increased tendency to arouse to external stimuli in fibromyalgia patients, and to the perception of more shallow sleep, but interestingly not related to pain (Perlis, et al., 1997). This increased arousability could be trans-diagnostic for functional symptoms; the tendency for patients to arouse more during sleep may result in more fragmented sleep, as suggested by Shneider-Helmert and Kumar (1995), which in turn has been implicated in daytime fatigue and nonrestorative sleep, (Stepanski et al., 1984), fundamental symptom complaints of patients with CFS.

Combining methods of sleep assessment enabled the examination of sleep variables derived from the different assessment modalities (subjective sleep diary vs objective PSG). Patients were accurate in their estimation of sleep duration. However,

estimations of wake duration and the time it took them to get to sleep were not concordant with the objectively derived measures. This finding mirrors the discrepancy found between subjective and objective measures of sleep, previously seen in CFS; Watson and colleagues (2003) demonstrated no differences between the healthy and CFS twins on objective measures of sleep abnormalities despite significant self-reported sleep complaints from the CFS twins. This suggests CFS patients require an objective assessment of their sleep pattern, and these objective methods, and the PSG and Actigraph have been shown to be feasible in this population. An overestimation of SOL and underestimation of TST, relative to objective measures, mirrors what is seen in patients with insomnia. Explanations for these important discrepancies have been offered by Perlis et al (1997), suggesting a potential preoccupation with sleep or cortical arousal during the onset of sleep. The presence of high frequency EEG activity around sleep-onset is associated with a range of *waking* cognitive functions, such as attention, perception, problem-solving, and memory, which results in blurred phenomenological distinction between sleep and wakefulness. However, the identification of such cortical arousal during the onset of sleep is measured by quanitative EEG (qEEG) and is therefore a consideration for future sleep studies.

Another finding of this feasibility study was that all sleep variables were shown to be stable across two nights of measured sleep. The PSG protocol therefore offers temporal stability and affords, if needed, the efficacy to carry out two rather than three nights of recording.

7.4.2 Conclusion

In addition to establishing protocol feasibility in this patient group, study 4 was also able to provide preliminary sleep results based on the data obtained from patients across the 3-day period. The study afforded the opportunity to establish a profile of sleep in patients. It also confirmed the temporal stability of sleep continuity and main architectural variables across two nights of assessment. Of note, variability of sleep was confirmed to exist in this population, and, as such, the establishment of a successful protocol for effective and thorough sleep assessment is a key advancement in this domain.

CHAPTER EIGHT
DISCUSSION

8.1 Introduction

This thesis intended to examine the role of sleep in CFS from a number of methodological perspectives, from the personal through to the biological. Firstly, a qualitative interview study with patients focused specifically on the patients' lived experience of sleep. This preceded an evaluation of patient sleep diaries and the examination of sleep quality and its association with key dimensions of the illness experience. A third study examined the largest PSG dataset of CFS patients to date, revealing a significant proportion of the sample had a PSD, and identified four sleep-specific phenotypes in the remaining patients. The final study combined subjective and objective methods of assessment and demonstrated feasibility of the most comprehensive sleep and cortisol protocol ever attempted in a group of CFS patients.

Importantly, the research has established that a range of research methods are possible and acceptable to CFS patients, and, the grounds have been established for a comprehensive protocol to assess sleep. It is evident from this work, and from existing sleep research in CFS, that sleep needs to be measured more effectively, and the feasibility study has demonstrated that this is possible. Further, by considering how sleep serves to exacerbate or maintain other symptoms in CFS patients, we can expand our existing theoretical models and integrate a fuller account of sleep into the interplay of social, behavioural, psychological and autonomic components that may contribute to this illness. These factors should be considered mutually, in both research and clinical settings when working with CFS patients to assess and manage/treat their sleep problems.

The following section will summarise the main findings of this biopsychosocial research programme, and will move on to revisit the biopsychosocial model and the specific role of sleep in CFS. The subsequent sections will describe a recommended gold standard protocol for sleep assessment in CFS, followed by the study limitations and the implications of this research programme for future clinical and research work.

8.2 Main Findings

The qualitative study highlighted how patients regarded their disturbed sleep as playing a key role in the maintenance of their symptoms and having a large impact on their quality of life; bodily pain, confusion and concentration problems were all exacerbated by poor sleep. Similarly, in the diary study, sleep emerged as a significant predictor of impaired daytime functioning; specifically, longer periods of wake time were associated with more daytime fatigue. In addition, afternoon napping (in combination with higher depression scores) was particularly detrimental to patients' objective cognitive functioning.

Sleep measured objectively via PSG in patients was shown to deviate from normal sleep parameters (Edinger, 2004). However, it is important to note that no *consistent* pattern in sleep abnormalities was identified. This lack of homogeneity in sleep complaints may be a reflection of the different phenotypes identified in study 3 (chapter 5). That study is the first to suggest, and identify, specific sleep-phenotypes in a large sample of patients with CFS. The critical finding here was that the sleep in those with CFS, without Sleep Apnoea or PLM Disorder, centred around four specific sleep-disturbed phenotypes, each group demonstrating a unique combination of sleep-specific complaints. These four sleep phenotypes are a crucial, albeit preliminary, finding, but may offer an indication as to why existing PSG studies with CFS patients may have gathered mixed results (Jackson & Bruck, 2012). Above all, the information from this cross-sectional study can be useful to inform, in conjunction with other assessments, actual clinical practice, discussed further in section 8.6.

Notably, the differential PSG findings from chapter 5 (marked objective sleep complaints) and chapter 7 (normal sleep) may be attributed to a potential "first-night effect" in the single night study. Alternatively, the discrepancies could be the result of sleep phenotypes, which were not accounted for in the mixed methods study (chapter 7). For example, a small % of SWS by one participant might be mirrored by a large % of SWS in another, and so averaging across the entire sample would blur extremes to give a relatively normal proportion of SWS.

Interestingly, when the subjective and objective methods were combined in the feasibility study, an evaluation of patients sleep derived from these measures discovered discrepancies between patient's retrospective evaluation of their sleep (baseline diaries & self-report sleep assessments prior to the study), and the objectively-derived measures (PSG) of their sleep continuity. Patients, despite being accurate in estimating their sleep duration, mis-estimated their sleep on all other continuity parameters. These discrepancies mirror what has been shown in previous sleep studies in patients with CFS (Watson et al., 2003; Neu et al., 2007), and this potential sleep-state misperception (SSM) may have implications for treatment, specifically, where sleep-based interventions such as CBT-I are effective in improving perceived sleep quality in patients.

A key underpinning message that emerged throughout all studies was the *heterogeneity* of patient's sleep problems. The variability in the nature and severity of sleep disturbances was first observed in the qualitative interviews with patients and continued to become apparent in the findings that developed throughout the trajectory of studies carried out. Analysis of self-reported sleep diaries (studies 2 & 4) demonstrated considerable variability in patients' sleep, and equally, the objectively derived sleep assessments (PSG; studies 3 & 4) established variance across each of the patient samples.

Taken together, the overall findings from this mixed methods research programme, demonstrate that sleep is a considerable issue in CFS. Importantly, the feasibility study that combined multiple methods of assessment, showed how a highly detailed protocol, combining a range of methods for sleep and cortisol assessment is acceptable to CFS patients. Ultimately this is the key finding, which suggests further research can feasibly apply this mixed-methods biopsychosocial sleep assessment, in an ambulatory setting with patients. However, it is debateable as to whether such a comprehensive and potentially costly programme of research would be commissioned and thus applied clinically. Perhaps the utilisation of effective self-report measures such as PSQI and ISI, are a more practical option to identify sleep complaints clinically without a PSG. Further, the ESS may offer a useful means of distinguishing between insomnia and hypersomnolence disorder (and identifying other PSDs) in patients in the clinic early

on, before moving on to consider implementing the complete mixed-methods assessment protocol.

8.3 Revisiting the model

To revisit the biopsychosocial model of CFS outlined in chapter 1, this model hypothesises that the combination of predisposing, precipitating and perpetuating factors serve to keep the condition going (Deary, Chalder & Sharpe, 2007). This model is particularly important when considering factors that might come into play in terms of mediating the exacerbation of sleep-related complaints in CFS. The perpetuating factors range from the physical, through to the behavioural, physiological and cognitive contributors, which may all serve to maintain symptoms, and disturbed sleep in particular. These factors are described below in relation to the study findings.

8.3.1 The role of sleep in CFS

Light sleep, restlessness and arousability

What has emerged throughout the findings of each of the studies presented throughout this thesis is the recurrent theme of 'light' and restless sleep, what might be expressed as *arousability* in patients. In study 1, most patients described frequently awakening during the night and over half of them considered their sleep to be disturbed by feelings of mental alertness. Interestingly, the second sleep phenotype identified in study 3 was also characterised by restlessness, a predominance of light sleep and feeling unrefreshed. This second phenotype displayed the highest percentage of stage 2 sleep and the highest number of arousals per hour, and markedly, this was the second largest group out of the four phenotypes. This stage 2 sleep has been associated with hormonal and autonomic dysregulation (Brandenberger et al., 2005) which are likely to relate to both higher levels of autonomic and cortical arousal which in turn play a role in inhibiting deep sleep. This links in with the concept of *arousability* and HPA axis dysfunction that has been shown in patients with CFS (Tomas, Newton & Watson, 2013). This warrants further investigation and future research should not only study cortisol but also the relationship between hormonal profiles and sleep (melatonin, cortisol) in patients. We have certainly shown that such mixed protocols are feasible.

REM Instability

REM sleep is the period by which learning and memory consolidation are believed to occur, it therefore seems plausible to consider this stage of sleep and how it may be involved in CFS, given this condition features key symptoms such as brain fog, memory and concentration difficulties. Also, in light of the findings from study 3 (chapter 5) where REM featured differentially between groups (i.e. longer REML and low amounts of REM in type 1, shorter REML and high amounts of REM in type 3), the concept of REM sleep instability (RSI) and its association with poor quality sleep (Riemann et al., 2012), might be a potential factor in keeping disturbed sleep going and in turn, impacting negatively on other symptoms, thus developing a perpetuating *cycle*.

The concept of RSI represents the most highly aroused brain state during sleep and appears the most vulnerable to fragmentation in individuals who demonstrate persistent hyperarousal. The instability of REM (i.e. increased micro- and macro-arousals during REM sleep) has been proposed as a contributor to the experience of disrupted and nonrestorative sleep, a result of enhanced arousal and more conscious perception of the environment during sleep (Riemann et al., 2012). REM sleep fragmentation over time can also lead to depression-like sleep abnormalities (REM sleep rebound) i.e. shortening of REM latency and increased REM density (Riemann, Berger & Voderholzer, 2001). RSI is also related to a reduced latency to the first REM cycle, in particular, these shorter REM latencies have been associated with depression (Palagini et al., 2013) and neurodegenerative diseases such as Parkinson's. Together, such disruptions in the normal sleep process might suggest that RSI may be an objective marker for these conditions.

The significance of vivid dreaming as highlighted by patients in the qualitative interview study (chapter 3) is also of interest. Vivid dreams are also observed in autoimmune conditions (i.e. Guillain-Barre syndrome (Cochen et al., 2005)) and is also associated with other CNS degenerative disorders (i.e. Parkinson's). Such instances highlight the biological nature of the dreaming state, and again emphasis architecturally, the importance that REM could have in CFS.

Coping and living

Overall, it is evident that patients utilise as much medical knowledge regarding CFS and their sleep as they can and in turn, utilise this information to maximise and manage their lifestyle. These more social factors became apparent in study 1 (chapter 3), factors that can have implications in the course and progression of CFS. Attempts at coping with sleep difficulties in conjunction with attempts at sleep-management were seen as additional "work" for patients already trying to manage their energy levels and pace daily activities. This was an additional contributory factor that created a disruption in the day to day living of these patients and mirrors the "illness burden" that is described by Bury (1982). Despite these attempts at self-managing their condition, the problems persist. As such, there is much scope to develop improved quality sleep interventions that would help patients to effectively *manage* their symptoms and thus *optimise* their lifestyle.

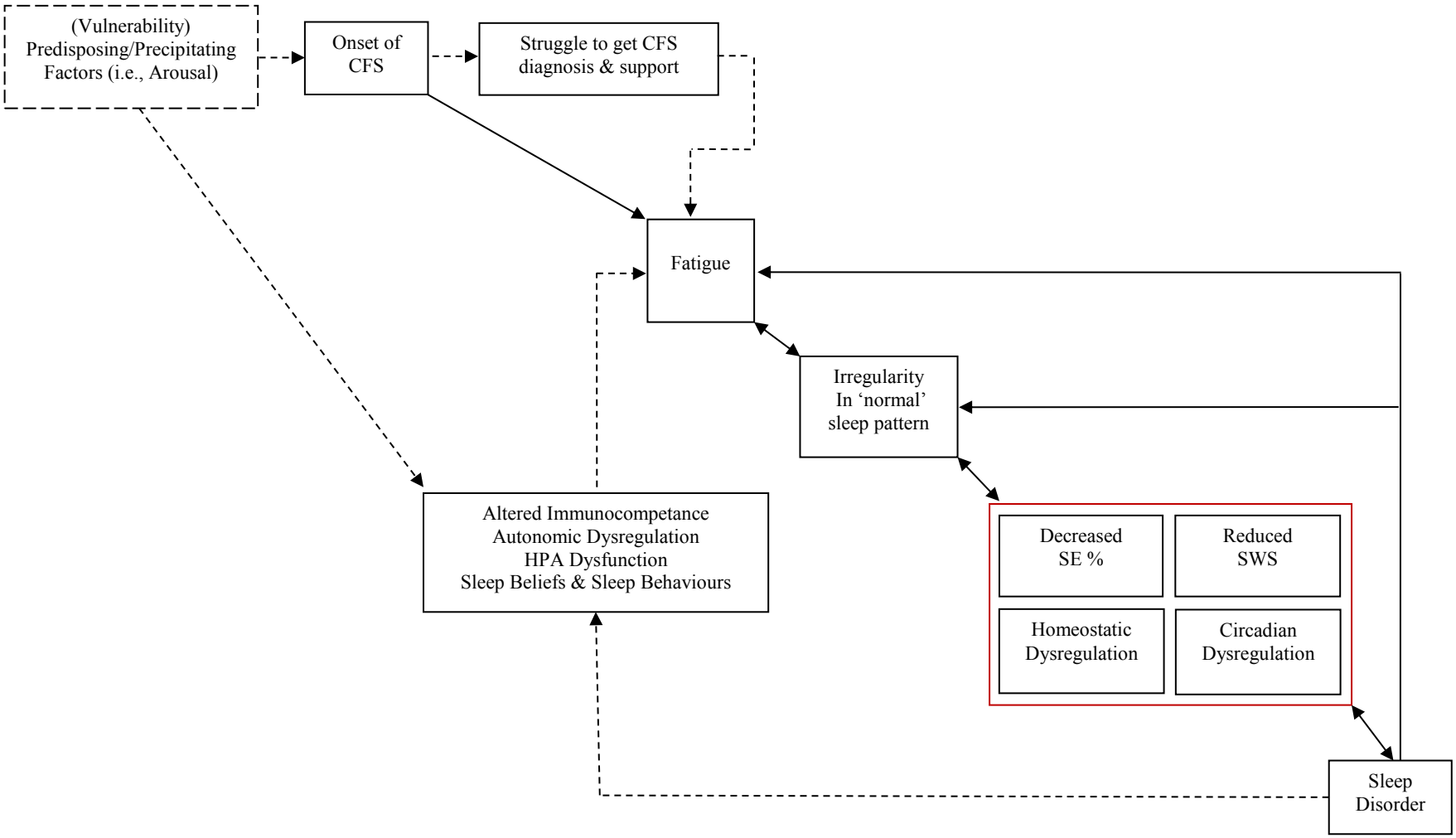

Figure 8.1: A theoretical model of sleep in CFS

Taking into account the range of findings presented throughout this thesis, and the existing biopsychosocial model of CFS, it is proposed that we should be mindful of a number of factors, which interact throughout the course of illness and ultimately keep disturbed sleep an ongoing problem in patients. In individuals who are more vulnerable to developing CFS (i.e increased arousal), sleep may act as a mediating factor between stress and disability and thus precipitate illness onset. A combination of socio-emotional factors (i.e. lack of support and understanding of the condition) in the early stages of the illness, and socio-economic factors (i.e. not being able to work, adapting to living on disability) that occur during the illness course, may contribute to CFS and feed into symptoms such as fatigue. A consequence of these factors being an irregular sleeping pattern which contributes to reductions in sleep efficiency, less deep (SWS) sleep, circadian and homeostatic dysregulation. Disruptions in these four features of sleep may lead to a sleep disorder which in turn reinforces the existing fatigue. The disordered sleep may also feed into HPA irregularities and autonomic dysregulation, and also have an impact on the cognitive and behavioural components of sleep with regard to patient's beliefs about their required amounts of sleep and the resulting sleep behaviours (i.e. SSM and napping). This reinforces the symptom of fatigue and thus the continuation of an irregular sleeping pattern (Figure 8.1).

Where other bio(psychosocial) models have been proposed (Maes et al., 2009; Harvey & Wessely, 2009), these emphasise the role of precipitants and the eventual perpetuation of symptoms in CFS. They focus on explaining how precipitating and perpetuating factors (i.e., prior stress, personality traits) induce the biological pathophysiology that accounts for specific symptoms. The proposed model above (Figure 8.1) therefore acknowledges such vulnerability factors that may predispose individuals to CFS. Prospective studies may wish to explore these further using birth cohorts, given it may infer arousability as a generic risk factor for ill health.

Considered together, this programme of studies of sleep in CFS has identified new biopsychosocial factors which may explain a process by which fatigue develops, is maintained and continues via a cycle of irregular sleeping patterns, biological dysregulation and cognitive and behavioural responses. This preliminary theoretical model of the *role* of sleep in CFS has been developed to integrate sleep into the picture, whilst being mindful to fit with existing models of CFS. The model might be

considered as a useful basis for CFS research and clinical work, helping to generate more multidisciplinary mixed methodology work to further understand this complex illness.

8.4 A gold-standard protocol

8.4.1 Measuring sleep in CFS

In a recent paper, Thabane et al (2010) note how the importance of pilot studies has been somewhat neglected. They argue that a true pilot study has the principle aim of assessing feasibility, not effectiveness. Our feasibility study was carried out in the same sense as Lancaster et al.'s (2004) and Thabane et al.'s (2010) use of the word pilot – a study on which a larger study can be built. The short answer to whether the 3-day sleep and cortisol assessment was feasible and acceptable to patients was "yes". In what had the potential to be too demanding for a patient group already experiencing a host of debilitating symptoms, the mixed methods study was shown to be acceptable to the group of CFS patients.

The findings are fundamental, because they provide an indication of the kinds of problems that might need to be addressed in the design of a larger study. The methods that were included in this protocol, measure and address the likely mediators of disturbed sleep that were discussed in the previous section; factors ranging from a possible instability in REM, increased amounts of light, restless sleep, through to functional impairment and a possible hypocortisolism. And so the success of this protocol is promising for a body of research that seeks to address this condition in a multidisciplinary fashion. The main issues and modifications for future work are highlighted and discussed in the following sections.

Recommendations

The understanding of sleep and its role in the early phases of CFS remains uncertain. This at times may coincide with the occurrence of misdiagnosis. As such, there is a necessity for thorough sleep assessment in this patient group to rule out other possible PSDs and to gauge the nature and severity of sleep complaints presenting in these

patients. The problems that have emerged from previous sleep studies in CFS have not only developed from the samples and diagnostic criteria difficulties, but quite notably the procedural aspects of these studies. Reflecting on this, it is essential to assess sleep in this patient group as early as possible and via the most effective and accurate means that are acceptable to patients.

To redress this, administering a standardised sleep diary during initial assessment stages would identify disturbed sleep early on. It is the early stages that are generally the most disturbed part of the illness, particularly in the coming to terms with the condition. Early assessment would enable the clinician to rule out a potential coexisting or misdiagnosed PSD, and even if no PSD is present, treating/managing sleep problems early on may help in the overall quality of life of patient in their experience of their CFS.

There are minor practical and technical issues to consider, as identified through reports by patients in the feasibility study, particularly in relation to pain and sensitivity to equipment and its application. It is recommended that as part of the study process, there should be a focus on working with the patients and their needs. Modifications to protocol may be required, for example, adaptations in the home, altering the type of paste used if needed, alternating the shoulder strap to a different side each night for comfort if needed.
Taking everything into account, these are some key elements to consider when measuring sleep in CFS;

- Consider the patient as an *individual*, each with their own unique collection of symptoms. Physical and mental limitations will differ for each patient. What one person finds comfortable, another may not. And so equipment and techniques of application should meet the tolerance of the individual.

- Be mindful of environmental and social factors that may restrict the usual conduct of assessment procedures, i.e, in an ambulatory setting, the household/bedroom may be limiting and social commitments of the patient could require scheduling modifications and advanced planning to be made.

- One night of PSG is enough to identify a PSD (Apnea and PLM) in patients, and tease apart the four other distinct sleep phenotypes. Two nights of PSG are sufficient to gain a basic characterisation of a patient's sleep. A third night, although ideal, is not compulsory, providing two consecutive nights of complete recordings are obtained.

- After ruling out PSDs, patients should be interviewed about their sleep (over the last month), given actigraphy (for identifying irregular sleep schedules) and a sleep diary (also measuring frequency and duration of *daytime* napping), to provide a subjective account that could be matched to the four phenotypes to inform a *tailored* treatment approach for the individual.

- In adjunct to direct measures of patient's sleep, there should be additional *biological* (cortisol), *cognitive* and *psychological* assessments, to clarify symptomatic correlates and any changes in severity.

Taken overall, the effective assessment of sleep in CFS patients has implications both in a clinical and research capacity. Working towards better modes of assessment and being mindful of different factors that could be contributing (i.e. taking on a holistic approach), can improve our understanding of sleep and its role in this illness.

8.5 Limitations

I have considered the limitations of the individual stages of this thesis as I have gone through each of the study chapters. However, it is worth reflecting on them as a whole prior to evaluating the collection of studies in their entirety.

As noted in chapter 1, there is much contention around the competing models that seek to explain CFS, and so, the identification of the multifactorial biosocial model to guide the trajectory of my research was perhaps a reflection of my own prior bias, partly based on a lack of other models integrating explanations from multiple angles. That said, the biopsychosocial model offered a flexible framework through which I was able to comprehend and describe the results that emerged over the course of studies, in a structured way.

In chapter three, despite the qualitative methodology that afforded the exploration of sleep-specific patient insights in great depth, it was not possible to express the full range of the topics raised in the narratives, topics that extended beyond the scope of sleep and its role in CFS. This should perhaps form the direction of further analyses of these transcripts, which could draw upon other elements of importance to the patients and their lived experience of their condition.

The shortcomings of the assessment-based studies of sleep in this programme of research, have been considered in their individual chapters (chapters 4, 5 and 6), but perhaps their imperfections are best addressed by ensuring that any future sleep studies in CFS, or sleep-based assessments with patients, are performed in light of the recommendations that are set out in section 8.6.3. These suggestions for conducting further work have been developed based upon a reflection of the issues identified throughout the research process, the limitations encountered and by being mindful of other factors that might present with CFS populations. Any future study, if performed as per the recommendations, will offer more robust data collection, given the potential for larger patient cohorts and more formal and detailed analysis of sleep variables amongst the patients under assessment.

Another flaw lays in partial data, mainly in chapter five and its respective phenotype PSG study findings. It was not possible to determine length of illness from the dataset. This would have been of interest in terms of identifying whether the sleep phenotypes are consistent across the illness course, i.e. to see if the phenotype is specific to the individual patient irrespective of illness duration or if the patients progressed through different sleep-phenotypes over time. This warrants further investigation using a longitudinal design.

As identified throughout the studies in chapters 3, 4 and 6, another flaw concerns the milieu of the results described. With several patients sleeping during the daytime as part of their *usual* sleeping pattern, there is the potential for this to have implications for their night-time sleep and in turn the ability to representatively evaluate it. This daytime sleep is a significant factor, given it may reflect the presence of a circadian dysregulation. Further, although the sleep diary utilised in the 3-day sleep assessment

feasibility study does provide a precise indication of the patient's perception of their sleep and fits with AASM criteria, it is missing the index of daytime napping, which, becomes a real issue in trying to interpret the data. Modification of this self-report tool (i.e. integrating a measure of frequency and duration of daytime naps into sleep diaries) should thus be a consideration for prospective sleep assessments. Finally, expansion of the objective PSG in terms of its recording duration, would ensure it captures patient's entire sleep period.

A further imperfection could be in the perspective of limited analyses performed on the sleep data. As discussed in chapters 6 and 7, whilst it was acknowledged throughout that the analysis of data from a feasibility study should be mainly descriptive (Lancaster, 2004), the nature of the analyses carried out on the cohort data might be considered premature; as such those data should be interpreted with a degree of caution. However, as expressed in chapter 7, these analyses were performed as a means of offering the reader a preliminary characterisation of sleep and cortisol in a *small* group of patients with CFS who undertook the first, most detailed protocol of its kind. Methodologically though, the study could be strengthened by a healthy control group, that would helpfully allow for results to be compared to healthy norms.. Ultimately, the statistical findings from this work should be used only as a means of informing the next stage of research and indicate what the parameters of interest for future research might be. The way this data will inform future work of our group is described in section 8.6.2. It will be the work of this subsequent study to demonstrate the effectiveness of utilising this protocol with a larger group of patients with CFS. Meanwhile, the reader is invited to take the data of the feasibility study as an early insight of what might be established in future studies of well-assessed sleep in CFS.

8.6 Implications (Clinical and Research)

Taking forward the findings that have been established throughout this thesis, derived from different modes of assessment, and the success of a protocol combining multiple sleep assessment modalities, it is possible to describe the implications for future work in the area of sleep in CFS. The following sections will consider implications for the clinical setting and research domain, in light of the research undertaken.

Clinical Implications

The therapeutic management of CFS is moving towards more *psychosocial* interventions. This mirrors recent work that shows the management of emotional distress is associated with lower levels of fatigue-related illness burden (Lattie et al., 2013). Considering the management of CFS from a multifactorial perspective, it is likely that this will lead to improved treatment outcomes for patients, given all potential mediators are targeted.

The best evidence treatments for CFS (GET and CBT) all involve a sleep management component, but it is not yet clear how significant the sleep component may be on its own, or how it specifically contributes to the efficacy of the overall treatments. As such, if sleep interventions such as CBT-I are utilised as an adjunct therapy to usual treatment in CFS, it could form a valuable component to the overall management process. It is therefore important that more attention is paid to sleep in the clinic. As a starting point, standardised sleep diaries should be incorporated into routine care to gauge the degree of sleep problems that present in the patient. The diary study, which established functional impairments via a self-reported sleep diary assessment, also provide the rationale to move forward with helping patients address and deal with the daytime complaints (i.e. cognitive symptoms), during treatment; tackling these coexisting symptoms will help to maximise quality of life for the patient. In chapter 6, patient's adherence to the consecutive completion of the sleep diaries is an important finding. These self-report measures of patient's sleep are vital in forming part of the therapeutic process in CBT-I. By continually reviewing the sleep diary, it is possible to monitor and reflect upon the improvements in sleep quality that occur as a result of sleep management during CBT-I.

Sleep is vital, but it is important to look at sleep in the broader context of other factors and the interplay between them all. Understanding the connection between the way the brain works and its connection with the biological processes that occur within the body is key. Most importantly the heterogeneity of CFS combined with the variability of sleep complaints identified highlights the necessity of patient-centred medicine. This way, the assessments and the treatments that follow, will be tailored to the patient.

It is important that the assessment process begins with the structured clinical interview, to understand the patient and their illness completely. This in combination with the use of a standardised diagnostic tool will be a move toward more standardised case definitions, which ultimately will aid the understanding of CFS and inevitably its treatment process. Given that the definition for CFS varies across different settings and countries between more standardisation will help both clinical and research work. Initiatives such as Jason et al's (2010) use of the DSQ as diagnostic tool in different settings (both research and clinical), will create an opportunity to increase the reliability of the criteria by reducing criterion variance.

Research Implications

Taken overall, the research findings demonstrate the usefulness of mixed methods of sleep assessment in CFS, and how these can be utilised to explore the condition in different ways. Ultimately, the *role* of sleep is only likely to be understood at its best by utilising the most effective measures available. First and foremost, there remains a lack of good quality assessment in CFS sleep research, and so utilising the range of methods established throughout the course of studies, would be a move forward methodologically in CFS sleep-related research. We have established a successful protocol for the comprehensive assessment of sleep and cortisol in patients with CFS, demonstrating the feasibility of using a range of assessment modalities Patient's fidelity to this complex protocol and 0% attrition rate is promising for recruitment in future studies.

As identified by the qualitative interview study, CFS affects not only the patients, but also immediate family members. This highlights the importance of considering others as part of the research process. Interview-based research in particular has the potential to include accounts from family members or friends, which could offer more insight into the impact of CFS as a whole and the role of sleep in particular.

The necessity for more objective tests for daytime sleep is warranted, given daytime sleep is often a *usual* pattern of sleep in CFS patients. The discouragement of napping during the course of sleep management interventions such as CBT-I, is a reflection of the negative impact such sleeping behaviours pose to the homeostatic drive (Manber et

al., 2012). Although research indicates brief naps (< 15min) can be beneficial to cognitive performance, it is the longer duration of napping and the circadian placement of these naps (i.e. when the nap is taken with respect to the 24h circadian rhythm) that are considered to have a negative impact upon the homeostatic sleep drive (process S), and thus impair the quality of night-time sleep (Lovato & Lack, 2010). This also has a reciprocal effect for daytime functioning the following day. Thus napping is a key factor and should be measured as part of the overall assessment of sleep in CFS.

Objective sleep studies in CFS may wish to also consider *daytime* PSG assessment, thus extending the monitoring of patient's sleep to ensure their entire sleep period is characterised. Given objective measures are key, sleep-based CFS research may also want to consider MSLTs or maintenance of wakefulness tests (MWT), this would address the difficulties that remain with regard to separating the symptoms of fatigue and daytime sleepiness (Neu et al., 2008); this is also pertinent in that these two complaints have different implications for diagnosis and treatment. In addition, the actigraph could also be used to disentangle discordance between subjective and objective sleep report, as it was shown to be possible to combine the methods, as detailed in chapter 6.

The first night effect has been regarded an issue in CFS (Le Bon, 2003) albeit a tentative one, and so two nights of PSG assessment are likely to be better than one. Adding to this, the stability of the sleep continuity and main architectural polysomnographic variables in the feasibility study is noteworthy. It provides the confidence for further research to be able to gain a true characterisation of patient's sleep via two rather than three nights of assessment. As well as this, we have demonstrated that a single night of PSG assessment is sufficient to identify patients as meeting criteria for a PSD and thus enable the exclusion from subsequent analyses in the research. Thus, it is possible after only one night of assessment, to tease apart a PSD from CFS, and this is also key in a clinical setting as early identification of PSD prevents misdiagnosis, enables the direction for correct treatment and prevents incorrect treatment delivery.

Future Directions; clinical and research work

Establishing the feasibility of the detailed sleep assessment protocol in patients forms a central part of informing the design and development of an intervention development project. Moving forward from a therapeutic viewpoint, it is of interest to determine the efficacy of sleep treatments in CFS, a group where sleep problems have been objectively confirmed.

The next proposed study of our group will identify and characterise in detail the sleep-related disturbances in CFS patients, and systematically develop and pilot a tailored sleep management intervention study to reflect these. By delivering a CBT-I intervention to CFS patients, it will be possible to determine whether CBT-I is an effective treatment in itself for improving perceived sleep quality, and if this in turn leads to improvements in daytime physical and mental symptoms in this condition. Conducting this CBT-I study will thus serve as a component analysis of existing CBT and activity management strategies that incorporate sleep management.

There is currently no research on the efficacy of CBT-I alone in CFS. Instead, we can make assumptions based on the effects of CBT-I in patients with Fibromyalgia (FM), and these have been shown to be beneficial, both in improving patients' subjective sleep, with additional favourable outcomes for pain and mental wellbeing (Edinger et al., 2005), but also in objectively increasing deep sleep and improving sleep efficiency in these patients (Sánchez et al., 2012). A recent randomised controlled trial also confirmed the effectiveness of CBT-I in FM, reporting significant improvements to sleep, fatigue and daily functioning, post-treatment, and emphasising the usefulness of CBT-I in the multidisciplinary management of this condition (Martínez et al., 2013). Based on these relatively new studies, it seems that CBT-I could offer a promising intervention for sleep disturbance and even daily functioning in CFS. CBT-I involves sleep hygiene/management components (i.e., establishing a consistent sleep routine, avoiding napping), and we know that these are necessary and already integrated into current CFS management programmes (GET, CBT), but is this sufficient? And might CBT-I be more effective? It will be interesting to assess how much it has an impact on the overall therapy for CFS.

The recent launch of the UK ME/CFS Research Collaborative (CMRC) (Krishna, 2013) shows how the government and associated funding bodies are making a commitment to pursue research into the understanding and treatment of this debilitating condition. If research progress is made, it is possible that we will see an enhanced understanding of CFS from a number of angles (HPA axis dysregulation, immune processes, symptoms and psychological aspects of CFS including sleep). Such facets should be examined by drawing upon multiple disciplines to determine the interplay of the factors that serve to maintain CFS. This may eventually lead to the furthering our understanding of the underpinning a etiology, which remains incomplete Future work should also consider CFS not a unitary construct but a syndrome that represents multiple illnesses with different causes albeit with similar symptom patterns.

8.7 Conclusions

CFS remains a complex and somewhat heterogeneous condition and equally, the sleep-related complaints that present in patients reflect this. Each patient experiences their very own personal combination of symptoms and, through a range of social, behavioural, cognitive and biological factors; these are maintained and often exacerbated. It is in this light, that the importance of the theoretical biopsychosocial model became crucial to the studies carried out in this thesis, (Deary, Chalder & Sharpe, 2007; Moss-Morris, Deary & Castell, 2013). This multi-factorial model enabled a structure of research to be established; utilising different assessment techniques that addressed sleep from a number of angles. The model was also fundamental when examining the data from these studies. It helped to understand how the sleep findings might feed into a model of mediating (biological, psychological and social) factors, and thus better explain the role of sleep in CFS.

The preliminary sleep findings from the feasibility of sleep protocol study mirrored the course of the other studies: all demonstrated the variability of sleep and sleep problems in CFS. As such, the establishment of a successful protocol for effective and thorough sleep assessment is key. It enables the identification of a PSD at an early stage. It affords a much more detailed examination of continuity and main architectural sleep variables than is currently being performed in research and in the clinic. Importantly,

the success of the three-night mixed-methods sleep protocol in patients underscores that methodologically, these (necessary) procedures and equipment are not regarded as invasive or detrimental to patient's experience of their CFS.

As suggested, sleep and its assessment in CFS needs to be considered from a number of angles, both clinically and through future research. Likewise, the management of CFS should be multi-disciplinary, addressing the biological, behavioural and psychological components that shape this condition. Specifically, any sleep management intervention should be delivered with the heterogeneity of sleep in CFS in mind, considering the nature of sleep disturbances presented by the individual prior to delivering treatment.

Above all, CFS continues to be only partially understood. A full understanding can only develop after we characterise this condition at every level from the biological through to the social, and understand how these mechanisms interact. By focussing in depth on one aspect - sleep - a greater understanding of the condition as a whole has emerged. As highlighted throughout, there is no cure for CFS, only symptom management. It is hoped through the dissemination of this work, and the insights gained, that this work will not only inform future research practice but also lead to enhanced therapeutic delivery, with more focus on the central role of sleep in CFS. This can only be to the benefit of those suffering from CFS.

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APPENDICES

APPENDIX A: Chapter 2 Table of study characteristics: Sleep in CFS

Author, Year	Methods	Population	Sample Size	Study Outcomes	Conclusions Drawn
Morriss et al., 1997	**Self-report**	Oxford Diagnosed CFS Patients	69 CFS without psychiatric disorder 58 CFS with psychiatric disorder 38 patients with chronic depressive disorders 45 healthy controls	Higher prevalence of sleepiness and daytime naps in CFS patients compared to depressed subjects and healthy controls. Periodic limb movements are more common in CFS patients than controls.	Difficulty maintaining sleep is the principle sleep complaint in CFS patients. Disrupted sleep appears to complicate the course of CFS and sleep complaints are unrelated to depression/anxiety in CFS.
Unger et al., 2004	Self-report	Fukuda diagnosed CFS	339 (24 met the Fukuda criteria) others fell into fatigue groups.	The Sleep Assessment Questionnaire (SAQ) revealed CFS subjects had increased risk of abnormal scores on the non-restorative and restlessness factors compared to non-fatigued, but not for factors of sleep apnea or excessive daytime somnolence.	Consistent with studies finding that, while fatigued, CFS subjects are not sleepy. SAQ factors describe sleep abnormalities associated with CFS and provide more information than the Epworth score.

Mariman et al., 2012	Self-report	Fukuda diagnosed CFS	415	High mean ESS and PSQI values (daytime sleepiness and poor sleep quality). Very low sleepiness and high levels of sleep disturbance clustered together, as well as high sleepiness and low sleep disturbance.	The associations at both ends of the ESS spectrum correspond to a clinical profile of insomnia and hypersomnia (insomnia – complaints of sleep disturbance associated with increased alertness; hypersomnia – excessive daytime sleepiness persists despite normal nocturnal sleep)
Ohinata et al., 2008	**Actigraphy**	Children (16-18) with Fukuda diagnosed CFS	12 CFS children 12 age-matched controls	Compared to controls, total sleep time was longer in CFS children and physical activity lower. Also the CFS children with irregular sleep had an impaired sleep/wake cycle, caused by disrupted night sleep and daytime napping.	Using actigraphy, several characteristics of sleep patterns could be identified. Actigraphic analysis is useful in detecting sleep/wake problems in children with CFS.
Rahman et al., 2011	Actigraphy	Fukuda diagnosed CFS	15 CFS 15 controls	Activity levels throughout the day did not differ between groups, although afternoon activity levels increased evening levels of fatigue in the CFS group. Patients and controls did not differ on sleep timing, duration or quality, so no evidence of impaired circadian rhythm in CFS.	Activity-symptom relationship demonstrated in a naturalistic setting (increased activity associated with increased symptoms of fatigue in CFS patients)
Buchwald et al., 1994	**PSG** (1 night)	50% met Holmes and modified CDC criteria for CFS (Schluederberg et al., 1992)	38 CFS 21 Non-CFS fatigue patients	No differences found in sleep symptoms or sleep disorders when comparing patients who met the CFS criteria and those that did not. Sleep disorders were equally as common in patients who did (82%) and did not (81%) meet the criteria for CFS.	Chronically fatigued patients have coexisting sleep disorders that are not considered to be associated with meeting the criteria for CFS.

Manu et al., 1994	PSG (1 night)	CFS patients who met modified CDC criteria for CFS (Schluederberg et al., 1992) & patients with chief complaint of fatigue	15 CFS 15 other chronic fatigue	Majority of CFS patients had nonpsychotic major depression – but not considered associated with alpha-delta sleep	Alpha-delta sleep is not considered a marker of CFS but may contribute to the illness of nondepressed patients with CFS (as was more common among patients who had chronic fatigue without major depression)
Fischler et al., 1997	PSG (2 and 3 nights)	Oxford Diagnosed CFS Patients	49 CFS 20 Healthy Controls	Sleep initiation problems – namely a significantly longer SOL was shown in CFS group compared to controls. Sleep continuity disturbances were characterised by significantly higher percentage movement time, number of awakenings greater than 1 min and number of stage/shifts per hour.	Both initiation and continuity anomalies contributed to significantly lower sleep efficiency index in CFS compared to controls. Sleep initiation and sleep maintenance disturbances are evident in CFS compared to healthy controls. This is also the first study to show significantly lower percentage stage 4 sleep in CFS.

Stores et al., 1998	Home PSG (1 night) case-control design	Teenagers with CFS (internationally agreed criteria – adapted fatigue duration for teenagers)	18 CFS 18 matched controls	Compared with controls, CFS teenagers showed significantly higher levels of sleep disruption (both brief and longer awakenings).	Disruption of sleep may contribute to daytime symptoms of young people with CFS.
Le Bon et al., 2003	PSG (2 nights)	Fukuda diagnosed CFS (without primary sleep disorders, 46/83 had at least one psychiatric diagnosis)	83	Significant observed differences from night 1-2 in TST, SE, NREM Sleep, SOL and Number of Sleep Cycles. Outcome attributed to first night effect.	CFS to be added to list of conditions where a clinically significant habituation effect takes place.
Ball et al., 2004	PSG (2 nights)	Fukuda diagnosed CFS	22 CFS-discordant twin pairs	No abnormalities observed in sleep architecture among CFS twins.	No strong evidence for role of abnormalities in sleep architecture in CFS. Co-twin control methodology highlights Importance of selecting well-matched control subjects.

Reeves et al., 2006	PSG (2 nights)	Fukuda diagnosed CFS	43 CFS 43 non-fatigued controls	No confirmation of statistically significant associations between sleep parameters and CFS.	Sleep abnormalities an unlikely contributor to pathophysiology of CFS. The illness may include sleep-state misperception.
Armitage et al., 2007	PSG (3 nights: sleep assessed night 2, sleep delayed by 4hrs night 3)	Fukuda diagnosed CFS	13 CFS-discordant twin pairs	CFS and healthy co-twins did not differ on slow wave activity.	Only after sleep challenge did CFS twins show less slow wave activity than co-twins.
Le Bon et al., 2007	PSG (2 nights – without habituation)	Fukuda Diagnosed CFS (without primary sleep/psychiatric disorders)	28 CFS 27 Sleep Apnea-Hypopnea syndrome patients 27 Healthy Controls	Stage 4 and SWS are more elevated in CFS.	Increase of deep sleep over light sleep in 'pure' cases of CFS
Kishi, et al., 2008	PSG (1 night)	Fukuda diagnosed CFS	22 CFS 22 Healthy Controls	Altered sleep-stage transition patterns. Lower REM to non-REM sleep transition in CFS than controls.	Normal continuation of sleep in light or REM sleep is disrupted in CFS.
Armitage et al., 2009	PSG (3 nights: only night 2 was used for purposes of	Fukuda diagnosed CFS	13 CFS-discordant twin pairs	No evidence of macro- or micro-architectural changes. Power spectral characteristics of sleep EEG do not differentiate twins with CFS from their healthy co-twins.	The sleep measures utilised cannot explain the chronic disabling fatigue experienced by the CFS twins.

	this study – night 3 reported by Armitage et al., 2007)				
Decker et al., 2009	PSG (2 nights)	Fukuda diagnosed CFS	35 CFS 40 Non-fatigued matched Controls	Sleep architecture did not differ (published as Reeves et al). Power spectra of EEG frequencies reduced in REM sleep	Reduced spectral power observed in CFS demonstrates impaired sleep homeostasis.
Kishi, et al., 2010	PSG (1 night)	Fukuda diagnosed CFS	14 CFS (without FMS) 12 CFS (with FMS) 26 Healthy Controls	Transitions between sleep stages differ between CFS (alone) and CFS (with FMS).	Suggests differences between CFS and FMS relating to different problems of sleep regulation
Krupp et al., 1993	**Mixed Methods** (Subjective reports and PSG (1 night))	Holmes diagnosed CFS patients	72 CFS 40 Healthy controls (PSG performed in 16 CFS)	CFS had significantly elevated seep disturbance, depression and fatigue (from subjective reports) 6 – major depression (only 2 with shorter REM latencies) 1 - CFS diagnosis changed to narcolepsy 4 – PLMD	In addition to severe fatigue and depressive symptoms, subjective sleep disturbance is common in CFS and some CFS patients may have sleep disorders.

Morriss et al., 1993	Mixed Methods (Subjective reports and home PSG (1 night) case-controlled)	Fukuda diagnosed CFS	12 CFS 12 matched controls	CFS patients spent more time in bed but slept less efficiently than controls, and had more time awake after initial sleep.	The disordered sleep in most CFS patients is likely to contribute to day time fatigue
Sharpley et al., 1997	Mixed Methods (Subjective reports and home PSG (1 night))	Fukuda diagnosed CFS (without primary sleep/psychiatric disorders)	20 CFS 20 matched controls	Complaints of poor quality sleep and unrefreshing experience of sleep. No sig abnormalities but more time in bed trying to sleep making sleep less efficient.	Abnormalities in sleep continuity only occur in a minority of CFS patients. Abnormalities of sleep not likely to be important in maintenance of symptoms.
Fossey et al., 2004	Mixed Methods (Subjective reports and PSG (1 night))	Fukuda diagnosed CFS	37 CFS 24 Narcolepsy 24 Controls	58% CFS group had previously undiagnosed primary sleep disorder. High rates of nonrestorative sleep in CFS group.	Primary sleep disorders (i.e. apnea, RLS, PLMD) are overlooked /misdiagnosed in CFS. Psychological disturbances may be result of living with poorly understood condition.
Watson et al., 2004	Mixed Methods (Self report and PSG (2 nights))	Fukuda diagnosed CFS	22 CFS-discordant twin pairs	CFS twins experienced more subjective sleepiness than their healthy co-twins despite similar mean sleep latencies.	CFS patients may mistake their chronic disabling fatigue for sleepiness. Future studies should examine mechanisms of the discrepancy between self-reported and measured sleep parameters in CFS.
Guilleminault et al., 2006	Mixed Methods Self-report scales and PSG (1 night))	Patients with unexplained chronic fatigue	14 unexplained fatigue 14 Controls	Complaints of chronic fatigue and unrefreshing sleep associated with abnormal CAP rate.	Abnormal sleep progression and NREM instability. Patterns related to undiagnosed sleep-disordered breathing

Majer et al., 2007	Mixed Methods (Self report and PSG (2 nights))	Fukuda diagnosed CFS	35 CFS 40 non-fatigued controls	CFS reported more sleep problems yet objective measures of architecture did not differ between groups	CFS patients may monitor their sleep behaviour more closely, which may contribute to their perceived sleep problems.
Neu et al., 2007	Mixed Methods (Self report scales and PSG (2 nights without habituation))	Fukuda diagnosed CFS (without sleep or mood disorders)	28 'pure' CFS 12 controls	PSQI – CFS significantly poorer subjective sleep quality than controls. SEI and amount of SWS did not differ between groups	Either a sleep quality misperception is present in CFS or the neurophysiological disturbances involved in the nonrecovering sensation are not expressed by sleep variables such as SEI or sleep stage distributions.
Van Hoof et al., 2007	Mixed Methods (Self report and PSG (2 nights))	Fukuda diagnosed CFS	48 CFS	Show extended onset latency compared to Fischler et al., (2007) patients. The high alpha-delta intrusion (% alpha waves in SWS) group reported the most self-reported anxiety	Shows extended sleep latency – as already suggested in the literature. Alpha-delta intrusion is associated with anxiety.
Neu et al., 2008	Mixed Methods (Self report scales and PSG (2 nights without habituation))	Fukuda diagnosed CFS (without sleep or mood disorders)	16 CFS 13 Apnea-Hypopnea syndrome patients 12 Controls	Higher levels of fatigue, anxiety and depression in CFS group. Also high level of idiopathic microarousal index in CFS group– almost as high as the SAHS group (even after PLMD and apnea were excluded – a usual contributor). Subjective scales showed CFS the most tired, SAHS most sleepy.	The data confirm the likely overlap in the perception of sleepiness and fatigue. This combined with discordance between subjective and objective sleepiness warrants the need to find more precise tools/analysis.

Togo et al., 2008	Mixed Methods (Self report and PSG (1 night))	Fukuda diagnosed CFS (without psychiatric disorders)	26 CFS (14 with coexisting fibromyalgia) 26 controls	CFS patients showed sleep disruption. They showed significantly reduced total sleep time, reduced sleep efficiency and shorter bouts of sleep than controls.	The sleep disruption may explain the fatigue, unrefreshing sleep and pain in this patient group.
Creti et al., 2010	Mixed Methods (Self-report scales, PSG (1 night), Actigraphy)	Fukuda diagnosed CFS	49 CFS	CFS reported poor sleep quality, non-refreshing sleep and daytime fatigue/sleepiness. But self-report TST was parameter most consistently reflected by objective measures. 65% met criteria for chronic insomnia. High percentage also had apnea.	Sleep apnea syndrome is considered a comorbidity of CFS rather than an exclusion criterion.
Schoofs, et al., 2004	**Qualitative** telephone interview	Fukuda diagnosed CFS (and FMS)	16	Social support, unlike healthcare support is related to quality of life	Subjects suffering from CFS/FMS do not experience high levels of social support. Physician-specific themes.
Anderson & Ferrans, 1997	Qualitative semi-structured interviews	Holmes diagnosed CFS patients	22	Explained quality of life in CFS	Cognitive dysfunction and disruption in social activities main concern.
Clarke, 1999	Qualitative Interviews via telephone	Non-specified diagnosed CFS	59	Gender differences in experience of CFS and treatment by medical profession	Main symptoms experienced –extreme fatigue, disabling pain and cognitive problems. Treatment options offered, varied by gender.

Lovell, 1999	Qualitative Interviews	Oxford Diagnosed CFS Patients	12	Symptoms Possible Causes	Main symptoms reported were debilitating fatigue, unrefreshing sleep, muscle and joint pain.
Soderlund, et al., 2000	Qualitative Focus Groups	Fukuda diagnosed CFS	12	Symptom Experience	Severe exhaustion and pain perceived as related to memory and concentration and sleep disturbances.

Notes: ESS, Epworth sleepiness scale; PSQI, Pittsburgh sleep quality index; SAQ, sleep assessment questionnaire; TST, total sleep time; SWS, slow wave sleep; SAHS, sleep apnoea-hypopnea syndrome; EEG, electroencephalography; SE, sleep efficiency; SOL, sleep onset latency; NREM, non-rapid eye movement; REM, rapid eye movement; CAP, cyclic alternating pattern; PLMD, periodic limb movement disorder; RLS, restless legs syndrome.

APPENDIX B: Chapter 3: Qualitative Interview Study Patient Consent Form

Qualitative Interview Informed Consent

v 1.0 03.03.2012

Interviews to explore the experience of sleep in CFS

Please initial in the appropriate box and sign below if appropriate for you

1. I confirm that I have read and understand the information sheet (Version 1.0, dated 03.03.2012) provided for the above study and have had the opportunity to ask questions. ☐
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. ☐
3. I understand that relevant sections of the data (including personal details) collected during the study may be looked at by responsible individuals from regulatory authorities or from the Newcastle upon Tyne NHS Foundation Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. ☐
4. I understand that if a significant disclosure is made, then appropriate action will be taken to ensure my safety, as a participant taking part in this study. ☐
5. I understand that I am free to stop the interview at any time, or refuse to answer any question, without this affecting my current or future care. ☐
6. I understand that notes will be taken and the session will be audio recorded and that these records will be anonymised and confidentially stored by the interviewer. ☐
7. I agree to take part in the above study. ☐

Name of participant		Date		Signature
Name of researcher		Date		Signature

One copy of this signed consent form will be kept by the researcher, one copy will be placed in your medical records and one copy will be given to you for your own records.

APPENDIX C: Chapter 3: Qualitative Interview Schedule

Interviews about Sleep in CFS:

Interview Schedule for Patients

Researcher makes introductions.

Hello, my name is Zoe & I am a PhD researcher from Northumbria University. The focus of my research is Chronic Fatigue Syndrome, otherwise called M.E. and I have a specific interest in sleep problems that people experience with the condition. Firstly, how would you like me to refer to your condition [CFS/ME/post-viral fatigue]?

You have kindly agreed to take part in an interview to talk about your experience of [CFS/ME]. The purpose of the interview will be to discuss your experience of this condition in some depth, with particular attention to your experience of sleep. This study will help us to better understand the links between this condition and sleep disturbances, which will help people like yourself – by allowing for more informed diagnoses & treatments.

The interview will last no longer than 90 minutes and if at any point you wish to stop the interview you may do so. Likewise, If you feel you do not want to speak about a particular topic or respond to a question then that is also fine. As you know, the interview will be audio recorded; however, these recordings are kept completely anonymous and in no way linked to you as an individual. All recordings will be transcribed following the interview and these too will be in no way linked to your name, but instead a code. I will switch on the Dictaphone now.

Having read the information sheet, do you have any questions before we begin?

Interview Questions:

1. **Can you please tell me a bit about your experience of having CFS/ME.**
   How does it make you feel?
   How does it affect your lifestyle/behaviour/ activities?
   How does it affect your relationship with others?

2. **What 3 things bother you the most about having CFS/ME?**
   How often do you experience this?
   How much of a problem is it for you?
   How does it affect your daily activities/behaviour?

How does it affect your relationships with others?

What makes this [better/worse]?

What kinds of things do you currently do to manage this?

3. **Can you describe a <u>typical</u> 24 hours..**
   - **Good**
   - **Bad**

   When you wake up, how do you feel, what do you do, do you doze, nap in day? What do you do next?

   Time you start to feel tired, time to bed, difficulty getting to sleep, things you do to help yourself get

   off to sleep, length of time sleeping, quality of sleep, interruptions during sleep, up during night, what

   you do when you're up in night, time awake in morning, how you feel when you wake, what you do

   when you get up… what next..

4. (If struggling to get to sleep) **What kind of things do you do to manage this?** What strategies would you use to help? (bed early, book, snack, TV, herbal remedy, medication, meditative breathing/relaxation techniques, tea/coffee, lie in, napping in day)

   Sleeping environment (pitch black, night light, full light, bed partner)?

5. **How is your sleep now compared to before having CFS/ME?**

   Any problems you encounter whilst sleeping that you did not experience <u>before</u> having CFS/ME (if not already discussed)?

6. **Have you looked up sleep problems on the Web/had any advice?**
7. **Have you ever raised sleep as an issue with your GP/clinician?**
8. (Beliefs/Expectations) **How much sleep do you feel you need a night in order to function?**
9. **How much sleep do you actually get on average a night?**

That's the end of my questions – thank you very much for sharing your experiences & thoughts with me about this. But before we finish, is there anything else important that I might have missed?

Thank you very much for your time today. If you have any queries following today, please feel free to contact me.

APPENDIX D: Chapter 4: 14-day Sleep Diary

SLEEP DIARY

Name _____

Date Started _____ Day of Week _____

Do you ever, at any time, take any medication (prescribed or purchased over the counter) to aid your sleep? ☐ Yes ☐ No
If yes, please detail name of medication, dose & time on back page.

Instructions:

- Please leave diary near your bedside
- It is important that you fill out this chart each morning
- Mark your diary in the following way:

ACTIVITIES

A - each alcoholic drink
C - each caffeinated drink includes coffee, tea, chocolate, cola
P - every time you take a sleeping pill or tranquilliser
M - meals
S - snacks
X - exercise
T - use of toilet during sleep-time
N - noise that disturbs your sleep
W - time of wake-up alarm (if any)

SLEEP TIME (including naps)

↓ - mark with a "down" arrow each time you got into bed.

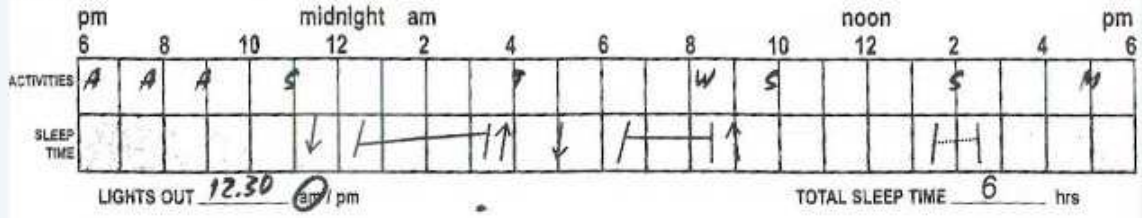
↑ - mark with an "up" arrow each time you got out of bed

| - mark with a line the time you began and the time you ended your sleep; then join the lines to indicate sleep periods.

| - mark with a line the time you began and the time you ended any naps, either in the chair or in bed; then join up lines with broken line to indicate nap periods.

Please describe (on the back page) any events that influenced your sleep.

Example:



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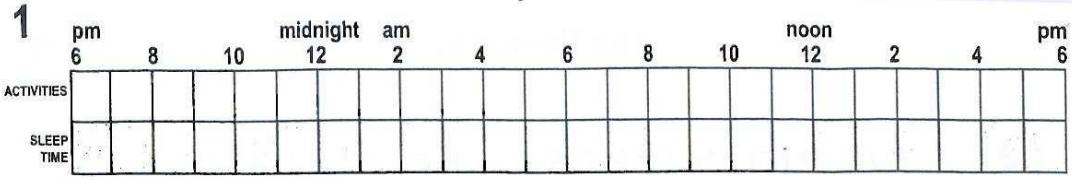
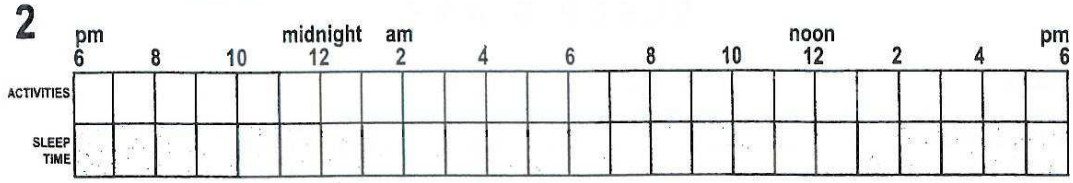


LIGHTS OUT_____ am / pm TOTAL SLEEP TIME _____ hrs

2



LIGHTS OUT_____ am / pm TOTAL SLEEP TIME _____ hrs

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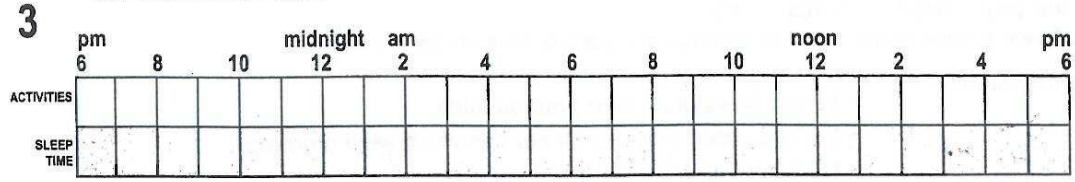
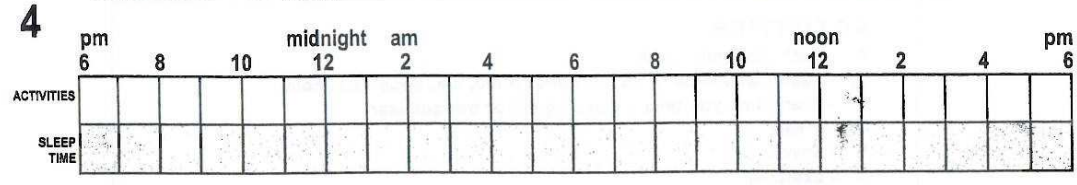


LIGHTS OUT_____ am / pm TOTAL SLEEP TIME _____ hrs

4



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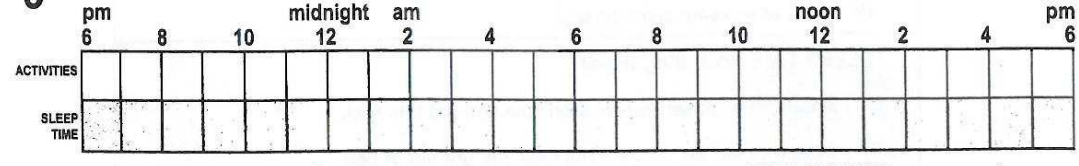

LIGHTS OUT_____ am / pm TOTAL SLEEP TIME _____ hrs

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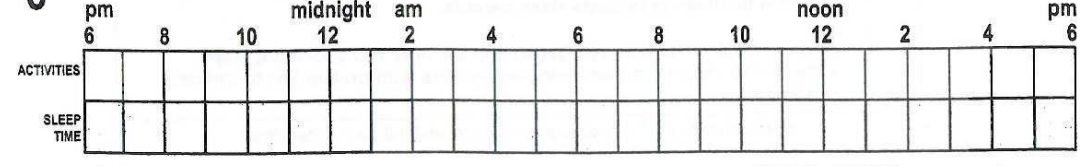

LIGHTS OUT_____ am / pm TOTAL SLEEP TIME _____ hrs

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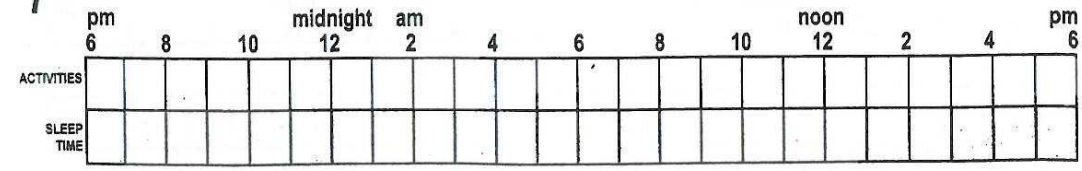

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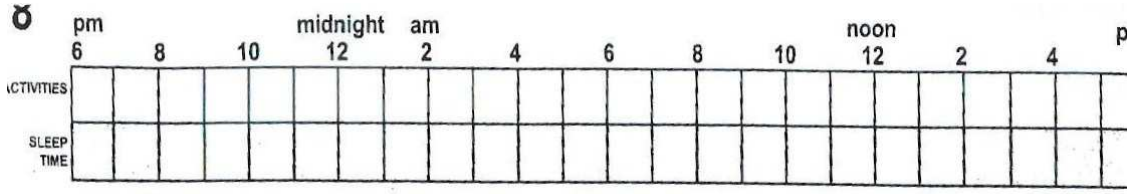

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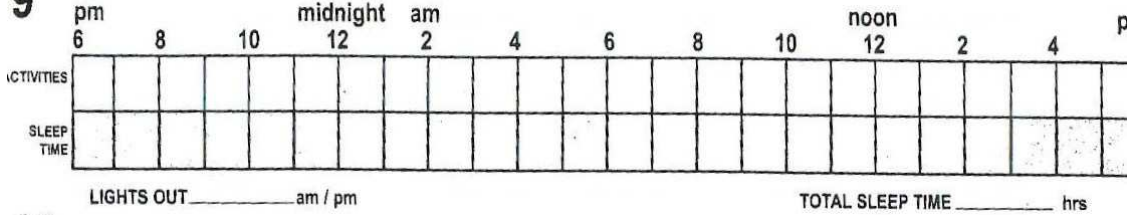
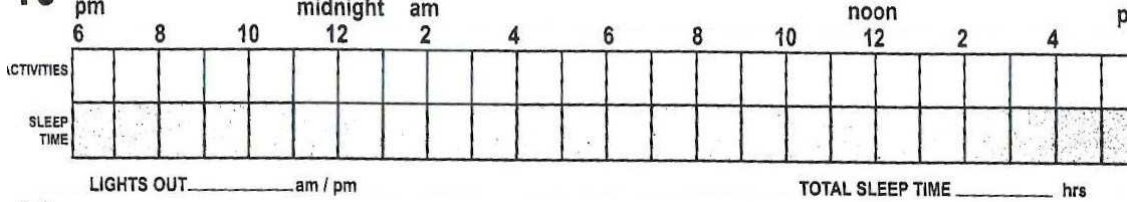


LIGHTS OUT _____ am / pm TOTAL SLEEP TIME _____ hrs

10



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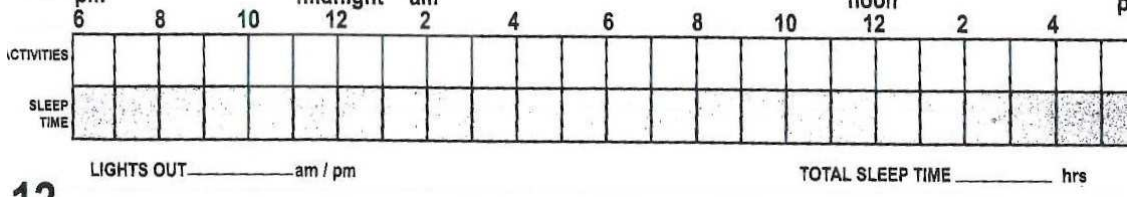
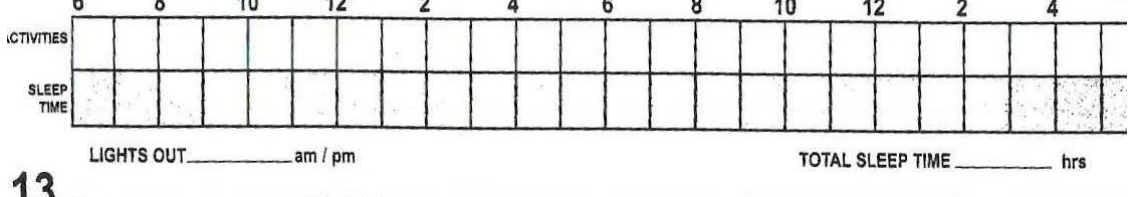
11



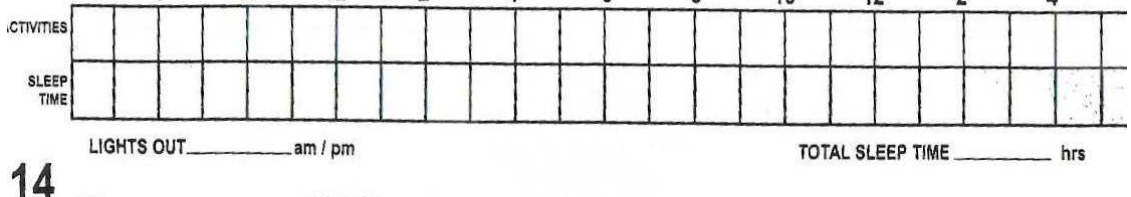
LIGHTS OUT _____ am / pm TOTAL SLEEP TIME _____ hrs

12



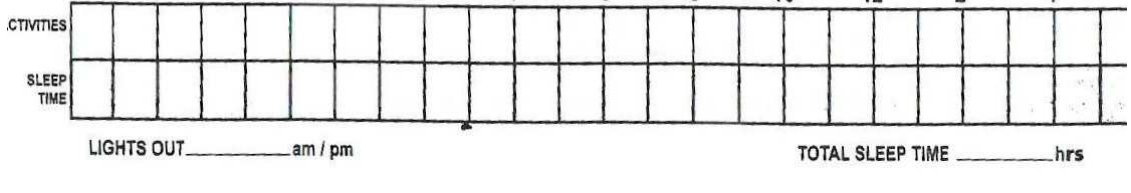
LIGHTS OUT _____ am / pm TOTAL SLEEP TIME _____ hrs

13



LIGHTS OUT _____ am / pm TOTAL SLEEP TIME _____ hrs

14



LIGHTS OUT _____ am / pm TOTAL SLEEP TIME _____ hrs

APPENDIX E: Chapter 4: Epworth Sleepiness Scale (ESS: Johns 1991).

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

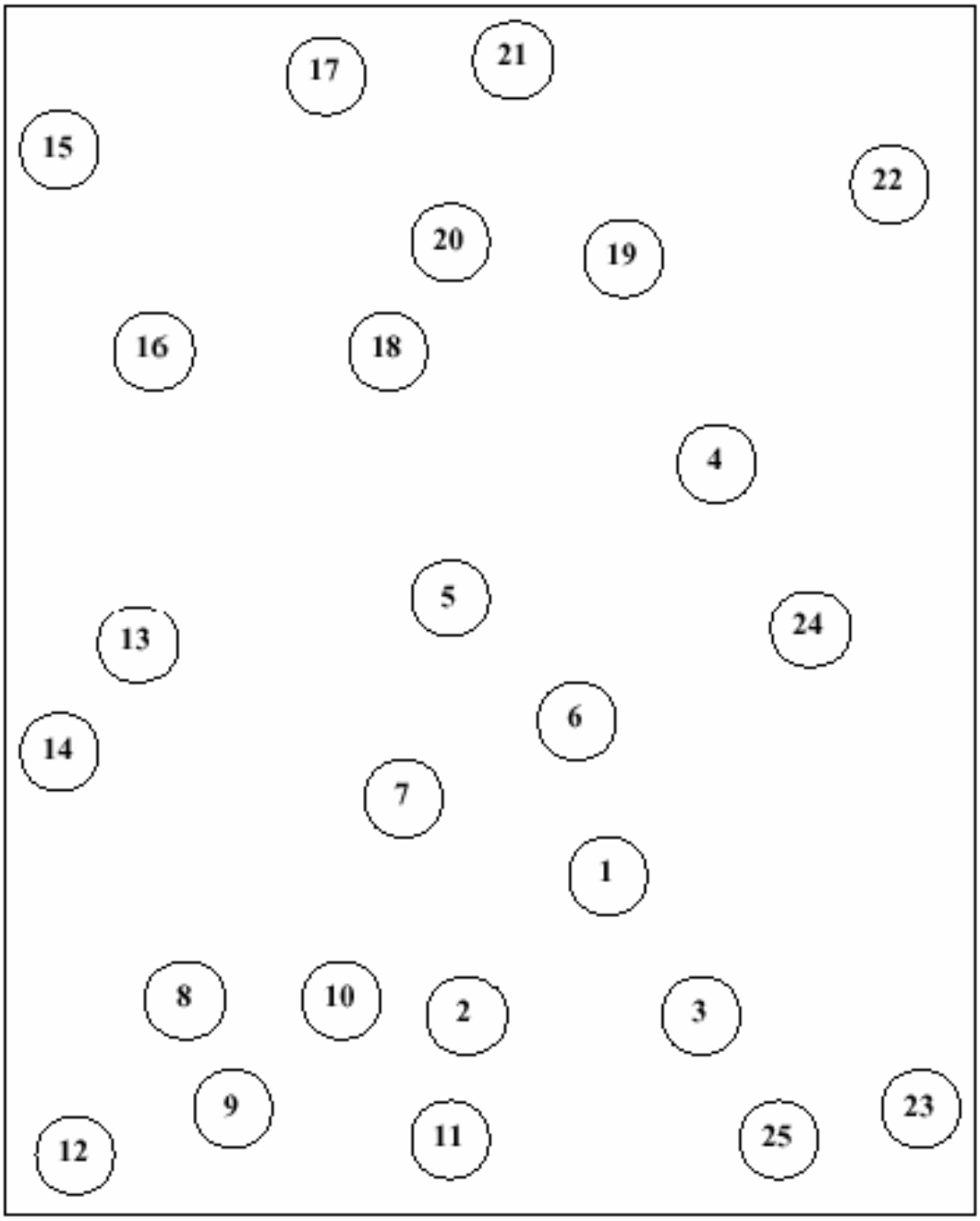
APPENDIX F: Chapter 4: Chalder Fatigue Scale (Chalder et al., 1993)

	Less than usual	No more than usual	More than usual	Much more than usual
Do you have problems with tiredness?				
Do you need to rest more?				
Do you feel sleepy or drowsy?				
Do you have problems starting things?				
Do you lack energy?				
Do you have less strength in your muscles?				
Do you feel weak?				
Do you have difficulty concentrating?				
Do you make slips of the tongue when speaking?				
Do you find it more difficult to find the correct word?				
	Better than usual	No worse than usual	Worse than usual	Much worse than usual
How is your memory?				

APPENDIX G: Chapter 4: Trail making Test (TMT: Reitan, 1958)

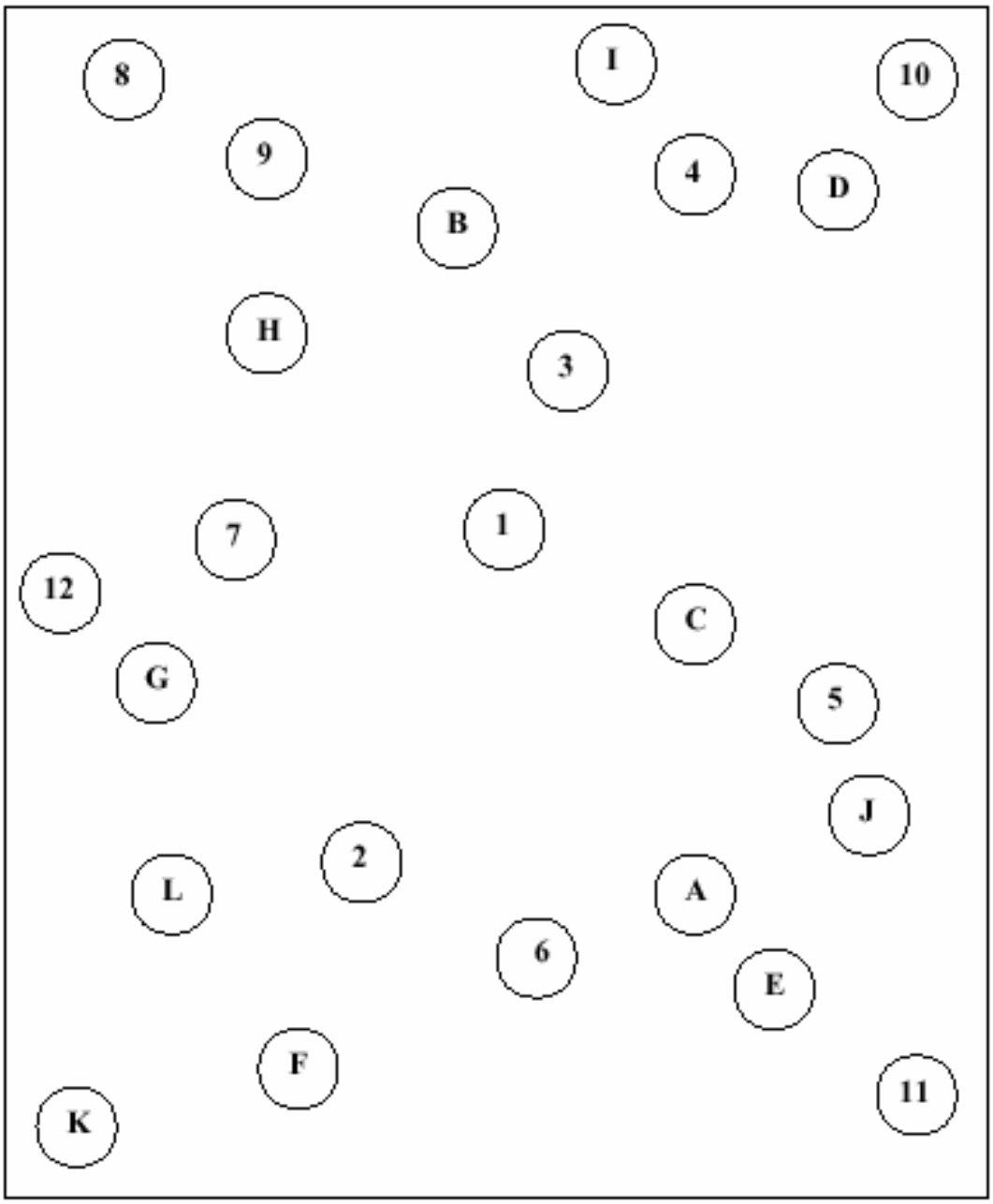
Trail Making Test Part A

Patient's Name: _____ Date: _____



Trail Making Test Part B

Patient's Name: _____ Date: _____



APPENDIX H: Chapter 4: Cognitive Failures Questionnaire (CFQ: Broadbent et al, 1982)

CFQ

The following questions are about minor mistakes which everyone makes from time *to* time, but some of which happen more often than others. We want to know how often these things have happened to you in the last six months. Please circle the appropriate number.

	Very often	Quite often	Occasionally	Very rarely	Never
1. Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2. Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3. Do you fail to notice signposts on the road?	4	3	2	1	0
4. Do you find you confuse right and left when giving directions?	4	3	2	1	0
5. Do you bump into people?	4	3	2	1	0
6. Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7. Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8. Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9. Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10. Do you lose your temper and regret it?	4	3	2	1	0
11. Do you leave important letters unanswered for days?	4	3	2	1	0
12. Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13. Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14. Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15. Do you have trouble making up your mind?	4	3	2	1	0
16. Do you find you forget appointments?	4	3	2	1	0
17. Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19. Do you daydream when you ought to be listening to something?	4	3	2	1	0
20. Do you find you forget people's names?	4	3	2	1	0
21. Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22. Do you find you can't quite remember something although it's 'on the tip of your tongue'?	4	3	2	1	0
23. Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24. Do you drop things?	4	3	2	1	0
25. Do you find you can't think of anything to say?	4	3	2	1	0

APPENDIX I: Chapter 4: Hospital Anxiety and Depression Scale (HADS: Zigmund & Snaith, 1983)

Read each item and tick the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response. ***Tick only one box in each section.***

1. I feel tense or "wound up"
- Most of the time. . . . . ☐
- A lot of the time. . . . . ☐
- Time to Time, Occasionally . . . . ☐
- Not at all . . . . . ☐

2. I still enjoy the things I used to enjoy
- Definitely as much. . . . . ☐
- Not quite as much. . . . . ☐
- Only a little. . . . . ☐
- Hardly at all . . . . . ☐

3. I get a sort of frightened feeling as if something awful is about to happen
- Very definitely and quite badly . . . ☐
- Yes, but not too badly . . . . . ☐
- Time to Time, Occasionally . . . . . ☐
- Not at all . . . . . ☐

4. I can laugh and see the funny side of things
- As much as I always could . . . . . ☐
- Not quite so much now . . . . . ☐
- Definitely not so much now . . . . . ☐
- Not at all . . . . . ☐

5. Worrying thoughts go through my mind
- A great deal of the time . . . . . ☐
- A lot of the time . . . . . ☐
- From time to time but not too often ☐
- Only occasionally . . . . . ☐

6. I feel cheerful
- Not at all . . . . . ☐
- Not often . . . . . ☐
- Sometimes . . . . . ☐
- Most of the time . . . . . ☐

7. I can sit at ease and feel relaxed
- Definitely . . . . . ☐
- Usually . . . . . ☐
- Not Often . . . . . ☐
- Not at all . . . . . ☐

8. I feel as if I am slowed down
- Nearly all the time . . . . . ☐
- Very often . . . . . ☐
- Sometimes . . . . . ☐
- Not at all . . . . . ☐

9. I get a sort of frightened feeling like butterflies in the stomach
- Not at all . . . . . ☐
- Occasionally . . . . . ☐
- Quite often . . . . . ☐
- Very often . . . . . ☐

10. I have lost interest in my appearance
- Definitely . . . . . ☐
- I don't take so much care as I should ☐
- I may not take quite as much care . . ☐
- I take just as much care as ever . . . . ☐

11. I feel restless as if I have to be on the move
- Very much indeed . . . . . ☐
- Quite a lot. . . . . ☐
- Not very much. . . . . ☐
- Not at all . . . . . ☐

12. I look forward with enjoyment to things
- As much as ever I did . . . . . ☐
- Rather less than I used to . . . . . ☐
- Definitely less than I used to . . . . . ☐
- Hardly at all . . . . . ☐

13. I get sudden feeling of panic
- Very often indeed . . . . . ☐
- Quite often . . . . . ☐
- Not very often . . . . . ☐
- Not at all . . . . . ☐

14. I can enjoy a good book or radio or TV programme
- Often . . . . . ☐
- Sometimes . . . . . ☐
- Not Often. . . . . ☐
- Very seldom . . . . . ☐

APPENDIX J: Chapter 6: Expression of Interest Form

The Roles of Sleep and Cortisol in CFS

Thank you for taking the time to read the information sheet regarding the above research study. Please tick the appropriate box below, and return the form in the enclosed reply-paid envelope. If you do not wish to take part you don't have to return the form, but it would be helpful for us if you could.

Yes, I am interested in taking part in the research study.

I understand that I can withdraw my interest at any time and that my current and future care will continue exactly as before. If I decide to withdraw, no further contact will be made with me regarding the study. ☐

Name (capitals)	
Date	
Signature	
Telephone number and/or email address	
Best time to contact me	

The Roles of Sleep and Cortisol in CFS

Please initial in the appropriate box and sign below if appropriate for you

8. I confirm that I have read and understand the information sheet (Version 2.0, dated 01.05.2012) provided for the above study and have had the opportunity to ask questions. ☐
9. 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. ☐
10. I understand that my sleep will be monitored for 3 nights. ☐
11. I understand that I will be required to provide my own saliva samples at 7 time points throughout each of the 3 days. ☐
12. I understand that relevant sections of the data (including personal details) collected during the study may be looked at by responsible individuals from regulatory authorities or from the Newcastle upon Tyne NHS Foundation Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. ☐
13. I understand that if a significant disclosure is made, then appropriate action will be taken to ensure my safety, as a participant taking part in this study. ☐
14. I agree to take part in the above study. ☐

Name of participant		Date		Signature
Name of researcher		Date		Signature

One copy of this signed consent form will be kept by the researcher, one copy will be placed in your medical records and one copy will be given to you for your own records.

FOR USE WHEN TISSUE IS BEING REMOVED AND STORED

Project Title: ***The Roles of Sleep and Cortisol in CFS***

Principal Investigator: Zoe Gotts

Participant Number: _____

I agree that the following tissue or other bodily material may be taken and used for the study:

Tissue/Bodily material	**Purpose**	**Removal Method**
e.g. saliva	*e.g. for cortisol analysis*	*e.g. via Salicaps*
Saliva	For cortisol analysis	Salivettes

I understand that if the material is required for use in any other way than that explained to me, then my consent to this will be specifically sought. I understand that I will not receive specific feedback from any assessment conducted on my samples, but should any kind of abnormality be discovered then the investigator will contact me.

I understand that the University may store this tissue in a Licensed Tissue Bank only for the duration of the study, it will then be destroyed.

Method of disposal:

Clinical Waste ☑

Other ☐

If other please specify.....

I consent to the University distributing this tissue to partners in this research study, outside of the University, for further testing (please tick the box if you agree). ☐

Signature of participant..... Date.....……..

Signature of researcher..... Date.....……..

APPENDIX L: Chapter 6: Standardised Sleep Diary: 14-day (baseline)

ID			
Initials			

Northumbria Centre for Sleep Research

Sleep Diary

Instructions:
The Sleep Diary is designed to provide a record of your experience of sleep. You will see information about seven nights (one week) can be recorded on each form. Please fill in both forms (2 weeks).

Please complete one column of the diary each morning, soon after you wake up. Take a few minutes to do this, trying to be as accurate as you can. It is your best estimate that we are looking for, but try not to get into the habit of clockwatching at night.

Please also indicate which day of the week it is (M, T, W, Th, Fr, Sa, Su) on Day 1 of the sleep diary by circling the appropriate response.

Study Title: The Roles of Sleep & Cortisol in CFS

Date _____

MEASURING THE PATTERN OF YOUR SLEEP	**Day 1 M,T,W,Th, Fr,Sa,Su**	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. What time did you wake this morning?							
2. At what time did you rise from bed?							
3. At what time did you go to bed last night?							
4. Lights Out:- At what time did you put the lights out to go to sleep?							
5. How long did it take you to fall asleep (minutes)? (After Lights Out)							
6. How many times did you wake up during the night?							
7. How long were you awake during the night (in total)?							
8. About how long did you sleep altogether (hours/mins)?							
9. How many sleeping pills did you take to help you sleep?							

MEASURING THE QUALITY OF YOUR SLEEP

1. How well do you feel this morning? 0 1 2 3 4 not at all moderately very							
2. How enjoyable was your sleep last night? 0 1 2 3 4 not at all moderately very							
3. How mentally alert were you in bed last night? 0 1 2 3 4 not at all moderately very							
4. How physically tense were you in bed last night? 0 1 2 3 4 not at all moderately very							

MEASURING THE PATTERN OF YOUR SLEEP	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
1. What time did you wake this morning?							
2. At what time did you rise from bed?							
3. At what time did you go to bed last night?							
4. Lights Out:- At what time did you put the lights out to go to sleep?							
5. How long did it take you to fall asleep (minutes)? (After Lights Out)							
6. How many times did you wake up during the night?							
7. How long were you awake during the night (in total)?							
8. About how long did you sleep altogether (hours/mins)?							
9. How many sleeping pills did you take to help you sleep?							

MEASURING THE QUALITY OF YOUR SLEEP

How well do you feel this morning? 0 1 2 3 4 not at all moderately very							
How enjoyable was your sleep last night? 0 1 2 3 4 not at all moderately very							
How mentally alert were you in bed last night? 0 1 2 3 4 not at all moderately very							

How physically tense were you in bed last night? 0 1 2 3 4 not at all moderately very							

For research use only:

SOL	WAKE	WASO	TST	TIB	SE

APPENDIX M: Chapter 6: Instructions for Questionnaire Booklet

ID# _____ Date_____

Welcome to the Northumbria Centre for Sleep Research (NCSR). The NCSR is designed to study and treat disorders of sleep and wakefulness and is located within Northumbria University's School of Life Sciences.

Our aim is two-fold:
We conduct research into the mechanisms underlying the transitions between sleep and wakefulness and how biological, psychological, social, and environmental circumstances affect these normal, albeit complex, transitions.

Our second aim is to help assess, diagnose, and treat sleep disorders, using a variety of techniques and methodologies, in different populations (children, adults, older adults, those with acute or chronic illnesses).

The NCSR has been designed to conduct research examining sleep and wakefulness using psychophysiologic assessment (e.g., EEG, EMG, EOG, ECG, ERP), indices of basal functioning of the endocrine and immune systems (e.g., diurnal cortisol, Cortisol Awakening Rise, cytokines, melatonin), and a variety of signal processing techniques, including power spectral analysis (PSA). We also utilise Bluetooth connectivity which means that we can do 'at-home' ambulatory studies.

The NCSR affords the opportunity to examine full physiological and sleep / wake parameters over the 24 hour cycle for short or long durations. Not only does it allow descriptive studies to be undertaken on objective markers of sleep quality, quantity, and timing; it also can be used as a diagnostic measure of 'clinically relevant' adverse nocturnal events which impact on sleep and daytime functioning in physically and psychologically ill populations and in patients with neurodegenerative disorders.

HOW TO FILL OUT THIS BOOKLET
This questionnaire is about your sleep, your general health and mood. The time it takes to fill in the questionnaire varies from person to person, but we estimate that it should take less or approximately half an hour. Most questions have multiple response choices. Choose the answer that best describes your situation. There is no right or wrong answer. Unless stated otherwise, give only one answer to each question and please answer all questions!

APPENDIX N: Chapter 6: DePaul Symptom Questionnaire (DSQ: Jason et al., 2010)

ABOUT YOU & YOUR HEALTH

DSQ

Please answer the following questions.

1. What is your height?_____

2. What is your weight?_____

3. What is your date of birth?_____

4. What is your gender?_____

5. To which of the following race(s) do you belong?

- □ Black, African-American
- □ White
- □ American Indian or Alaska Native
- □ Asian or Pacific Islander
- □ Other race (*Please specify*)_____

6. Are you of Latino or Hispanic origin?

□ Yes □ No

7. What is your current marital status?

- □ Married or living with partner
- □ Separated
- □ Widowed
- □ Divorced
- □ Never married

8. Do you have any children?

□ Yes □ No (*Skip to Question 9)*

8a. How many children do you have?_____

8b. How many of your children are under 18 years old?_____

9. How many people live in your home?_____

10. What grade or degree have you completed in school?

- □ Less than high school
- □ Some high school
- □ High school degree or GED
- □ Partial college (at least one year) or specialized training
- □ Standard college degree
- □ Graduate professional degree including masters and doctorate

11. What is your current work status? **(Check all that apply)**

- □ On disability
- □ Student
- □ Homemaker
- □ Retired
- □ Unemployed
- □ Working part-time
- □ Working full-time

11a. If you are on disability, for what condition do you receive disability compensation?

Please Specify_____

12. What is your current occupation?

Current_____

12a. If you are currently not working, what was your most recent occupation?

Most Recent_____

For the following questions (13-66), we would like to know **how often you have had each symptom** and **how much each symptom has bothered you over the last 6 months**. For each symptom please circle **one number for frequency and one number for severity**. Please fill the chart out from left to right.

Symptoms	*Frequency:* Throughout the **past 6 months**, **how often** have you had this symptom? For each symptom listed below, circle a number from: **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**	*Severity:* Throughout the **past 6 months**, **how much** has this symptom bothered you? For each symptom listed below, circle a number from: **0 = symptom not present** **1 = mild** **2 = moderate** **3 = severe** **4 = very severe**
13) Fatigue/extreme tiredness	0 1 2 3 4	0 1 2 3 4
14) Dead, heavy feeling after starting to exercise	0 1 2 3 4	0 1 2 3 4
15) Next day soreness or fatigue after non-strenuous, everyday activities	0 1 2 3 4	0 1 2 3 4
16) Mentally tired after the slightest effort	0 1 2 3 4	0 1 2 3 4
17) Minimum exercise makes you physically tired	0 1 2 3 4	0 1 2 3 4
18) Physically drained or sick after mild activity	0 1 2 3 4	0 1 2 3 4
19) Feeling unrefreshed after you wake up in the morning	0 1 2 3 4	0 1 2 3 4
20) Need to nap daily	0 1 2 3 4	0 1 2 3 4
21) Problems falling asleep	0 1 2 3 4	0 1 2 3 4
22) Problems staying asleep	0 1 2 3 4	0 1 2 3 4
23) Waking up early in the morning (e.g. 3am)	0 1 2 3 4	0 1 2 3 4
24) Sleep all day and stay awake all night	0 1 2 3 4	0 1 2 3 4
25) Pain or aching in your muscles	0 1 2 3 4	0 1 2 3 4
26) Pain/stiffness/tenderness in more than one joint without swelling or redness	0 1 2 3 4	0 1 2 3 4
27) Eye pain	0 1 2 3 4	0 1 2 3 4
	Frequency:	*Severity:*

Symptoms	Throughout the **past 6 months**, **how often** have you had this symptom? For each symptom listed below, circle a number from: **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**					Throughout the **past 6 months**, **how much** has this symptom bothered you? For each symptom listed below, circle a number from: **0 = symptom not present** **1 = mild** **2 = moderate** **3= severe** **4 = very severe**				
28) Chest pain	0	1	2	3	4	0	1	2	3	4
29) Bloating	0	1	2	3	4	0	1	2	3	4
30) Abdomen/stomach pain	0	1	2	3	4	0	1	2	3	4
31) Headaches	0	1	2	3	4	0	1	2	3	4
32) Muscle twitches	0	1	2	3	4	0	1	2	3	4
33) Muscle weakness	0	1	2	3	4	0	1	2	3	4
34) Sensitivity to noise	0	1	2	3	4	0	1	2	3	4
35) Sensitivity to bright lights	0	1	2	3	4	0	1	2	3	4
36) Problems remembering things	0	1	2	3	4	0	1	2	3	4
37) Difficulty paying attention for a long period of time	0	1	2	3	4	0	1	2	3	4
38) Difficulty finding the right word to say or expressing thoughts	0	1	2	3	4	0	1	2	3	4
39) Difficulty understanding things	0	1	2	3	4	0	1	2	3	4
40) Only able to focus on one thing at a time	0	1	2	3	4	0	1	2	3	4
41) Unable to focus vision and/or attention	0	1	2	3	4	0	1	2	3	4
42) Loss of depth perception	0	1	2	3	4	0	1	2	3	4
43) Slowness of thought	0	1	2	3	4	0	1	2	3	4
44) Absent-mindedness or forgetfulness	0	1	2	3	4	0	1	2	3	4
45) Bladder problems	0	1	2	3	4	0	1	2	3	4
46) Irritable bowel problems	0	1	2	3	4	0	1	2	3	4

Symptoms	*Frequency:* Throughout the **past 6 months**, **how often** have you had this symptom? For each symptom listed below, circle a number from: **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**	*Severity:* Throughout the **past 6 months**, **how much** has this symptom bothered you? For each symptom listed below, circle a number from: **0 = symptom not present** **1 = mild** **2 = moderate** **3= severe** **4 = very severe**
47) Nausea	0 1 2 3 4	0 1 2 3 4
48) Feeling unsteady on your feet, like you might fall	0 1 2 3 4	0 1 2 3 4
49) Shortness of breath or trouble catching your breath	0 1 2 3 4	0 1 2 3 4
50) Dizziness or fainting	0 1 2 3 4	0 1 2 3 4
51) Irregular heart beats	0 1 2 3 4	0 1 2 3 4
52) Losing or gaining weight without trying	0 1 2 3 4	0 1 2 3 4
53) No appetite	0 1 2 3 4	0 1 2 3 4
54) Sweating hands	0 1 2 3 4	0 1 2 3 4
55) Night sweats	0 1 2 3 4	0 1 2 3 4
56) Cold limbs (e.g. arms, legs, hands)	0 1 2 3 4	0 1 2 3 4
57) Feeling chills or shivers	0 1 2 3 4	0 1 2 3 4
58) Feeling hot or cold for no reason	0 1 2 3 4	0 1 2 3 4
59) Feeling like you have a high temperature	0 1 2 3 4	0 1 2 3 4
60) Feeling like you have a low temperature	0 1 2 3 4	0 1 2 3 4
61) Alcohol intolerance	0 1 2 3 4	0 1 2 3 4
62) Sore throat	0 1 2 3 4	0 1 2 3 4
63) Tender/sore lymph nodes	0 1 2 3 4	0 1 2 3 4
64) Fever	0 1 2 3 4	0 1 2 3 4
65) Flu-like symptoms	0 1 2 3 4	0 1 2 3 4
66) Some smells, foods, medications, or chemicals make you feel sick	0 1 2 3 4	0 1 2 3 4

67. Have you **always** had persistent or recurring **fatigue/energy problems**, even back to your earliest memories as a child? (By persistent or recurring, we mean that the fatigue/energy problems are usually ongoing and constant, but sometimes there are good periods and bad periods.)

□ Yes □ No □ Not having a problem with fatigue/energy

68. Since your **fatigue/energy related illness** began, do your headaches either happen more often, feel worse or more severe, or are they in a different place or spot?

□ Yes □ No □ Not having a problem with fatigue/energy

69. How long ago did your problem with **fatigue/energy** begin?

□ Less than 6 months
□ 6-12 months
□ 1-2 years
□ Longer than 2 years
□ Had problem with fatigue/energy since childhood or adolescence
□ Not having a problem with fatigue/energy

70. Have you been diagnosed with Chronic Fatigue Syndrome or Myalgic Encephalomyelitis?

□ Yes □ No

70a. If yes, what year were you diagnosed?_____

70b. Do you currently have a diagnosis of Chronic Fatigue Syndrome or Myalgic Encephalomyelitis?

□ Yes □ No

70c. Who diagnosed you with Chronic Fatigue Syndrome or Myalgic Encephalomyelitis?

□ Medical Doctor □ Alternative Practitioner □ Self-Diagnosed

70d. Have any of your family members been diagnosed with Chronic Fatigue Syndrome or Myalgic Encephalomyelitis?

□ Yes □ No

If yes, please list their relation to you and current age_____

71. Did you experience any of the following symptoms regularly and repeatedly in the months and
years before your fatigue/energy problems began?

□ Sore throat
□ Tender/sore lymph nodes
□ Unrefreshing sleep
□ Impaired memory and concentration
□ Prolonged fatigue following physical or mental exertion
□ Muscle pain
□ Headaches
□ Joint Pain
□ Not having a problem with fatigue/energy

72. If you rest, does your problem with **fatigue/energy** go away? **(Check one)**

□ Entirely

□ Partially

□ My fatigue/energy problem is not improved by rest *(Skip to Question 73)*

□ I am not having a problem with fatigue/energy *(Skip to Question 73)*

72a. How long do you have to rest for your problem with **fatigue/energy** to entirely or partially go away?

□ less than 30 minutes □ 30 to 59 minutes □ 1-2 hours □ more than 2 hours

73. If you were to become exhausted after actively participating in extracurricular activities, sports, or outings with friends, would you recover within an hour or two after the activity ended?

□ Yes □ No

74. Do you reduce your activity level to avoid experiencing problems with **fatigue/energy**?

□ Yes □ No □ Not having a problem with fatigue/energy

75. Do you experience a worsening of your **fatigue/energy related illness** after engaging in minimal physical effort?

□ Yes □ No □ Not having a problem with fatigue/energy

75a. Do you experience a worsening of your **fatigue/energy related illness** after engaging in mental effort?

□ Yes □ No

75b. If you feel worse after activities, how long does this last? **(Check one)**

□ 1 hour or less □ 2-3 Hrs □ 4-10 Hrs □ 11-13 Hrs

□ 14-23 Hrs □ More than 24 Hrs (Please specify_____)

76. Are you currently engaging in any form of exercise?

□ Yes *(Skip to Question 77)* □ No

76a. If you do not exercise, why aren't you exercising? **(Check all boxes that you agree with)**

□ Not interested

□ No time

□ Would like to but cannot because of problems with fatigue/energy

□ Cannot because exercise makes symptoms worse

77. Over what period of time did your **fatigue/energy related illness,** develop? **(Check one)**

□ Within 24 hours

□ Over 1 week

□ Over 1 month

□ Over 2-6 months

□ Over 7-12 months

□ Over 1-2 years

□ Over 3 or more years

□ I am not ill

78. How would you describe the course of your **fatigue/energy related illness? (Check one)**

□ Constantly getting worse

□ Constantly improving

□ Persisting (no change)

□ Relapsing & remitting (having "good" periods with no symptoms & "bad" periods)

□ Fluctuating (symptoms periodically get better and get worse, but never disappear completely)

□ No Symptoms/I am not ill

79. Which statement best describes your **fatigue/energy related illness** during the **last 6 months**? **(Check one)**

□ I am not able to work or do anything, and I am bedridden.

□ I can walk around the house, but I cannot do light housework.

□ I can do light housework, but I cannot work part-time.

□ I can only work part-time at work or on some family responsibilities.

□ I can work full time, but I have no energy left for anything else.

□ I can work full time and finish some family responsibilities but I have no energy left for anything else.

□ I can do all work or family responsibilities without any problems with my energy.

80. Did your **fatigue/energy related illness** start after you experienced any of the following? **(Check one or more and please specify)**

□ An infectious illness_____

□ An accident_____

□ A trip or vacation_____

□ An immunization (shot at doctor's office)_____

□ Surgery_____

□ Severe stress (bad or unhappy event(s))_____

□ Other_____

□ I am not ill

81. Have you ever consulted a medical doctor or health professional about your **fatigue/energy** problem?

□ Yes □ No *(Skip to Question 83)*

82. Do you currently have a medical doctor overseeing your **fatigue/energy** problem?

□ Yes □ No

83. Do you have any medical illness (es) that might be causing your symptoms?

□ Yes □ No *(Skip to Question 84)*

83a. What medical illnesses do you have?
Illness name(s) and year it began:_____

_____

_____

83b. For which of these conditions are you currently receiving treatment?

_____

84. Are you currently taking any medications (over the counter or prescription)?

□ Yes □ No *(Skip to Question 86)*

84a. What medications are you taking?

_____

85. Do you think any medication(s) is (are) causing your problem with **fatigue/energy**?

□ Yes □ No *(Skip to Question 86)*

□ I do not have a problem with fatigue/energy *(Skip to Question 86)*

85a. Please specify which medications:_____

_____

86. Have you ever been diagnosed and/or treated for any of the following: **(Check all that apply and write year (s) experienced, years treated, and medication (if applicable) in the blank)**

□ Major depression_____

□ Major depression with melancholic or psychotic features_____

□ Bipolar disorder (Manic-depression)_____

□ Anxiety_____

□ Schizophrenia_____

□ Eating disorder_____

□ Substance abuse_____

□ Multiple chemical sensitivities_____

□ Fibromyalgia_____

□ Allergies_____

□ Other (*Please specify*)_____

□ No diagnosis/treatment

87. What do you think is the cause of your problem with **fatigue/energy**? **(Check one)**

□ Definitely physical

□ Mainly physical

□ Equally physical and psychological

□ Mainly psychological

□ Definitely psychological

□ No problem with fatigue/energy

88. Do you think anything specific in your personal life or environment accounts for your problem with **fatigue/energy**?

□ Yes □ No *(Skip to Question 89)*

□ I do not have a problem with fatigue/energy (*Skip to Question 89)*

88a. Please specify:_____

89. In the **past 4 weeks**, approximately how many hours per week have you spent doing:

Household related activities?_____hours per week

Social/Recreational related activities?_____hours per week

Family related activities?_____hours per week

Work related activities?_____hours per week

90. In the **past 4 weeks**, have you had to reduce the number of hours you previously spent (prior to your illness) on occupational, social or family activities because of your health or problems with **fatigue/energy**?

□ Yes □ No *(Skip to Question 91)* □ Not having a problem with fatigue/energy

90a. **Before your fatigue/energy related illness**, approximately how many hours did you used to spend on:

Household related activities? _____hours per week

Social/Recreational related activities? _____hours per week

Family related activities? _____hours per week

Work related activities?_____hours per week

91. Please rate the amount of **energy** you had available **yesterday**, using a scale from 1 to 100 where 1= no energy and 100 = your pre-illness energy level. **(If you don't have a fatigue/energy related illness, a score of 100 = having abundant energy such that you could work full time and complete your family responsibilities)**

_____

92. Please rate the amount of **energy** you expended (used) **yesterday**, using a scale from 1 to 100 where 1 = no energy and 100 = your pre-illness energy expended

_____

93. Please rate the amount of **fatigue** you had **yesterday**, using a scale from 1 to 100 where 1 = no fatigue and 100 = severe fatigue_____

94. For the **past week**, please rate the amount of **energy** you had available using a scale from 1 to 100 where 1 = no energy and 100 = your pre-illness energy level _____

95. For the **past week**, please rate the amount of **energy** you have expended (used) using a scale from 1 to 100 where 1 = no energy and 100 = your pre-illness energy expended____

96. For the **past week**, please rate the amount of **fatigue** you have had using a scale from 1 to 100 where 1 = no fatigue and 100 = severe fatigue_____

97. Since the onset of your problems with fatigue/energy, have your symptoms caused a 50% or greater reduction in your activity level?

□ Yes □ No □ Not having a problem with fatigue/energy

98. Do you experience frequent viral infections with prolonged recovery periods?

□ Yes □ No

99. Are you intolerant of extremes of temperatures (when it is extremely hot or cold)?

□ Yes □ No

APPENDIX O: Chapter 6: SF-36: (Ware & Sharebourne, 1992), from the Medical Outcomes Study

MOS SURVEY

INSTRUCTIONS:

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is: ***(Please circle one)***

Excellent 1
Very good 2
Good 3
Fair 4
Poor 5

2. **Compared to one year ago,** how would you rate your health in general now? ***(Please circle one)***

Much better than one year ago 1
Somewhat better now than one year ago 2
About the same as one year ago 3
Somewhat worse now than one year ago 4
Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your health Now limit you in these activities? If so, how much?

Activities	**Yes, Limited A Lot**	**Yes, Limited A Little**	**No, Not Limited At All**
Vigorous activities: running, lifting heavy objects, participating in strenuous sports	1	2	3
Moderate activities: moving a table, pushing a vacuum cleaner, bowling, playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing **several** flights of stairs	1	2	3
Climbing **one** flight of stairs	1	2	3
Bending, kneeling, or stooping	1	2	3
Walking **more than a mile**	1	2	3
Walking **several blocks**	1	2	3
Walking **one** block	1	2	3
Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of your **physical health**?

Problems	**Yes**	**No**
Cut down on the **amount of time** you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Were limited in the **kind** of work or other activities	1	2
Had **difficulty** performing the work or other activities (For example, it took extra effort)	1	2

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

Problems	**Yes**	**No**
Cut down the **amount of time** you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Didn't do work or other activities as **carefully** as usual	1	2

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, neighbors, or groups?
(Please circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the **past 4 weeks**?

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very Severe 6

8. During the **past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**.

For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time **during the past 4 weeks**

Questions	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
Did you feel full of pep?	1	2	3	4	5	6
Have you been a nervous person?	1	2	3	4	5	6
Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
Have you felt calm and peaceful?	1	2	3	4	5	6
Did you have a lot of energy?	1	2	3	4	5	6
Have you felt down-hearted and blue?	1	2	3	4	5	6
Did you feel worn out?	1	2	3	4	5	6
Have you been a happy person?	1	2	3	4	5	6
Did you feel tired?	1	2	3	4	5	6

10. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time 1
Most of the time..... 2
Some of the time 3
A little of the time..... 4
None of the time..... 5

11. How **TRUE** or **FALSE** is each of following statements for you?

Statements	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
I seem to get sick a little easier than other people	1	2	3	4	5
I am as healthy as anybody I know	1	2	3	4	5
I expect my health to get worse	1	2	3	4	5
My health is excellent	1	2	3	4	5

APPENDIX P: Chapter 6: Demographic, Diet & Exercise Questions

If you are female

	Yes	No
Are you currently taking the contraceptive pill? (please tick)	☐	☐

Please let us know which stage of your menstrual cycle you are in (*the first day of bleeding is the first day of your cycle)*:

First half	Second half	Not applicable
☐	☐	☐

Would you describe yourself as: (please tick box)

Pre-menopausal	☐
Experiencing the menopause now	☐
Post-menopausal	☐

Diet & Exercise

How many **caffeinated beverages** do you drink, on average, per day? (eg. cola, tea, coffee, hot chocolate)? _____ (per day)

How many alcoholic drinks per day, on average, do you have (in units)? _____(per day)

Do you smoke? (please tick) Yes ☐ No ☐ Recently Quit ☐

If yes,
How many cigarettes (cigars or pipes) per day do you smoke (on average)? _____(per day)

How many times per week do you exercise? (please tick)

- ☐ Every day
- ☐ At least 4 times a week
- ☐ About 3 times a week
- ☐ About twice a week
- ☐ About once a week
- ☐ Never

APPENDIX Q: Chapter 6: The General Health Questionnaire (GHQ-28; Goldberg, 1978)

GHQ-28

Please read this carefully.

We would like to know if you have had any medical complaints and how your health has been in general, **over the past few weeks**. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

Have you recently					
A1	been feeling perfectly well and in good health?	Better than usual	Same as usual	Worse than usual	Much worse than usual
A2	been feeling in need of a good tonic?	Not at all	No more than usual	Rather more than usual	Much more than usual
A3	been feeling run down and out of sorts?	Not at all	No more than usual	Rather more than usual	Much more than usual
A4	felt that you are ill?	Not at all	No more than usual	Rather more than usual	Much more than usual
A5	been getting any pains in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A6	been getting a feeling of tightness or pressure in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A7	been having hot or cold spells?	Not at all	No more than usual	Rather more than usual	Much more than usual
B1	lost much sleep over worry?	Not atall	No more than usual	Rather more than usual	Much more than usual
B2	had difficulty in staying asleep once you are off?	Not at all	No more than usual	Rather more than usual	Much more than usual
B3	felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
*					
B4	been getting edgy and bad-tempered?	Not at all	No more than usual	Rather more than usual	Much more than usual
B5	been getting scared or panicky for no good reason?	Not at all	No more than usual	Rather more than usual	Much more than usual
B6	found everything getting on to of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
B7	been feeling nervous and	Not	No more	Rather more	Much more

Have you recently

C1	been managing to keep yourself busy and occupied?	More so than usual	Same asusual	Rather less than usual	Much less than usual
C2	been taking longer over the things you do?	Quicker than usual	Same as usual	Longer than usual	Much longer than usual
C3	felt on the whole you were doing things well?	Better than usual	About the same	Less well than usual	Much less well
C4	been satisfied with the way you've carried out your task?	More satisfied	About same as usual	Less satisfied than usual	Much less satisfied
C5	felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less useful
C6	felt capable of making decisions about things?	More so than usual	Same as usual	Less so thanusual	Much less capable
C7	been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual
D1	been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
D2	felt that life is entirely hopeless?	Not atall	No more than usual	Rather more than usual	Much more than usual
D3	felt that life isn't worth living?	Not at all	No more than usual	Rather more than usual	Much more than usual
D4	thought of the possibility that you might make away with yourself?	Definitely not	I don't thinkso	Has crossed my mind	Definitely have
D5	found at times you couldn't do anything because your nerves were too bad?	Not atall	No more than usual	Rather more than usual	Much more than usual
D6	found yourself wishing you were dead and away from it all?	Not at all	Nomore than usual	Rather more than usual	Much more than usual
D7	found that the idea of taking your own life kept coming into your mind?	Definitely not	I don't think so	Has crossed my mind	Definitely has

A	B	C	D	Total

APPENDIX R: Chapter 6: Chalder Fatigue Questionnaire (CFQ; Chalder et al., 1993)

CHALDER FATIGUE QUESTIONNAIRE

We would like to know more about any problems you have had with feeling tired, weak or lacking in energy **in the last month**. Please answer ALL the questions by ticking the answer which applies to you most closely. If you have been feeling tired for a long while, then compare yourself to how you felt when you were last well. (Please tick only one box per line).

	Less than usual	No more than usual	More than usual	Much more than usual
Do you have problems with tiredness?				
Do you need to rest more?				
Do you feel sleepy or drowsy?				
Do you have problems starting things?				
Do you lack energy?				
Do you have less strength in your muscles?				
Do you feel weak?				
Do you have difficulty concentrating?				
Do you make slips of the tongue when speaking?				
Do you find it more difficult to find the correct word?				
	Better than usual	No worse than usual	Worse than usual	Much worse than usual
How is your memory?				

APPENDIX S: Chapter 6: Hospital Anxiety and Depression Scale (HADS: Zigmond and Snaith, 1983)

Read each item and tick the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response. ***Tick only one box in each section.***

1. I feel tense or "wound up"
- Most of the time. . . . . ☐
- A lot of the time. . . . . ☐
- Time to Time, Occasionally . . . . ☐
- Not at all . . . . . ☐

2. I still enjoy the things I used to enjoy
- Definitely as much. . . . . ☐
- Not quite as much. . . . . ☐
- Only a little. . . . . ☐
- Hardly at all . . . . . ☐

3. I get a sort of frightened feeling as if something awful is about to happen
- Very definitely and quite badly . . . ☐
- Yes, but not too badly . . . . . ☐
- Time to Time, Occasionally . . . . . ☐
- Not at all . . . . . ☐

4. I can laugh and see the funny side of things
- As much as I always could . . . . . ☐
- Not quite so much now . . . . . ☐
- Definitely not so much now . . . . . ☐
- Not at all . . . . . ☐

5. Worrying thoughts go through my mind
- A great deal of the time . . . . . ☐
- A lot of the time . . . . . ☐
- From time to time but not too often ☐
- Only occasionally . . . . . ☐

6. I feel cheerful
- Not at all . . . . . ☐
- Not often . . . . . ☐
- Sometimes . . . . . ☐
- Most of the time . . . . . ☐

7. I can sit at ease and feel relaxed
- Definitely . . . . . ☐
- Usually . . . . . ☐
- Not Often . . . . . ☐
- Not at all . . . . . ☐

8. I feel as if I am slowed down
- Nearly all the time . . . . . ☐
- Very often . . . . . ☐
- Sometimes . . . . . ☐
- Not at all . . . . . ☐

9. I get a sort of frightened feeling like butterflies in the stomach
- Not at all . . . . . ☐
- Occasionally . . . . . ☐
- Quite often . . . . . ☐
- Very often . . . . . ☐

10. I have lost interest in my appearance
- Definitely . . . . . ☐
- I don't take so much care as I should ☐
- I may not take quite as much care . . ☐
- I take just as much care as ever . . . . ☐

11. I feel restless as if I have to be on the move
- Very much indeed . . . . . ☐
- Quite a lot. . . . . ☐
- Not very much. . . . . ☐
- Not at all . . . . . ☐

12. I look forward with enjoyment to things
- As much as ever I did . . . . . ☐
- Rather less than I used to . . . . . ☐
- Definitely less than I used to . . . . . ☐
- Hardly at all . . . . . ☐

13. I get sudden feeling of panic
- Very often indeed . . . . . ☐
- Quite often . . . . . ☐
- Not very often . . . . . ☐
- Not at all . . . . . ☐

14. I can enjoy a good book or radio or TV programme
- Often . . . . . ☐
- Sometimes . . . . . ☐
- Not Often. . . . . ☐
- Very seldom . . . . . ☐

APPENDIX T: Chapter 6: Work and Social Adjustment Scale (WSAS: Mundt et al., 2002)

WSAS

The Following questionnaire asks how much your illness or condition affects different areas of your life, on a scale from Not At All (0) to Very Severely (8). Please circle the number you feel is closest to how much your problem affects you.

BECAUSE OF MY ILLNESS MY ABILITY TO **WORK** IS IMPAIRED								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at all		Slightly		Definitely		Markedly		Very Severely

BECAUSE OF MY ILLNESS MY **HOME MANAGAMENT** IS IMPAIRED (cleaning, tidying, shopping, cooking, looking after home or children, paying bills)								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at all		Slightly		Definitely		Markedly		Very Severely

BECAUSE OF MY ILLNESS MY **SOCIAL LESIURE ACTIVITIES** ARE IMPAIRED (with other people, such as parties, bars, clubs, outings, visits, dating, home entertainment)								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at all		Slightly		Definitely		Markedly		Very Severely

BECAUSE OF MY ILLNESS MY **PRIVATE LEISURE ACITVITIES ARE** IMPAIRED (done alone, such as reading, gardening, collecting, sewing, walking alone)								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at all		Slightly		Definitely		Markedly		Very Severely

BECAUSE OF MY ILLNESS MY ABILITY TO FORM AND MAINTAIN **RELATIONSHIPS** IS IMPAIRED (close relationships with others, including those you live with)								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at all		Slightly		Definitely		Markedly		Very Severely

APPENDIX U: Chapter 6: Perceived Stress Scale (PSS: Cohen et al., 1983)

The questions in this scale ask you about your feelings and thoughts during the **last month**. In each case, you will be asked to indicate how often you felt or thought in a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each one as a separate question. That is, don't try to count up the number of times you felt a particular way, but rather indicate the number that seems like a reasonable estimate. Please circle the most appropriate response.

	1.Never	2.Almost Never	3.Some Times	4.Fairly Often	5.Very Often
In the last month, how often have you been upset because of something that happened unexpectedly?	1	2	3	4	5
In the last month, how often have you felt that you were unable to control the important things in your life?	1	2	3	4	5
In the last month, how often have you felt nervous and stressed?	1	2	3	4	5
In the last month, how often have you dealt with irritating life hassles?	1	2	3	4	5
In the last month, how often have you felt that you were effectively coping with important changes that were occurring in your life?	1	2	3	4	5
In the last month, how often have you felt confident about your ability to handle your personal problems?	1	2	3	4	5
In the last month, how often have you felt that things were going your way?	1	2	3	4	5
In the last month, how often have you found that you could not cope with all the things you had to do?	1	2	3	4	5
In the last month, how often have you been able to control irritations in your life?	1	2	3	4	5
In the last month, how often have you felt that you were on top of things?	1	2	3	4	5
In the last month, how often have you been angered because of things that happened that were outside of your control?	1	2	3	4	5
In the last month, how often have you found yourself thinking about things that you have to accomplish?	1	2	3	4	5
In the last month, how often have you been able to control the way you spend your time?	1	2	3	4	5
In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	1	2	3	4	5

APPENDIX V: Chapter 6: Brief Illness Perception Questionnaire (IPQ; Broadbent, et al., 2006)

The following questions relate to your views about **your illness** (CFS).

For the following questions, please circle the number that best corresponds to your views:

How much does your illness affect your life?

0	1	2	3	4	5	6	7	8	9	10
no affect at all										severely affects my life

How long do you think your illness will continue?

0	1	2	3	4	5	6	7	8	9	10
a very short time								forever		

How much control do you feel you have over your illness?

0	1	2	3	4	5	6	7	8	9	10
Absolutely no control										extreme amount of control

How much do you think your treatment can help your illness?

0	1	2	3	4	5	6	7	8	9	10
not at all										extremely helpful

How much do you experience symptoms from your illness?

0	1	2	3	4	5	6	7	8	9	10
no symptoms at all										many severe symptoms

How concerned are you about your illness?

0	1	2	3	4	5	6	7	8	9	10
not at all concerned										extremely concerned

How well do you feel you understand your illness?

0	1	2	3	4	5	6	7	8	9	10
don't understand at all										understand very clearly

How much does your illness affect you emotionally? (eg. does it make you angry, scared, upset or depressed?)

0	1	2	3	4	5	6	7	8	9	10
not at all affected emotionally										extremely affected emotionally

Please list in rank-order the three most important factors that you believe caused <u>your illness</u>.

The most important causes for me:-

1. _____

2. _____

3. _____

APPENDIX W: Chapter 6: The Pittsburgh Sleep Quality Index (PSQI: Buysse et al., 1989)

PSQI

ABOUT YOUR SLEEP

The following questions relate to your usual sleep habits during the **past month *only***. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month.

Please answer *all* of the questions.

1. During the past month, when have you usually gone to bed at night?

USUAL BED TIME: _____
(i. e. 10pm or 22.00)

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES: _____

2b. How long have you usually been awake during the night?

NUMBER OF MINUTES: _____

3. During the past month, when have you usually got up in the morning?

USUAL GETTING UP TIME: _____

4. During the past month, how many hours of *actual* sleep did you get at night? This may be different to the number of hours you spend in bed.

HOURS OF SLEEP PER NIGHT: _____

4b. How many nights per week do you usually have difficulties sleeping?

NUMBER OF NIGHTS PER WEEK: _____

5. During the past month, how often have you had trouble sleeping because you:

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) Cannot get to sleep within 30 minutes				
(b) Wake up in the middle of the night or early morning				
(c) Have to get up and use the bathroom				
(d) Cannot breathe comfortably				
(e) Cough or snore loudly				
(f) Feel too cold				
(g) Feel too hot				
(h) Had bad dreams				
(i) Have pain				

Other reason(s), please describe_____

How often during the past month have you had trouble sleeping because of this?

[ ] Not during the past month
[ ] Less than once a week
[ ] Once or twice a week
[ ] Three or more times a week

6. During the past month, how would you rate your sleep quality overall?

[ ] Very good
[ ] Fairly good
[ ] Fairly bad
[ ] Very Bad

7. During the past month, how often have you taken medicine (prescribed or 'over the counter') to help you sleep?

[ ] Not during the past month
[ ] Less than once a week
[ ] Once or twice a week
[ ] Three or more times a week

8. During the past month, how often have you had trouble staying awake while driving, eating meals or engaging in social activity?

[ ] Not during the past month
[ ] Less than once a week
[ ] Once or twice a week
[ ] Three or more times a week

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

[ ] No problem at all
[ ] Only a very slight problem
[ ] Somewhat of a problem
[ ] A very big problem

10. Do you have a bed partner or room-mate?

[ ] No bedroom partner or room-mate
[ ] Partner/ room-mate in other room
[ ] Partner in same room, but not same bed
[ ] Partner in same bed

If you have a room-mate or bed partner, ask him/ her how often in the past month you have had:

(a) Loud snoring

[ ] Not during the past month
[ ] Less than once a week
[ ] Once or twice a week
[ ] Three or more times a week

(b) Long pauses between breaths while asleep

[ ] Not during the past month
[ ] Less than once a week
[ ] Once or twice a week
[ ] Three or more times a week

(c) Legs twitching or jerking while you sleep

[ ] Not during the past month
[ ] Less than once a week
[ ] Once or twice a week
[ ] Three or more times a week

(d) Episodes of disorientation or confusion during sleep

[ ] Not during the past month
[ ] Less than once a week
[ ] Once or twice a week
[ ] Three or more times a week

(e) Other restlessness while you sleep; please describe

_____

[ ] Not during the past month
[ ] Less than once a week
[ ] Once or twice a week
[ ] Three or more times a week

(f) Do you consider yourself to have a sleep problem?
[ ] Yes
[ ] No

If Yes, how long has the problem been present? _____

APPENDIX X: Chapter 6: Insomnia Severity Index (ISI: Morin et al., 2011)

ISI

Please rate your current situation (i.e. last month) by selecting one response for each question.

1). Please rate the current severity of your insomnia problem(s).

	None	Mild	Moderate	Severe	Very
a. Difficulty falling asleep:	0	1	2	3	4
b. Difficulty staying asleep:	0	1	2	3	4
c. Problem waking up too early	0	1	2	3	4

2). How SATISFIED/DISSATISFIED are you with your current sleep pattern?

Very Satisfied				Very Dissatisfied
0	1	2	3	4

3). To what extent do you consider your insomnia problem to INTERFERE with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.).

Not at all Interfering	A little	Somewhat Interfering	Much	Very much Interfering
0	1	2	3	4

4). How NOTICEABLE to others do you think your insomnia problem is in terms of impairing the quality of your life?

Not at all Noticeable	A little	Somewhat	Much	Very much Noticeable
0	1	2	3	4

5). How WORRIED/DISTRESSED are you about your current insomnia problem?

Not at all Worried	A little	Somewhat	Much	Very much Worried
0	1	2	3	4

APPENDIX Y: Chapter 6: Ford Insomnia Response to Stress Test (FIRST: Drake et al., 2004)

FIRST

When you experience the following situations, how likely is it for you to have difficulty sleeping? Please circle an answer even if you have not experienced these situations recently situations recently.

Before an important meeting the next day

Not likely Somewhat likely Moderately likely Very likely

After a stressful experience during the day

Not likely Somewhat likely Moderately likely Very likely

After a stressful experience in the evening

Not likely Somewhat likely Moderately likely Very likely

After getting bad news during the day

Not likely Somewhat likely Moderately likely Very likely

After watching a frightening movie or TV show

Not likely Somewhat likely Moderately likely Very likely

After having a bad day at work

Not likely Somewhat likely Moderately likely Very likely

After an argument

Not likely Somewhat likely Moderately likely Very likely

Before having to speak in public

Not likely Somewhat likely Moderately likely Very likely

Before going on holiday the next day

Not likely Somewhat likely Moderately likely Very likely

THANK YOU!
Now please return the questionnaire booklet to the researcher.

APPENDIX Z: Chapter 6: Saliva Collection Instructions

SALIVA COLLECTION INSTRUCTIONS

To assess concentrations of the stress hormone, cortisol, we would like you to collect saliva on **THREE CONSECUTIVE WEEKDAYS**. You have been provided with three zip lock bags, labelled **D1** *(day 1)*, **D2** *(day 2) and* **D3** *(day 3)*. Inside each bag, you will find seven saliva collection tubes**.
** *saliva collection tubes have been labelled to help you decide which tube to use, and at which time point***
Please collect saliva at the following time **(T)** points,

Day 1 (D1)
D1_**T1**_S : Wake (**Immediately** after waking)
D1_**T2**_S : Wake + 15 min (15 minutes after you wake)
D1_**T3**_S : Wake + 30 min (30 minutes after you wake)
D1_**T4**_S : Wake + 45 min (45 minutes after you wake)
D1_**T5**_S : Wake + 60 min (60 minutes after you wake)
D1_**T6**_S : Afternoon Sample (between 2-4pm)
D1_**T7**_S : Before Bed (brush teeth after sample is taken)

Please refrain from brushing teeth/eating breakfast until after the 60 minute sample is taken

Day 2 (D2)
D2_**T1**_S : Wake (**Immediately** after waking)
D2_**T2**_S : Wake + 15 min (15 minutes after you wake)
D2_**T3**_S : Wake + 30 min (30 minutes after you wake)
D2_**T4**_S : Wake + 45 min (45 minutes after you wake)
D2_**T5**_S : Wake + 60 min (60 minutes after you wake)
D2_**T6**_S : Afternoon Sample (between 2-4pm)
D2_**T7**_S : Before Bed (brush teeth after sample is taken)

Day 1 (D3)
D3_**T1**_S : Wake (**Immediately** after waking)
D3_**T2**_S : Wake + 15 min (15 minutes after you wake)
D3_**T3**_S : Wake + 30 min (30 minutes after you wake)
D3_**T4**_S : Wake + 45 min (45 minutes after you wake)
D3_**T5**_S : Wake + 60 min (60 minutes after you wake)
D3_**T6**_S : Afternoon Sample (between 2-4pm)
D3_**T7**_S : Before Bed (brush teeth after sample is taken)

Please also complete the **sample log booklet** provided. This allows you to note the dates and times of your samples, including how you are feeling at those times.

WHAT IS THE BEST WAY TO ACCURATELY COLLECT SALIVA?

- Leave at least **45 minutes** between eating any food and taking a sample
- Rinse your mouth with cold water *(not essential)*
- Remove the cotton roll from the collection tube
- Place in your mouth
- Chew for 1-2 minutes, until the cotton roll is **COMPLETELY** saturated
- Deposit the saturated roll back into the collection tube
- Make sure the cap is secure
- Place back into the zip-lock bag & **REFRIGERATE** until returned to the research team

WHAT SHOULD I DO IF THINGS GO WRONG, OR I HAVE QUESTIONS?

Please contact the researcher, Zoe Gotts, **Tel:** 0191 243 7018 **E-mail:** zoe.gotts@northumbria.ac.uk

APPENDIX AA: Chapter 6: Standardised Sleep Diary & Saliva Sample Log: 3-day (assessment)

V1.0_03/02/12

ID			
Initials			

HOW TO FILL OUT THIS BOOKLET

Please complete the questions in this booklet carefully. On each day please indicate the date. Please could you record the time at which you wake and the time at 15 minutes, 30 minutes, 45 minutes and 1 hour after you wake. Could you also record the times at which you take your saliva samples – these should match as far as possible the times that you indicate for wake and for the 15 minutes, 30 minutes, 45 minutes and 1 hour after waking.

For the first hour after you wake, you will not be allowed to eat or brush your teeth as this can interfere with the measurements we are taking. Please also do not eat for at least 30 minutes prior to taking the afternoon and bed samples. You will be allowed to drink water.

Following your 1 hour after waking sample, you will be required to answer questions relating to your sleep and mood. You will also be required to record the time you take your afternoon sample and bed sample and answer questions relating to your mood at these times.

Please complete the booklet carefully in the morning, afternoon and prior to sleeping for 3 days.

DAY 1

Today's date ____ / ____ / _____

MORNING

Please provide the exact time that you provide each of the samples

	Wake	Wake +15	Wake +30	Wake +45	Wake +60
Time					
Time of sample					

Please complete the following questions following your 'Wake +60' sample

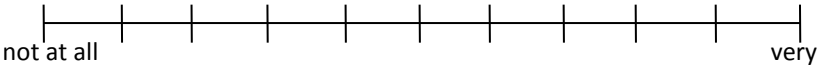
	MEASURING THE PATTERN OF YOUR SLEEP	
1	What time did you wake this morning?	
2	At what time did you rise from bed?	
3	At what time did you go to bed last night?	
4	Lights Out: At what time did you put the lights out to go to sleep?	
5	How long did it take you to fall asleep (minutes)? (After Lights Out)	
6	How many times did you wake up during the night?	
7	How long were you awake during the night (in total)?	
8	About how long did you sleep altogether (hours/mins)?	
9	How many sleeping pills did you take to help you sleep?	

	MEASURING THE QUALITY OF YOUR SLEEP			
	not at all	**moderately**		**very**
10	How well do you feel this morning? 0 1	2	3	4
11	How enjoyable was your sleep last night? 0 1	2	3	4
12	How mentally alert were you in bed last night? 0 1	2	3	4
13	How physically tense were you in bed last night? 0 1	2	3	4

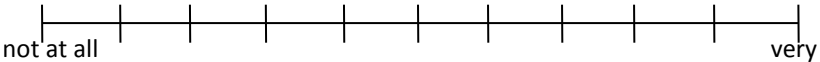
Please read each statement then circle the most appropriate point to indicate

how you feel right now

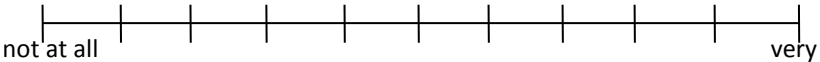
I feel calm



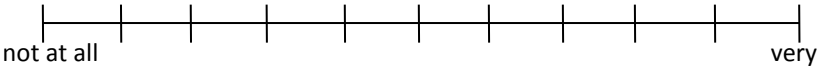
I feel tense



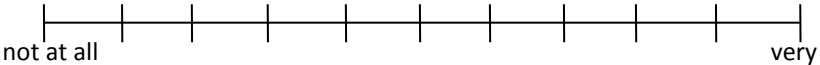
I am upset



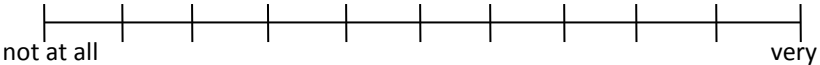
I feel relaxed



I feel content



I feel worried



AFTERNOON

Please provide the exact time that you provide the 'Afternoon' sample

	Afternoon
Time of sample	

Please complete the following questions following your 'Afternoon' sample

Please read each statement then circle the most appropriate point to indicate

how you feel right now

I feel calm

not at all very much

I feel tense

not at all very much

I am upset

not at all very much

I feel relaxed

not at all very much

I feel content

not at all very much

I feel worried

not at all very much

BED

Please provide the exact time that you provide the 'Bed' sample

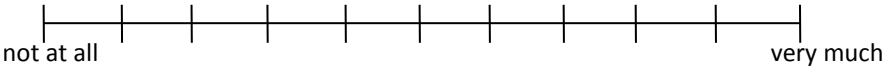
	Bed
Time of sample	

Please complete the following questions following your 'Bed' sample

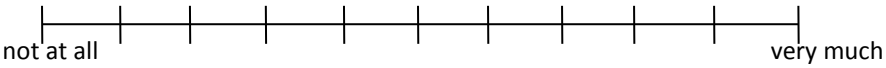
Please read each statement then circle the most appropriate point to indicate

how you feel right now

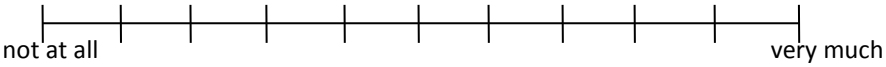
I feel calm



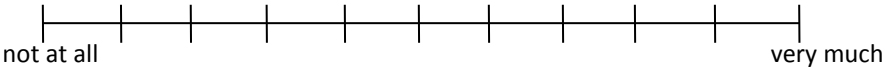
I feel tense



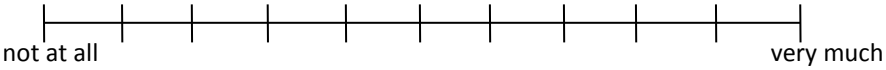
I am upset



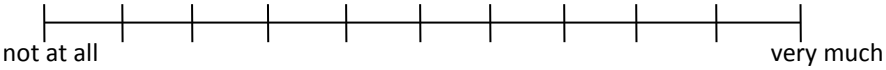
I feel relaxed



I feel content



I feel worried



DAY 2

Today's date ____ / ____ / _____

MORNING

Please provide the exact time that you provide each of the samples

	Wake	Wake +15	Wake +30	Wake +45	Wake +60
Time					
Time of sample					

Please complete the following questions following your 'Wake +60' sample

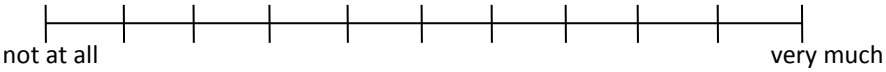
	MEASURING THE PATTERN OF YOUR SLEEP	
1	What time did you wake this morning?	
2	At what time did you rise from bed?	
3	At what time did you go to bed last night?	
4	Lights Out: At what time did you put the lights out to go to sleep?	
5	How long did it take you to fall asleep (minutes)? (After Lights Out)	
6	How many times did you wake up during the night?	
7	How long were you awake during the night (in total)?	
8	About how long did you sleep altogether (hours/mins)?	
9	How many sleeping pills did you take to help you sleep?	

	MEASURING THE QUALITY OF YOUR SLEEP				
	not at all		**moderately**		**very**
6	How well do you feel this morning?				
	0	1	2	3	4
7	How enjoyable was your sleep last night?				
	0	1	2	3	4
8	How mentally alert were you in bed last night?				
	0	1	2	3	4
9	How physically tense were you in bed last night?				
	0	1	2	3	4

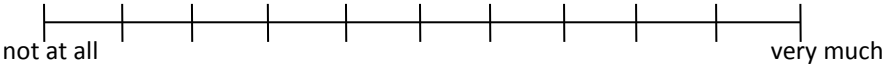
Please read each statement then circle the most appropriate point to indicate

how you feel right now

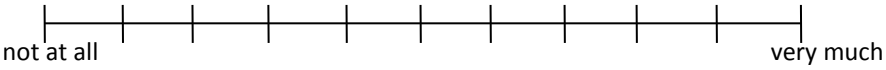
I feel calm



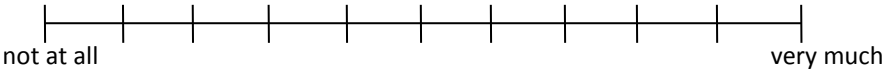
I feel tense



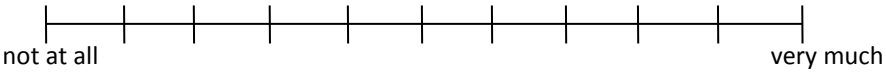
I am upset



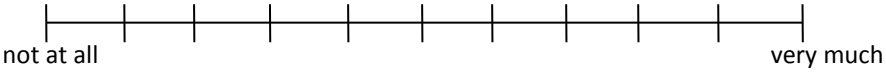
I feel relaxed



I feel content



I feel worried



AFTERNOON

Please provide the exact time that you provide the 'Afternoon' sample

	Afternoon
Time of sample	

Please complete the following questions following your 'Afternoon' sample

Please read each statement then circle the most appropriate point to indicate

how you feel right now

I feel calm

not at all very much

I feel tense

not at all very much

I am upset

not at all very much

I feel relaxed

not at all very much

I feel content

not at all very much

I feel worried

not at all very much

BED

Please provide the exact time that you provide the 'Bed' sample

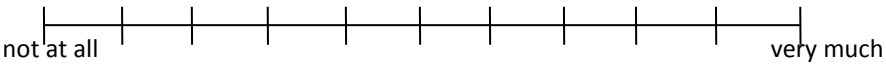
	Bed
Time of sample	

Please complete the following questions following your 'Bed' sample

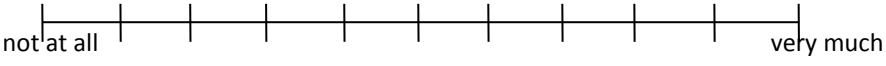
Please read each statement then circle the most appropriate point to indicate

how you feel right now

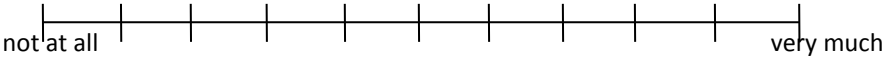
I feel calm



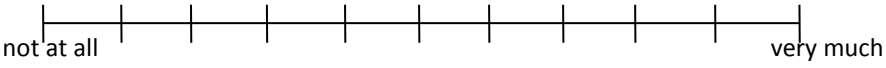
I feel tense



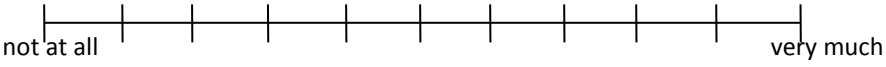
I am upset



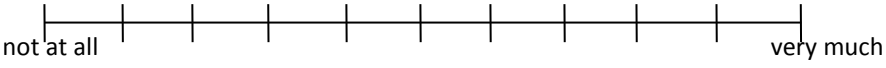
I feel relaxed



I feel content



I feel worried



DAY 3

Today's date ____ / ____ / _____

MORNING

Please provide the exact time that you provide each of the samples

	Wake	Wake +15	Wake +30	Wake +45	Wake +60
Time					
Time of sample					

Please complete the following questions following your 'Wake +60' sample

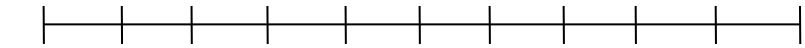
	MEASURING THE PATTERN OF YOUR SLEEP	
1	What time did you wake this morning?	
2	At what time did you rise from bed?	
3	At what time did you go to bed last night?	
4	Lights Out: At what time did you put the lights out to go to sleep?	
5	How long did it take you to fall asleep (minutes)? (After Lights Out)	
6	How many times did you wake up during the night?	
7	How long were you awake during the night (in total)?	
8	About how long did you sleep altogether (hours/mins)?	
9	How many sleeping pills did you take to help you sleep?	

	MEASURING THE QUALITY OF YOUR SLEEP				
	not at all		**moderately**		**very**
6	How well do you feel this morning?				
	0	1	2	3	4
7	How enjoyable was your sleep last night?				
	0	1	2	3	4
8	How mentally alert were you in bed last night?				
	0	1	2	3	4
9	How physically tense were you in bed last night?				
	0	1	2	3	4

Please read each statement then circle the most appropriate point to indicate

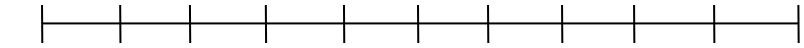
how you feel right now

I feel calm



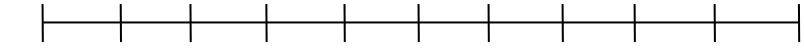
not at all very much

I feel tense



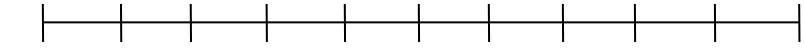
not at all very much

I am upset



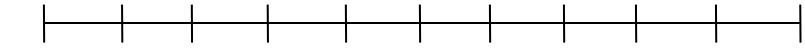
not at all very much

I feel relaxed



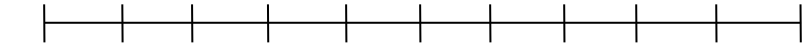
not at all very much

I feel content



not at all very much

I feel worried



not at all very much

AFTERNOON

Please provide the exact time that you provide the 'Afternoon' sample

	Afternoon
Time of sample	

Please complete the following questions following your 'Afternoon' sample

Please read each statement then circle the most appropriate point to indicate

how you feel right now

I feel calm

not at all very much

I feel tense

not at all very much

I am upset

not at all very much

I feel relaxed

not at all very much

I feel content

not at all very much

I feel worried

not at all very much

BED

Please provide the exact time that you provide the 'Bed' sample

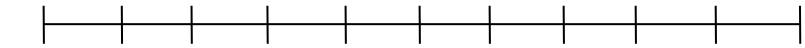
	Bed
Time of sample	

Please complete the following questions following your 'Bed' sample

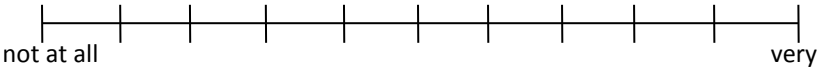
Please read each statement then circle the most appropriate point to indicate

how you feel right now

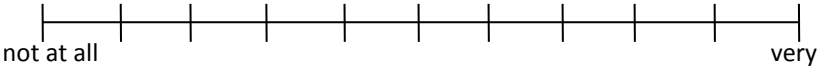
I feel calm



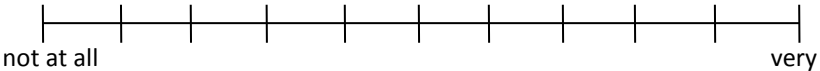
I feel tense



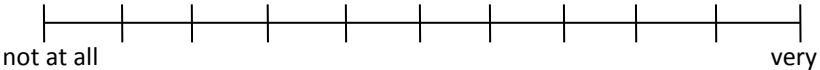
I am upset



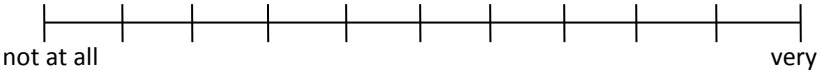
I feel relaxed



I feel content



I feel worried



APPENDIX BB: Chapter 7: Sleep characteristics of normal sleepers derived from self-reported and objectively (PSG) assessed measures

Sleep Characteristics	**Mean (SD)**		
Self-report			
PSQI (subjective sleep quality)	0.64 (0.49)		
PSQI (sleep latency)	0.82 (0.59)		
PSQI (sleep duration)	0.18 (0.39)		
PSQI (habitual sleep efficiency)	0.18 (0.50)		
PSQI (sleep disturbances)	1.00 (0.44)		
PSQI (use of sleep medication)	0.09 (0.43)		
PSQI (daytime dysfunction)	0.59 (0.50)		
PSQI (global)	3.45 (1.77)		
FIRST	19.14 (4.43)		
ISI	2.64 (2.19)		
PSG Variables	**(n2)**	**(n3)**	**(average n2 & n3)**
TST (min)	437.82 (32.13)	430.43 (30.08)	434.13 (30.02)
SOL (min)	12.39 (9.53)	14.73 (11.41)	13.55 (10.08)
WASO (min)	13.82 (10.63)	15.86 (12.41)	14.84 (11.14)
SEI (%)	97.04 (1.97)	96.52 (2.37)	96.78 (2.07)
%N1 (of TST)	3.34 (1.35)	3.70 (1.39)	3.52 (1.26)
%N2 (of TST)	53.84 (5.50)	52.08 (4.47)	52.96 (4.53)
%N3 (of TST)	19.34 (4.85)	20.02 (4.43)	19.68 (4.24)
%REM (of TST)	23.48 (4.54)	24.33 (4.91)	23.91 (4.01)
REM Latency (min)	102.30 (42.59)	89.45 (30.91)	95.88 (35.73)
Number of awakenings (over TSP)	13.68 (5.68)	13.64 (4.88)	13.66 (5.07)
% wake (over TSP)	5.52 (2.66)	6.54 (3.75)	6.03 (3.11)
Subjective Sleep Diary	**(n2)**	**(n3)**	**(average n2 & n3)**
TST (min)	455.91 (30.81)	450.50 (37.15)	447.84 (33.77)
SOL (min)	14.32 (7.76)	14.23 (9.60)	14.48 (7.89)
WASO (min)	9.77 (10.15)	5.00 (6.12)	6.86 (5.85)
SEI (%)	87.76 (6.10)	86.02 (6.19)	86.93 (5.55)

Note: $N = 22$. PSQI, Pittsburgh sleep quality index; FIRST, ford insomnia response to stress test; ISI, insomnia severity index; PSG, polysomnography; SOL, sleep onset latency; WASO, wake after sleep onset; TST, total sleep time; %N1, percentage of stage 1 sleep; %N2, percentage of stage 2 sleep; %N3, percentage of slow wave sleep; %REM, percentage of rapid eye movement sleep; SEI, sleep efficiency index; TSP, total sleep period.

APPENDIX CC

Gotts, Z. M., Deary, V., Newton, J., Van der Dussen, D., De Roy, P., & Ellis, J. G. (2013). Are there sleep-specific phenotypes in patients with chronic fatigue syndrome? A cross-sectional polysomnography analysis. *BMJ open*, *3*(6).