THE UNIVERSITY
of EDINBURGH

Development of a Psychological Intervention for Post-Stroke Fatigue

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PhD

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2015

Declaration

I declare that this thesis has been composed solely by myself and that the work has not been submitted in any previous application for a degree or professional qualification. I confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

Part of the work presented in Chapters 1 and 2 was previously published in *Stroke* (2015); 46: 893-898 as Model of understanding fatigue after stroke by Wu, S., Mead, G.E., Macleod, M.R., & Chalder, T. This study was conceived by all of the authors. I conducted the literature searches and drafted the manuscript. All authors contributed substantially to the manuscript revision and approved the final version. Mead and Macleod are my academic supervisors.

Part of the work presented in Chapter 2 was previously published in *Stroke* (2014); 45: 1778-1783 as Psychological associations of post-stroke fatigue: a systematic review and meta-analysis by Wu, S., Barugh, A.J., Macleod, M.R., & Mead, G.E. This study was conceived together with my supervisors (Mead and Macleod) and I wrote the protocol. I conducted the literature search, study selection, data analysis, and manuscript drafting. Barugh helped with study selection. All authors contributed substantially to the manuscript revision and approved the final version.

The work presented in Chapter 5 was previously published in *Cochrane Database of Systematic Reviews* (2015) as Interventions for post-stroke fatigue by Wu, S., Kutlubaev, M.A., Chun, H-Y.Y., Cowey, E., Pollock, A., Macleod, M.R., Dennis, M., Keane, E., Sharpe, M., & Mead, G.E. A previous version of this review was published in 2009. Pollock, Mead and Macleod provided advice on modifying the protocol and I wrote the protocol. The protocol was agreed by all authors before the literature searches were conducted by the Cochrane Stroke Group co-ordinators (Hazel Fraser and Brenda Thomas). Kutlubaev, Chun, Cowey, Mead and I selected

studies. Kutlubaev, Chun and I extracted data. I analysed data and drafted the manuscript. All authors contributed substantially to the manuscript revision and approved the final version.

Signature _____ Date _____

Abstract

Background

Post-stroke fatigue (PSF) is a common and distressing problem after stroke. It impedes patients' participation in daily activities and is associated with higher risks of institutionalisation and death following stroke. Despite its high prevalence and detrimental consequences, little research has been conducted to develop effective treatments for PSF. Psychological interventions are effective in treating fatigue in other conditions such as cancer and chronic fatigue syndrome. This thesis described the development of a psychological intervention for PSF.

Methods

This thesis was based on the theoretical, modelling and part of the piloting phases of the Medical Research Council (MRC) framework for designing and evaluating complex interventions. This intervention was developed in collaboration with a multidisciplinary group of stroke clinicians, clinical psychologists, a psychotherapist, and stroke survivors. Both qualitative and quantitative methods were used. Systematic reviews were conducted to explore the natural history of PSF and to identify potential targets for a psychological intervention for PSF. The format of the intervention was adapted from existing psychological interventions for cancer-related fatigue and chronic fatigue syndrome. The intervention was delivered by a clinical psychologist (i.e. the therapist) to 12 patients with PSF (i.e. the participants) to test its acceptability and feasibility in the local health system. After the feasibility study, the intervention was refined according to the feedback from the participants and the therapist. A Cochrane review of interventions for PSF was updated to identify any new evidence that could inform future studies.

Results

Systematic reviews suggested that PSF often occurred early after stroke and persisted over time (which justified the need for interventions for PSF) and that PSF was associated with distressed mood, lower self-efficacy, reduced physical activity and

sleeping problems (which were potential targets for the treatment of PSF). Based on interventions that have been used to treat fatigue in other conditions, these psychological and behavioural factors could be addressed by psychological interventions that challenge patients' thoughts and behaviours (i.e. the cognitive behavioural therapy, CBT). Thus a manualised CBT was developed for PSF. This CBT was delivered to each participant individually, through six face-to-face treatment sessions over a period of 12 weeks, followed by a telephone-delivered review session one month later. Both the participants and the therapist gave favourable opinions on the acceptability of the intervention. The recruitment and follow-up procedures were feasible in the local health system. Following the feedback from participants and therapist, the intervention manual was refined for future use, where the last two treatment sessions will be combined to a single session and the review session will be delivered in person by the therapist. There were statistically significant improvements in fatigue, mood, mobility, and participation in social activity from baseline to three months after the end of treatment. The updated Cochrane review concluded that there was insufficient evidence to recommend any specific intervention for PSF; psychological interventions are one type of interventions worth being investigated in future trials.

Conclusions

PSF is associated with distressed mood, lower self-efficacy, reduced physical activity and sleeping problems, which are potential targets for the treatment of PSF. Although there was insufficient evidence to recommend any intervention for the treatment of PSF, psychological interventions are one type of promising interventions worth future investigation. The promising results from this uncontrolled feasibility study support the need for a subsequent exploratory randomised controlled trial (RCT) of this brief psychological intervention.

Lay Summary

Background

Post-stroke fatigue (PSF) is a common and distressing problem after stroke, but we know little about how to treat fatigue in people with stroke. Talking therapies are effective in treating fatigue in other conditions such as cancer and chronic fatigue syndrome. Thus, in this thesis I have developed and tested a talking therapy for PSF.

Methods

I developed this therapy together with stroke clinicians, clinical psychologists, a psychotherapist, and stroke patients. I reviewed the existing research studies of PSF to develop the theory for this therapy. I adapted the current therapy from existing talking therapies for cancer-related fatigue and chronic fatigue syndrome. The therapy was delivered by a clinical psychologist (i.e. the therapist) to 12 stroke patients with PSF (i.e. the participants), to test whether it would be acceptable and feasible in the local health system. I refined the therapy according to the feedback from participants and therapist. I also reviewed studies to identify if there is any new evidence to guide treatment of PSF.

Results

Based on existing studies, I identified that distressed mood, reduced physical activity, and sleeping problems were associated with PSF. Thus the therapy was developed to treat these factors with an aim to reduce fatigue. We delivered the current talking therapy to each participant through six face-to-face treatment sessions and gave a review session by telephone one month after the final treatment session. Both participants and therapist reported that the intervention was acceptable to them. The study procedures worked well in the local health system. There were significant improvements in fatigue, mood, mobility, and participation in social activity from before treatment to three months after the end of treatment. Following the feedback from participants and therapist, I made changes to the therapy for future studies, which included the combination of the last two treatment sessions into a single

treatment session and delivering the review session in person by the therapist. My review of literature suggested no new evidence to inform the treatment of PSF.

Conclusions

In this thesis, I present information which increases our knowledge of people with fatigue after stroke. I have tried to develop a talking therapy to reduce PSF and tested it with a small group of stroke patients. The next stage would be a clinical study to test this therapy in treating PSF as against with usual medical care.

Acknowledgements

I would like to thank my supervisors Professor Gillian Mead and Professor Malcolm Macleod for their guidance, support and encouragement throughout my PhD study. They are always positive and inspiring. It has been a fantastic experience working with them.

I am grateful to my collaborators who contributed substantially to the published work related to this PhD study. They are Gillian Mead, Malcolm Macleod and Trudie Chalder for the study entitled *Model of understanding fatigue after stroke* in *Stroke* (2015); Amanda Barugh, Malcolm Macleod and Gillian Mead for the study entitled *Psychological associations of post-stroke fatigue: a systematic review and meta-analysis* in *Stroke* (2014); Mansur Kutlubaev, Ho-Yan Yvonne Chun, Eileen Cowey, Alex Pollock, Malcolm Macleod, Martin Dennis, Elizabeth Keane, Michael Sharpe and Gillian Mead for the study entitled *Interventions for post-stroke fatigue* in *Cochrane Database of Systematic Reviews* (2015). These studies provided the theoretical evidence for the current intervention.

This research would not be possible without the stroke survivors and their caregivers who participated in my study. I greatly appreciate the time and commitment of these participants. I would like to thank my colleagues who helped with the recruitment; those included colleagues of the UK Stroke Research Network (Anne Forster and Zena Jones), colleagues at the Stroke Clinic of Western General Hospital (Martin Dennis and Maggie Scott), Stroke Research Nurses at the Royal Infirmary of Edinburgh (Seona Burgess, Katrina McCormack, and Ruth Paulton), and Stroke Nurses from the Chest Heart & Stroke Scotland (Audrey Bruce, Thomas Jones, Fiona Ryan, and Kay Walkinshaw).

I would like to thank my colleagues at the Department of Geriatric Medicine (Amanda Barugh, Maureen Harding, and Sharon Moncrieff) and at the Clinical Research Facility (Audrey Kuchnowski and Liz Fraser) of the Royal Infirmary of Edinburgh for their help to co-ordinate the study. I would like to thank colleagues at

the Department of Clinical Psychology of Astley Ainslie Hospital (Jo Gouick) for providing a clinical room for the intervention delivery.

I would like to thank Gillian Mead, Malcolm Macleod, Trudie Chalder, Kirstin Anderson and David Gillespie for their collaboration in developing this intervention and conducting the feasibility study.

I would like to thank Professor Ming Liu, my previous academic supervisor in China, who inspired my interest in stroke research and encouraged me to study aboard. Thanks to the Chinese government and the University of Edinburgh, which provided the opportunity and funding for me to study in Edinburgh.

Last but not least, thank you to all my family, particularly my mum (Xiaochun Gao), dad (Zhimin Wu) and grandpa (Zhonggui Wu), for your understanding and love, who supported me all these years.

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Full publications

- Wu, S., Mead, G., Macleod, M. & Chalder, T. (2015). Model of understanding fatigue after stroke. *Stroke*, 46, 893-898. (Appendix 1.1)

- Wu, S., Barugh, A., Macleod, M. & Mead, G. (2014). Psychological associations of poststroke fatigue: a systematic review and meta-analysis. *Stroke*, 45, 1778-1783. (Appendix 1.2)

- Wu, S., Kutlubaev, M. A., Chun, H. Y. Y., Cowey, E., Pollock, A., Macleod, M. R., Dennis, M., Keane, E., Sharpe, M. & Mead, G. E. (2015). Interventions for post-stroke fatigue. *Cochrane Database of Systematic Reviews*, Art. No.: CD007030. doi:10.1002/14651858.CD007030.pub3. (Appendix 1.3)

  (I have obtained the formal permission from the publishers to include a copy of these publications in this thesis)

Conference abstracts

- Wu, S., Barugh, A., Macleod, M. & Mead, G. (2013). Psychological associations of post-stroke fatigue: a systematic review. *International Journal of Stroke*, 8 (Suppl. 3), S71. UK Stroke Forum 2013 Conference. 3-5 December 2013. Harrogate International Centre, North Yorkshire, UK. (This abstract has been awarded the Poster Presentation Prize by the UK Stroke Forum, see Appendix 2.1 for the abstract, poster and the prize certificate)

- Wu, S., Kutlubaev, M. A., Chun, H. Y. Y., Cowey, E., Pollock, A., Macleod, M. R., Dennis, M., Keane, E., Sharpe, M. & Mead, G. E. (2015). Interventions for post-stroke fatigue: A systematic review and meta-analysis. *International Journal of Stroke*, 10 (Suppl. 2), S111. The European Stroke Organisation Annual Conference. 17-19 April 2015. Scottish Exhibition and Conference Centre, Glasgow, UK. (This abstract has been awarded the Best Poster Award by the European Stroke Organisation, see Appendix 2.2 for the abstract, poster and the award certificate)

- Wu, S., Chalder, T., Anderson K.E., Gillespie, D.C., Macleod, M.R. & Mead, G.E. (2015). Development and evaluation of a complex intervention for post-stroke fatigue. *International Journal of Stroke*, 10 (Suppl. 2), S417. The European Stroke Organisation Annual Conference. 17-19 April 2015. Scottish Exhibition and Conference Centre, Glasgow, UK. (see Appendix 2.3 for the abstract and poster)

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List of Abbreviation

Abbreviation	Full expression	Initial page number
95% CI	95% Confidence Interval	48
ACTH	Adrenocorticotropic Hormone	45
ADLs	Activities in Daily Living	17
APA	Adaptive Physical Activity	169
CAM-COG	Cambridge Cognitive Examination	44
CBT	Cognitive Behavioural Therapy	20
CHSS	Chest Heart & Stroke Scotland	92
CIS	Checklist Individual Strength	15
COGRAT	Cognitive Treatment plus Graded Activity Training	19
CPAP	Continuous Positive Airway Pressure	19
CRF	Clinical Research Facility	117
CRP	C-reactive Protein	45
CT	Computed Tomography	42
DALYs	Disability-adjusted Life Years	4
df	Degrees of Freedom	67
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition	101

DWI	Diffusion-weighted Imaging	42
FAS	Fatigue Assessment Scale	11
FSS	Fatigue Severity Scale	11
GBD	Global Burden of Diseases	3
GM-SAT	Greater Manchester Stroke Assessment Tool	12
GP	General Practitioner	102
HPA	Hypothalamic-pituitary-adrenal	45
HRQoL	Health-related Quality of Life	95
IADL	Instrumental Activities of Daily Living	105
ICF	International Classification of Functioning, Disability and Health	4
IL1RN	Interleukin-1 Receptor Antagonist Gene	45
LACI	Lacunar Infarcts	3
MCID	Minimal Clinically Important Difference	104
MD	Mean Difference	134
MFSI	Multidimensional Fatigue Symptom Inventory	11
MFI	Multidimensional Fatigue Inventory	15
MFS	Mental Fatigue Scale	14
MMSE	Mini-mental State Examination	44
MoCA	Montreal Cognitive Assessment	44
MRC	Medical Research Council	22

MRI	Magnetic Resonance Imaging	5
NEADL	Nottingham Extended Activities of Daily Living	105
NHS	National Health System	22
NICE	National Institute for Health and Care Excellence	20
NIHR	National Institute for Health Research	82
OCSP	Oxfordshire Community Stroke Project	2
OR	Odds Ratio	48
OXVASC	Oxford Vascular Study	2
PACI	Partial Anterior Circulation Infarcts	3
PET	Positive Emission Tomography	43
PHQ-9	Patient Health Questionnaire-9	101
PICO	Studied Populations, Treatment Intervention, Control Intervention, and Outcome Measures	159
POCI	Posterior Circulation Infarcts	3
POMS	Profile of Mood States	11
PSF	Post-stroke fatigue	1
PTSD	Post-traumatic Stress Disorder	52
RCT	Randomised Controlled Trial	1
RR	Risk Ratio	150

SF-36	Short Form-36	11
SIS	Stroke Impact Scale	105
SMD	Standardised Mean Difference	150
SNP	Single Nucleotide Polymorphism	45
SOL	Self-observation List	165
SSQOL	Stroke-specific Quality of Life	14
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology	63
TACI	Total Anterior Circulation Infarcts	3
TCM	Traditional Chinese Medicine	163
TIA	Transient Ischaemic Attack	124
TMS	Transcranial Magnetic Stimulation	43
TOAST	Trial of Org 10172 in Acute Stroke Treatment	3
UK	United Kingdom	7
WHO	World Health Organisation	3

CHAPTER I Introduction

The purpose of this PhD study was to develop a psychological intervention for post-stroke fatigue (PSF). This thesis has six chapters. Chapter 1 provides an overview of stroke and a general introduction of PSF, a common symptom after stroke. Chapter 2 explores the natural history and clinical correlates of PSF, and then focuses on its psychological associations. Based on the factors identified as being associated with PSF, a conceptual model is proposed for understanding PSF, which indicates that psychological and behavioural factors play important roles in maintaining fatigue symptoms. Chapter 3 describes a multi-stage and iterative process of developing a manualised intervention for PSF, which involves identifying the evidence, developing the treatment rationale, and designing the intervention programme. In Chapter 4, a feasibility study is conducted to test the acceptability of the intervention and the feasibility of the study design. Chapter 5 is an update of the Cochrane review of interventions for PSF, which aims to identify any new evidence that could be included in future studies. This review suggests that psychological interventions are promising treatment strategies for PSF, whilst their efficacy should be investigated in further randomised controlled trials (RCTs). Finally, Chapter 6 discusses clinical implications of the current study and directions for future research.

This initial chapter (Chapter 1) starts with a brief introduction of stroke, followed by a focus on PSF. Section 1.1 introduces the definition, epidemiology, and common consequences of stroke. Section 1.2 discusses PSF in general, reviewing its prevalence, definition, measurement, potential mechanisms, and impacts on life after stroke. This section also reviews interventions for fatigue after stroke and in other conditions, with a conclusion that psychological interventions are promising strategies to treat PSF. Section 1.3 introduces a framework for the development of complex interventions and discusses how the aim and objectives of this thesis fit the framework.

Section 1.1 Overview of stroke

1.1.1 Definition and types of stroke

Stroke is defined as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" (Aho et al., 1980). Stroke occurs when the blood flow that supplies the brain is disrupted, resulting in death of brain cells due to the lack of oxygen and nutrients. There are two types of stroke, depending on whether the brain blood flow is disrupted by the blockage (i.e. ischaemic stroke) or the rupture (i.e. haemorrhagic stroke) of a blood vessel. According to the Oxfordshire Community Stroke Project (OCSP) in 1980s, ischaemic stroke accounts for 80% of all stroke events and haemorrhagic stroke accounts for 15%, with the other 5% of the uncertain type (Bamford et al., 1990). A later study (the Oxford Vascular Study, OXVASC) with the same general population of the OCSP study reported that of 262 first-ever incident stroke occurred between 2002 and 2004, 223 (85%) were ischaemic stroke, 33 (13%) were haemorrhagic stroke and six (2%) were of the unknown type (Rothwell et al., 2004). Similar results were reported in North America that, of all stroke events, 87% are ischaemic stroke and 13% are haemorrhagic stroke (American Heart Association, 2014).

Ischaemic stroke

There are mainly two subtypes of ischaemic stroke: thrombotic stroke (the blood clot develops in the brain blood vessel, known as atherosclerosis) and embolic stroke (the blood clot develops in other part of the body, usually from carotid arteries or heart, and travels through the bloodstream to the brain). In addition, ischaemic stroke can be caused by some rare aetiologies such as non-atherosclerotic vasculopathies. Furthermore, the stenosis or occlusion of brain blood vessels can occur in either large arteries or small arteries, or both. Thus according to the aetiologies, ischaemic stroke can be classified to five subtypes: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined aetiology, and stroke of

undetermined aetiology, which is known as the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification (Adamas et al., 1993).

Different blood vessels supply different brain areas, which control different body functions. The disruption of blood flow to certain brain area could impair the corresponding functions. Thus according to the presenting impairments (i.e. symptoms and signs), the OCSP classification suggests four subtypes of ischaemic stroke: lacunar infarcts (LACI), total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), and posterior circulation infarcts (POCI) (Bamford et al., 1991).

Haemorrhagic stroke

Haemorrhagic stroke occurs when a blood vessel that supplies the brain ruptures and bleeds into the brain. Apart from the death of brain cells due to the lack of oxygen and nutrients, the leaking blood can cause pressure and swelling to the surrounding brain tissues, which can result in further brain damage. There are two major causes of haemorrhagic stroke: intracerebral haemorrhage and subarachnoid haemorrhage. Intracerebral haemorrhage is the bleeding of blood vessels within the brain parenchyma, of which hypertension is an important risk factor. Subarachnoid haemorrhage is the bleeding in the subarachnoid space between the brain parenchyma and the membrane that covers it (i.e. arachnoid mater), which is often caused by an aneurysm or arteriovenous malformation.

1.1.2 Epidemiology of stroke

The World Health Organisation (WHO) estimates that approximately 15 million people suffer a stroke worldwide each year (Mackay et al., 2004). Based on the findings of the Global Burden of Diseases (GBD) study, it is estimated that 33 million people had stroke in the year 2010 and 17 million of them were incident stroke (Feigin et al., 2014). Despite the difference in the incidence trends of stroke across countries, the global burden of stroke continues to increase due to the ageing population (Mackay et al., 2004). Over the past few decades, the stroke incidence has decreased in high-income countries but increased substantially in low to middle

income countries (Feigin et al., 2009). From 1990 to 2010, the absolute number of people with incident stroke has increased worldwide , while the mortality rate has decreased during this period, resulting in a significant increase (by 84%) of the absolute number of stroke survivors (Feigin et al., 2014). It is estimated that the global burden of stroke would rise from 38 million disability-adjusted life years (DALYs, a measure of overall illness burden, i.e. the number of years lost due to ill-health, disability, and early death, compared with life expectancy) in 1990 to 61 million DALYs in 2020 (Mackay et al., 2004).

1.1.3 Consequences of stroke

Although the survival rate following stroke has increased, stroke is still the second most common cause of death in the world (Lozano et al., 2013). It is estimated that stroke caused 6.7 million deaths in 2012 worldwide (World Health Organization, 2014). Immediate mortality of stroke is high and about 20% of people die within 30 days following their stroke (Scottish Intercollegiate Guidelines Network, 2010). The reported survival rates differ between stroke subtypes: patients who have ischaemic stroke have higher survival rates than patients who have haemorrhagic stroke (Krishnamurthi et al., 2013); in addition, patients with anterior circulation ischaemic stroke have relatively low survival rates by one year after stroke than patients with posterior circulation ischaemic stroke (Bamford et al., 1991). The outcome also varies across different countries, for example, for both ischaemic and haemorrhagic stroke, the survival rates are relatively high in high-income countries than those in the countries with lower income (Krishnamurthi et al., 2013).

The increased number of people with incident stroke and the improved survival rate following stroke result in an increase in the number of stroke survivors. Stroke is the third most common cause of disability in the world (Murray et al., 2013). The American Heart Association suggests classifying clinical outcomes of stroke as impairments, functional disabilities, and handicap (American Heart Association, 1998), which is consistent with the International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2001). Impairments are symptoms and signs of underlying pathology of brain damage, which can present as

dysfunctions in the following one or more domains: movement, sensory, vision, affect, cognition, or language (American Heart Association, 1998). Disabilities are the result of functional impairments, presenting as restriction in performing daily functional activities. Handicap is the loss of role in daily living and social life because of the inability in functional activities. According to the ICF framework (World Health Organization, 2001), impact of stroke can be further categorised as functioning and disability. Functioning refers to integrity of body functions and structures, as well as adequate performance in activities and participation; disability refers to having problems in any of these domains, i.e. functional impairments, activity limitations, or participation restrictions. This framework also considers the external (i.e. environmental factors) and internal (i.e. personal factors) factors that influence functioning and disability (World Health Organization, 2001).

A stroke may result in impairments in all aspects of body functions (American Heart Association, 1998). Symptoms of stroke vary from person to person based on the size and location of stroke lesions. Dysfunctions following stroke correspond to the responsible brain areas that have been damaged. When brain cells in a certain area are damaged by a stroke, the function controlled by this area may be impaired. For example, anterior circulation stroke can be characterised by higher cerebral dysfunctions such as dysphasia and visuospatial disorders, and posterior circulation stroke can be characterised by symptoms of cerebellar dysfunctions and the damage in brainstem can affect vital functions such as breathing. Lesion size is a determinant of the severity of stroke symptoms. A mild stroke may only cause limb weakness, whilst a severe stroke can result in paralysis or even death. Although activities and participation may be primarily limited by functional impairments, other factors such as emotions (personal factors) and social relationships (environmental factors) may also play roles in affecting functional abilities.

Although the location and size of stroke lesions are important determinants of stroke symptoms, some people with pathological brain lesions do not have stroke symptoms. For example, research studies reported that 8% to 28% of the general population had brain infarcts on Magnetic Resonance Imaging (MRI) but did not

have any history of stroke symptoms (Vermeer et al., 2007). In contrast, about 30% of patients with symptomatic lacunar stroke syndromes did not have any visible subcortical infarct on MRI (Doubal et al., 2011).

In general, stroke has multi-level and diverse impacts on individuals, from body functioning (impairments), independence in daily activities (disabilities), to roles in participating in family and social life (handicap), and involves personal factors and relationships with other people. Taking account these factors, clinical guidelines recommend that rehabilitation of stroke should target the individual needs of stroke patients, and aim to maximise the individual's activity, participation and quality of life, and minimise the distress to caregivers (Scottish Intercollegiate Guidelines Network, 2010).

Section 1.2 Post-stroke fatigue

In the United Kingdom (UK), about 150,000 incident strokes occur each year and there are 1.2 million stroke survivors (Stroke Association, 2015). Stroke is the leading cause of adult disability and approximately half of all stroke survivors have a disability and more than one third of stroke survivors are dependent on others (Stroke Association, 2015). Of the wide range of symptoms experienced after stroke, fatigue is one of the most common and debilitating problems. In 2011, a UK-based James Lind Alliance survey was conducted with stroke patients, their caregivers and stroke-related health professionals, which reported that 'how to manage fatigue' was ranked among the top ten research priorities of all 226 unique unanswered treatment uncertainties relating to life after stroke (Pollock et al., 2012).

This section outlines a comprehensive account of PSF, including its prevalence, definition, measurement, potential mechanisms, impacts on life, and treatment interventions. This section is based on a systematic review of studies of PSF published previously (Wu et al., 2015b), with an updated search of the recent literature. Although briefly introduced in this section, the natural history and clinical correlates of PSF will be discussed in detail in the next chapter, as they provided the theoretical basis for the development of the psychological intervention for PSF described in this thesis.

1.2.1 Prevalence of post-stroke fatigue

Fatigue is ubiquitous but is more common and more severe in people with acute and chronic conditions, including stroke. Observational studies reported that the prevalence of self-reported fatigue in stroke patients could be twice or more as high as that in general controls (Ingles et al., 1999, van der Werf et al., 2001, Naess et al., 2005, Christensen et al., 2008, Smith et al., 2008). In addition, some patients reported that their fatigue after stroke was different from the fatigue that they had experienced prior to their stroke, because of its persistent presence and negative impacts on daily life (Barbour and Mead, 2011). PSF is often present early after stroke and tends to be persistent in some stroke patients (Duncan et al., 2012). The reported proportion of

patients with fatigue after stroke ranges from 23% to 75% (Choi-Kwon and Kim, 2011). The variation in proportion reflects the heterogeneity in the studied populations, time since stroke, and assessment methods of PSF.

1.2.2 Definition of post-stroke fatigue

The perception of fatigue is subjective (Chalder et al., 1993). Many different synonyms have been used in clinical practice and research studies to describe the feeling of fatigue, such as tiredness, exhaustion, weariness, drowsiness, lassitude, asthenia, boredom, sleepiness, lethargy, low vitality, and lack of energy or motivation. This diversity in terminology reflects that fatigue is a complex phenomenon, which can be defined from different perspectives.

Some researchers distinguish between 'physiological fatigue' (i.e. a state of general tiredness that is the result of excessive physical and/or mental activities, and can be improved after rest) and 'pathological fatigue' (i.e. a constant state of weariness that is unrelated to previous activity levels, and is usually not improved by rest) (de Groot et al., 2003). Physiological fatigue is a normal experience in daily life, usually with a single, readily identifiable cause and characterised as acute (i.e. with rapid onset and short duration), whilst pathological fatigue is perceived as abnormal or excessive, usually with multiple or unknown causes and characterised as chronic (i.e. with persistent presence) (de Groot et al., 2003). In neurological disorders such as stroke, fatigue can occur during the acute phase and persist to the chronic phase, and the persistent fatigue is usually considered pathological, which is of interest in this thesis.

Persistent fatigue after stroke (i.e. PSF) is different from the feeling of tiredness triggered by sustained physical activity. Tseng and colleagues found that aerobic fitness was the only independent predictor of the level of fatigue immediately after physical exercise, whereas depression was the only independent predictor of chronic fatigue in stroke patients (Tseng et al., 2010). In addition, the presentation of PSF is not limited in the physical domain. In qualitative studies, stroke patients described their fatigue as "a general feeling of tiredness", "a tiredness in the muscles", or

"mental tiredness" (Barbour and Mead, 2011). Thus the concept of PSF should encompass physical as well as mental fatigue. To identify fatigue that matters to stroke patients and warrants clinical assessment and treatment, Lynch and colleagues developed a case definition for PSF, which reads "over the past month, there has been at least a 2-week period when the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities" (Lynch et al., 2007). This definition describes fatigue as a feeling of lack of energy or need to rest rather than lack of motivation, boredom, or sleepiness (Lynch et al., 2007). Also it reflects the chronic nature of PSF and emphasises its impact on everyday activities, both physical and mental.

Our understanding of the causes of PSF is limited. Fatigue can be classified as 'primary' if it is present in the absence of any obvious causes apart from stroke itself, or 'secondary' if it develops in relation to any other comorbidities (e.g. depression, anaemia, or hypothyroidism) or the use of certain medications (e.g. beta-blockers, antidepressants, or anticonvulsants) (Kutlubaev et al., 2015). Also it can be divided into 'somatic fatigue' if related to organic diseases, 'psychological fatigue' if associated with poor motivation, 'physical fatigue' if occurring after muscular exertion, and 'mental fatigue' if appearing with cognitively demanding tasks (Staub and Bogousslavsky, 2001b). However, these subtypes are not mutually exclusive and there is little empirical evidence for the concept of these subtypes from stroke studies (Hackett et al., 2014).

Considering the pathophysiology, fatigue in neurological disorders can be classified as 'central fatigue' and 'peripheral fatigue' (Chaudhuri and Behan, 2004). Central fatigue is a subjective sense of fatigue perceived at the level of central nervous system, which is due to the failure of signal transmission in the central nervous system during the physical and/or mental activities. Peripheral fatigue refers to muscle weakness (i.e. fatigability) due to disorders of muscle and/or neuromuscular junction. However, the pathophysiological mechanism of fatigue in stroke patients is underinvestigated, which was recently reported in a small study with 70 stroke

patients that the reduced motor cortex excitability was associated with higher levels of fatigue after stroke (Kuppuswamy et al., 2015). No study has explored the peripheral mechanisms of PSF and yet the association between the subjective sense of fatigue and muscle weakness is unknown.

1.2.3 Measurement of post-stroke fatigue

Self-reported fatigue scales

Clinical assessment of fatigue often relies on patients' subjective reporting. A number of structured self-report scales have been used to assess the presence or severity of fatigue in stroke patients. However, these scales, which are usually devised in non-stroke populations, may lack validity in patients with stroke. Among over one hundred fatigue scales that have been used in research studies (Egerton et al., 2015), only 11 (as far as I am aware) have been specifically tested for their psychometric properties in stroke populations (see Table 1.1). Other scales were frequently used in stroke studies but their psychometric properties have not been established in stroke populations (see Table 1.2). Some of these scales are multidimensional scales, reflecting the multidimensional nature of PSF that may involve physical, cognitive, psychological, and behavioural components. However, there is no distinct boundary between different subtypes of fatigue. Due to complex interactions between physical and mental elements in completing tasks in daily life, it is difficult to separate these elements.

Table 1.1 summarises the scales that have been specifically tested for their psychometric properties in measuring fatigue in stroke patients. Although all of these scales showed satisfactory results of the tested psychometric properties, none of them satisfied all criteria for assessing the quality of self-report scales (i.e. reliability, validity, responsiveness, and interpretability (Mokkink et al., 2010)). Furthermore, it is difficult to determine the criterion validity of these scales, as there is no generally accepted definition of PSF.

With an aim to identify a fatigue scale that is most valid, feasible, and reliable in stroke patients, Mead and colleagues reviewed fatigue scales used in research studies

(Mead et al., 2007). They identified five scales with best face validity as these captured the phenomenon of PSF and was free from items indistinguishable from the effects of stroke. Of these five scales, the Brief Fatigue Inventory (Mendoza et al., 1999) was excluded for further analysis after the initial selection because some stroke patients had difficulty in completing this scale (i.e. poor feasibility in stroke patients). The other four scales showed moderate to good test-retest reliability and good inter-rater reliability in measuring fatigue in stroke patients. These four scales were the Fatigue Assessment Scale (FAS) (Michielsen et al., 2003), the fatigue subscale of the Profile of Mood States (POMS-fatigue) (McNair and Lorr, 1964), the general subscale of the Multidimensional Fatigue Symptom Inventory (MFSI-general) (Stein et al., 1998), and the vitality subscale of the Short Form-36 version 2.0 (SF-36 v2-vitality) (Jenkinson et al., 1999). In addition, these four scales showed good convergent validity against each other, which reflects the common or similar items they share. Mead and colleagues recommended using the FAS to measure PSF as it had good feasibility in stroke patients, best test-retest reliability and high convergent validity as compared to the other three scales (Mead et al., 2007). Although the internal consistency of the FAS was low in this study, this might be due to that the FAS measures both physical and mental aspects of fatigue (Mead et al., 2007).

Fatigue Assessment Scale

Considering its good feasibility, validity, and reliability in measuring fatigue in stroke patients (Mead et al., 2007), I used the FAS to assess fatigue severity in this thesis. Another reason for choosing this scale was that it measures not only patients' subjective feelings but also the impact of fatigue on daily life. I did not use fatigue scales that only measure subjective feelings (see Table 1.1), as focusing on fatigue itself would make patients feel worse. Although the Fatigue Severity Scale (FSS) (Krupp et al., 1989) is the most commonly used fatigue scale in research studies, I did not use it because it does not contain any item related to the mental aspect of fatigue, which is a common presentation of PSF.

The FAS has items for both physical (e.g. 'physically, I feel exhausted') and mental (e.g. 'I have problems thinking clearly') aspects of fatigue, whilst it still has good unidimensionality in measuring fatigue severity as indicated by the exploratory factor analysis that the FAS showed a unique factor on the scree plot (Michielsen et al., 2003). In addition, the FAS has good divergent validity against depression. The principal component analysis on a combined pool of items from the FAS and depression scales showed a two-factor construct in both the health working population (Michielsen et al., 2003) and the stroke population (Smith et al., 2008). This psychometric property is important for the FAS to be used in this thesis. Fatigue is often confounded by depressive symptoms but the current study was not intended to target patients with severe depression, thus a fatigue scale that has good divergent validity against depression (i.e. FAS) is preferable as it would help to identify patients with fatigue that is not because of depression.

Case definition of post-stroke fatigue

'Clinically significant' fatigue is usually defined by certain cut-off scores of fatigue scales. However, dichotomising patients on the basis of a single cut-off score does not fully characterise fatigue. To identify fatigue that matters to stroke patients and warrants clinical assessment and treatment, Lynch and colleagues developed a case definition of PSF (which I have introduced in Section 1.2.2) (Lynch et al., 2007). This case definition showed good test-retest and inter-rater reliability in identifying the clinically significant fatigue with a mixture of 55 stroke patients from hospital and community (36% met the case definition) and also good convergent validity with other four fatigue scales including the FAS (Lynch et al., 2007). I used this case definition in this thesis as a dichotomous measure (i.e. for the presence or absence) for clinically significant fatigue in stroke patients.

A screening question for post-stroke fatigue

Although the case definition is a good measure for the clinically significant fatigue, it may be too strict to be used as a screening tool for PSF because it has specific requirements for the frequency and duration of fatigue. The Greater Manchester

Stroke Assessment Tool (GM-SAT) is a feasible tool to assess the unmet needs of community-dwelling stroke patients, which covers 35 common problems after stroke (Rothwell et al., 2013). In a survey using the GM-SAT to assess the needs of 137 stroke patients who were six months after stroke, fatigue was identified as the most frequent (34%) unmet need among all 35 proposed problems, by a single question 'Do you feel tired all the time or get tired very quickly since your stroke?' (Rothwell et al., 2013). This is consistent with the proportion of stroke patients with PSF (33%) as identified by the PSF case definition in a longitudinal cohort study (Duncan et al., 2014). There, I used this single fatigue question from the GM-SAT to screen for PSF in this thesis.

Table 1.1 Fatigue scales specifically developed or validated in stroke populations

Fatigue scales	Constructs assessed	No. of items	Validation studies (No. of stroke patients)	Validated language version
Unidimensional (sub)scales				
Fatigue Severity Scale-9 (FSS-9)	Fatigue feeling and impact	9	Valko 2008 (n=235) (Valko et al., 2008)	German
			Lerdal 2011 (n=119) (Lerdal et al., 2009)	Norwegian
Fatigue Severity Scale-7 (FSS-7)	Fatigue feeling and impact	7	Lerdal 2011 (n=119) (Lerdal et al., 2009)	Norwegian
Fatigue Assessment Scale (FAS)	Fatigue feeling and impact	10	Mead 2007 (n=55) (Mead et al., 2007)	English
Fatigue subscale of Profile of Mood States (POMS-fatigue)	Fatigue feeling	7	Mead 2007 (n=55) (Mead et al., 2007)	English
General subscale of Multidimensional Fatigue Symptom Inventory (MFSI-general)	Fatigue feeling	6	Mead 2007 (n=55) (Mead et al., 2007)	English
Vitality subscale of Short Form-36 version 2.0 (SF-36v2-vitality)	Fatigue feeling	4	Mead 2007 (n=55) (Mead et al., 2007)	English
Brief Fatigue Inventory (BFI)	Fatigue feeling and impact	9	Mead 2007 (n=55) (Mead et al., 2007)	English
Fatigue subscale of Newcastle Stroke-specific Quality of Life (NEWSQOL-fatigue)	Fatigue feeling and impact	3	Buck 2004 (n=106) (Buck et al., 2004)	English
Fatigue subscale of Functional Assessment of Chronic Illness Therapy (FACIT-fatigue)	Fatigue feeling and impact	13	Butt 2013 (n=51) (Butt et al., 2013)	English
Multidimensional scales				
Neurological Fatigue Index for Stroke (NFI-stroke)	Physical symptoms, cognitive symptoms, responsiveness to rest/sleep, and sleep	22	Mills 2012 (n=282) (Mills et al., 2012)	English
Mental Fatigue Scale (MFS)	Affective, cognitive and sensory symptoms, duration of sleep, and daytime variation in symptoms severity	15	Johansson 2014 (n=93) (Johansson and Ronnback, 2014)	Swedish

Table 1.2 Fatigue scales used in stroke studies without being previously investigated for psychometric properties in stroke populations

Fatigue scales	Domains assessed	No. of items	Original target populations	Examples of stroke studies using the scale
Single question for fatigue	Unidimensional: presence of fatigue	1	Different versions	(Appelros, 2006, Glader et al., 2002)
Visual Analogue Scale for Fatigue (VAS-fatigue)	Unidimensional: fatigue severity	1	Different versions	(Choi-Kwon et al., 2007, Michael et al., 2006)
Fatigue subscale of Checklist Individual Strength (CIS-fatigue)	Unidimensional: fatigue severity	8	Chronic fatigue syndrome (Vercoulen et al., 1994)	(van der Werf et al., 2001, Zedlitz et al., 2012)
Chalder Fatigue Scale (CFS)	Physical symptoms Mental symptoms	11	Patients in general hospitals and health controls (Chalder et al., 1993)	(Winward et al., 2009)
Multidimensional Fatigue Inventory (MFI)	General fatigue Physical fatigue Mental fatigue Reduced motivation Reduced activity	20	Cancer (Smets et al., 1995)	(Christensen et al., 2008, Andersen et al., 2012)
Fatigue Scale for Motor and Cognitive Functions (FSMC)	Cognitive fatigue Motor fatigue	20	Multiple sclerosis (Penner et al., 2009)	(Hubacher et al., 2012)
Fatigue Assessment Instrument (FAI)	Fatigue severity Situation specificity Consequences of fatigue Responsiveness to rest/sleep	29	Mixed clinical groups (multiple sclerosis, chronic fatigue, Lyme disease, lupus, and dysthymia) and health controls (Schwartz et al., 1993)	(Brioschi et al., 2009, Radman et al., 2012)
Fatigue Impact Scale (FIS)	Cognitive functioning Physical functioning Psychosocial functioning	40	Chronic fatigue syndrome, multiple sclerosis and hypertension (Fisk et al., 1994)	(Ingles et al., 1999, Jaracz et al., 2007, Parks et al., 2012)

1.2.4 Mechanisms of post-stroke fatigue

Mechanisms of PSF are unclear. Qualitative studies reported that PSF might be triggered by factors that occur at the time of stroke (e.g. the stroke lesion or admission to hospital) and then be exacerbated by behavioural changes such as poor sleep and boredom (Barbour and Mead, 2011). Observational studies suggested that the development of PSF involved an interaction of biological, psychological, behavioural and environmental factors (Chaudhuri and Behan, 2004). Our understanding of how PSF develops is mainly based on potential associations rather than definite causal relationships. To identify clinical factors that are associated with PSF, I conducted a systematic review of observational studies of PSF. Drawing on the literature, I developed a conceptual model of PSF, which illustrates the development of PSF as a temporal process that involves a mixture of pre-existing factors, stroke-specific impairments, and co-existing conditions (Wu et al., 2015b). Of these factors, some are shown as predictors of PSF in longitudinal studies, such as depressive symptoms (Wu et al., 2014b) and reduced physical activity (Duncan et al., 2015). In addition, some associated factors, such as reduced physical activity and sleeping problems, are modifiable. Thus management of these psychological and behavioural factors may help to reduce the impact of PSF on daily life. (The systematic review of observational studies of PSF and the model of PSF will be discussed in detail in Chapter 2)

1.2.5 Impact of post-stroke fatigue

Fatigue is a common and detrimental problem for stroke patients. In a study with 90 stroke patients who were at least one year after stroke, 50% of patients reported fatigue as their main complaint following stroke (van der Werf et al., 2001). Similarly, in another study with 88 stroke patients between three and 13 months after stroke, 40% of patients reported fatigue as the, or one of the worst, sequelae of their stroke, and 68% of them attributed their functional limitations to fatigue (Ingles et al., 1999). A population-based study found that, at two years after stroke, the presence of PSF was associated with being dependent on other people in daily living,

higher risk of institutionalisation, and having a poorer self-perception of general health (Glader et al., 2002). In addition, fatigued patients had a higher mortality rate at follow-up than those without fatigue (Glader et al., 2002) and a higher level of fatigue was associated with shorter subsequent survival (Mead et al., 2011).

PSF may be present as an "on and off" feeling in some patients but in others it is a feeling of tiredness "nearly every day" (White et al., 2012). Some researchers reported that the impact of PSF on daily living was more severe on physical domain as compared with cognitive or psychosocial domains (Choi-Kwon et al., 2005), whilst in the clinical practice we have observed that some stroke patients, who were physically active, reported their fatigue to be characterised by problems with concentration and thinking.

PSF impedes patients' participation in daily activities and stroke rehabilitation (Michael, 2002). In a qualitative study of the consequences of living with PSF, patients attributed their limitations in carrying out activities to fatigue (Carlsson et al., 2004). A small study suggested that fatigue was related to mobility deficits and cardiovascular deconditioning and resulted in the reduced ambulatory activities in daily living (Michael et al., 2006). Cross-sectional studies found that PSF was associated with patient-perceived disability (van der Werf et al., 2001, Appelros, 2006). Another study found that higher fatigue scores were associated with poorer performance in activities in daily living (ADLs) (Chen et al., 2015). In a pilot study with 20 stroke patients, physiotherapists reported that six patients had been limited by their fatigue to participate in rehabilitation sessions (Morley et al., 2005). In addition, stroke patients with PSF had a lower rate of returning to work and more deductions in work load at two years after stroke than non-fatigued stroke patients (Pihlaja et al., 2014).

PSF is associated with profound deterioration of several aspects of life after stroke. Cross-sectional studies found that fatigue scores were negatively associated with total scores of the Stroke-specific Quality of Life (SSQOL) (Chen et al., 2015) as well as scores on all of its subscales (including physical, cognitive, emotional, and social domains) (Visser-Meily et al., 2009). Similar results were reported by studies

that assessed quality of life using the Short Form-36 (SF-36). One study found that higher fatigue scores were associated with lower scores on all subscales of the SF-36, including physical functioning, physical role, mental health, emotional role, vitality, bodily pain, social functioning, and general health (Tang et al., 2010b). However, another study found associations between PSF and all subscales of SF-36 except for emotional role (Naess et al., 2006), whilst the third study reported that poorer outcomes of both mental health and emotional role function were associated with increased fatigue in stroke patients (Mead et al., 2011). Furthermore, a longitudinal study found significant cross-sectional associations between fatigue and both physical and mental health as assessed by the SF-36, at both acute phase and 18 months after stroke; and acute phase fatigue was an independent predictor for poor physical health at 18 months (Lerdal and Gay, 2013).

Fatigue could be present in patients with minor stroke (Carlsson et al., 2003) or those having made good neurological recovery (Powell et al., 2004). Some researchers proposed that fatigue could be a particularly salient problem in stroke patients with minor or no physical impairment (Ingles et al., 1999); this might be because of the relative lack of other sequelae of stroke, and that patients with subtle disability would have higher expectation for full recovery and attempt to take part in more activities in daily life (de Groot et al., 2003).

1.2.6 Treatment for fatigue after stroke and in other conditions

Cochrane review of interventions for post-stroke fatigue

Despite its high prevalence and detrimental consequences, little research has been carried out to develop effective treatments for PSF. A Cochrane review of interventions for post-stroke fatigue, which was published in 2009, concluded that there was insufficient evidence to inform the management of PSF (McGeough et al., 2009).

This Cochrane review included three completed RCTs which investigated the efficacy of interventions in stroke patients and measured fatigue as an outcome. One trial recruited 83 stroke patients with self-reported fatigue and randomised them to

receive either fluoxetine or placebo 20 mg daily for three months. After correcting for the effect of baseline fatigue severity, there was no difference in fatigue severity between groups at either three months or six months after the start of treatment (Choi-Kwon et al., 2007). The second trial recruited 31 women patients with subarachnoid haemorrhage and randomised them to receive either tirilazad mesylate or placebo 150 mg daily for 10 consecutive days after the onset of subarachnoid haemorrhage. Of 18 patients available for neuropsychological tests three months later, the tirilazad group had lower percentage of patients with fatigue than that in the placebo group (Ogden et al., 1998). The third trial investigated a Chronic Disease Self-management Programme (CDSMP) in 1140 patients with chronic diseases, of whom 125 were stroke patients. Patients were randomised to either the immediate treatment group (who immediately received seven weekly sessions of the CDSMP after randomisation) or the wait-list group (who received the CDSMP six months after randomisation). Fatigue scores were assessed at baseline and at six months, and mean changes of scores were calculated for each group. In the subgroup of 125 stroke patients, there was no significant between-group difference in the change of fatigue scores (Lorig et al., 2001).

This Cochrane review also identified two ongoing trials (McGeough et al., 2009). One trial investigated the continuous positive airway pressure (CPAP) for stroke patients with sleep-disordered breathing. This trial was terminated due to the poor recruitment. The interim results suggested no difference in fatigue scores after treatment between the active treatment group and the sham group (Brown et al., 2013). The other ongoing trial was completed and published in 2012, in which 83 stroke patients with fatigue were randomised to receive either a group-based cognitive treatment or the cognitive treatment plus graded activity training (COGRAT) for 12 weeks (Zedlitz et al., 2012). Fatigue scores were decreased significantly from before treatment to immediately after treatment in both groups, but changes of scores were not significantly different between groups. At six-month follow-up, the COGRAT group showed better clinically relevant improvement (i.e. higher proportion of patients with a decrease of CIS-fatigue $\geq$ 8 points) in fatigue than the cognitive treatment group (Zedlitz et al., 2012). This trial suggested that

both cognitive treatment and physical training are feasible with stroke patients and are promising to treat fatigue, and COGRAT is better than cognitive treatment alone. However, this trial did not have a 'usual care' arm thus the specific efficacy of either cognitive treatment or physical training is unknown.

Clinical management of post-stroke fatigue

Although some clinical guidelines for stroke management have incorporated a section for PSF, there is insufficient evidence to recommend any specific strategies for its management. The UK national clinical guideline for stroke (2012) offers two recommendations: fatigue should be assessed in medically stable patients, and fatigued patients should be given information and reassured that the symptom is likely to improve with time (Intercollegiate Stroke Working Party, 2012). The Canadian Stroke Best Practices (2015) also recommends the routine assessment of fatigue in stroke patients and providing information for fatigue education (Heart Stroke Foundation Canada, 2015). In addition, the Canadian guideline suggests a number of strategies to manage PSF, which include treatment of co-morbid conditions that could cause fatigue (e.g. mood disorders and sleep disorders), prioritising daily activities, exercise scheduling, sleep hygiene, communication with other people, and care by health professionals with knowledge of PSF (Heart Stroke Foundation Canada, 2015). However, these recommendations are all based on the level C evidence, that is, determined by the writing group consensus and supported by limited research evidence (Heart Stroke Foundation Canada, 2015). In addition, both the UK and Canadian guidelines suggest that there is insufficient evidence to recommend specific pharmacological treatment for PSF (Intercollegiate Stroke Working Party, 2012, Heart Stroke Foundation Canada, 2015).

Psychological interventions for fatigue in other conditions

Given that little evidence is available from stroke research to guide the treatment of PSF, interventions used to treat fatigue in other conditions may be informative. The UK National Institute for Health and Care Excellence (NICE) has recommended the cognitive behavioural therapy (CBT) and the graded exercise training for the

management of chronic fatigue syndrome (National Institute for Health and Care Excellence, 2007). This recommendation is further supported by a multicentre RCT, which found that both CBT and graded exercise training were effective in improving outcomes of chronic fatigue syndrome as compared to the specialist medical care (White et al., 2011). Furthermore, this RCT demonstrated that, compared with graded exercise training and specialist medical care, CBT was the most cost-effective strategy in managing chronic fatigue syndrome (McCrone et al., 2012). CBT is a type of psychological interventions that targeting people's thoughts and behaviours, which is also effective in treating fatigue in patients with cancer (Armes et al., 2007) and multiple sclerosis (Thomas et al., 2013). Patients with PSF have some psychosocial characteristics comparable to patients with chronic fatigue syndrome, cancer, and multiple sclerosis, such as lower self-efficacy, maladaptive coping patterns, and lower social support (Zedlitz et al., 2011). Therefore, psychological interventions are promising strategies to treat PSF.

Section 1.3 Aim and objectives of the thesis

Aim

The aim of this PhD study was to develop a psychological intervention for PSF and to evaluate its feasibility in stroke patients in the UK National Health System (NHS). Psychological interventions are complex interventions that consist of multiple therapeutic components. The UK Medical Research Council (MRC) has proposed a framework for the development and evaluation of complex interventions (Figure 1.1), illustrating a phased process from identifying the evidence to long-term implementation, which is analogue to the four-phased drug development (Campbell et al., 2000, Craig et al., 2008a). This framework suggests that the early stages of identifying theory, modelling and piloting should be taken as an iterative activity (Campbell et al., 2007), which is the focus of this thesis. The framework also suggests that complex interventions may work best if they are tailored to local contexts (Craig et al., 2013). Therefore, although a number of psychological interventions have shown to be effective in reducing fatigue in other conditions (Armes et al., 2007, Thomas et al., 2013, White et al., 2011), they need to be adapted to the local health system for stroke care.

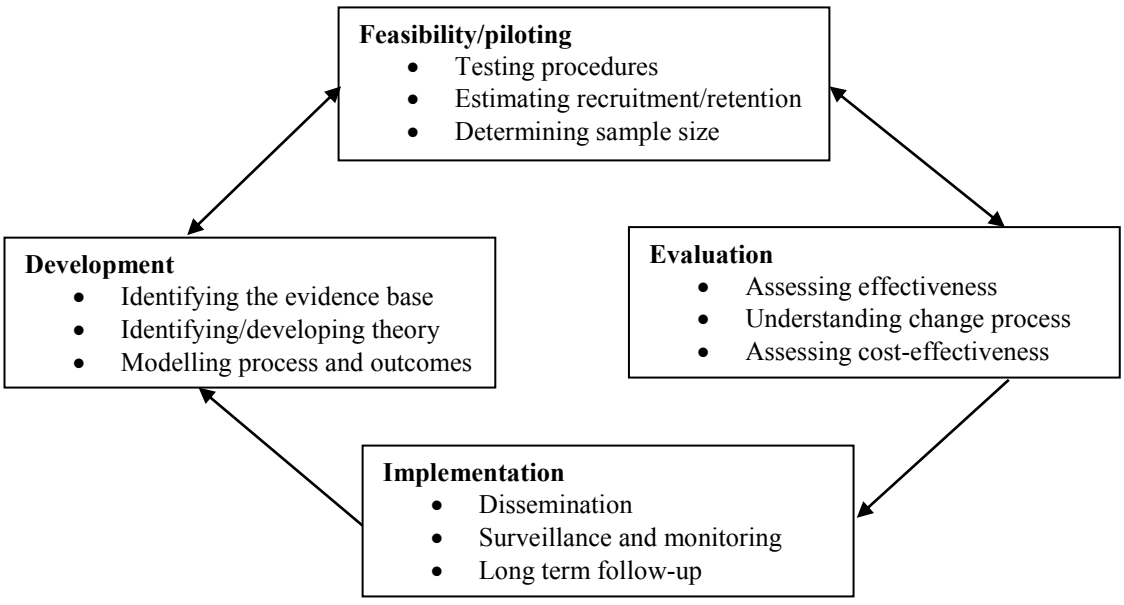

Figure 1.1 Key elements of the design and evaluation of complex interventions (Craig et al., 2008a)

Objectives

This chapter has provided an overview of PSF. I started with an introduction of stroke, and then focused on PSF, which is a common symptom after stroke. I have covered the following topics in this chapter:

- Section 1.1 Overview of stroke: definition, epidemiology, and consequences
- Section 1.2 Introduction of post-stroke fatigue: prevalence, definition, measurement, potential mechanisms, impacts on life after stroke, and interventions for fatigue after stroke and in other conditions
- Section 1.3 Aim and objectives of this thesis

In the following chapters of this thesis, I will describe how I developed a psychological intervention for PSF, from identifying evidence, developing treatment rationale, modelling intervention, testing feasibility, updating evidence, to refining intervention. This was an evidenced-based process following the MRC framework of developing complex interventions (Craig et al., 2008a). It is important to note that this development process is not a linear but an iterative approach, although it will be described in a linear pattern in the subsequent chapters.

The objectives of each chapter of this thesis are:

- Chapter 1: to provide an overview of stroke and post-stroke fatigue
- Chapter 2: to identify evidence to justify the choice of a psychological intervention and identify intervention targets
- Chapter 3: to develop the treatment rationale and design the intervention programme
- Chapter 4: to assess the feasibility of the intervention and study process
- Chapter 5: to update knowledge of interventions for post-stroke fatigue
- Chapter 6: to discuss the clinical implication of the current study and directions for future research

CHAPTER II: Theoretical Basis of a Psychological Intervention for Post-stroke Fatigue

In Chapter 1, I provided a general introduction of PSF. In brief, fatigue is a common and chronic problem in stroke patients. PSF has negative associations with stroke recovery and quality of life after stroke. Our understanding of its mechanisms is mainly based on potential associations, but the causal mechanisms of PSF are unknown. Despite its high prevalence, there is insufficient evidence to recommend any intervention for the treatment of PSF (McGeough et al., 2009). Psychological interventions are effective in reducing fatigue in conditions other than stroke, such as cancer (Armes et al., 2007), multiple sclerosis (Thomas et al., 2013), and chronic fatigue syndrome (White et al., 2011). As patients with PSF share some psychosocial characteristics with patients of these other conditions (Zedlitz et al., 2011), psychological interventions may be also effective to treat fatigue in stroke patients. Therefore, the aim of this thesis was to develop a psychological intervention for PSF.

This chapter is the initial stage of the intervention development, which aims to explore the evidence to justify the choice of the contents of a psychological intervention for PSF. In this chapter, I begin with a literature review of observational studies of PSF on its natural history (Section 2.1) and clinical correlates (Section 2.2), and then focus on psychological associations of PSF (Section 2.3). Drawing on the evidence from literature, I propose a conceptual model for understanding PSF (Section 2.4). This model suggests that the development of PSF is a temporal process and involves interactions of various biological, psychological, and behavioural factors. Although it is unclear whether these relationships are causal, many of these psychological and behavioural factors have bidirectional associations with PSF and are usually modifiable. Thus a psychological intervention targeting these psychological and behavioural factors is a promising approach to treat PSF.

Section 2.1 Natural history of post-stroke fatigue

2.1.1 Fatigue, an early and chronic problem after stroke

Fatigue is common immediately after stroke. In a qualitative study exploring the experience of PSF in 31 community-dwelling stroke patients, all patients reported that their fatigue first became evident during the hospital admission (White et al., 2012). In another study that recruited 220 patients who were between three and 27 months after stroke, 125 (57%) had self-reported PSF; of these fatigued patients, 77% reported that their fatigue started within the first week after stroke (Choi-Kwon et al., 2005). Similarly, in observational studies that investigated the presence of fatigue within the first two weeks after stroke, more than one third (30% to 60%) of stroke patients had fatigue at this early stage (Christensen et al., 2008, Lerdal et al., 2011, Chen et al., 2015, Wu et al., 2014a). Emerging early after stroke, fatigue is also common at the chronic stage after stroke. The longest research observation of PSF was reported in a Dutch study, which found that fatigue was present in 41% of 325 patients at a mean follow-up of 9.8 years after stroke (Maaijwee et al., 2014).

If PSF is a persistent problem rather than a transitory phenomenon, this will justify the development of interventions to manage it. Also a better understanding of natural history of PSF will allow clinicians and researchers to determine the optimum timing for intervention delivery. Therefore, I updated a systematic review of natural history of PSF (Duncan et al., 2012), by searching for longitudinal studies that investigated the presence of fatigue at more than one time point after stroke. Through the updated search, I identified four new studies (Duncan et al., 2014, Radman et al., 2012, van Eijsden et al., 2011, Pihlaja et al., 2014) in addition to the nine studies included in the previous review, making a total of 13 longitudinal cohort studies included.

Table 2.1 summarises these 13 longitudinal studies, by presenting proportions of patients with PSF at each assessment time point. Of these studies, the observational period of PSF ranges from within the first 10 days to three years after stroke. Although the estimates of prevalence vary according to the participant

characteristics, time since stroke and assessment methods of PSF, the general pattern of fatigue prevalence is consistent across studies. A considerable proportion of stroke patients (25% to 59%) had fatigue at the initial assessment, which was usually within the first few months after stroke. Also, in most studies, more than one third of patients had fatigue at a later assessment, which was usually at one year or later after stroke. In summary, fatigue is common at the acute phase as well as the chronic phase after stroke.

Attrition is a common problem in longitudinal studies. According to how the attrition data were managed, these 13 studies listed in Table 2.1 can be categorised into two groups. The first group (i.e. the first eight studies in Table 2.1) analysed and reported the data of patients who completed all assessments (Schepers et al., 2006, Snaphaan et al., 2011, van Eijsden et al., 2011, Pihlaja et al., 2014, van de Port et al., 2007, Sisson, 1995, Christensen et al., 2008, Duncan et al., 2014). These studies investigated the time course of PSF (i.e. changes of proportions or severity of fatigue over time), which I will discuss shortly in this section (in Subsection 2.1.2). The second group (i.e. the remaining five studies in Table 2.1) calculated proportions of patients with PSF at each assessment based on different numbers of patients at different assessment time points (Radman et al., 2012, Hellawell et al., 1999, Noble et al., 2008, Ogden et al., 1994, Skaner et al., 2007). For these five studies, it is difficult to interpret their results of the comparison of fatigue severity or proportions of patients with fatigue between different time points in individual studies, because the number of patients changed over time and the reasons for dropouts were not reported. If the dropouts were associated with more severe fatigue, the reported prevalence of PSF at follow-up might have been underestimated, as it was based on patients retained in the study (i.e. those who had less severe fatigue). Thus, I will not discuss the time course of PSF in these five studies, although the initial assessment of PSF in these studies could have provided useful information of the incidence of PSF.

Table 2.1 Numbers and proportions of stroke patients with post-stroke fatigue (PSF) at different time points after stroke

Studies (fatigue measures)	Number of patients with PSF/total number of patients (proportions of patients with PSF)								
	10 days	**1 month**	**2 months**	**3 months**	**6 months**	**1 year**	**18 months**	**2 years**	**3 years**
(Christensen et al., 2008) (MFI-20 general)	81/138 (59%)			61/138 (44%)		52/138 (38%)		55/138 (40%)	
(Sisson, 1995) (Single question)		12/13 (92%)			11/13 (85%)				
(Schepers et al., 2006) (FSS)		86/167 (52%)			107/167 (64%)	116/167 (69%)			
(Snaphaan et al., 2011) (CIS)			38/108 (35%)				36/108 (33%)		
(van Eijsden et al., 2011) (FSS)				141/242 (58%)		133/242 (55%)			
(Pihlaja et al., 2014) (POMS-Fatigue)				33/133 (25%)	34/133 (26%)			25/133 (19%)	
(van de Port et al., 2007) (FSS)					152/223 (68%)	165/223 (74%)			129/223 (58%)
(Duncan et al., 2014) (PSF case definition and FAS)		43/132 (33%) 24/86 (28%)			23/105 (22%) 20/86 (23%)	18/91 (20%) 18/86 (21%)			
(Ogden et al., 1994) (Single question)			10 weeks: 79/89 (89%)			57/66 (86%)			
(Skaner et al., 2007) (Single question)				72/106 (69%)		61/97 (58%)			
(Hellawell et al., 1999) (Single question)					18/28 (64%)	13/22 (59%)		13/19 (68%)	
(Radman et al., 2012) (FAI)					33/109 (30%)	34/99 (34%)			
(Noble et al., 2008) (MFSI-SF)				24 – 251 days (mean 109 days): 43/73 (59%)		335 – 672 days (mean 406 days): 31/87 (36%)			

CIS, Checklist Individual Strength; FAI, Fatigue Assessment Instrument; FAS: Fatigue Assessment Scale; FSS, Fatigue Severity Scale; MFI-20, Multidimensional Fatigue Inventory; MFSI-SF: Multidimensional Fatigue Symptom Inventory – Short Form; POMS, Profile of Mood States.

2.1.2 Time course of fatigue after stroke

Presence or absence of fatigue over time

Of the eight studies that reported the data of patients who completed all assessments (the first eight studies in Table 2.1), seven reported a general trend of decrease in proportions of patients with PSF over time (Duncan et al., 2014, Sisson, 1995, Snaphaan et al., 2011, van Eijsden et al., 2011, Christensen et al., 2008, Pihlaja et al., 2014, van de Port et al., 2007) and one reported an increase in proportions (Schepers et al., 2006). It is important to note that in some studies the changes of proportions were small (i.e. less than 5%) and some changes fluctuated over time (i.e. first increase and then decrease, or vice versa). In addition, in one study with a general trend of decrease, the proportion decreased significantly from 10 days (59%) to three months (44%) after stroke, but no major change afterwards (38% at one year and 40% at two years) (Christensen et al., 2008). Furthermore, none of these eight studies performed any statistical analysis to compare the proportions at different time points, thus we do not know whether these differences were statistically significant.

Of these eight studies, six studies also investigated the natural history of PSF in individual patients (Table 2.2). In general, about half of stroke patients in each study did not have fatigue at any assessments; in the other half of patients, the majority of patients had fatigue at all assessments, about 10% of patients had fatigue at the initial assessment but recovered at a later assessment, and another 10-15% of patients did not have fatigue at the initial assessment but developed it at a later assessment. In addition, a small proportion (less than 5%) of patients had a fluctuating course of fatigue over time, i.e. some had fatigue at the initial assessment, recovered later, but relapsed by the final assessment.

Table 2.2 Natural history of post-stroke fatigue (PSF) in patients who completed all assessments over the study course

Studies (number of patients): Assessment time points (Proportions of patients with PSF)	**Numbers (proportions) of patients with or without PSF at each assessment**	**Proportions in patients who completed all assessments**	**Proportions in patients with (or without) PSF at the initial assessment**
Snaphaan 2011 (n=108):	*38 (35%) patients with fatigue at the initial assessment*		
1st: 2 months (35%)	• 28 patients had fatigue at both assessments	**26%** (persistent fatigue)	**74%**
2nd: 18 months (33%)	• 10 patients had fatigue at 2 months but not 18 months	9% (recovered fatigue)	26%
(Snaphaan et al., 2011)	*70 (65%) patients without fatigue at the initial assessment*		
	• 9 patients developed fatigue between 2 and 18 months	8% (late onset fatigue)	13%
	• 61 patients did not have fatigue at either assessment	57% (no fatigue)	87%
van Eijsden 2011 (n=242):	*141 (58%) patients with fatigue at the initial assessment*		
1st: at discharge (97±46.9 days)	• 98 patients had fatigue both at discharge and 24 weeks later	**40%** (persistent fatigue)	**70%**
(58%)	• 43 patients had fatigue at discharge but not at 24 weeks later	18% (recovered fatigue)	30%
2nd: 24 weeks later (55%)	*101 (42%) patients without fatigue at the initial assessment*		
(van Eijsden et al., 2011)	• 35 patients developed fatigue after discharge	15% (late onset fatigue)	35%
	• 66 patients did not have fatigue at either assessment	27% (no fatigue)	65%
Christensen 2008:	*81 (59%) patients with fatigue at the initial assessment*		
1st: 10 days (59%)	• 72% remained either fatigued or non-fatigued between 10 days and 3 months	(persistent fatigue or no fatigue)	
2nd: 3 months (44%)	• 75% remained either fatigued or non-fatigued during the interval between 3 months and 2 years	(persistent fatigue or no fatigue)	
3rd: 1 year (38%)			
4th: 2 years (40%)	• 9% developed fatigue between 3 months and 2 years	(late onset fatigue)	
(Christensen et al., 2008)			

Table 2.2 Natural history of post-stroke fatigue (PSF) in patients who completed all assessments over the study course (continued)

Studies (number of patients): Assessment time points (Proportions of patients with PSF)	Numbers (proportions) of patients with or without PSF at each assessment	Proportions in patients who completed all assessments	Proportions in patients with (or without) PSF at the initial assessment
Schepers 2006 (n=167): 1st: at admission (6±4 weeks) (52%) 2nd: 6 months (64%) 3rd: 12 months (69%) (Schepers et al., 2006)	*86 (52%) patients with fatigue at the initial assessment*		
	• 63 patients had fatigue at all three assessments	**38%** (persistent fatigue)	**73%**
	• 7 patients had fatigue at admission, and recovered by 6 months	4% (recovered fatigue)	8%
	• 10 patients had fatigue at both admission and 6 months, and recovered by 12 months	6% (recovered fatigue)	12%
	• 6 patients had fatigue at initial assessment, recovered by 6 months, and relapsed between 6 and 12 months	4% (early onset fatigue with fluctuating course)	7%
	81 (48%) patients without fatigue at the initial assessment		
	• 29 patients developed fatigue between the admission and 6 months, and persisted at 12 months	17% (late onset fatigue)	36%
	• 18 patients developed fatigue between 6 and 12 months	11% (late onset fatigue)	22%
	• 5 patients developed fatigue by 6 months, and recovered at 12 months	3% (late onset recovered fatigue)	6%
	• 29 patients did not have fatigue at any assessment	17% (no fatigue)	36%
Duncan 2014 (n=86): 1st: 1 month (28%) 2nd: 6 months (23%) 3rd: 12 months (21%) (Duncan et al., 2014)	*24 (28%) patients with fatigue at the initial assessment*		
	• 7 patients had fatigue at all three assessments	**8%** (persistent fatigue)	**29%**
	• 13 patients had fatigue at 1 month, and recovered by 6 months	15% (recovered fatigue)	54%
	• 1 patient had fatigue at both 1 and 6 months, and recovered between 6 and 12 months	1% (recovered fatigue)	4%
	• 3 patients had fatigue at 1 month, recovered by 6 months, and relapsed between 6 and 12 months	4% (early onset fatigue with fluctuating course)	13%
	62 (72%) patients without fatigue at the initial assessment		
	• 3 patients developed fatigue between 1 and 6 months, and persisted to 12 months	4% (late onset fatigue)	5%
	• 5 patients developed fatigue between 6 and 12 months	6% (late onset fatigue)	8%
	• 9 patients developed fatigue between 1 and 6 months, and recovered between 6 and 12 months	10% (late onset recovered fatigue)	14%
	• 45 patients did not have fatigue at any assessment	52% (no fatigue)	73%

Table 2.2 Natural history of post-stroke fatigue (PSF) in patients who completed all assessments over the study course (continued)

Studies (number of patients): Assessment time points (Proportions of patients with PSF)	Numbers (proportions) of patients with or without PSF at each assessment	Proportions in patients who completed all assessments	Proportions in patients with (or without) PSF at the initial assessment
Pihlaja 2014 (n=133): 1st: 3 months (25%) 2nd: 6 months (26%) 3rd: 24 months (19%) (Pihlaja et al., 2014)	*33 (25%) patients with fatigue at the initial assessment*		
	• 13 patients had fatigue at all three assessments	**10%** (persistent fatigue)	**39%**
	• 9 patients had fatigue at 3 months, and recovered by 6 months	7% (recovered fatigue)	27%
	• 7 patients had fatigue at both 3 and 6 months, and recovered between 6 and 12 months	5% (recovered fatigue)	22%
	• 4 patients had fatigue at 3 months, recovered by 6 months, and relapsed fatigue between 6 and 24 months	3% (early onset fatigue with fluctuating course)	12%
	100 (75%) patients without fatigue at the initial assessment		
	• 5 patients developed fatigue between 3 and 6 months, and persisted at 24 months	4% (late onset fatigue)	5%
	• 3 patients developed fatigue between 6 and 24 months	2% (late onset fatigue)	3%
	• 9 patients developed fatigue between 3 and 6 months, and recovered between 6 and 24 months	7% (late onset recovered fatigue)	9%
	• 83 patients did not have fatigue at any assessment	62% (no fatigue)	83%

Although the proportion varies across studies, findings from the longitudinal studies revealed four general trajectories of the temporal course of fatigue after stroke, i.e. persistent fatigue, recovered fatigue, late onset fatigue, and fluctuating fatigue. A 'persistent fatigue' is present at all assessments over time after stroke; a 'recovered fatigue' is present at early but not late assessment after stroke; a 'late onset fatigue' is not present at the early assessment but develops during the follow-up and is present at a later assessment; and a 'fluctuating fatigue' is developed early, recovered later, but relapsed again. Table 2.3 summarises the exact proportions of patients with persistent fatigue, recovered fatigue, late onset fatigue, and a fluctuating course of fatigue in each longitudinal studies.

Table 2.3 Proportions of stroke patients with persistent fatigue, recovered fatigue, late onset fatigue, or a fluctuating course in individual longitudinal studies

Study ID	No. of patient	Patients with fatigue at the initial assessment			Patients without fatigue at the initial assessment	
		Persistent fatigue	Recovered fatigue	Fluctuating course	Late onset fatigue	No fatigue at any assessment
Snaphaan 2011	108	26%	9%	NA	8%	57%
van Eijsden 2011	242	40%	18%	NA	15%	27%
Radman 2012	99	25%	8%	NA	9%	58%
Schepers 2006	167	38%	10%	4%	31%	17%
Duncan 2014	86	8%	16%	4%	20%	52%
Pijlaja 2014	133	10%	12%	3%	13%	62%
Christensen 2008	138	NA	NA	NA	9%	NA

NA: not applicable

Severity of fatigue over time

Some studies investigated the change of fatigue severity over time, assessed by mean scores of fatigue of the entire cohort. A Dutch study (167 patients) reported a significant contribution of time ($p < 0.001$) on the variation of fatigue scores, with an increase of fatigue scores from admission, to three months and later one year after stroke (Schepers et al., 2006). In contrast, a Norwegian study (95 patients) assessed the fatigue severity at the acute phase, six months, 12 months and 18 months after stroke and found no effect of time on fatigue scores (Lerdal et al., 2012). However,

these two studies only investigated the general effect of time over the entire course of observation rather than comparing fatigue scores between specific time points. A Danish study (138 patients) found a significant decrease of fatigue scores from 10 days after stroke to three months ($p < 0.05$), but no further significant changes from three months to two years (Christensen et al., 2008). This change of fatigue scores might reflect the change of proportions of patients with PSF in this longitudinal study as discussed previously. Similarly, another study (86 patients) found a significant decrease of fatigue scores from one month to six months ($p = 0.03$) but no significant change from six months to one year ($p = 0.19$) (Duncan et al., 2014). In addition, a small study (58 patients) found no significant changes of fatigue scores from the initial assessment at a mean of three months to a later assessment at a mean of 13 months after stroke (Noble et al., 2008). Another Dutch study (242 patients) explored changes of fatigue severity in individual patients from the initial assessment at a mean of three months to the assessment six months later, which found no significant change of fatigue scores in the majority of patients (161 patients, 66%), and only 16% had a significant increase and another 18% had a significant decrease during this period (van Eijsden et al., 2011). These studies reported a common observation that fatigue severity tends to be stable over time, but if it does resolve naturally, it often occurs in the first few months after stroke. Thus the best timing for implementing interventions for PSF may be the chronic phase of stroke (e.g. three months or six months after stroke onset), as at this stage fatigue is usually a persistent problem that does not resolve spontaneously.

2.1.3 The concept of early fatigue and late fatigue

When studying fatigue after stroke, we should take into consideration that the prevalence of fatigue in the general population is relatively high (prevalence of chronic fatigue in general population ranges from 15% to 32%), and that fatigue present at an early stage after stroke may be not necessarily caused by stroke. The presence of fatigue after stroke is associated with the presence of fatigue prior to stroke (I will return to the issue of pre-stroke fatigue in the next section of factors associated with PSF). Similarly, for fatigue present at a later stage after stroke, it is

unclear whether this is a persistent status since when the fatigue is first present, or if it is developed later, or even there is a fluctuation over time, as the presence of fatigue is not continuously monitored in research studies. For example, "persistent fatigue" represents the fatigue present at all assessments over the course of the study, but we do not know the status of fatigue in-between these assessments. Thus the identified temporal course of fatigue may vary depends on the length of follow-up, the number of assessments, and the time of each assessment since stroke. To investigate whether these factors affect the identified temporal course of PSF, I compared the proportions of patients with 'persistent fatigue', 'recovered fatigue', 'late onset fatigue', 'fluctuating fatigue' and those 'without fatigue' between different numbers and time points of assessments, using the data from a longitudinal study (Schepers et al., 2006) that reported the numbers of patients who had fatigue at admission, six months and 12 months after stroke (Table 2.4).

Table 2.4 Influence of the length of follow-up and times of assessments on the identified pattern of temporal course of post-stroke fatigue

Schepers 2006 (n=167)	Persistent fatigue	Recovered fatigue	Late onset fatigue	Fluctuating course	No fatigue
Three assessments: at admission, 6 months, and 12 months	63 (38%)	17 (10%)	52 (31%)	6 (4%)	29 (17%)
Two assessments: admission and 12 months	69 (41%)	17 (10%)	47 (28%)	NA	34 (21%)
Two assessments: admission and 6 months	73 (44%)	13 (8%)	34 (20%)	NA	47 (28%)
Two assessments: 6 months and 12 months	92 (55%)	15 (9%)	24 (14%)	NA	36 (22%)

NA: not applicable.

Table 2.4 shows that comparing the results of having two assessments at different time points in the first year after stroke (i.e. at admission and 12 months, versus at admission and six months, versus at six and 12 months), there is no significant difference in proportions of the identified patterns of temporal course of PSF, except that there is a lower proportion of patients with 'late onset fatigue' and a higher proportion of 'persistent fatigue' if assessed between six and 12 months, compared with those assessed between admission and six months or those between admission

and 12 months. This suggests that more patients had fatigue that started in the first six months after stroke and the fatigue status tended to be stable after six months. Also compared with any two assessments during the first year, three assessments during this period identified no significant difference in the proportions of any temporal pattern of PSF, except that three assessments rather than two identified a small proportion of patients (4%) who had a fluctuating course of fatigue. In summary, fatigue tends to be present early after stroke and persist in long term, regardless of the number and time points of assessments. This implies that the clinical observation of fatigue does not need to be frequent, as two assessments, one at an early stage (e.g. acute phase) and the other at a later stage (e.g. several months after stroke onset), would be sufficient to reveal temporal course of fatigue in most stroke patients.

Because of the difficulty in determining the starting time of fatigue and limitations in continuous monitoring of fatigue status, here I propose the concepts of "early fatigue" and "late fatigue" which will be used in the subsequent chapters of this thesis. "Early fatigue" describes the presence of fatigue at an early stage after stroke (i.e. at the initial assessment, usually within the first few weeks after stroke) and "late fatigue" describes the presence of fatigue at a later assessment after stroke (usually several months or years after stroke onset). These concepts are focused on the presence of fatigue at certain time points, regardless of when the fatigue starts and whether it persists to a later time point (Figure 2.1).

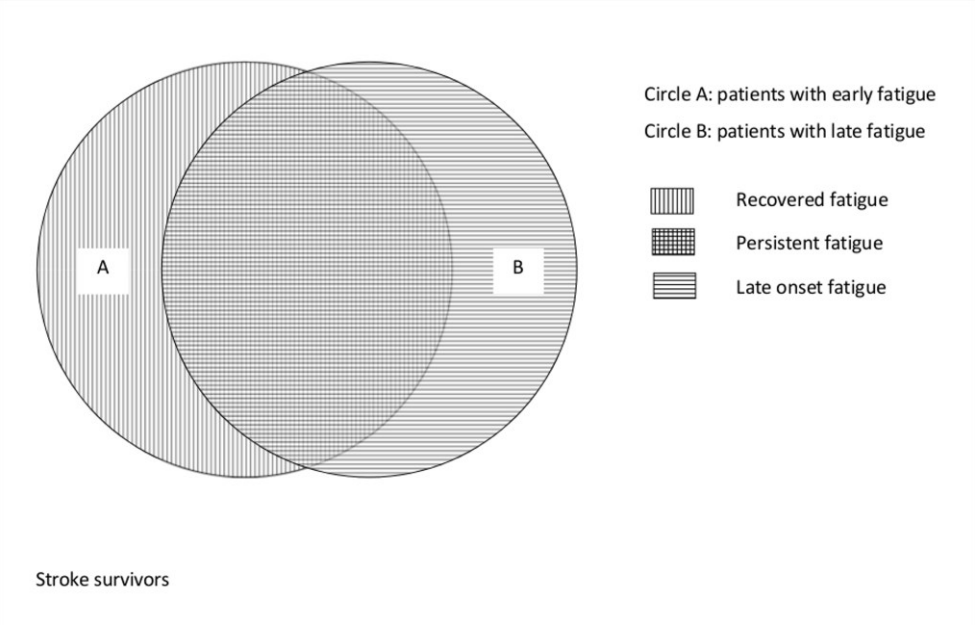

Figure 2.1 Concepts of early fatigue and late fatigue after stroke

It is important to note that fatigue present early after stroke (i.e. early fatigue) and fatigue present at a later stage after stroke (i.e. late fatigue) should be viewed as part of an evolving process. In longitudinal studies of PSF, early fatigue is always associated with, or the independent predictor of, late fatigue (Lerdal and Gay, 2013, Snaphaan et al., 2011). However, it is plausible that different factors contribute to fatigue present at different time points after stroke. Two studies investigated factors associated with fatigue at different time points after stroke. In one study, infratentorial stroke was associated with fatigue at two months but not 18 months after stroke, whilst baseline depressive symptoms and anxiety were associated with fatigue at both assessments (Snaphaan et al., 2011). In the other study, the three strongest correlates of fatigue at six months after stroke were stroke severity, functional disability and depressive symptoms, whilst at one year the strongest correlates were depressive symptoms, anxiety, and language impairment (Radman et al., 2012). These findings suggest that the nature of the stroke itself may be a more important determinant of early rather than late fatigue, with psychological factors important for both phases.

2.1.4 Summary

Understanding the natural history of PSF informs whether an intervention is necessary and helps us to determine the optimum timing for delivering the intervention. About half of stroke patients experienced PSF at some time after their stroke, and most of them had fatigue at an early stage after stroke. PSF is a persistent problem as the majority of patients who had fatigue at an early stage also had fatigue at a later stage, with only a small proportion of patients recovering from fatigue. Some studies reported the decrease of proportions or severity of fatigue occurred during the first few months after stroke, but in the chronic phase (e.g. three months after stroke onset) the status of fatigue often tended to be stable. In general, PSF is a common and persistent problem that requires medical interventions.

Due to the difficulties in continuous observation of fatigue in research studies and clinical practice, I proposed the concepts of 'early fatigue' and 'late fatigue', which are focused on the presence of fatigue at different time points after stroke. Some studies indicated that the nature of stroke itself may be a more important determinant of early rather than late fatigue, with psychological factors are important for both phases. This may explain the natural resolution of fatigue during the first few months after stroke, that is, early fatigue, which is more attributable to stroke lesions, would be relieved as the neurological deficits gradually recover over time. Also some patients reported that changes in life following stroke (e.g. hospitalisation) caused their fatigue, and as they gradually adapted their life to these changes the feeling of fatigue could resolve. Therefore, the target population of interventions to treat PSF need be those who had fatigue during the chronic phase after stroke rather than those during the acute phase, because some patients with early fatigue can recover spontaneously.

The lack of effective intervention for PSF is partly due to our lack of understanding of its aetiologies and mechanisms. In the next section, I will systematically review factors that are associated with PSF and explore whether and how these factors contribute to fatigue at different stages after stroke. These contributing factors may help us to understand PSF and identify potential targets for the management of PSF.

Section 2.2 Factors associated with post-stroke fatigue

Although PSF is a common problem, its aetiologies are unknown and our understanding of its mechanisms is mainly based on potential associations. A number of clinical factors have been reported to be associated with PSF. Given the concepts of early and late fatigue after stroke and the observation that specific lesion sites of stroke were associated with early but not late fatigue (Snaphaan et al., 2011), it is important to consider the time at which any related factors might exert most influence on PSF. This section reviews factors associated with fatigue at early and late stages after stroke and explores possible causal relationships. The concepts of early and late fatigue indicate that the development of PSF is a temporal process, thus in this section I will discuss factors associated with PSF according to the time of their presence in relation to stroke onset, i.e. pre-stroke factors, stroke-specific factors, and co-existing factors.

2.2.1 Pre-stroke factors

Some factors that exist prior to stroke may contribute to people's vulnerability to fatigue or may be indicators of this vulnerability.

Age

The reports regarding the influence of age on PSF are conflicting. Many studies found no significant associations between age and the presence or severity of PSF (Appelros, 2006, Carlsson et al., 2003, Chen et al., 2015, Choi-Kwon et al., 2005, Christensen et al., 2008, Crosby et al., 2012, Harbison et al., 2009, Hoang et al., 2012, Ingles et al., 1999, Kutlubaev et al., 2013, Lerdal et al., 2011, Lerdal and Gay, 2013, Naess et al., 2005, Passier et al., 2011, Pihlaja et al., 2014, Stokes et al., 2011, Tang et al., 2010a, Tang et al., 2013, Tang et al., 2010b, van Eijsden et al., 2011, Vuletic et al., 2011, Wang et al., 2014, Wu et al., 2014a). However, some studies reported that patients with older age were more likely to have fatigue than younger patients or the advancing age was related to more severe fatigue (Feigin et al., 2012, Glader et al., 2002, Jaracz et al., 2007, Mead et al., 2011, Naess et al., 2012, Radman

et al., 2012, Schepers et al., 2006), whilst other studies found that younger age was associated with a greater likelihood of fatigue (Parks et al., 2012, Snaphaan et al., 2011). One may assume that elderly people are prone to fatigue due to the declined body function with ageing, while others may argue that fatigue is more evident in younger people as they are likely to lead a more active life.

Sex

Of studies that investigated the association between sex and PSF, not all of them found a significant association. However, of studies that found a significant effect of sex on PSF, all reported that women patients were more likely to have PSF (Crosby et al., 2012, Glader et al., 2002, Naess et al., 2005, Tang et al., 2010a, Tang et al., 2013) or the fatigue level was higher in women than men (Christensen et al., 2008, Kutlubaev et al., 2013, Lerdal et al., 2011, Mead et al., 2011, Schepers et al., 2006, Tang et al., 2010b). The higher perception of fatigue in women than men is also reported in the general population, which may be explained by the sex difference in understanding the phenomenon of fatigue (Meeuwesen et al., 2002). As fatigue has a significant effect on participation in daily activities, another possible explanation is the sex difference in roles in daily activities. For example, traditionally housework is mainly performed by women, which would result in women more prone to fatigue in daily living.

Pre-stroke fatigue

Five studies (954 patients) asked stroke patients about the presence of fatigue prior to stroke and all found that patients who suffered fatigue before stroke were more likely to have fatigue after stroke (Choi-Kwon et al., 2005, Duncan et al., 2014, Lerdal et al., 2011, Chen et al., 2015, Wang et al., 2014). However, these findings should be interpreted with caution as there is no validated tool to measure pre-stroke fatigue and there is a risk of recall bias. In spite of this, these findings imply the possibility that factors predisposing fatigue prior to stroke may also contribute to fatigue after stroke. Factors such as personality and genetic factors were reported as predisposing factors for fatigue in non-stroke populations (Lievesley et al., 2014), but whether

these factors are associated with PSF is yet to be documented. In addition, PSF is also common in patients without pre-stroke fatigue. In a study where patients with pre-stroke fatigue were excluded at recruitment, 40% of the remaining 312 patients had PSF within the first 10 to 15 days after stroke onset (Wu et al., 2014a).

Pre-stroke depression and white matter changes

One study (108 patients) reported no association between PSF and pre-stroke depression or age-related white matter changes at either two months or 18 months after stroke; however, it should be noted that this was an underpowered study as only 14 patients had pre-stroke depression and none had white matter changes (Snaphaan et al., 2011). In a larger study (377 patients), patients with pre-stroke depression or those with leucoaraiosis (non-specific white matter changes) were more likely to have PSF at six months after stroke (Naess et al., 2012). However, in another study (107 patients), which had a higher proportion of patients with white matter lesions (50%), there was no significant association between fatigue scores and the severity of white matter lesions (none, mild, moderate, severe) as assessed both globally and in different regions of the brain (Kutlubaev et al., 2013).

Pre-stroke disability and activity patterns

One study found that pre-stroke disability was associated with higher levels of cognitive, psychosocial and physical fatigue at 12 months after stroke (Parks et al., 2012). In addition, dependence in daily activities before stroke was associated with the presence of fatigue at six months (Feigin et al., 2012) and two years after stroke (Glader et al., 2002). One study found that the lack of exercise before stroke was an independent predictor for the presence of fatigue within two weeks after stroke (Wang et al., 2014), whilst other studies found no significant association between pre-stroke exercise pattern and PSF (Choi-Kwon et al., 2005, van Eijsden et al., 2011). These physical factors present prior to stroke are likely to also exist after stroke. If associations between these physical factors and PSF are confirmed in future studies, this may help us to identify patients who are vulnerable to PSF and to promote physical activity at an early stage to prevent PSF.

2.2.2 Stroke-specific factors

In qualitative studies, some patients considered their fatigue as a direct result of stroke or part of the recovery process and reported that PSF was different from their experience of fatigue prior to stroke (Barbour and Mead, 2011, Flinn and Stube, 2010). This is consistent with the idea that PSF might be triggered by specific stroke lesion(s). If this is the case, we might expect associations between PSF and the type, size and site of stroke lesions.

Type of stroke

Some studies investigated the effect of stroke type on PSF. There is no difference between patients with ischaemic stroke and those with haemorrhagic stroke in proportions of patients with PSF (Glader et al., 2002, Lynch et al., 2007) or fatigue severity (Duncan et al., 2015, Schepers et al., 2006). A study further illustrated that the presence of PSF was not different between patients with intracerebral haemorrhage, large vessel infarct, lacunar infarct, or those with embolic infarct (Appelros, 2006). Therefore, patients with different types or subtypes of stroke will not be discussed separately in this thesis.

Stroke severity at admission

No clear pattern has emerged for the association between PSF and stroke severity (a surrogate marker of the stroke lesion size, usually measured by scales for neurological deficits). Among 11 studies that investigated the association between stroke severity at admission and the presence or severity of fatigue at follow-up, eight studies (1502 patients) found no significant association (Appelros, 2006, Christensen et al., 2008, Ingles et al., 1999, Kutlubaev et al., 2013, Naess et al., 2005, Snaphaan et al., 2011, Tang et al., 2010a, Wu et al., 2014a). Although the other three studies (377 patients) found a significant association between stroke severity and fatigue in patients within six months after stroke, this association was no longer significant after the effects of psychological factors (e.g. depression and anxiety)

were controlled for in the regression analysis (Jaracz et al., 2007, Radman et al., 2012, Chen et al., 2015).

Site of stroke lesions

Despite the observation in one study that infratentorial strokes were associated with early (but not late) fatigue, a systematic review of biological correlates of PSF found no conclusive evidence on the association between PSF and stroke lesion sites (Kutlubaev et al., 2012). However, the uncertainty regarding any association between PSF and lesion sites might be attributed to two factors: the time of fatigue assessment and how lesion sites were classified. In studies where a significant association between PSF and lesion sites was reported, fatigue was usually assessed within the first few months after stroke and the associations were found with specific brain structures, such as brainstem, basal ganglia, internal capsule, or insular lobe (Naess et al., 2005, Snaphaan et al., 2011, Staub and Bogousslavsky, 2001a, Tang et al., 2010a, Manes et al., 1999, Tang et al., 2013). In contrast, in studies that reported no significant association, fatigue was often assessed at a later stage (e.g. six months) after stroke and the lesion sites were classified more broadly as anterior or posterior circulation, or by the affected hemisphere (Appelros, 2006, Carlsson et al., 2003, Choi-Kwon et al., 2005, Christensen et al., 2008, Ingles et al., 1999, Jaracz et al., 2007, Lynch et al., 2007).

In addition, some of the existing studies classified the lesion sites by clinical presentations and some used computed tomography (CT), which are not sensitive enough to detect specific lesion sites. The growing use of magnetic resonance imaging (MRI) in stroke care, along with improvements in techniques, is leading to the identification of more specific regional stroke damage. Prospective MRI studies are helpful to explore the association between regional stroke damage and the presence of PSF. Tang and colleagues assessed the lesion sites in 500 stroke patients by the diffusion-weighted imaging (DWI) MRI, reporting that caudate infarct was an independent predictor of the presence of PSF at three months after the index stroke (Tang et al., 2013).

Functional disconnection of nervous system

Functional brain imaging may be more sensitive than structural imaging to reflect the link between stroke damage and PSF. It is hypothesised that neurological fatigue is mediated by dysfunction of the reticular activating system (Chaudhuri and Behan, 2004). Although there is no direct evidence to support this hypothesis, it is consistent with the observation that PSF was associated with infarct in brainstem (Staub and Bogousslavsky, 2001a) and in subcortical white matter (Tang et al., 2014), which are components of the reticular activating pathways. Also, wakefulness and attention, two major functions regulated by the reticular activating system (Kinomura et al., 1996), are impaired in patients with PSF (please see the section for Cognitive impairments).

A positive emission tomography (PET) study for patients with multiple sclerosis reported that, compared with non-fatigued patients, fatigued patients had reduced metabolism in both the prefrontal cortex and caudate nucleus (Roelcke et al., 1997). Although there is no functional brain imaging study for PSF, Tang *et al*. reported in their DWI/MRI study that caudate infarct was associated with PSF (Tang et al., 2013). Studies of brain functional connectivity demonstrated that caudate was linked with executive frontal areas including dorsolateral prefrontal cortex, anterior cingulate cortex and orbitofrontal cortex on transcranial magnetic stimulation (TMS) (Knoch et al., 2006, Strafella et al., 2001), PET and functional MRI (Postuma and Dagher, 2006). These findings indicate a possible association between PSF and executive functions.

Motor cortex is another brain area that may be responsible for PSF. One recent study (70 patients) using TMS (applied to the primary motor cortex area) and electromyography techniques found that reduced excitability of corticospinal motor output contributed to higher levels of fatigue in stroke patients (Kuppuswamy et al., 2015).

Cognitive impairments

PSF can be characterised by cognitive deficits, as some patients describe their fatigue as “mental tiredness” or “difficulty in concentration”. The difficulty in exploring the relationship between PSF and cognitive deficits lies in the measures of cognitive functioning. In studies which assessed cognition using the Mini-mental State Examination (MMSE), no association was found between PSF and the total score of MMSE (Appelros, 2006, Carlsson et al., 2003, Kutlubaev et al., 2013, Naess et al., 2005, Park et al., 2009, Schepers et al., 2006, Snaphaan et al., 2011, van Eijsden et al., 2011). A limitation in these studies was that MMSE does not measure executive functioning, whilst brain imaging studies have suggested a possible link between PSF, caudate, and executive frontal cortex. To compensate for this weakness of MMSE, the Cambridge Cognitive Examination (CAM-COG) incorporates a number of additional items including those for abstract thinking and perception (Roth et al., 1986). Also, the Montreal Cognitive Assessment (MoCA), a cognitive scale which is commonly used for stroke patients, contains items for executive functions (Nasreddine et al., 2005).

In a study (108 patients) which included a detailed cognitive examination (for memory, verbal learning, non-verbal recall, attention, visuospatial functioning, and executive functioning (assessed by the Brixton Spatial Anticipation Test for strategic thinking and with phonological fluency for concept generation)), the presence of cognitive impairments at three months after stroke was associated with greater fatigue at one-year follow-up (Passier et al., 2011). Another study (109 patients) further illustrated that attentional (phasic alert and divided attention) and executive dysfunction (assessed by a modified Stroop test) was associated with PSF at both six months and 12 months after stroke (Radman et al., 2012). The executive functioning assessed in these studies is associated with dorsolateral prefrontal cortex (Alvarez and Emory, 2006). Therefore, cognitive scales measuring these executive functions, such as CAM-COG and MoCA, need to be used in patients with PSF.

The association between PSF and two other executive frontal regions, anterior cingulate cortex and orbitofrontal cortex, has not yet been investigated in patients

with PSF. These two brain regions are associated with decision-making, empathy, impulse control and emotion. Their associations with PSF need to be explored in future studies, for example, by observational studies for the association between PSF and apathy or functional imaging studies for the association between PSF and blood flow or metabolism in anterior cingulate cortex.

Neuroendocrine changes

Some researchers proposed that fatigue in neurological disorders was associated with dysfunctions of hypothalamic-pituitary-adrenal (HPA) axis (Chaudhuri and Behan, 2004). The underactive HPA axis and related neuroendocrine changes were found in patients with chronic fatigue syndrome (Scott and Dinan, 1999), but there is scarce evidence from stroke studies. One study (109 patients) investigated levels of cortisol and adrenocorticotropic hormone (ACTH) in stroke patients, but found no association of these hormones with PSF at either six months or 12 months after stroke (Radman et al., 2012).

Inflammatory biomarkers

Fatigue in neurological disorders is often associated with both central nervous system and systemic inflammation (Morris et al., 2015). Inflammation is an important pathophysiological response to stroke, which is characterised by the changed levels of peripheral inflammatory markers (Emsley and Tyrrell, 2002). A genetic study (39 patients) found that stroke patients carrying the minor C allele of the rs4251961 single nucleotide polymorphism (SNP) in the interleukin-1 receptor antagonist gene (IL1RN, the gene for IL1rα) had higher fatigue scores than patients without this SNP at one month and three months after stroke, respectively (both $p < 0.05$), but not at six months or one year (Becker et al., 2015).

The SNP rs4251961 C allele is associated with higher plasma levels of both C-reactive protein (CRP) and IL-6 and lower levels of IL-1rα in the general population (Reiner et al., 2008). However, there is no robust evidence in stroke population for the association between PSF and any of these inflammatory biomarkers. In a pilot study with 28 patients within three months after stroke, the mean CRP level was not

significantly different between patients with and those without PSF (McKechnie et al., 2010). In addition, another small study (45 patients) found that the CRP level at acute phase was not associated with fatigue severity at six months, 12 months, or 18 months (Ormstad et al., 2011). In this same cohort of stroke patients, higher levels of acute phase glucose were associated with greater fatigue at six months and 12 months, higher levels of acute phase IL-1β were associated with greater fatigue at six months, and lower levels of acute IL-1rα and IL-9 were associated with greater fatigue at 12 months (Ormstad et al., 2011). This study also found that lower bioavailability for serotonin synthesis at acute phase was associated with the presence of PSF at 12 months (Ormstad et al., 2014). However, we should be cautious when interpreting the results of this study, as the critical level for statistical significance might have to be adjusted due to the multiple comparisons.

One interesting finding in the study described above was that none of these biomarkers was associated with fatigue at 18 months. Given that the fatigue level observed in this study did not decline by 18 months, the investigators speculated that other factors such as psychosocial factors might have contributed to the sustained level of fatigue (Ormstad et al., 2011). This is consistent with our observation in an exploratory study for associations between CRP and PSF in 65 stroke patients, where there was a significant cross-sectional association between CRP and PSF at six months after stroke, but this association was no longer significant after controlling for the effect of anxiety, depression, and physical activity, with anxiety as the only significant association of PSF at six months. In addition, anxiety, depression and reduced physical activity but not CRP at 12 months were independently associated with PSF at 12 months. These findings imply that CRP is associated with early but not late fatigue, and the association with early fatigue is confounded by psychological and behavioural factors. However, this is an exploratory study with a relatively small sample size so the results should be repeated in larger studies in future. (I am the leading author of this CRP study. This work is currently in preparation for submission to academic journals for peer review)

Physical impairments

Fatigue after stroke may also be attributed to the increased physical effort associated with neurological deficits. One study (377 patients) found that in patients at one year after stroke the presence of PSF was associated with the residual neurological deficits (measured by the National Institutes of Health Stroke Scale) and perceived disability (measured by the modified Rankin Scale), respectively (Appelros, 2006). Cross-sectional associations between PSF and disability were found in patients from the acute phase to several years after stroke (Choi-Kwon et al., 2005, Naess et al., 2005, van der Werf et al., 2001, Wu et al., 2014a). In addition, one study (108 patients) reported that physical impairments at three months after stroke were associated with fatigue at one-year follow-up (Passier et al., 2011).

However, fatigue is also present in stroke patients with minor or no residual neurological deficits (Winward et al., 2009) or those with minor physical impairments (Kuppuswamy et al., 2015). This suggests the possibility of other contributing factors to PSF. For example, one longitudinal study (108 patients) found that higher level of disability (by the modified Rankin Scale) at baseline was associated with the presence of fatigue at baseline but not at 18 month after stroke; furthermore, the baseline association was no longer significant after controlling for the effects of age, lesion site, anxiety, and depressive symptoms (Snaphaan et al., 2011). Similar results were reported in another study (109 patients) where higher levels of neurological deficits (by the National Institutes of Health Stroke Scale) and disability (by the modified Rankin Scale) were each associated with more severe fatigue at six months but not 12 months after stroke; and these associations were no longer significant after controlling for the effects of anxiety and depressive symptoms (Radman et al., 2012).

2.2.3 Co-existing factors

Psychological factors

Stroke or stroke-induced changes in life can make patients feel distressed. Psychological factors are the most commonly reported associations of PSF. This is because fatigue is often a symptom of many psychological conditions, such as depression and anxiety. However, some patients reported that they did not have any of these psychological conditions and fatigue was their only problem after stroke. In addition to affective factors, other psychological factors, such as sense of control and physical cause attribution, have been found to be associated with fatigue in patients with multiple sclerosis and those with chronic fatigue syndrome (Vercoulen et al., 1998). These factors may also play a role in the development of fatigue after stroke.

Affective factors

To explore associations between PSF and depressive symptoms and anxiety, I conducted a systematic review and performed meta-analyses to determine the strength of these associations (Wu et al., 2014b). Details of the methods and results of this systematic review will be discussed in Section 2.3. In brief, I identified 31 studies that reported the association between PSF and depressive symptoms, of which 19 studies (6712 patients) provided data suitable for meta-analysis. The pooled data indicated a significant association between PSF and depressive symptoms (pooled Odds Ratio, OR = 4.14, 95% confidence interval, 95% CI 2.73 to 6.27); this association was significant even in patients who did not meet clinical criteria of depression (433 patients, pooled OR = 1.39, 95% CI 1.27 to 1.53), or in studies that used depression measures without any fatigue item (4554 patients, pooled OR = 5.41, 95% CI 1.54 to 18.93). Of seven studies that reported the association between PSF and anxiety, four studies (3934 patients) provided data for meta-analysis and found a trend towards an association between PSF and anxiety (pooled OR = 2.34, 95% CI 0.98 to 5.58). Subgroup analyses indicated that this association was weaker ($p < 0.01$) in studies that controlled for the effect of depression (two studies, 3717 patients, pooled OR = 1.25, 95% CI 1.14 to 1.38) than

studies that did not control for depression (two studies, 217 patients, pooled OR = 5.34, 95% CI 4.70 to 6.07).

The above results were based on the literature search in October 2012 and have been published in *Stroke* (2014); 45: 1778-1783. Several new studies reporting psychological associations of PSF have been published since the last search, which were not included in the above meta-analyses. Through an updated search in August 2015, I identified 11 additional studies (2548 patients) that had reported associations between PSF and depressive symptoms (Chen et al., 2015, Galligan et al., 2015, Lerdal and Gay, 2013, Maaijwee et al., 2014, Naess and Nyland, 2013, Pihlaja et al., 2014, Tang et al., 2014, Tang et al., 2013, Wang et al., 2014, Wu et al., 2014a, Duncan et al., 2015) and four of them (955 patients) had also reported associations between PSF and anxiety (Chen et al., 2015, Maaijwee et al., 2014, Duncan et al., 2015, Galligan et al., 2015). The significant association between PSF and depressive symptoms was consistently reported across all studies. Also four studies investigating the association between PSF and anxiety all found a significant association; however, this association might have been confounded by depressive symptoms, as two of these studies found that depressive symptoms and anxiety were highly correlated (Chen et al., 2015, Duncan et al., 2015).

Although the causal mechanisms of PSF could not been established in observational studies, existing studies suggested that PSF and depressive symptoms (or anxiety) were associated over time and were predictors for each other, indicating a bidirectional relationship. Cross-sectional studies have found significant associations between PSF and both depressive symptoms and anxiety, with observational periods ranging from the first few days (Wang et al., 2014, Wu et al., 2014a) to several years after stroke (Maaijwee et al., 2014, Naess and Nyland, 2013). Longitudinal studies further illustrated that PSF was associated with these affective factors at both early (i.e. within the first few months) and late (i.e. beyond one year) stages after stroke (Radman et al., 2012, Snaphaan et al., 2011, Duncan et al., 2015). In addition, levels of depression and levels of anxiety at baseline were positively associated with, and the independent predictors for, fatigue levels at follow-up (Lerdal and Gay, 2013,

Snaphaan et al., 2011, Chen et al., 2015, Duncan et al., 2015); one the other hand, patients with PSF at baseline had more depressive symptoms at follow-up (Pihlaja et al., 2014). Furthermore, patients who had fatigue at both baseline and follow-up (i.e. persistent fatigue) had higher levels of depression and anxiety at baseline, compared to those who did not have fatigue or those who only had fatigue at either baseline or follow-up (Snaphaan et al., 2011, Tang et al., 2014).

It is important to note that fatigue and depression are two distinct concepts, even though they often coexist in stroke patients and their associations are bidirectional. Factor analysis of the combined pool of items of the FAS and the Beck Depression Inventory revealed two factors that represented fatigue and depression as two separate constructs (Smith et al., 2008). This is consistent with the observation that many patients with PSF do not have depression (Choi-Kwon et al., 2005). In summary, PSF is significantly associated with depressive symptoms and anxiety, and they may have reciprocal causal relationships, but PSF could also occur in patients without depression and anxiety.

Illness perceptions

Patients' cognitive responses to fatigue (i.e. their illness perceptions or beliefs about fatigue) may in turn have an impact on fatigue. In models for fatigue in multiple sclerosis and chronic fatigue syndrome, illness attribution to physical problems has negative impacts on PSF through the effect of reduced physical activity (Vercoulen et al., 1998). In qualitative studies of PSF, some patients attributed their fatigue to stroke or the relevant recovery process, while other patients were aware of other problems such as physical impairments, depression, medication, and ageing (Barbour and Mead, 2011, Flinn and Stube, 2010). However, there is no quantitative study investigating the association between illness attributions and fatigue in stroke patients.

Self-efficacy and sense of control

Sense of control or self-efficacy is the perceived ability to control one's own life or to achieve a goal in a particular situation (e.g. after stroke or with PSF). A

longitudinal study (167 patients) found that stroke patients who had a locus of control more directed to significant others (e.g. their families and doctors) at baseline were more likely to develop fatigue at one-year follow-up (Schepers et al., 2006). Another study (77 patients) reported that, in patients who were at least six months after their stroke, higher levels of fatigue were associated with both the decreased activity and the lower self-efficacy in keeping balance and in managing chronic diseases (Miller et al., 2013). The negative associations of PSF with self-efficacy and levels of daily activities were also reported in another study with 55 patients more than one year after stroke; this study also found that stroke specific self-efficacy and levels of daily activities were positively associated with each other (Muina-Lopez and Guidon, 2013). Therefore, it is possible that fatigue, lower self-efficacy, and lower level of activities after stroke are mutually linked.

Behavioural factors

Physical activity

Decreased mobility or inactivity is common in many medical conditions including stroke. Low level of physical activity has been identified in both hospitalised (West and Bernhardt, 2011) and community-dwelling stroke patients (Alzahrani et al., 2011). A hypothesis is that the reduced activity after stroke leads to physical deconditioning and in turn exertional fatigue, and that exertional fatigue leads to further avoidance of physical activity, which then contributes to chronic fatigue (Kutlubaev and Mead, 2011). However, the relationship between PSF and physical deconditioning is unclear. One study (66 patients) reported that lower leg strength on the unaffected side was associated with higher levels of fatigue in stroke patients (Lewis et al., 2011), whilst another study (48 patients) found no association between PSF and walking activity or fitness measures (Michael et al., 2006). A pilot study (9 patients) found a significant association between the peak oxygen uptake and fatigue levels immediately after the six-minute-walk test (Tseng and Kluding, 2009), but the investigators further illustrated in a larger study (21 patients) that the peak oxygen uptake was associated with the exercise-induced fatigue rather than the pathological chronic fatigue (Tseng et al., 2010).

The association between PSF and physical activity is likely to be bidirectional, although whether physical deconditioning plays a role in this is unknown. A longitudinal study (84 patients) reported significant cross-sectional associations between lower levels of physical activity and higher levels of fatigue at one, six and 12 months after stroke, respectively, and that the lower level of physical activity at one month was an independent predictor of higher levels of fatigue at both six and 12 months (Duncan et al., 2015). On the other hand, another longitudinal study (96 patients) found that acute phase fatigue was an independent predictor for lower physical health at 18-month follow-up (Lerdal and Gay, 2013).

Coping patterns

Coping is the way that people respond to stressful events, which involves an interaction of emotional, cognitive and behavioural processes. Qualitative studies revealed a spectrum of potential strategies for coping with PSF, ranging from struggling to cope (patients who seek explanations for their fatigue and search for strategies to overcome it, often feeling frustrated, guilty or out of control because of their fatigue) to adjusting by taking fatigue into account (accepting fatigue as part of life and adjusting their daily routines to adapt) (Eilertsen et al., 2013). A cross-sectional study (50 patients) found that, in patients at three months after stroke, both emotional-oriented coping (i.e. focusing on personal emotions) and avoidance-oriented coping (i.e. attempting to avoid difficult situations) were associated with higher fatigue scores, whilst task-oriented coping (i.e. cognitively restructuring the problem or altering the situations) was associated with lower fatigue scores (Jaracz et al., 2007). A longitudinal study (108 patients) reported that patients who adopted a passive coping pattern at three months after subarachnoid haemorrhage were more likely to have fatigue at one-year follow-up (Passier et al., 2011). Another study (109 patients) found no direct correlation between maladaptive coping (e.g. denial and avoidance) and PSF, but maladaptive coping at three months after subarachnoid haemorrhage was associated with post-traumatic stress disorder (PTSD) at both three months and 13 months, and scores of PTSD were associated with fatigue scores at both time points (Noble et al., 2008).

These findings imply that the way people response to stressful events may affect how they feel emotionally and the emotional distress is associated with fatigue symptoms. Given the positive associations between PSF and both emotional-oriented coping and avoidance-oriented coping and the negative association between PSF and task-oriented coping, it is possible that adopting the active coping with fatigue problems and the combat with emotional conditions and avoiding-behaviours could help to reduce PSF.

Social support

Some stroke patients reported that the lack of understanding by their significant others (e.g. their families and doctors) complicated their coping process and invoked emotional distress, and they believed that appropriate understanding and support from their significant others would be beneficial for the management of fatigue (Eilertsen et al., 2013). However, external support for stroke patients is limited. Patients with PSF often felt disbelief and a lack of understanding from other people (Eilertsen et al., 2015) and complained insufficient and ineffective medical advice on PSF from health professionals (White et al., 2012). In a group of 41 stroke patients who reported fatigue as a frequent problem, only 8 (19.5%) had discussed fatigue with their clinical team (Crosby et al., 2012). In addition, fatigued patients often reported lower levels of family function (Wang et al., 2014) and poorer social support (Michael et al., 2006), as compared with non-fatigued stroke patients.

Comorbidities and medications

Sleeping problems

About 20-40% of stroke patients experience sleep disturbances, mostly with hypersomnia, insomnia, daytime somnolence and sleep-disordered breathing (Hermann et al., 2003). Some patients thought that their fatigue was related to the poor sleep in hospital during the acute phase (Barbour and Mead, 2011). This is consistent with the observation that higher levels of fatigue were associated with lower quality of sleep in patients within the first week after stroke (Lerdal et al., 2011). Sleep apnoea is common after stroke but no study has directly investigated its

association with PSF, apart from a small study (32 patients) which used a scale for daytime sleepiness "to evaluate symptoms of sleep apnoea" and found the mean scores of daytime sleepiness were not different between patients with and without PSF (Hoang et al., 2012). A larger study (136 patients) found cross-sectional associations between PSF and daytime sleepiness at one, six and 12 months after stroke, though sleepiness at one month did not predict fatigue at follow-up (Duncan et al., 2015). In addition, presence of other sleep disturbances (e.g. insomnia or frequent wakening during night) were associated with PSF (Naess et al., 2012, Schepers et al., 2006, Choi-Kwon et al., 2005, Appelros, 2006, Galligan et al., 2015, Tang et al., 2014, Wang et al., 2014). However, this association did not exist in regression models, when controlling for effects of other contributing factors to PSF (Park et al., 2009, Naess et al., 2012, Schepers et al., 2006, Appelros, 2006, Galligan et al., 2015, Tang et al., 2014, Wang et al., 2014).

Depression is an important confounder for the association between PSF and sleeping problems. Suh and colleagues (282 patients) reported that depression but not fatigue was independently associated with poor quality of sleep at night, and both poor sleep at night and fatigue were independently associated with daytime sleepiness (Suh et al., 2014). Pain is possibly another confounder. Tang and colleagues recruited 97 patients who had PSF at three months after stroke and found that patients who had subcortical white matter infarct, insomnia, pain or higher depression scores at three months were more likely to had fatigue at 15 months; adding these factors in multiple regression model, the other three factors but not insomnia were independent predictors for PSF (Tang et al., 2014). The potential association between PSF and subcortical white matter infarct has been discussed previously in this thesis, but whether it influences PSF directly or through the effect of other symptoms such as pain or depression is unclear. In addition, we do not know whether fatigue is a direct result of poor sleep or the use of sleeping pills, of which the latter usually have sedative effects. Two studies found that PSF was associated with both the presence of sleep disturbances and the use of sleeping pills, but one of these studies (312 patients) reported that in the multivariate model only the association with sleeping pills was significant but not with sleep disturbances (Wang et al., 2014), whilst the

other study (377 patients) reported that adding the use of sleeping pills in the model did not change the significant association between PSF and sleep disturbances (Naess et al., 2012).

Although there might be some confounding factors, PSF is associated with sleeping problems, either directly or indirectly. Thus stroke survivors with fatigue should be asked about their sleep patterns. For fatigued patients with sleeping problems, they should be provided advice on developing regular sleep patterns and keeping sleep hygiene, or even be advised to consult their doctors for more specific treatment.

Pain

Pain is common after stroke, of which the reported prevalence ranges from 11% to 55% in stroke patients (Harrison and Field, 2015). Some studies reported that about 30% of stroke patients had co-existing fatigue and pain (Naess et al., 2012, Miller et al., 2013). In a population-based study with 3667 patients at two years after stroke, self-reported feeling of tiredness was significantly associated with self-reported feeling of pain (Glader et al., 2002). Another study reported that 71% of fatigued patients had pain, which was about two times of the proportion of pain in non-fatigued stroke patients (36%), although this difference was not statistically significant in this small sample of 32 stroke patients (Hoang et al., 2012). One study (77 patients) reported that PSF and pain were individually associated with lower self-efficacy and reduced activity, and patients with coexisting fatigue and pain had lower self-efficacy and reduced activity than those without coexisting symptoms (Miller et al., 2013). These findings suggest that PSF and pain may have synergic effect on or may be affected simultaneously by self-efficacy and participation in activities, although there may be no direct association between the two symptoms (Appelros, 2006, Miller et al., 2013). In addition, similar to sleeping problems, the association between PSF and pain may be confounded by the use of relevant medication. One study (377 patients) reported that the use of analgesics was associated with the presence of PSF (Naess et al., 2012).

Altered blood pressure

One study (100 patients) found that patients with episodes of daytime hypertension and those with episodes of daytime hypotension had higher fatigue scores as compared with patients with normal blood pressure as recorded on 24-hour ambulatory blood pressure monitoring (Harbison et al., 2009). This study also found that patients receiving anti-hypertensive medication were more fatigued than those who did not take the medication (Harbison et al., 2009). These findings imply two possibilities: firstly, there may be a significant association between fatigue and hypertension or hypotension. The association between fatigue and lower blood pressure has been reported in the general population (Wessely et al., 1990); secondly, fatigue may be a result of the use of anti-hypertensive medication, of which fatigue is a common side effect (Joshi et al., 2010). Future studies comparing patients with normal blood pressure to patients who had medication-controlled hypertension may help to clarify the effect of anti-hypertensive drugs on PSF.

Medications

In addition to the medications discussed above (i.e. sleeping pills, analgesics and anti-hypertensive drugs), other medications commonly used in stroke patients can also cause fatigue. For example, one study (218 patients) found that higher fatigue scores was associated with the use of antidepressants (Chen et al., 2015). Also, statins are often used in stroke patients, of which muscle weakness and fatigue are the most common adverse effects (Golomb and Evans, 2008). In an audit (64 patients) to assess the frequency and impact of fatigue after stroke, there was a trend towards statistically significant associations between the presence of PSF and the use of statin ($p = 0.07$) (Crosby et al., 2012). In addition, in a study investigating the impact of discontinuation of statin therapy in 631 stroke patients, 246 patients discontinued their statin therapy in the first year after discharge and 16 (7%) of these statin withdrawal were for the reason of fatigue (Colivicchi et al., 2007).

If the patient thinks that certain medication causes his/her fatigue, clinicians may need to consider using alternative medications. However, clinicians and patients should be cautious to stop using the medication simply because of fatigue. This is because withdrawal of certain drugs may cause more adverse consequences to the

patient; for example, discontinuation of statin therapy was an independent predictor for mortality in the first year after stroke (Colivicchi et al., 2007) and controlling blood pressure and blood lipid is important for the secondary prevention of stroke (American Heart Association Stroke Council, 2014). Clinicians need to inform patients of both benefits (e.g. to prevent recurrent stroke) and potential side effects (e.g. fatigue) of using certain medication so that patients will be able to weigh the pros and cons of using or not using the medication.

2.2.4 Summary

In summary, the development of PSF is a temporal and dynamic process, which is associated with a myriad of biological (e.g. stroke lesions and inflammation), psychological (e.g. depressive symptoms and anxiety symptoms), behavioural (e.g. reduced physical activity and sleeping problems) and environmental factors (e.g. inadequate external support). Some people may be more vulnerable than others to fatigue. This vulnerability may be accounted for factors that exist prior to stroke and can be reflected in symptoms such as fatigue and depression, either prior to or after stroke. However, predisposing factors for this vulnerability is unknown in stroke patients and need to be investigated in future studies. Associations between PSF and stroke lesions and related biological changes are reported in some but not all studies. These stroke-specific factors may result in physical and cognitive impairments, which would require patients to consume more energy to complete physical and mental tasks in daily living thus make them feel fatigued. If PSF is associated with these stroke-related changes, then it is expected to resolve with stroke recovery. This is consistent with the observation of natural resolution of fatigue early after stroke in some patients. Future studies are expected to clarify how stroke triggers PSF, as our current understanding of its mechanisms is merely based on the observation of associations.

Although the early resolution of fatigue is reported in some studies, PSF is more commonly to be reported as a chronic problem that persists in patients several months or years after stroke. Findings from longitudinal studies indicate that the presence and severity of fatigue tends to be stable in the chronic stage. Factors that

perpetuate fatigue include distressed mood, lower self-efficacy, and reduced physical activity, which are reflected as maladaptive coping patterns (e.g. emotional-oriented, avoidance-oriented, or passive patterns). There is evidence that associations between PSF and some of these psychological and behavioural factors are bidirectional, although the causal mechanisms are still elusive. Inadequate social support may influence PSF through the effects of emotional distress and coping patterns. In addition, other medical conditions (such as sleeping problems, pain, and altered blood pressure) and some medications commonly used in stroke patients (e.g. sleeping pills, analgesics, anti-hypertensive drugs, antidepressants, and statins) can also contribute to the development of PSF, thus need to be screened and managed in fatigued patients.

These findings suggest that PSF is an early and persistent problem after stroke. Given its high prevalence and detrimental consequences, interventions to prevent and treat PSF are urgently needed. Although the causal mechanisms of PSF is unclear, some of its clinical correlates are possible targets for interventions for PSF. In Section 2.4, I will discuss how the findings in this section informed the development of a psychological intervention for the management of PSF.

Section 2.3 Psychological associations of post-stroke fatigue: a systematic review and meta-analysis

Psychological factors are the most commonly reported associations of PSF, particularly depressive symptoms. These associations might represent targets for treatment. In this section, I conducted a systematic review of psychological correlates of PSF and, where data were suitable, performed meta-analyses to determine the strength of associations.

2.3.1 Abstract

Background

Fatigue is common after stroke but there is no effective treatment. Psychological interventions improve fatigue in other conditions by targeting psychological factors such as patients' thoughts and behaviours. If these psychological factors correlate with fatigue in stroke patients, this would justify the development of similar psychological interventions for post-stroke fatigue (PSF). This systematic review and meta-analysis aimed to explore psychological factors that are associated with PSF.

Methods

Online databases (MEDLINE, EMBASE, CINAHL plus, AMED, and PsycINFO) were searched for observational studies that reported psychological associations of PSF. Odds ratios (ORs) were used to estimate the strength of associations and were pooled in a random-effects model. Subgroup analyses were used to investigate the impact of study design. Sensitivity analyses were limited to studies that had excluded patients with clinical depression, and to studies that had used depression scales which did not have any fatigue item.

Results

A total of 5863 citations were retrieved and full texts were obtained for 288 studies. Thirty five studies (9268 patients) fulfilled the inclusion criteria, which reported the association between PSF and at least one psychological factor. Nineteen studies

(6712 patients) reported the association between PSF and depressive symptoms (pooled OR = 4.14, 95% confidence interval, 95% CI 2.73 to 6.27); this association existed in patients without clinical depression (2 studies, 433 patients, pooled OR = 1.39, 95% CI 1.27 to 1.53) and in studies using depression scales without fatigue items (6 studies, 4554 patients, pooled OR = 5.41, 95% CI 1.54 to 18.93). Four studies (3884 patients) reported the association between PSF and anxiety (pooled OR = 2.34, 95% CI 0.98 to 5.58). Two studies (123 patients) found an association with poor coping styles and one study (167 patients) found an association with loss of control. Six studies (1978 patients) reported associations between PSF and other emotional or behavioural symptoms.

Conclusions

PSF is associated with depressive symptoms, anxiety, poor coping, loss of control, and other emotional and behavioural symptoms. These psychological factors are potential targets for the treatment of PSF.

2.3.2 Background

Post-stroke fatigue (PSF) is a distressing symptom that affects more than a third of stroke patients (Lerdal et al., 2009). However, little research has been conducted to develop effective interventions and there is insufficient evidence to guide its treatment (McGeough et al., 2009). Psychological interventions improve fatigue in other conditions such as cancer, multiple sclerosis, and chronic fatigue syndrome. These interventions primarily aimed to change patients' thoughts and behaviours, as well as to improve their emotional well-being. To determine whether to develop similar interventions for fatigue after stroke, we need evidence about associations between PSF and those factors that could be targeted as part of a psychological intervention.

Although a number of narrative reviews have reported psychological associations of PSF (Annoni et al., 2008, Barker-Collo et al., 2007, Barritt and Smithard, 2011, Choi-Kwon and Kim, 2011, Colle et al., 2006, de Groot et al., 2003, Duncan et al., 2012, Lerdal et al., 2009, Staub and Bogousslavsky, 2001a), their results are conflicting. For example, three reviews concluded that PSF was associated with depression (Barritt and Smithard, 2011, Lerdal et al., 2009, Duncan et al., 2012) but other six reviews reported that PSF could occur independently of depression (Annoni et al., 2008, Barker-Collo et al., 2007, Choi-Kwon and Kim, 2011, Colle et al., 2006, de Groot et al., 2003, Staub and Bogousslavsky, 2001a). Similarly, three reviews reported that PSF was associated with anxiety (Annoni et al., 2008, Duncan et al., 2012, Lerdal et al., 2009) but another review reported no association (Barker-Collo et al., 2007). Importantly, none of these reviews used meta-analysis to estimate the strength of associations. Thus, we need more evidence about the nature of the association between PSF and psychological factors, including, but not limited to, depressive symptoms, anxiety, sense of control, and coping patterns.

This systematic review and meta-analysis aimed to determine whether PSF is associated with psychological factors that could be targets for a psychological intervention.

2.3.3 Methods

Electronic search

An electronic search was conducted in October 2012 to identify publications of observational studies of PSF in the following databases MEDLINE, EMBASE, CHINAHL, AMED, and PsycINFO. The search strategy was adapted from a Cochrane review of interventions for PSF (McGeough et al., 2009), using "stroke" and its synonyms in combination with search terms relating to "fatigue".

Study selection

Observational studies of stroke patients were included if they reported measures of both PSF and at least one psychological factor, either as dichotomous variables (e.g. the presence or absence of fatigue) or continuous variables (e.g. scales for the severity of fatigue). For studies only reporting qualitative data for the associations, they were not included in the meta-analysis but presented in the section of descriptive analysis. Studies were excluded if they a) contained insufficient data to allow reporting of any association, b) included any patients aged 18 or younger, c) used unstructured assessment for PSF, or d) provided data for patients with stroke that could not be disaggregated from other types of patients.

To ensure that eligible studies were not missed, I screened all titles and abstracts on two separate occasions. Apparently irrelevant studies were excluded and full texts were obtained for potentially eligible studies. I read all full texts to determine whether they met the inclusion criteria. Another two review authors (Amanda Barugh, AB and Gillian Mead, GM) each read half of the full texts, independently of me. Any disagreement regarding whether a study was eligible for the review was solved by discussion between the review authors. I also scrutinised reference lists of included studies and previous reviews of PSF, and obtained full texts for potentially relevant studies.

Data extraction

The second review author (AB) and I independently extracted data on study design, demographics of patients (including whether patients with a clinical diagnosis of depression were included or excluded at recruitment), measures of PSF, measures of psychological factors, and statistics for the association(s) between PSF and psychological factors.

Quality assessment

We (AB and I) also independently applied the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Vandenbroucke et al., 2007) to assess the methodological quality of each included studies.

Statistical analysis

For each study which provided raw data of the number or proportion of patients with PSF and the number or proportion of patients with any psychological factor(s), I calculated odds ratios (ORs) and 95% confidence intervals (95% CI) for associations between PSF and each psychological factor. If raw data were unavailable, I used ORs reported by study investigators for meta-analysis. If study investigators only reported correlation coefficients rather than raw data or ORs, I converted the correlation coefficients to ORs using established methods (Borenstein et al., 2009). If ORs could not be obtained by any of these methods, I summarised the study qualitatively not quantitatively in this review. I assessed publication bias using funnel plotting (Borenstein et al., 2009).

I pooled summary estimates of ORs in the random-effects model (Borenstein et al., 2009) for associations between PSF and depressive symptoms and between PSF and anxiety, respectively. I assessed between-study heterogeneity using the Cochran Q statistic, with a pre-specified critical level of 0.05 for significant heterogeneity (Borenstein et al., 2009). I had intended to conduct meta-analysis for psychological associations other than depressive symptoms and anxiety, but this was not possible because these studies only reported regression coefficients and *p* values.

For the association between PSF and depressive symptoms, some studies investigated the association using multiple regression where ORs were adjusted by controlling for the effects of potential confounders (e.g. age, sex, lesion site, and dependence in daily living), whilst other studies investigated the association using binary analysis where ORs were not adjusted by other factors. I compared studies reporting adjusted ORs with those reporting unadjusted ORs, and partitioned heterogeneity between these two subgroups (Borenstein et al., 2009). I conducted sensitivity analyses a) for studies that had excluded patients with a clinical diagnosis of depression at recruitment, and b) by excluding studies that had used a depression measure that contained any item for fatigue.

2.3.4 Results

5863 citations were retrieved from electronic searches and 288 full texts were screened to assess whether they fulfilled the inclusion criteria. The process of study selection and data analysis is summarised in Figure 2.2.

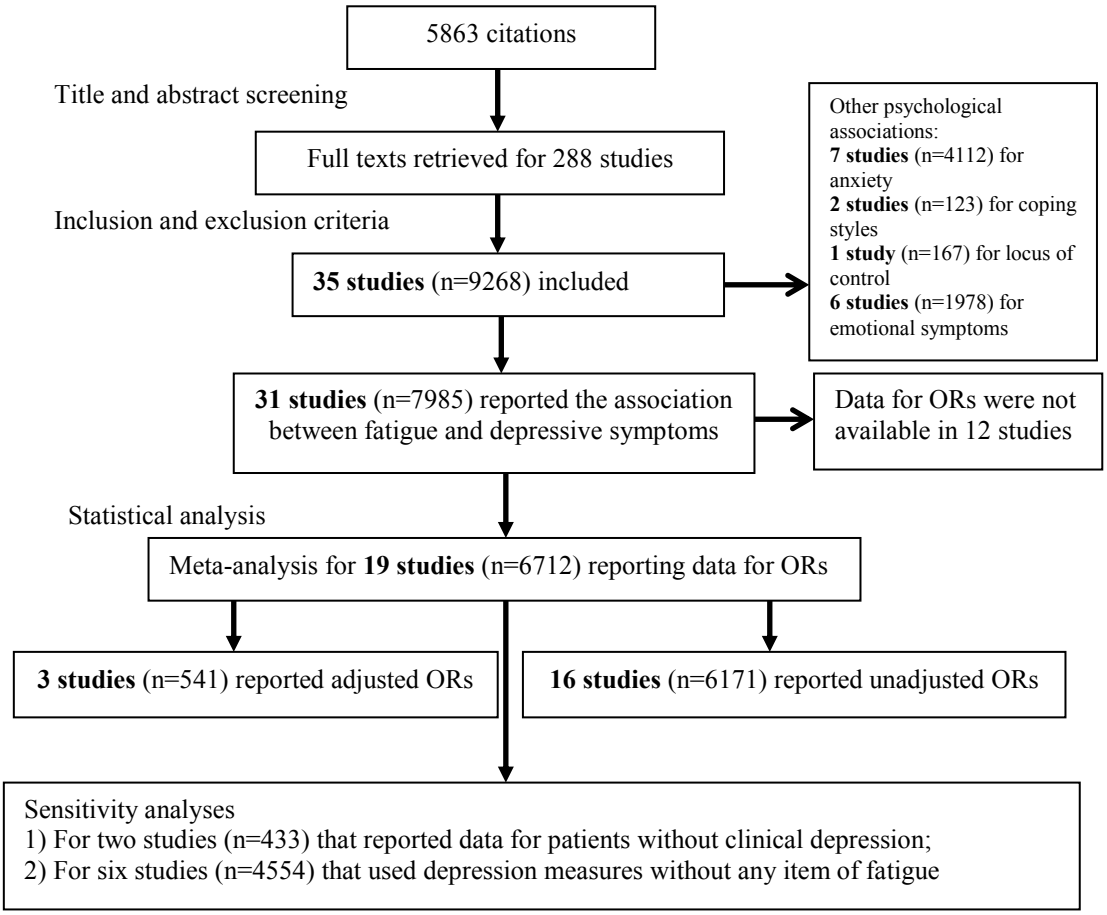

Figure 2.2 Flowchart of electronic search, study selection, and data analysis for a systematic review of psychological associations of post-stroke fatigue. ORs indicate odds ratios

A total of 35 studies with 9268 patients were included in this review. The mean age of patients ranged from 51 years (Hubacher et al., 2012) to 75 years (Appelros, 2006) and the women proportion ranged from 19% (Hubacher et al., 2012) to 67% (Crosby et al., 2012). Five studies recruited patients with ischaemic stroke (Coster et al., 2005, Parks et al., 2012, Snaphaan et al., 2011, Tang et al., 2010a, Tang et al., 2010b), two studies with subarachnoid haemorrhage (Noble et al., 2008, Visser-Meily et al., 2009), 18 studies included both ischaemic and haemorrhagic stroke (Almborg et al., 2010, Appelros, 2006, Crosby et al., 2012, Glader et al., 2002, Hoang et al., 2012, Hubacher et al., 2012, Ingles et al., 1999, Jaracz et al., 2007, Lynch et al., 2007, Mead et al., 2011, Naess et al., 2012, Park et al., 2009, Radman et al., 2012, Sibon et al., 2012, Skaner et al., 2007, Tseng et al., 2010, van de Port et al., 2007, Zedlitz et al., 2011), and the other 10 studies did not specify the type of stroke

(Choi-Kwon et al., 2005, Harbison et al., 2009, Lerdal et al., 2011, Lewis et al., 2011, Schepers et al., 2006, Smith et al., 2008, Spalletta et al., 2005, Stokes et al., 2011, van der Werf et al., 2001, Vuletic et al., 2011).

Of the 35 included studies, the depressive symptom was the most commonly investigated psychological association of PSF (31 studies with 7985 patients), followed by the symptom of anxiety (seven studies with 4112 patients). Other reported associations included coping patterns (two studies with 123 patients), sense of control (one study with 137 patients), and general emotional status or other symptoms (six studies with 1978 patients).

The study quality was generally good. The median number of the STROBE checklist items scored was 19 (interquartile range, 18 to 20, out of a maximal possible score of 22; higher scores indicate better quality). Common weaknesses included not describing details of recruitment, not addressing potential bias, or not declaring sources of funding. In addition, no study reported how the sample size was determined.

Depressive symptoms

Summary meta-analysis

Of 31 studies that investigated the association between PSF and depressive symptoms, ORs could be obtained from 19 studies; from these I calculated ORs from raw data (i.e. numbers of patients with or without the case of fatigue, and numbers for depression) of seven studies (Choi-Kwon et al., 2005, Crosby et al., 2012, Glader et al., 2002, Harbison et al., 2009, Ingles et al., 1999, Naess et al., 2012, Spalletta et al., 2005), extracted ORs from four studies (Appelros, 2006, Radman et al., 2012, Snaphaan et al., 2011, Tang et al., 2010a), and converted ORs from correlation coefficients from the other eight studies (Coster et al., 2005, Jaracz et al., 2007, Lerdal et al., 2011, Park et al., 2009, Schepers et al., 2006, Smith et al., 2008, Tang et al., 2010b, Tseng, 2009). The odds of fatigue in patients with depressive symptoms were 4.14 (95% CI 2.73 to 6.27) times of the odds in patients without depressive

symptoms (Figure 2.3), with no significant between-study heterogeneity (Q = 15.58, degrees of freedom (df) = 18, p = 0.62).

Subgroup analysis

The strength of the association in 16 studies of unadjusted ORs (6171 patients, pooled OR = 5.46, 95% CI 3.58 to 8.32) was higher ($p < 0.0001$) than the association in three studies where ORs were adjusted by other factors (541 patients, pooled OR = 1.36, 95% CI 1.26 to 1.46). This difference might have contributed to an asymmetrical funnel plot (Figure 2.4), as the three studies reporting adjusted ORs were located in the upper left-hand corner of the plot (indicating smaller effect sizes with smaller variance) away from the other 16 studies.

Sensitivity analyses

Of the 19 studies included in meta-analysis, one study (334 patients) excluded patients with major depression at recruitment (Tang et al., 2010a) and another study (99 patients) provided data of patients without depression (Radman et al., 2012); pooled estimate of these two adjusted ORs was 1.39 (95% CI 1.27 to 1.53, which was not statistically different from the summary estimate of all three adjusted ORs, p = 0.91). The other 17 studies did not specify whether they had distinguished patients with current clinical depression.

Thirteen studies assessed depression using a measure that contained a single item for fatigue (Appelros, 2006, Choi-Kwon et al., 2005, Coster et al., 2005, Ingles et al., 1999, Jaracz et al., 2007, Lerdal et al., 2011, Park et al., 2009, Radman et al., 2012, Smith et al., 2008, Spalletta et al., 2005, Tang et al., 2010a, Tang et al., 2010b, Tseng et al., 2010) and two of them also assessed the presence of fatigue by this fatigue item of the depression measure (Coster et al., 2005, Spalletta et al., 2005). For the remaining six studies (4554 patients) that used depression measures without any fatigue item, the pooled OR was 5.41 (95% CI 1.54 to 18.93), which was not significantly different from either the summary estimate for the other 13 studies (pooled OR = 3.45, 1.82 to 6.57; p = 0.53) or from that of the total 19 studies (pooled OR = 4.14, 95% CI 2.73 to 6.27; p = 0.84).

ID	No.	OR	95% CI
Tseng(2010)	21	20.36	2.58-160.7(
Tang(2010b)	458	15.74	10.37-23.9(
Glader(2002)	3820	14.54	11.06-19.1
Naess(2012a)	352	11.31	3.86-33.12
Crosby(2012)	57	11.20	1.30-96.64*
Lerdal(2011)	115	6.90	3.25-14.66
Park(2009)	40	6.90	1.90-25.06
Smith(2008)	80	5.91	2.43-14.39
Schepers(2006)	167	4.65	2.55-8.47
Choi-Kwon(2005)	220	4.48	2.11-9.51
Coster(2005)	206	3.41	2.02-5.75
Appelros(2006)	247	3.20	1.70-6.01
Spalletta(2005)	200	2.84	1.59-5.07
Jaracz(2007)	50	2.77	0.96-7.97
Harbison(2009)	50	2.75	0.83-9.09
Ingles(1999)	88	1.61	0.63-4.13
Tang(2010a)	334	1.37	1.24-1.51
Snaphaan(2011)	108	1.36	1.17-1.58
Radman(2012)	99	1.33	1.14-1.55

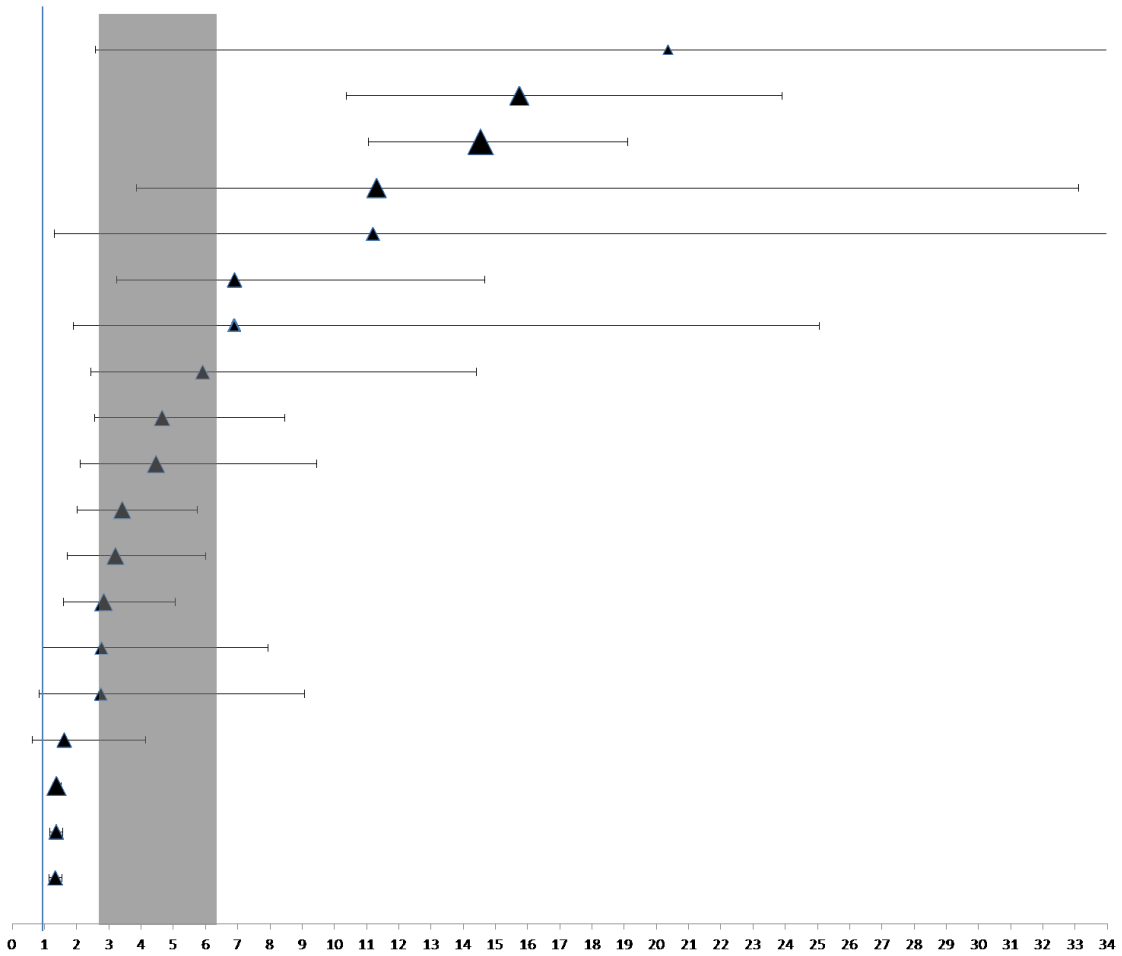

Figure 2.3 Random-effects meta-analysis for the association between post-stroke fatigue and depressive symptoms. The horizontal axis is the odds ratio (OR) comparing the occurrence of depressive symptoms in patients with and without fatigue after stroke. Horizontal error bars represent the 95% confidence interval (CI) of OR in individual studies, and vertical gray bar represents the 95% CI of the summary estimate of OR. The triangle symbol size represents the log of the number of patients in that study. *The upper limit of the 95% CI of OR beyond 34 was not shown in the plot.

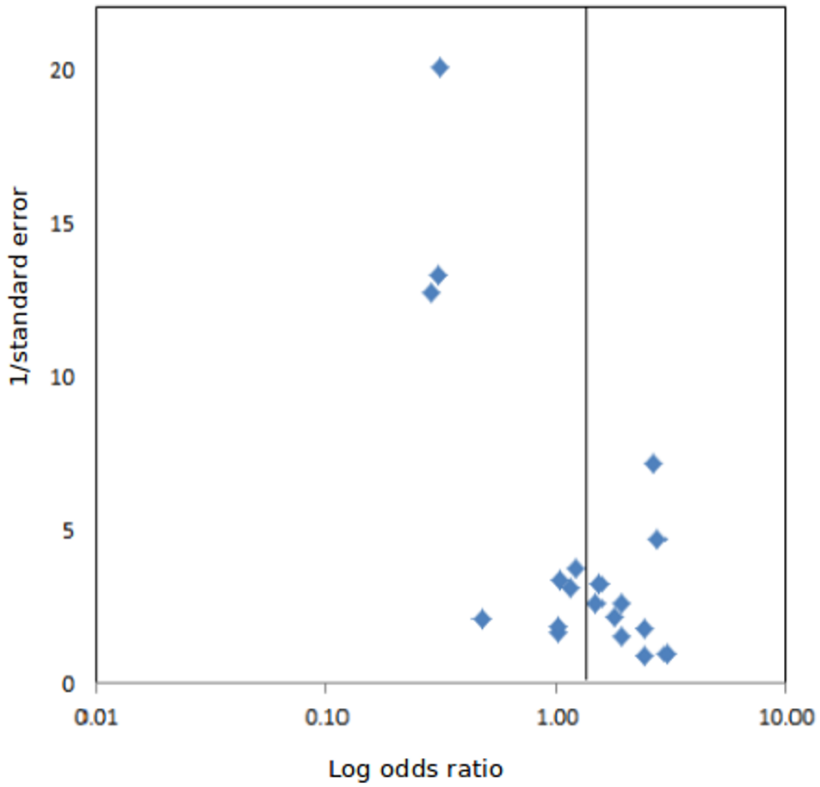

Figure 2.4 Funnel plot for publication bias. The horizontal axis represents the log odds ratios (ORs) for the association between post-stroke fatigue and depressive symptoms, and the vertical axis represents the inverse standard error.

Qualitative analysis

Twelve studies investigated the association between PSF and depressive symptoms but did not report sufficient data to be included in meta-analysis. Of these studies, nine studies (1053 patients) reported a significant association between PSF and depression (Almborg et al., 2010, Hubacher et al., 2012, Lynch et al., 2007, Parks et al., 2012, Sibon et al., 2012, Skaner et al., 2007, van de Port et al., 2007, van der Werf et al., 2001, Vuletic et al., 2011), whereas one small study (32 patients) reported 'no significant difference' in depression scores between fatigued and non-fatigued groups (Hoang et al., 2012), another study (100 patients) reported that depressive symptoms were associated with mental fatigue but not with other fatigue domains (Stokes et al., 2011), one further study (88 patients) used two measures for

PSF and two measures for depression, but reported four conflicting results of the association (Zedlitz et al., 2011).

Anxiety

Seven studies reported the association between PSF and anxiety, of which four studies (3934 patients) provided data for meta-analysis (Glader et al., 2002, Harbison et al., 2009, Radman et al., 2012, Snaphaan et al., 2011). The summary estimate of OR was 2.34 (95% CI 0.98 to 5.58) with no significant between-study heterogeneity (Q = 2.36, df = 3, p = 0.50). Subgroup analysis indicated that the strength of association between PSF and anxiety in two studies (Radman et al., 2012, Snaphaan et al., 2011) not having controlled for the effect of depression (217 patients, pooled OR = 5.34, 95% CI 4.70 to 6.07) was higher (p < 0.01) than that in the other two studies (Glader et al., 2002, Harbison et al., 2009) having controlled for the effect of depression (3717 patients, pooled OR = 1.25, 95% CI 1.14 to 1.38).

Of the three studies that had provided insufficient data to be included in the meta-analysis, two studies (90 patients) reported a significant association between fatigue and anxiety (Lynch et al., 2007, Vuletic et al., 2011), whereas the other study (88 patients) excluded patients with depression at recruitment and found a non-significant association between PSF and anxiety (Zedlitz et al., 2011).

Other psychological factors

Associations between PSF and coping styles were investigated by two studies. One study (50 patients) reported that patients focusing on personal emotions and self-blame were more likely to have a higher level of PSF (p < 0.01) (Jaracz et al., 2007). Another study (73 patients) found that 'maladaptive coping' (e.g. denial and self-distraction) was the main cause of Post-traumatic Stress Disorder (PTSD, p < 0.0001) and the latter was associated with PSF (p < 0.0001) (Noble et al., 2008). One study (167 patients) reported that patients who were not confident in their own ability to control their health had more severe fatigue (p = 0.002) (Schepers et al., 2006). Three studies (1527 patients) assessed mental health and emotional role by the SF-36 and all reported that PSF was associated with poor outcomes of both mental and

emotional subscales (Lewis et al., 2011, Mead et al., 2011, Tang et al., 2010b). Such an association was also reported by another study (141 patients) using the emotional subscale of Stroke-specific Quality of Life (SSQOL) (Visser-Meily et al., 2009). PSF was also associated with inappropriate laughing (one study, 220 patients) (Choi-Kwon et al., 2005) and alertness behaviour (measured by the Sickness Impact Scale in one study, 90 patients) (van der Werf et al., 2001).

2.3.5 Discussion

This is, to our knowledge, the first meta-analysis to report associations between post-stroke fatigue, and mood or other psychological factors. We found a statistically significant association between PSF and depressive symptoms, and a trend towards an association between PSF and anxiety. Two studies reported associations with inadequate coping styles, one study for loss of control, and six studies for other emotional or behavioural symptoms. The named psychological factors, i.e. depressive symptoms, anxiety, locus of control and coping patterns, have already been targeted by psychological interventions for fatigue in other conditions such as cancer and multiple sclerosis. This review provides the necessary evidence to justify the development of a similar intervention for fatigue in stroke patients. However, our findings should be interpreted with caution because only a small number of studies investigated each factor except for depressive symptoms. Also there are some weaknesses in the quality of the included studies in that most of them did not report how patients were recruited and how study size was achieved; thus it is difficult to determine whether the sample is representative of the entire stroke population.

PSF is associated with depressive symptoms, even in patients not meeting clinical criteria for depression. A previous study reported the presence of depressive symptoms in stroke patients without clinical depression, where 41% of the patients reported depressed mood but only half of them met clinical criteria for depression (Fedoroff et al., 1991). This suggests that clinicians should be aware of depressive symptoms in stroke patients and screen for them in patients with PSF, even in those without a clinical depression. We also noticed that some of the included studies had measured depression by using scales or criteria that contain a single item of fatigue.

We therefore performed a sensitivity analysis to determine whether this might result in an overestimation of the strength of the association between fatigue and depressive symptoms. The result indicated that this association remained significant even after excluding studies that had used a depression measure containing a fatigue item. In fact in these depression measures, fatigue only contributes a small proportion to the total score of depression (from one out of nine points to one out of 66 points). Thus the association that we identified was not because of the overlap between fatigue and depression measures.

In some of the included studies, age, sex, lesion site and dependence in daily life were considered as confounders for the association between PSF and depressive symptoms. Based on the current data, however, we could not analyse the effect of each individual confounder on the association. Previous studies reported that age and sex are associated with fatigue (Mead et al., 2011) but not with depression (Allan et al., 2013). There is insufficient evidence for the association between lesion site and either fatigue (Kutlubaev et al., 2012) or depression (Carson et al., 2000). The association between PSF and dependence in daily living has been widely reported in the studies included in this review. Dependence was also reported to be associated with post-stroke depression (Kutlubaev and Hackett, 2014) . Future research is expected to investigate the effect of these confounders.

There is a trend towards an association between PSF and anxiety, but the association was weaker after controlling for the effect of depressive symptoms. One study (included in our systematic review but not in meta-analysis) which had excluded patients with depression at recruitment reported no significant association between PSF and anxiety (Zedlitz et al., 2011). It is reported that anxiety is strongly correlated with depression after stroke (Barker-Collo, 2007). To better clarify whether depressive symptoms are confounders, the association between PSF and anxiety needs to be compared between stroke patients with and without depressive symptoms.

Our study has several strengths. It is the first systematic review to pool the results from studies that reported the associations between PSF and depressive symptoms or

anxiety. We performed a comprehensive search, had a pre-specified protocol, and used a well-established statistical approach. We also used a funnel plot to detect publication bias, where the asymmetrical plot might indicate certain publication bias caused by the 'missing' studies in the bottom left-hand corner of the plot. These studies are likely to be of small sample size and/or reported less significant results. A possible source for this publication bias might be the exclusion of conference abstracts and studies not published in English, although we have attempted to obtain further data by contacting the study authors but did not get any response. One limitation of our study is that only one author read all the abstracts to identified potentially eligible studies. However, this was done on two separate occasions to reduce the possibility of missing any relevant studies.

2.3.6 Conclusions

This review provides robust evidence for the association between post-stroke fatigue and depressive symptoms. This implies the screening and treatment of PSF in stroke patients needs to integrate strategies targeting mood. PSF is also associated, either directly or indirectly, with anxiety, loss of control, poor coping styles, emotional and behavioural symptoms; these factors are potential targets for the treatment of PSF.

Section 2.4 Implications for the management of PSF

In this Chapter, I have systematically reviewed the literature to explore the natural history and clinical correlates of PSF. In this section, I will discuss how these findings from the literature facilitate our understanding of PSF and inform its clinical management.

2.4.1 A conceptual model for understanding post-stroke fatigue

Drawing on the literature on natural history and clinical correlates of PSF, here I propose a conceptual model of potential mechanisms of PSF (Figure 2.5). This model illustrates the development of PSF as a temporal process that involves interactions of various biological, psychological, behavioural and environmental factors. A previous version of this model has been published in *Stroke* (2015); 46: 893-898 (Wu et al., 2015b). Here I present an updated version, by incorporating the perpetuating factors for chronic fatigue into a vicious cycle.

Factors existing prior to stroke predispose the vulnerability to fatigue. Fatigue present early after stroke is associated with specific lesion sites of stroke and some stroke-related impairments; together with the observation that PSF resolved spontaneously in some patients in the first few months after stroke, this suggests that early fatigue might be a result of stroke lesion or restorative response to the stroke event. Although fatigue resolves spontaneously in some patients, most patients had their fatigue persist over time. Patients' cognitive representation of fatigue (e.g. their illness beliefs, sense of control and self-efficacy) interact with their distressed mood and reduced physical activity, together with environmental factors, forming a vicious cycle that perpetuate fatigue symptoms. Thus the cognitive presentation of fatigue would be a potential treatment target to break this vicious cycle and thus reduce fatigue.

Although factors contributing to fatigue present early and late after stroke might be different, it is better to view these two types of fatigue as a continuous process, as early fatigue is associated with, or the most important predictor for, chronic fatigue

(van Eijsden et al., 2011, Lerdal and Gay, 2013, Snaphaan et al., 2011). Also, no single factor could fully explain the phenomenon of PSF. Even depressive symptoms, which is the most commonly reported association of PSF, explains only less than 20% of variance in fatigue scores in stroke patients (van der Werf et al., 2001). In addition, there are interactions between different contributing factors. For example, depressive symptoms and anxiety are highly correlated in stroke patients (Chen et al., 2015, Duncan et al., 2015), and fatigue, lower self-efficacy and reduced activities after stroke are linked with each other (Muina-Lopez and Guidon, 2013). Furthermore, there is no distinct boundary between predisposing, triggering and perpetuating factors, and they may overlap with each other. For example, symptoms of depression and anxiety at baseline were predictors for follow-up fatigue. However, these factors are not exclusively developed after stroke but may be present prior to stroke, thus it is unclear whether these factors play roles in predisposing or triggering PSF. Also, longitudinal studies found cross-sectional associations between these psychological factors with both early and late fatigue, indicating a role in perpetuating fatigue.

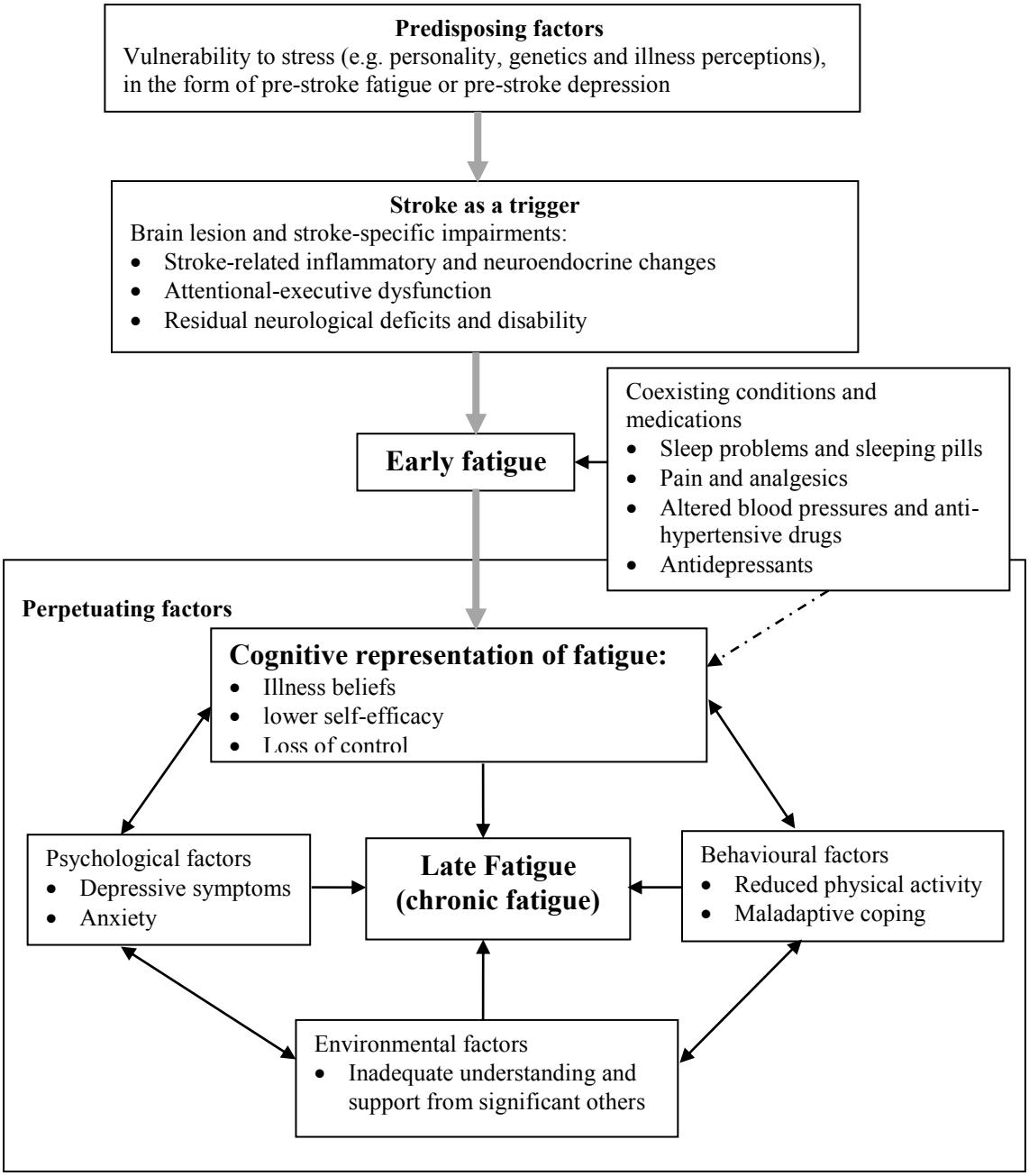

Figure 5.2 Conceptual model of post-stroke fatigue. The unidirectional arrows indicate a potential causal direction to PSF; the bidirectional arrows indicate bidirectional associations between factors.

2.4.2 Potential targets for the management of PSF

This conceptual model broadens our understanding of PSF from focusing on its potential triggers to factors that predispose fatigue and factors that prevent fatigue to resolve. The development of PSF involves interactions of a mixture of biological, psychological, behavioural and environmental factors. Some of these factors are potential targets for the management of PSF.

Although our understanding of PSF is mainly based on observational studies and its causal mechanisms are unknown, some identified factors are modifiable and their associations with PSF are bidirectional, i.e. they are independent predictors for and are also predicted by fatigue in longitudinal studies. These factors include distressed mood, lower self-efficacy and reduced physical activity. Interventions targeting these factors may help to reduce PSF. Also other potential causes for fatigue, including sleeping problems, pain, altered blood pressures and fatigue-inducing medications, can be readily identified and need to be managed in fatigued patients in clinical practice.

Predisposing factors

Studies for chronic fatigue syndrome suggest that some people may be more vulnerable than others to fatigue; this vulnerability can be attributed to personality or genetics and reflected in pre-existing conditions such as depression (Lievesley et al., 2014). This vulnerability hypothesis may apply to PSF because associations were found between PSF and some pre-stroke conditions (such as pre-stroke fatigue and pre-stroke depression), which are potential indicators of the fatigue vulnerability. However, predisposing factors for such vulnerability to fatigue in stroke patients are unknown. Future research is expected to explore these predisposing factors. This will help clinicians and researchers to identify people who are vulnerable to PSF and to develop strategies to adjust the predisposing factors. Early interventions to the predisposing factors in vulnerable people, where possible, will help to prevent PSF.

Other medical conditions and medications

Some medical conditions, including sleep disturbances, pain and altered blood pressure, are common in stroke patients and often coexist with PSF. These conditions need to be screened for, and properly treated in patients with PSF. Some medications that are often prescribed to stroke patients can cause muscle weakness or have sedative effects, resulting in the feeling of fatigue. These drugs include sleeping pills, analgesics, anti-hypertensive drugs, antidepressants, and statins. If the fatigue is suspected to be caused by certain drugs, it may be worth trying alternative medications. However, clinicians and patients should cautiously weigh the pros and cons of stopping using certain drugs only for avoiding the side effect of fatigue. This is because withdrawal of certain drugs may cause more adverse consequences to the patient; for example, drugs for controlling hypertension and dyslipidemia are important strategies for the secondary prevention of stroke (American Heart Association Stroke Council, 2014).

Stroke lesions and related impairments

Some studies reported that PSF was associated with specific lesion sites, residual neurological deficits, attentional-executive dysfunction, and inflammatory and neuroendocrine changes after stroke. These findings fit a brain fatigue model which was proposed for post-polio fatigue and chronic fatigue syndrome (Bruno et al., 1998). In this model, brain lesions interrupt the neural networks regulating attention and wakefulness function, which consequently lead to impaired concentration and the feeling of drowsiness. However, existing stroke studies on the biological mechanisms of PSF are small and the results are inconsistent, thus future studies are needed.

If this brain fatigue model is justified in stroke patients, PSF is expected to be resolved over time as neurological symptoms tend to get better. This is consistent with the observation of natural resolution of PSF in the first few months after stroke in some patients (Christensen et al., 2008, Duncan et al., 2014), during which the stroke recovery is most active but would subside afterwards (Jørgensen et al., 1995,

Newman, 1972). However, this does not mean that fatigue present at the early stage after stroke should be ignored. Early fatigue is always associated with or the most important predictor for late fatigue (Lerdal and Gay, 2013, Snaphaan et al., 2011). Early identification of and interventions for PSF may prevent it from becoming entrenched.

PSF could be present in patients who have minor or no neurological deficits (Carlsson et al., 2004, Powell et al., 2004) and the status of fatigue tends to be stable in the chronic stage after stroke (Christensen et al., 2008, Duncan et al., 2014). In addition, associations between PSF and stroke lesion sites or related biological changes are often found at an early but not late stage following stroke. These findings suggest that there might be other factors contributing to PSF than stroke per se, particularly in chronic stage.

Psychological and behavioural factors

Stroke patients who recover physically may be left with emotional and psychological dysfunctions (Tyrrell and Smithard, 2005). Affective factors are the most commonly reported associations of PSF. Quantitative analyses indicated a strong association between PSF and depressive symptoms and a trend of association between PSF and anxiety (Wu et al., 2014b). Furthermore, longitudinal studies demonstrated that these associations existed over time after stroke, and baseline depressive symptoms and anxiety were predictors for fatigue at follow-up (Lerdal and Gay, 2013, Snaphaan et al., 2011, Chen et al., 2015, Duncan et al., 2015). In addition, lower self-efficacy is common in people with chronic conditions such as stroke, and is associated with both fatigue and reduced activity in stroke patients (Muina-Lopez and Guidon, 2013). Although causal relationships between these psychological factors and PSF are elusive, there is evidence that their associations are bidirectional, i.e. they are predictors for each other in longitudinal studies. Therefore, clinical management of these psychological factors may help to reduce PSF.

Reduced physical activity at one month after stroke is an independent predictor for PSF at both six and 12 months (Duncan et al., 2015) and, vice versa, baseline fatigue

is an independent predictor for poor physical health at follow-up (Lerdal and Gay, 2013). These findings suggest a vicious cycle between PSF and inactivity, where the reduced activity after stroke leads to physical deconditioning and in turn exertional fatigue, and that exertional fatigue leads to further avoidance of physical activity, which then contributes to chronic fatigue (Kutlubaev and Mead, 2011). This hypothesis is further supported by the observation that stroke patients who had the avoidance coping pattern were more likely to have fatigue (Jaracz et al., 2007), which implies the possibility that the avoidance of physical activity in response to the feeling of fatigue in turn perpetuates fatigue symptoms. Increased physical activity is effective in improving physical fitness in stroke patients (Saunders et al., 2014), which may be helpful to combat the self-perpetuating cycle of inactivity, deconditioning, and PSF.

Conclusions

Future studies are needed to explore predisposing factors and biological mechanisms of PSF. Psychological and behavioural factors often coexist with fatigue in stroke patients. Some of these factors (i.e. distressed mood, lower self-efficacy and reduced physical activity) have bidirectional associations with PSF and are often modifiable, which are potential targets for the treatment of PSF. In addition, other medical conditions (i.e. sleep disorders, pain and altered blood pressure) and some medications (i.e. sleeping pills, analgesics, anti-hypertensive drugs, antidepressants and statins) can cause the feeling of fatigue, thus need to be screened for and managed in patients with PSF. These psychological and behavioural factors are important targets to be incorporated in a complex intervention for the treatment of PSF.

CHAPTER III: Development of a Psychological Intervention for Post-stroke Fatigue

Section 3.1 Introduction

In Chapter 2, I reviewed the evidence for the potential targets of a psychological intervention for the treatment of PSF. In brief, although PSF may be triggered by stroke, the persistent presence of fatigue is not necessarily associated with site or size of stroke lesions or the presence of neurological deficits. Psychological and behavioural factors probably play important roles in triggering and maintaining symptoms of PSF. Some of these factors, such as depressive symptoms and reduced physical activity, have bidirectional associations with PSF and are readily modifiable by psychological interventions. Interventions targeting these psychological and behavioural factors may be effective in reducing PSF.

In this chapter and the next chapter, I will explain how a psychological intervention was developed based on the modifiable clinical correlates of PSF. Psychological interventions are 'complex interventions' that consist of multiple therapeutic components (Craig et al., 2013). The UK Medical Research Council (MRC) has proposed a phased process of developing complex interventions, with an emphasis on early phase development and piloting and suggesting that these early stages are iterative (Campbell et al., 2007). The current chapter is focused on Phase 1, which includes the processes of identifying evidence, developing theory, and part of the modelling stage (Craig et al., 2008a). The next chapter will be discussing Phase 2, which includes part of the modelling stage and part of the piloting stage (Craig et al., 2008a).

Section 3.2 Methods

I developed this intervention in collaboration with a stroke physician (Gillian Mead, GM), a stroke neurologist (Malcolm Macleod, MM), two clinical psychologists (Kirsten Anderson, KA and David Gillespie, DG), and a CBT psychotherapist (Trudie Chalder, TC). The stroke physician and the stroke neurologist (GM and MM, both my academic supervisors) had both clinical and research experience with stroke patients, as well as expertise in designing clinical trials. The clinical psychologists (KA and DG) had more than ten years' experience of the psychological treatment of stroke patients. The psychotherapist (TC) had expertise in cognitive behavioural psychotherapies for chronic fatigue and clinical experience with stroke patients. I met these members of this multidisciplinary group (i.e. the project team) frequently to discuss and decide on theoretical and practical issues of this intervention, with perspectives from both stroke care and clinical psychology in the local health system. In addition, I sought service user involvement from two groups of stroke patients through the Stroke Research Network of the UK National Institute for Health Research (NIHR).

Both qualitative and quantitative approaches were used, which complemented each other. Given the subjective nature of PSF, patients' perspective is essential for the current study, for which qualitative approaches allow for in-depth exploration of the patients' perspectives. Quantitative approaches further investigate the issues revealed by qualitative studies in larger samples and test the statistical significance. For example, the qualitative approach (e.g. focus group with stroke patients) suggested that psychological factors such as low mood were potentially associated with PSF, and the quantitative approach (e.g. meta-analysis) explored how strong these associations were and whether they were statistically significant. The evidence was accumulated through a phased but iterative process, which involved literature review and meta-analysis, expert opinions (by project team meetings), and service user feedback (by focus groups and individual consultations with stroke patients). The work of each stage was built on the evidence obtained from the previous stage and updated through the repetitive cycles of planning – identifying evidence – developing

intervention – reviewing evidence – refining the intervention. Figure 3.1 is the flowchart of the initial phase (Phase 1) of developing this psychological intervention. In this Chapter, I sometimes use the present or future tense to introduce this intervention programme, as it will be tested in the next Chapter.

Phase 1 (October 2012 to June 2014)

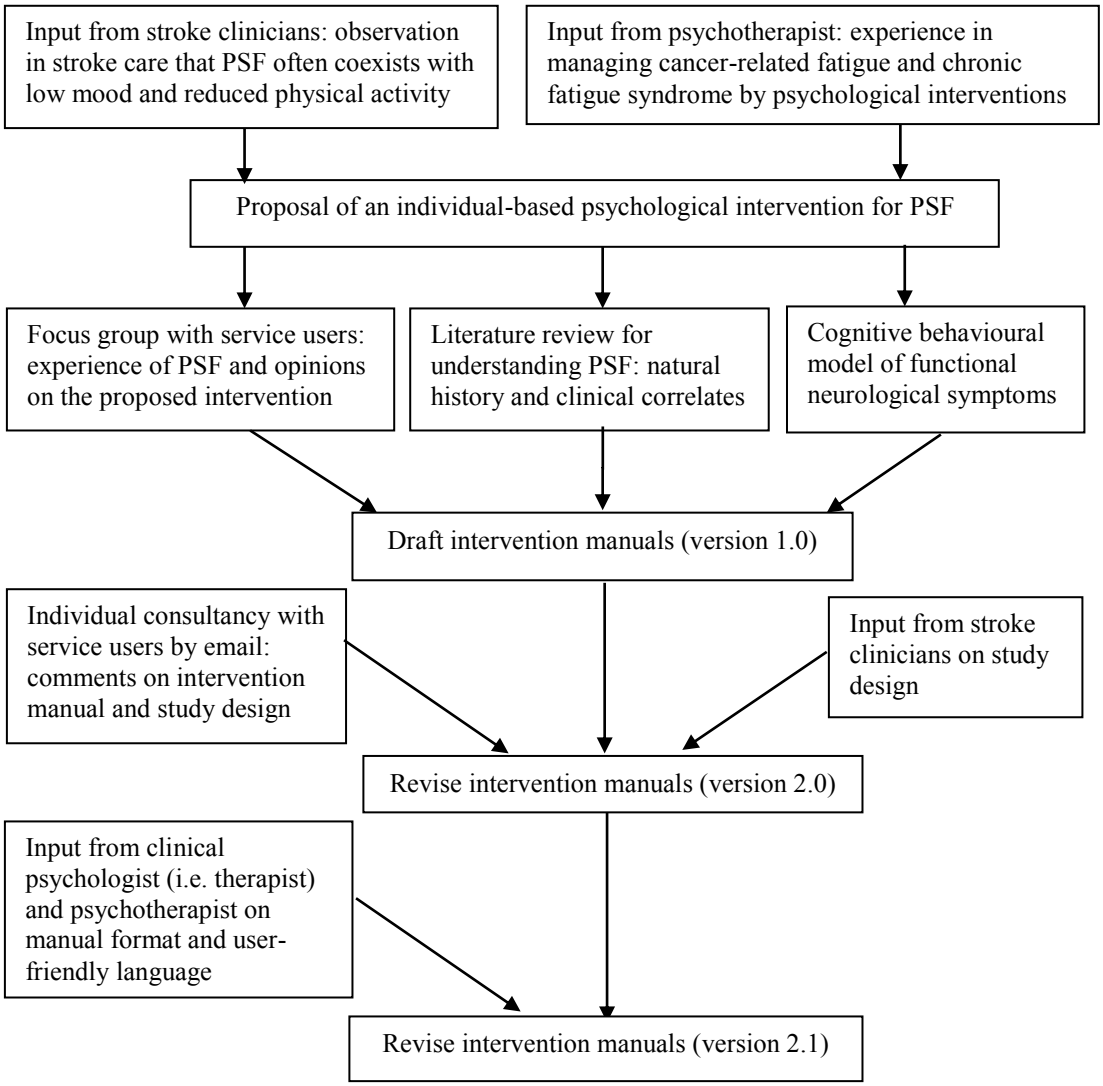

Figure 3.1 Development of a psychological intervention for post-stroke fatigue (PSF): identifying evidence, developing theory, and designing the intervention programme.

3.2.1 Proposal of a psychological intervention for PSF

A psychological intervention

The project team proposed a psychological intervention targeting stroke patients' thoughts and behaviours to treat PSF. The choice of the intervention was based on stroke clinicians' clinical observation that PSF often coexists with low mood,

emotional distress and reduced physical activity, and the psychotherapist's experience in managing chronic fatigue in other conditions such as cancer-related fatigue and chronic fatigue syndrome.

The intervention was adapted from two fatigue management programmes that the psychotherapist (TC) had been involved in: the content of the intervention was adapted from a manualised self-management cognitive behavioural approach for chronic fatigue syndrome, with aims to provide fatigue education, challenge unhelpful thoughts, and promote physical activity (Burgess and Chalder, 2005); the session arrangement and delivery modes were adapted from a psychological intervention for cancer-related fatigue, which was an intervention programme of three individual, face-to-face, nurse-delivered sessions (Armes et al., 2007). We developed the current intervention for PSF based on these two psychological intervention programmes because patients with PSF share some common psychosocial characteristics with patients with cancer-related fatigue and chronic fatigue syndrome (Zedlitz et al., 2011). Also these two psychological intervention programmes were feasible to be administered in the UK NHS.

Target population

We chose to recruit patients who were at three months after stroke onset with self-reported fatigue. The choice of this time window was based on the findings of our systematic review of natural history of PSF (as discussed in Chapter 2), where longitudinal studies indicated that in most stroke patients, if fatigue is going to develop, it usually develops by the first few months after stroke. Also, patients' medical conditions, including fatigue status, tend to be stable after three months after stroke.

Patients with severe depression would be excluded because these patients are usually under current treatment for depression, e.g. antidepressants and/or psychological interventions. The clinical psychologist (DG) suggested including patients with mild or moderate depressive symptoms, as in the local health system these patients usually do not receive treatment for depression, and psychological interventions for fatigue

are similar to the interventions for mood. Thus these patients with PSF might benefit from this psychological intervention for fatigue even though they had some depressive symptoms.

Therapist

Previous psychological interventions for PSF were group-based and delivered by clinical psychologists (Zedlitz et al., 2012, Clarke et al., 2012), which one could argue are not practical in the UK NHS because of the shortage of trained clinical psychologists in routine stroke care (Bowen et al., 2005). In the local health system in the Lothian area of Scotland, stroke patients in the community are routinely visited by stroke nurses at home. Thus an individual-based nurse-delivered approach may be more practical. In addition, symptoms of fatigue are diverse among different patients and their main complaint may be different, thus interventions for PSF should be personalised and focused on individual problems. A study in London has shown that the nurse-delivered individual psychological intervention was feasible in the NHS and effective in improving physical functioning in patients with cancer-related fatigue (Armes et al., 2007). Thus our intention was that the current intervention would ultimately be delivered by stroke nurses on an individual basis, so that it would be feasible and affordable in the NHS.

In this thesis, which was related to the early development stage of the intervention, this psychological intervention would be delivered by a clinical psychologist (KA), who had more than ten years' experience of psychological treatment of stroke patients. This would help to test if this intervention was comparable to psychological interventions normally used in clinical practice and if it was acceptable to the therapist from the perspective of a clinical psychologist.

The current intervention was a 'brief' psychological intervention in that it did not require the therapist to have complex psychological expertise, as it was adapted from other self-management or nurse-delivered interventions. If the intervention was acceptable for delivery by the clinical psychologist, in future studies it will be further tested for the feasibility of delivery by stroke nurses. In a study investigating the

effect of a CBT for the treatment of chronic fatigue syndrome, there was no difference in the therapist effect between clinical psychologists and specialist nurses, given that same orientation, training and supervision were provided (Cella et al., 2011). Thus a nurse-delivery psychological intervention for the treatment of PSF might be feasible.

3.2.2 Focus group on the acceptability of the proposed intervention

I approached a service user group at the Annual User Meeting of the Yorkshire Stroke Research Network (in November 2012, Bradford). Ten stroke patients (six men and four women) and five caregivers, who were interested in the topic on PSF, were invited to a round-table discussion. I held two focus groups with these users, each with five stroke patients and their caregivers. With each focus group, I introduced the proposed intervention programme and facilitated a 45 minutes' discussion to elicit users' opinions about the proposed intervention. The discussion also covered the topics of patients' experiences of PSF as well as helpful and unhelpful strategies that they had used to manage fatigue. A co-facilitator and I took notes of the discussion independently. I compared the notes and analysed the transcripts qualitatively using the thematic content analysis (Burnard, 1991).

The themes and categories raised by the users are summarised in Table 3.1. Users were satisfied with the proposed strategies to provide fatigue education, challenge unhelpful thoughts, and promote physical activity, as they thought that their fatigue was caused by the distressed mood and boredom, and also some of them found that regular physical activity (such as workout in the gym and doing routine housework) were helpful in relieving their fatigue. In addition, some users reported that sleeping problems contributed to their fatigue and keeping a regular sleep pattern relieved fatigue. This indicated the need to incorporate the strategies for developing good quality sleep in the current intervention. Finally, all users acknowledged that optimistic attitude and family support were important not only for improving fatigue but overall recovery of stroke. Therefore, keeping positive attitude towards fatigue and sharing experience with family members might help to reduce fatigue.

One limitation of this focus group study was that I did not take audio record, so that I could not report quotes of the users in Table 3.1. This annual user meeting was held shortly after the current intervention was conceived by our project team and we wanted to obtain some user feedback on the acceptability of the proposed intervention. I was invited to be one of the facilitators of this user meeting and so I organised this focus group discussing PSF and the proposed intervention. Ethical approval was not needed for this meeting with service users, but had I wanted to audio record the meeting I almost certainly would have needed ethics approval to do this but there was insufficient time to obtain the approval.

Table 3.1 Focus group's views on their experience of and strategies for post-stroke fatigue

Themes	Major categories	Minor categories
Fatigue presentation	Symptoms	Physical exhausted
		Mental tiredness
		Sleepiness
	Timing	Afternoon or end of the day
		Anytime during the day
		In the middle of an activity
Contributing factors	Biological factors	Stroke
		Older age
		Family history
		Raised blood pressure
	Psychological and behavioural factors	Anxiety and mental stress
		Boredom
		Sleeping problems
	Medication	Multiple medication
		Antidepressants
Helpful factors or strategies	Automatically getting better with time	
	Being physically active	Physical activity
		Routine exercise
		Daily housework
	Taking rest	Regular rest during the day
		One day off during the week
	Regulating sleep patterns	Not sleeping during the day
	Attitude	Optimism of patients
		Family support and encouragement
	Keeping a diary to schedule things	
	Fresh air	
Unhelpful strategies	Antidepressants	

3.2.3 Identifying evidence basis for the intervention

Although both stroke-related health professionals and service users had provided favourable opinions on our proposed psychological intervention, further evidence was needed to justify the choice of the intervention in a broader context of stroke studies. Therefore, I conducted systematic reviews to explore the natural history and clinical correlates of PSF (as discussed in Chapter 2). Drawing on the evidence from observational studies of PSF, I developed a stroke-specific model of PSF, which suggested that the development of PSF was a temporal process that involved interactions of various biological, psychological, behavioural and environmental factors (see Section 2.4). Although fatigue in the first few months after stroke might be related to biological factors, fatigue persisting in the chronic phase of stroke might be more attributable to psychological (e.g. low mood and anxiety) and behavioural (e.g. reduced physical activity and sleep disorders) factors (see Section 2.2) (Wu et al., 2015b). Also, I performed meta-analyses to determine the strength of associations between PSF and psychological factors, which found a significant association between PSF and depressive symptoms, even in patients who did not meet clinical criteria for depression (see Section 2.3) (Wu et al., 2014b). In summary, depressive symptoms, anxiety, lower self-efficacy, passive coping, reduced physical activity, sleeping problems, and inadequate social support are important associations of PSF (see Section 2.4) (Wu et al., 2015b). Based on the psychotherapist's (TC) experience in managing chronic fatigue, these associations could be addressed by psychological interventions that target people's thoughts and behaviours (i.e. using a cognitive behavioural approach). By modifying these psychological and behavioural associations, it is possible that fatigue symptoms can be reduced.

3.2.4 Developing rationale for the intervention

Findings from systematic reviews and meta-analyses indicated that PSF was associated with depressive symptoms, anxiety, lower self-efficacy, passive coping, reduced physical activity, sleeping problems, and inadequate social support (Wu et al., 2015b). These factors can be incorporated into a cognitive behavioural model of

neurological functional symptoms (Williams et al., 2011), where physical symptoms of fatigue, patients' thoughts, emotions, behaviours and relationships with other people are held both to interact with each other and perpetuate fatigue symptoms (Figure 3.2).

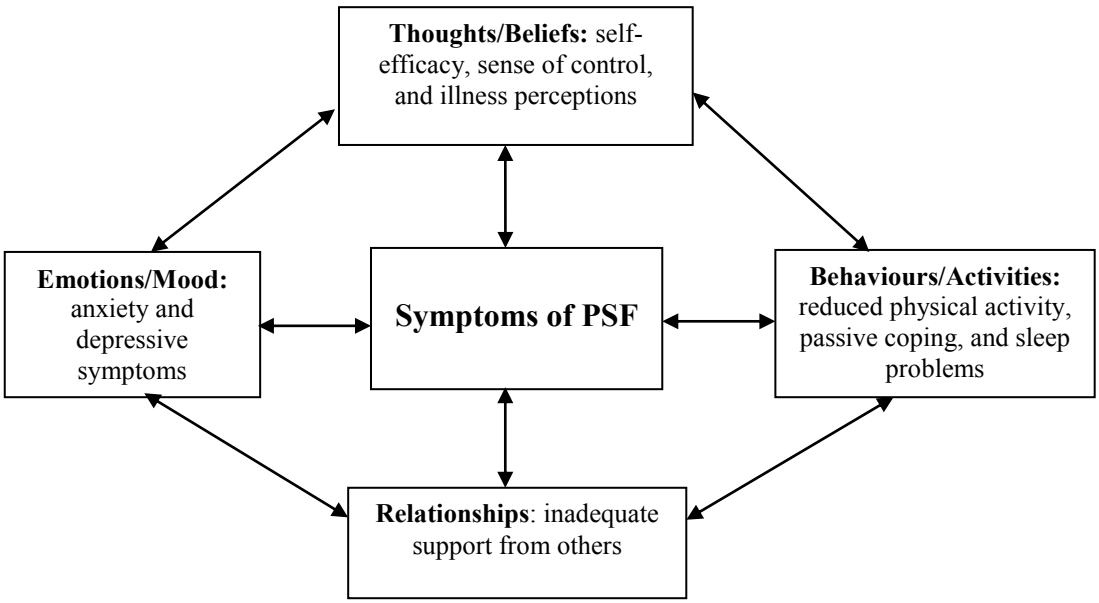

Figure 3.2 Cognitive behavioural model for post-stroke fatigue (adapted from (Williams et al., 2011))

Psychological interventions targeting patients' thoughts and behaviours (i.e. CBT) may help to break this cycle and thus reduce fatigue symptoms. The CBT has been widely used in mental health conditions and are effective in treating fatigue in patients with cancer (Armes et al., 2007), multiple sclerosis (Thomas et al., 2013), and chronic fatigue syndrome (White et al., 2011). In the situation of PSF, we hypothesised that the increase of activity will break the vicious cycle of fatigue and reduced physical activity, and that the increased activity will improve patients' confidence in taking physical activity and thus improve their self-efficacy and mood distress.

3.2.5 Modelling the intervention programme and outcomes

The initial intervention programme

The content and format of the initial intervention programme were adapted from two intervention programmes for fatigue in other conditions in the UK (Burgess and Chalder, 2005, Armes et al., 2007). In addition, information for education about PSF was developed from theories of PSF (based on the existing literature discussed in Chapter 2) and adapted from self-help materials for PSF by local stroke charities (i.e. Stroke Association, and Chest Heart & Stroke Scotland, CHSS).

The programme consisted of three individual, face-to-face sessions, with two hours for each session and two-week intervals between sessions:

- Session 1: introduction and education about PSF
- Session 2: learning skills to facilitate the improvement of PSF
- Session 3: progress assessment and making future plans

User feedback on the initial programme

I drafted the Participant Manual (version 1.0) to provide participants with an outline of the contents for each session. Another user group of five stroke patients (i.e. service users from the Scottish Stroke Research Network) were invited by email to feedback on the acceptability of the manual and the feasibility of the study design. I distributed the manual by email to each user, with an outline of the study and questions regarding the session arrangement, inclusion criteria, and mode of delivery. The responses of the users are summarised in Table 3.2.

Table 3.2 Users' feedback on the initial version of intervention manual and study design

Topics	Responses
Acceptability of manual	
Length of the manual	'At first I thought the participant manual was a bit long and wordy but having looked at it a second time it's the nature of the study and I cannot see how it can be reduced'
More examples and pictures	'The patient would benefit from more examples and a more conversational tone, and use of more diagrams and pictures'
Arrangement of sessions	
Three sessions, each two weeks apart	'Probably but may depend on the individual and their attention span'
	'I would suggest that a light touch treatment will need to take place over at least 1-2 years'
	'No, I doubt it [that three sessions would be enough]. There is a large amount of quite abstract materials to internalise'
	'For rollout in the future a maintenance group session after the course, say monthly, would be a good way to ensure that the lessons endure, and provides an opportunity for staff observations and training'
Assessment immediately after treatment	'The final assessment should be delayed to ensure the therapy has had an effect and to identify whether it has persisted. The patient may feel obliged to be positive about the therapy because the researcher has spent time helping them. A postal questionnaire three months after completing the therapy might provide a different answer'
Inclusion criteria	
Including patients at 3 months after stroke	'I agree [including patients at three months after stroke]. Earlier than that life is in too much turmoil anyway; by 6 months the problem may be entrenched'
	'3 months is still too early to address these post stroke complications. The patient is still overwhelmed by the dramatic change in their circumstances at 3 months'
	'This problem [fatigue] is widespread and involves those with stroke more than 3 months ago'
Including mild or moderate depressive symptoms, but excluding severe depression	'Seems fair enough'
	'I thoroughly approve of you including people with mild depressive symptoms'
	'Yes, strategies for addressing fatigue problems may rollover into other areas of life, e.g. coping with low mood'
Mode of delivery	
Delivery by nurses	'Yes, this is reasonable, but the training should be thorough'
	'Yes, it does. Could it also involve survivors who have beaten the fatigue effects?'
	'Probably better for the patient as I suspect that it will remove the additional stigma of being referred to and treated by a psychologist and hence probably lower anxiety levels in the patient'

Revision of the intervention programme

In response to users' feedback, I modified the intervention manual and the study design as follows: a) extending three treatment sessions to six treatment sessions and halving the length of each session to one hour; b) adding a review session one month after the last treatment session to consolidate patients' gains from the intervention; c) adding an assessment of clinical outcomes at three months after the last treatment session by postal questionnaires; and d) extending the criterion for including patients at three months to between three months and two years after the recent stroke.

The revised Participant Manual (version 2.0) was discussed within the project team, following which the manual was modified to a more user-friendly version (e.g. named the current intervention as a 'rehabilitation therapy' in the manual) (version 2.1). Based on this version of the Participant Manual, I developed a corresponding Therapist Manual to provide the therapist with detailed content of each session and guidance on delivery, which was discussed with and finally approved by all members of the project team.

Of this final version of manuals, Sessions 1 and 6 and feedback session were developed by the project team (100%). Session 1 was based on the theories of PSF that we had developed (as discussed in Chapter 2). Session 6 and feedback session were based on the content delivered in the previous sessions. For sessions 2 and 5, introduction sections and 'tasks to do at home' were written by the project team (100%); examples and worksheets were adapted from a self-management programme for CFS and a nurse-delivered intervention for cancer-related fatigue (80%), of which some content were adjusted to the stroke-specific situations (20%).

Defining outcome measures

Some researchers suggested that the selection of outcome measures to assess functional recovery after stroke should incorporate the International Classification of Functioning, Disability and Health (ICF) framework (Barak and Duncan, 2006). Also clinical guidelines recommend that rehabilitation of stroke should target the individual needs of stroke patients, and aim to maximise the individual's activity,

participation and quality of life, and minimise the distress to caregivers (Scottish Intercollegiate Guidelines Network, 2010).

As PSF often impedes stroke rehabilitation and recovery, I considered the ICF framework to determine the outcome measures for the current intervention. This intervention primarily targeted patients' thoughts and behaviours, with aims to improve how people feel physically (i.e. fatigue symptoms) and emotionally (i.e. mood). Thus the expected outcomes were the improvement in both fatigue and mood. In addition, one of the key strategies of this intervention was to promote physical activity in daily living, thus the participation in daily activities was assessed. Furthermore, the overall health-related quality of life (HRQoL) after stroke was assessed. In summary, the determined outcomes fit the ICF framework of recovery from fatigue after stroke, where fatigue and depressive symptoms relate to impairments, dependence in daily activities relates to limitations, and HRQoL relates to all three levels of impairments, limitations and restrictions (World Health Organization, 2001).

To choose the measure for each outcome, I considered two criteria (Barak and Duncan, 2006): a) the measures should have good psychometric properties in stroke patients, and b) the measures should be feasible for postal delivery. The individual outcome measures will be discussed in the result section.

Section 3.3 Results

3.3.1 Theoretical issues

Rationale of a CBT-based psychological intervention for PSF

The premise of CBT is that changing unhelpful thoughts and behaviours would affect how people feel physically (physical symptoms) and emotionally (emotional feelings) (Beck, 2011). A CBT typically consists of two interacting therapeutic approaches: the cognitive approach is to help people correctly understand their symptoms and situations and develop correct beliefs about themselves, other people and the world; and the behavioural approach is to encourage people carry out behavioural experiments to test out the accuracy of alternative thoughts and beliefs, and thus adopt new ways of perceiving and acting (Grazebrook and Garland, 2005). Thus the key strategies of the current intervention for PSF were to reassure participants that the impact of PSF is reversible if factors that perpetuate fatigue are properly treated and to encourage them to overcome their fear of taking physical activity (i.e. the cognitive approach), and to promote a balance between daily activities, rest and sleep and then gradually increase their level of physical activity (i.e. the behavioural approach).

Cognitive strategies

Education about PSF is provided to reassure participants that fatigue is common after stroke and its impact on life is reversible. Firstly, PSF is potentially triggered by stroke, thus the expected outcome of this intervention is not to help participants go back to the normal life prior to stroke but to establish a new life of balance. Secondly, although fatigue may be triggered by stroke, the persistent presence of fatigue is not necessarily related to stroke lesions but associated with psychological and behavioural factors such as distressed mood, inactivity, and erratic sleep patterns. These psychological and behavioural factors are often modifiable. If these factors can be properly identified and managed, the impact of fatigue on these areas may be reduced.

Specific thoughts related to unpleasant emotions in the situation with fatigue are identified and challenged, with a particular attention paid to the fear-avoidance responses to fatigue. Fatigue is a common experience in chronic conditions such as stroke. The fear of activity-induced fatigue can lead to the avoidance of activities, which may in turn result in a vicious cycle of the reduced physical activity or inactivity – physical deconditioning – exertional fatigue – further avoidance of physical activity – chronic fatigue. Overcoming the fear about activity-induced fatigue is the starting point to break this vicious cycle.

Behavioural strategies

One of the key strategies of this intervention is to promote the participation in activities of daily living, which is also the 'behavioural experiment' to test out the theory that keeping active would break the vicious cycle of fatigue and inactivity. The first step is to encourage participants to develop a regular routine of daily activities and scheduled rests rather than act and rest in response to fatigue. This is because erratic activity pattern could consume more energy and thus make fatigue worse. After developing a routine of daily activities and scheduled rests, participants will be encouraged to gradually increase their daily activities (including social activities) and reduce the amount of rests, by a series of practice of goal setting, activity and rest planning, progress assessment, and goal modification.

Sleep is another behavioural target for this intervention, as sleeping problems are common after stroke and often coexist with fatigue. A detailed sleep diary for the timing and quality of sleep is used to identify the individual sleep pattern and any sleeping problems that could be improved. Information about sleep hygiene is provided to help participants develop a regular and good quality sleep.

Other strategies

Information of identification and management of other potential causes for fatigue such as pain and certain medications is also provided in the manual, although they are not the key targets of this intervention. If any of these factors identified, participants will be suggested to consult their doctors for further advice or potential

treatment. In addition, because inadequate external support would confound people's psychological and behavioural responses to fatigue thus worsen fatigue symptoms, information is provided regarding how to get help from significant others and how others can be of best help. Participants are encouraged to share their experience of fatigue with family and friends. Understanding from 'significant others' and their support are important for participants to keep positive attitude towards their fatigue.

Structure and content of the intervention programme

The intervention will be delivered by a therapist to individual participant through six face-to-face treatment sessions and one telephone-delivered review session. Table 3.3 summarises the structure and content of the intervention programme. The duration of the first session is 90 minutes and the subsequent sessions are 60 minutes each. The extra 30 minutes in the first session would allow for the development of a collaborative therapeutic relationship between the participant and the therapist. There are two-week intervals between the sessions, during which participants will be encouraged to complete some home tasks (e.g. keeping a diary or increasing daily activities), as negotiated between the participant and the therapist during the session. The therapist will provide praise and encouragement throughout the intervention to enhance participants' self-confidence in making changes to overcome fatigue.

One month after the final treatment session (i.e. after Session 6), the project team will mail the postal questionnaires to each participant for the assessment for their clinical outcomes. Based on the result of this assessment, the therapist will have a review session (on the telephone) with each participant to discuss his/her progress and to negotiate plans for making further improvement in overcoming PSF.

Table 3.3 Structure and content of a psychological intervention for post-stroke fatigue (PSF)

Sessions	Cognitive strategies	Behavioural strategies
Session 1: Introduction and fatigue education	Education about PSF: To reassure the participant that impact of PSF is reversible	Activity and sleep diaries: To identify targets to facilitate the improvement of PSF
Two weeks' interval		
Session 2: Goal setting and activity planning	Goal setting: Based on the participant current mental and physical abilities, set goals to develop a balance between daily activities, rest and sleep	Activity planning: Divide goals into small and manageable steps and specify activities to work toward the goals
Two weeks' interval		
Session 3: Progress assessment and goal modification	Goal modification: Modify goals according to the participant's progress and, where applicable, gradually increase the activity level	Activity rescheduling: To adjust the activity plan according to the new goals
Two weeks' interval		
Session 4: Cognitive restructuring	Challenging unhelpful thoughts: Identify thoughts about PSF that invoke unpleasant emotions and their impact on behavioural responses; develop alternative, more positive and realistic thoughts	Acting against unhelpful thoughts: Foster behavioural changes according to the alternative thoughts
Two weeks' interval		
Session 5: Dealing with blocks and setbacks	Identifying factors that block the progress: Review the diaries and discuss potential factors that block the progress; reinforce the challenge of unhelpful thoughts	Managing blocks and setbacks: Take action to overcome factors that block the progress
Two weeks' interval		
Session 6: Overview and future planning	Review of the learned skills; Summary of achieved goals; Making future plans	Providing worksheets used during the programme to encourage the continue using of the learned skills
One month's interval		
Review session	Reviewing the progress in overcoming fatigue Negotiating future plans to make further improvement	

3.3.2 Practical issues

Participants

Inclusion criteria

a) ≥18 years old, b) recent stroke (including minor stroke) three months to two years previously, c) self-reported fatigue, and d) living in the Lothian area, Scotland, UK.

Time window after stroke

I used three months after stroke as the lower limit for inclusion because longitudinal studies indicated that most patients had their fatigue developed at this early stage after stroke, and also there is a natural resolution of PSF in some patients in the first few months after stroke (as discussed in Chapter 2). This early resolution is possibly because that fatigue present early after stroke is associated with stroke lesions and thus resolves as stroke recovers (Wu et al., 2015b). Also at an early stage after stroke patients' feeling of fatigue may be influenced by hospitalisation and possible lifestyle changes (Choi-Kwon et al., 2005). This type of transitory fatigue is not of the interest of this thesis, thus I only included patients who had fatigue after three months as beyond this time point fatigue tends to be chronic. PSF is a persistent problem in many patients, so I included patients up to two years after their stroke. I did not include patients over two years because some service users suggested that by two years after stroke, most patients would have adapted themselves to the life after stroke, thus their lifestyle might have been entrenched and difficult to change.

Self-reported fatigue

The presence of fatigue was screened by a single question 'Do you feel tired all the time or get tired very quickly since your stroke?' This question is part of the Greater Manchester Stroke Assessment Tool (GM-SAT), a structured evidence-based needs assessment tool that is feasible in a community setting and acceptable to stroke patients (Rothwell et al., 2013). I limited possible responses only to 'yes' or 'no' and

included patients who answered 'yes' to this question as it indicated that fatigue was a problem for the patient.

Exclusion criteria

a) severe depression, b) significant impairments in cognition or verbal communication, c) medically unstable or living in nursing home, or d) currently took part in other research studies that might affect fatigue or add significant burden to the participant (e.g. studies providing physical training). The rationale for excluding these people is explained in the text below.

Severe depression

Depression was screened by the Patient Health Questionnaire-9 (PHQ-9), which is a self-administered questionnaire that establishes the diagnosis of depression based on the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (Spitzer et al., 1999). A total PHQ-9 score less than 10 seldom occur in individuals with major depression whereas a score of 15 or more usually signifies the presence of major depression (Kroenke et al., 2001). The PHQ-9 is a valid screening tool for depression after stroke, of which a total score of 10 or more had 91% sensitivity and 89% specificity for major depression (Williams et al., 2005).

In the current study, I used a cut-off score of 15 for exclusion. This was because a PHQ-9 score of 15 or more indicates at least moderately severe major depression (15 to 19 for moderately severe depression; 20 to 27 for severe depression) (Kroenke and Spitzer, 2002). As suggested by a clinical psychologist (DG) in the project team, such patients would require for immediate medical management for depression (e.g. antidepressant or psychotherapy, or both), thus they were excluded from the current study. Patients with moderate depressive symptoms (with a PHQ-9 score between 10 and 14) were included, because in the local health system these patients usually do not receive treatment for depression and the current intervention for fatigue was similar to the intervention for mood, thus these patients with fatigue and depressed mood might benefit from this intervention. For patients with moderate depression, I informed them that they potentially had some symptoms of depression, and

suggested them to either take part in the current study or consult their General Practitioners (GPs) for further advice on depression.

Severe deficits in cognition and significant difficulties in verbal communication

The current psychological intervention was delivered through therapeutic conversations between the therapist and the participant. This required participants to have adequate capability in cognition and verbal communication, so that they could understand the manual content and participate in the intervention. These capabilities were determined by my contacting with their GPs or responsible stroke clinicians, and by my judgement through the telephone and face-to-face conversations with each participant.

Unfavourable medical conditions

Patients with other acute or severe medical conditions were excluded because fatigue is a ubiquitous and common symptom in many medical conditions, and could be aggravated by unstable medical status.

Other research studies

Patients in other research studies were excluded, if by attending such studies participants could be overburdened or their feeling of fatigue could be affected. For example, a study providing physical training may have synergic effect with the current psychological intervention on fatigue; also a study requiring much travelling from home to hospital may increase the amount of physical activity thus induce fatigue.

Assessment of clinical outcomes

Outcomes were assessed four times for each participant: at baseline (i.e. before treatment, T0), immediately after the final treatment session (i.e. immediately after Session 6, T1), one month after the final treatment session (before the review session, T2), and three months after the final treatment session (T3).

Presence of clinically significant fatigue

The presence of clinically significant fatigue was assessed by a case definition of PSF (Lynch et al., 2007). This case definition contains seven probe questions, which was particularly designed to identify fatigue that is clinically relevant to stroke patients (Lynch et al., 2007). This case definition is feasible and reliable in measuring fatigue in stroke survivors and has good convergent validity with the Fatigue Assessment Scale (FAS) (Lynch et al., 2007).

To fulfil this case definition, the experience of fatigue should meet the following criteria: a) is a feeling of fatigue, lack of energy, or an increased need to rest, rather than sleepiness or lack of motivation; b) lasts for more than 50% of waking hours of the day; c) has been present every day or nearly every day for at least two weeks in the past month; and d) is perceived by patients as a problem and affects their everyday activities (Lynch et al., 2007).

Our project team had discussed whether to use this case definition as an inclusion criterion and finally decided not to use it in this feasibility study. Instead, we used a simple screening question for fatigue in order to include a broader range of patients as long as they perceived fatigue as a problem for them.

Severity of fatigue

The severity of fatigue was assessed by the FAS (Michielsen et al., 2004). I chose this scale because it assesses the fatigue severity from both the patient's subjective feelings of fatigue and its impact on daily life. I did not use scales that only measure subjective feelings, because focusing on fatigue itself might make patients feel worse. In addition, the FAS has good psychometric properties in measuring fatigue in stroke patients, in terms of face validity, feasibility, and reliability (Mead et al., 2007). Furthermore, the FAS has good divergent validity to distinguish fatigue from depression (Smith et al., 2008, Michielsen et al., 2003), of which the latter is a common confounder of fatigue. Finally, this is a self-rating scale and is feasible for postal delivery (Michielsen et al., 2003).

The FAS has ten items asking about the frequency of different aspects of fatigue, with each item on a 5-point Likert rating scale from 1 = "never" and 5 = "always". The total score, which was used in the current study as an index of fatigue severity, ranges from 10 to 50, with a higher score indicating more severe fatigue. It is important to note that for two items of this scale (i.e. "I have enough energy for everyday life" and "when I am doing something, I can concentrate quite well"), a higher score indicates better outcome; whilst for the other eight items (e.g. "I am bothered by fatigue"), a higher score indicates poorer outcome. Thus for data analysis, scores of these two items were converted by deducting the individual score from 6 (for example, a score of 1 would be transformed to 5 i.e. 6-1=5). A study suggested a 4-point difference on FAS as the minimal clinically important difference (MCID) in patients with sarcoidosis (de Kleijn et al., 2011), however, this MCID has not been established in stroke patients. Therefore, I used this scale as a continuous measure of fatigue and assessed the change of scores from before to after treatment.

Depressive symptoms

The depression severity was assessed by the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001), which was also used as the screening questionnaire for depression at recruitment. This scale was chosen because it was designed based on the nine criteria for depressive disorders of the fourth version of the DSM-IV, thus it could be used for both the diagnosis of depression and monitoring depression severity over time or in response to treatment (Kroenke et al., 2001). In addition, this scale has good reliability and validity in stroke patients (Williams et al., 2005, Janneke et al., 2012) and it is readily delivered through telephone (Pinto - Meza et al., 2005).

The PHQ-9 consists of nine items, in corresponding to the DSM-IV criteria for depression. Each item can be scored from 0 = "not at all" to 3 = "nearly every day", with a total score ranging from 0 to 27 and a higher score indicating more severe symptoms. Cut-off points of 5, 10, 15 and 20 represent the thresholds for mild, moderate, moderately severe, and severe depression, respectively. The PHQ-9 also has an item in addition to the diagnostic section, which is a general rating of

functional impairment (Kroenke et al., 2001). It is suggested that a decline of 5 points as the MCID on the PHQ-9 (Kroenke and Spitzer, 2002), but this has not been validated in stroke patients. This scale was used as a continuous measure of the severity of depressive symptoms in the current study.

Participation in activities of daily living

Independence in daily activities is an important functional outcome for stroke patients. Encouraging participants to take more daily activities was a key strategy of the current psychological intervention. Thus the Nottingham Extended Activities of Daily Living (NEADL) (Nouri and Lincoln, 1987) was chosen to measure the independence of daily life. I did not choose scales of basic ADL (e.g. Barthel Index) because some studies suggested that PSF was associated with instrumental activities of daily living (IADL) but not basic ADL (van de Port et al., 2007). Another concern for not using the Barthel Index is that the floor and ceiling effects are a particular issue of this scale in stroke trials (Quinn et al., 2011).

The NEADL is a self-rating scale that particularly designed to assess the independence in activities thought to be important to stroke patients for daily living at home (Nouri and Lincoln, 1987). The scale contains 22 activities of four domains (mobility, kitchen, domestic, and leisure). Patients are asked whether they actually did the activity rather than if they were capable to do it, with an aim to assess the level of activity rather than the capacity (Nouri and Lincoln, 1987). Four answers are provided on a Guttmann scale for each activity (i.e. for each activity, the answers are arranged in an order so that the patient who agrees with a particular answer also agrees with all answers of lower rank-order). Patients are coded as either independent (scored 1) if they respond ‘on my own’ or ‘on my own with difficulty’, or dependent (scored 0) if they ‘need help’ or ‘did not do’ the activity (Nouri and Lincoln, 1987). Thus the total score ranges from 0 (very dependent) to 22 (fully independent), with a higher score indicating better independence. This scale is feasible for postal delivery to stroke patients in community (Nouri and Lincoln, 1987).

Health-related quality of life

The general health status was assessed because fatigue could affect different domains of life after stroke. The Stroke Impact Scale (SIS) 3.0 is a stroke-specific, self-rating scale that assesses different aspects of stroke recovery (Duncan et al., 2003). This scale was designed for repeated administration to track change over time, and has been recommended for assessing general changes after stroke rehabilitation, for its good responsiveness to changes as compared with another stroke-specific scale for health-related quality of life (Lin et al., 2010a). The SIS is feasible for both postal (Duncan et al., 2002) and telephone (Duncan et al., 2005) delivery.

The SIS contains 59 items measuring eight domains, including physical strength, ADL/IADL, mobility, hand function, communication, emotion, memory and thinking, and participation/role function (Duncan et al., 2003). The first four of these domains may be combined into one physical domain, but the others must be scored separately. Each item can be scored from 1 to 5; for most items a higher score indicates a better outcome, but for three items in the emotion subscale (i.e. 3f, 3h, and 3i) a higher score indicates a poorer outcome. For these three items (3f, 3h, and 3i), their individual scores are transformed by the equation: transformed score = 6 – individual raw score. The SIS uses the scoring algorithm of the SF-36 (Stewart and Ware, 1992), thus for each domain the transformed score ranges from 0 to 100 (with higher scores indicating better outcomes) based on the following equation:

Score = ((actual raw score - lowest possible raw score) / possible raw score range) × 100

In addition, the SIS includes a question assessing the patient's perceived overall recovery from stroke, with 0 indicating 'no recovery' and 100 indicating 'full recovery'. One study suggested the MCIDs on the physical strength, ADL/IADL, mobility, and hand function subscales of SIS were 9.2, 5.9, 4.5 and 17.8 points, respectively (Lin et al., 2010b), but no MCID has been established for non-physical subscales.

Section 3.4 Discussion

This chapter has described an evidence-based process of developing a psychological intervention for PSF, which is related to the processes of identifying evidence, developing the treatment rationale, and modelling the intervention programme and outcomes as described in the MRC framework (Craig et al., 2008a). The targets of the intervention were chosen based on the clinical observation and justified by a thorough, systematic review of the literature. The intervention manuals were developed with iterative input from stroke clinicians, psychological therapists, and stroke patients, considering both theoretical and practical issues in local stroke care and clinical psychology. In summary, a continuum of evidence was accumulated from three interactive strands throughout the study, which included literature review on mechanisms of and interventions for PSF, expert opinions from health professionals in stroke care and clinical psychology, and user input from stroke patients.

A manualised psychological intervention has been developed. This is a complex intervention in that it has a number of interacting therapeutic components, involves multidisciplinary work, and has multiple outcome measures (Craig et al., 2013). The intervention is not focused on fatigue itself because paying attention to the fatigue may make symptoms worse, instead, this intervention aimed to reduce the impact of fatigue on daily life through a cognitive behavioural approach. The intervention challenges peoples' fear-avoidance responses to fatigue with an aim to promote physical activity in daily living. This type of intervention has shown to be feasible and effective in treating fatigue in other chronic conditions (Armes et al., 2007, White et al., 2011). However, little is known about the feasibility and efficacy of this intervention in the context of stroke.

Therefore, in the next chapter, I will describe a feasibility study which tests the acceptability of this intervention to both the stroke patients and the therapist. Also, to inform the design of future definitive trials, I tested the feasibility of the recruitment process, intervention delivery, and follow-up assessment.

CHAPTER IV: Feasibility Study of a Psychological Intervention for Post-stroke Fatigue

Section 4.1 Introduction

In Chapter 3, I described how a manualised psychological intervention for PSF was developed following the MRC framework of development and evaluation of complex interventions (Campbell et al., 2000, Craig et al., 2008a). I developed this psychological intervention in collaboration with a multidisciplinary group of stroke clinicians, psychological therapists, and stroke patients, considering both theoretical and practical issues in stroke care and clinical psychology in the local health system in the UK.

In this chapter, I will introduce how this intervention was tested in a feasibility study, in terms of its acceptability to both the participants (stroke patients with PSF) and the therapist (a clinical psychologist), and the feasibility of the trial process of recruitment, intervention delivery, and follow-up assessment. This chapter is related to part of the modelling phase and part of the piloting phase of the MRC framework, with aims to test intervention procedures and to estimate recruitment and retention (Craig et al., 2008a). However, this single-arm feasibility study did not inform the sample size calculation, which needs to be clarified in future pilot studies with the randomised controlled design.

As the clinical psychologist is not normally involved in routine health care of stroke patients, I also collected feedback from both the participants and the therapist for their opinions on our plans to deliver the intervention using approaches that are more affordable to the NHS, for example, delivering the intervention by stroke nurses or using telephone or internet. In addition, I performed the before-and-after analysis for clinical outcomes to obtain some preliminary data of the intervention effect on fatigue.

Aims and objectives

The aim of this feasibility study was to pilot a psychological intervention with stroke patients who had self-reported fatigue.

The primary objectives were a) to investigate the acceptability of the intervention programme to both the stroke patients and the clinical psychologist, b) to assess the feasibility of the trial process (i.e. procedures of recruitment, intervention delivery, and follow-up assessments), c) to test the feasibility of questionnaires for assessing clinical outcomes, and d) to collect opinions from stroke patients and the clinical psychologist on plans to adapt the intervention for nurse-delivery, and whether delivery through telephone or internet would be acceptable to patients.

The secondary objectives were to investigate whether this intervention could improve any of the pre-specified clinical outcomes (i.e. for fatigue, mood, independence in daily life, and overall health-related quality of life; measures for these outcomes have been discussed in Chapter 3 and will be summarised in the Methods section of this chapter).

Section 4.2 Methods

4.2.1 Study design

This feasibility study had two stages: the screening stage and the intervention stage. The screening stage (including a survey for post-stroke fatigue) was to pilot the recruitment process and to identify potentially eligible participants for the intervention stage. The intervention stage (i.e. a single-arm feasibility study) was to test the feasibility of the intervention programme, delivery process, and follow-up procedures.

4.2.2 Ethical approvals and trial registration

Ethical approvals for this study were granted by the NHS Lothian Board, South East Scotland Research Ethics Committee (14/SS/0093, Appendix 3.1) and the NHS Lothian R&D Office (2014/0237, Appendix 3.2). Separate consent was obtained from participants for the survey for post-stroke fatigue and for the intervention stage. This feasibility study was registered at https://www.clinicaltrials.gov/ (the ClinicalTrials.gov Identifier NCT02131532).

4.2.3 Participants

Inclusion and exclusion criteria

Rationale for the inclusion and exclusion criteria has been discussed in Chapter 3. In brief, patients were eligible for this study if they a) ≥ 18 years old, b) had had a stroke (including minor stroke) three months to two years previously, c) had self-reported fatigue, and d) live in the Lothian area, Scotland, UK. Patients were excluded if they had a) severe depression, b) significant impairments in cognition or verbal communication, c) medically unstable or living in the nursing home, or d) currently took part in other research studies that might affect fatigue or add significant burden to the participant.

The eligibility was determined through a multi-stage process (details of the recruitment process will be discussed shortly in this section):

- Screening the discharge summary of stroke patients stored in the TRAK system (which is the electronic database of the NHS that holds medical information of patients, e.g. for age, home address, time since stroke, current medical conditions, and whether deceased)
- Contacting GPs of the potential participant to determine the presence of current depression, communication capacity, medical stability, unfavourable conditions, and whether in other research studies.
- Reviewing the result of survey questionnaires completed by the potential participant (i.e. questionnaires for post-stroke fatigue and depression)
- Telephone conversations and face-to-face meetings with the potential participant (e.g. for capacity of cognition and verbal communication)

Sample size

Sample size calculation is not normally required for feasibility or pilot studies (Arain et al., 2010). Some researchers suggested that a sample of 10 or fewer would be sufficient for studies assessing acceptability of formatting or ease of administration of an instrument (Hertzog, 2008). Such a small group of participants had been used in the development and preliminary evaluation of a cognitive behavioural approach to manage fatigue in patients with multiple sclerosis (Thomas et al., 2010), which successfully informed the design of a multi-centre RCT (Thomas et al., 2013). Thus I pre-specified a sample size of 12 for this feasibility study to allow for two dropouts. This sample size was anticipated to be achievable in the limited time (three to four months) available for the recruitment in this feasibility study.

4.2.4 Study process

4.2.4.1 Screening stage

The recruitment process is presented in Figure 4.1. Potential participants were identified through three approaches, i.e. from the Stroke Clinic of Western General Hospital in Edinburgh, from the Stroke Unit of Royal Infirmary of Edinburgh, and through the Chest Heart & Stroke Scotland (CHSS, which is a health charity organisation that supports stroke nurses routinely visit stroke patients in the community). The recruitment processes through these three approaches were similar, with the main difference lying in the personnel who initially identified and contacted the potential participants; that is, colleagues who were members of the medical care team of stroke patients at each of these three sites identified potential participants for this study. In the text below, I will explain in detail how participants were recruited from the Stroke Unit and summarise the difference in the recruitment from the Stroke Clinic and by the CHSS.

1) Initial screening of eligibility before contacting potential participants

The Scottish Stroke Research Network nurses (Seona Burgess, Katrina McCormack and Ruth Paulton), who were part of the clinical team, helped with the recruitment. The nurses obtained discharge summaries from the ward secretary of all stroke patients discharged from the Royal Infirmary of Edinburgh in the past two years. They screened these discharge summarises to identify adult patients (18 years or over) who had their stroke three months to two years previously and currently lived in the Lothian area. Then the nurses contacted GPs of these patients to check that they did not meet any exclusion criteria.

In the Stroke Clinic, the above process was conducted by the responsible stroke consultant (Martin Dennis and his clinical secretary Maggie Scott). In the CHSS, the Stroke nurses (Audrey Bruce, Thomas Jones, Fiona Ryan and Kay Walkinshaw) identified potential participants (i.e. those who potentially had fatigue) during their home visits to community-dwelling stroke patients.

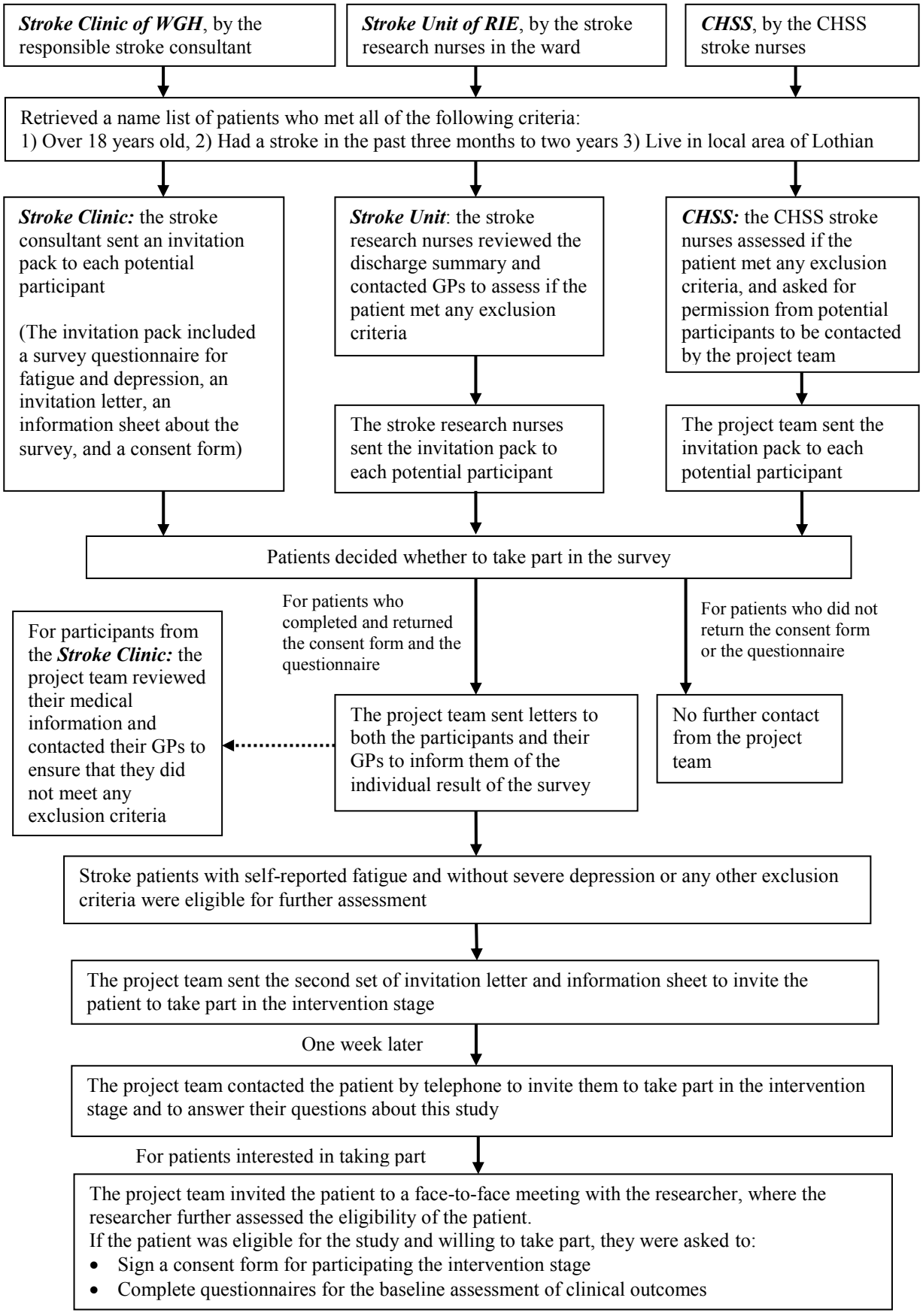

Figure 4.1 Flowchart of the recruitment for a feasibility study of a psychological intervention for post-stroke fatigue.

2) A survey for post-stroke fatigue and depression

For patients from the Stroke Unit who appeared eligible during the initial screening, the Stroke Research Network nurses mailed an invitation pack (see Appendix 4) to invite them to complete a survey for post-stroke fatigue and depression. For patients from the Stroke Clinic, the invitation letters were mailed out by their responsible stroke consultant in the clinic; for patients identified by the CHSS nurses, the invitation letters were mailed out by me. This questionnaire pack contained an invitation letter (signed by the stroke consultants who had been responsible for the patient's clinical care, see Appendix 4.1), an information sheet about the survey (see Appendix 4.2), a consent form (see Appendix 4.3), and a survey questionnaire for post-stroke fatigue and depression (see Appendix 4.4). By signing the consent form, the patient gave his/her consent a) to complete the survey, b) to receive further contact from the project team, c) for the project team to access his/her medical information held by the NHS, and d) for his/her GP to be informed of his/her participation in and the result of this survey. A stamped addressed envelope was enclosed in the questionnaire pack for each patient to return the signed consent form and the completed survey questionnaire to me.

The survey questionnaire contained a single question for post-stroke fatigue 'Do you feel tired all the time or get tired very quickly since your stroke?' (this question is part of the Greater Manchester Stroke Assessment Tool, GM-SAT, which is a feasible tool to identify unmet needs of stroke patients in community (Rothwell et al., 2013)) and the Patient Health Questionnaire-9 (PHQ-9, a valid screening tool for depression in stroke patients (Williams et al., 2005)).

For patients who completed and returned the questionnaire, I assessed their eligibility following the criteria as listed in Table 4.1 and sent a written report with individual results to each patient and their GPs. In brief, stroke patients who answered 'yes' to the fatigue question and had a PHQ-9 score of 14 or less were eligible for further assessment, to whom I mailed another set of invitation letter (Appendix 5.1) and information sheet (Appendix 5.2) to invite them to take part in the intervention stage. For patients who had a PHQ-9 score between 10 and 14, I explained in the report that

they might have some symptoms that we commonly see in patients with depression, and provided them with the choice of either taking part in this study or consulting their GPs about possible depression. I excluded patients who had a total PHQ-9 score of 15 or more, as this score indicated the presence of at least moderately severe depression (Kroenke and Spitzer, 2002). For these 'ineligible' patients, I wrote a letter (Appendix 5.3) explaining why this intervention was not suitable for them and recommending that they should seek advice from their GPs for further assessment and treatment for possible depression (Figure 4.2).

Table 4.1 Screening criteria for post-stroke fatigue and depression

Question for fatigue	Total score of PHQ-9	Eligibility for further assessment
'Yes'	9 or less (no or mild depression)	**Eligible**
	Between 10 and 14 (moderate depression)	**Eligible**
	15 or more (at least moderately severe depression)	Ineligible
'No'	9 or less (no or mild depression)	Ineligible
	10 or more (at least moderate depression)	Ineligible

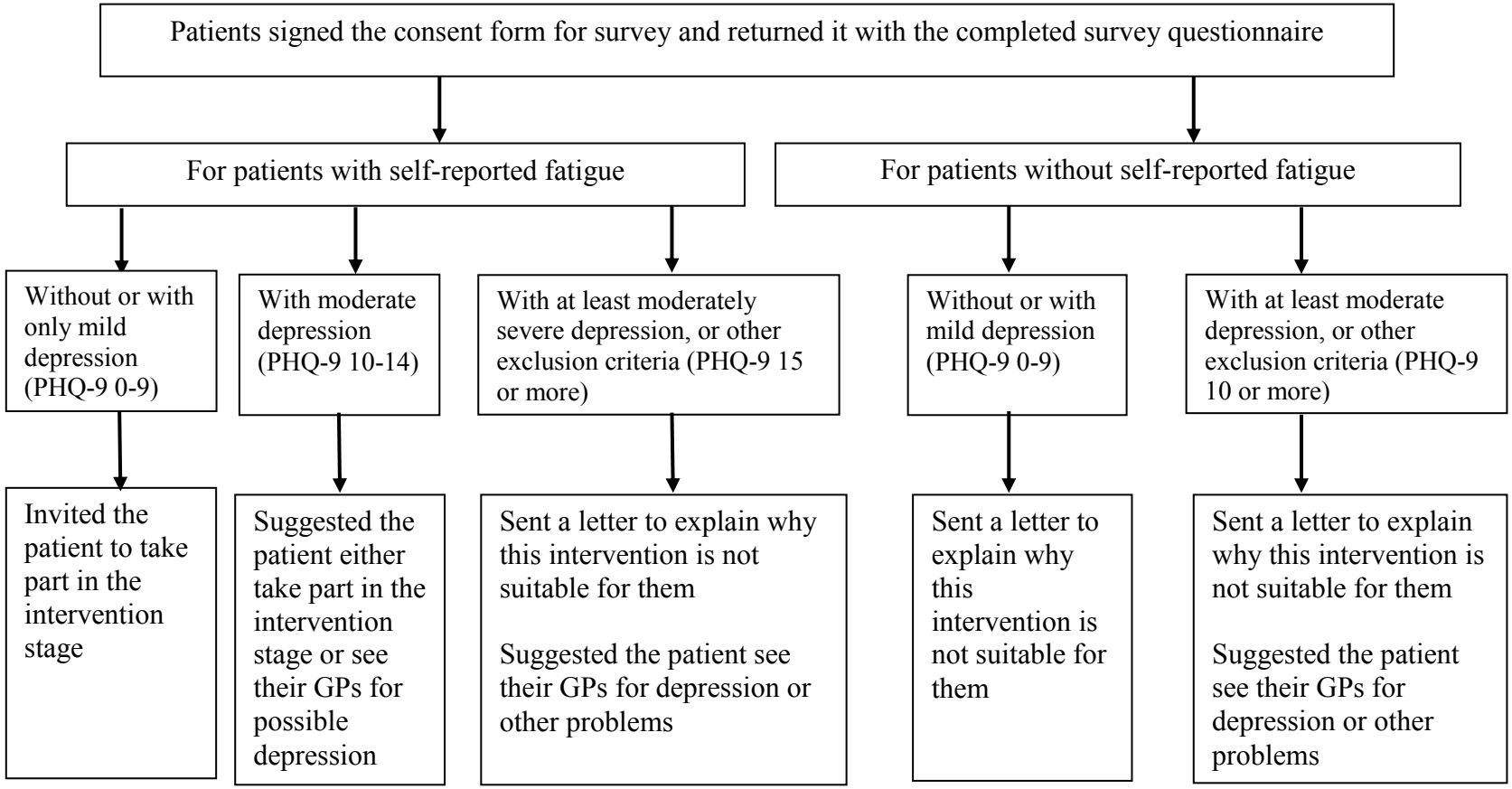

Figure 4.2 Flowchart of the survey for post-stroke fatigue and depression.

3) Final assessment and consent for participating the intervention stage

One week after sending out the invitation letter to potentially eligible patients, I contacted each patient by telephone a) to check if they had received the invitation letter, b) to answer their questions about this study, and c) to invite them to take part in the intervention stage. For patients who agreed to take part, I invited them to attend a one-to-one, face-to-face meeting with me at the Clinical Research Facility (CRF) of the Royal Infirmary of Edinburgh. This meeting had three aims: a) to confirm eligibility of the patient; b) to obtain written consent from the eligible patient; and c) to conduct the baseline assessment of clinical outcomes for each participant.

At the beginning of the meeting, I explained the study process to the patient and answered any questions that the patient had. Then I asked the patient when their fatigue started; only those who stated that their fatigue occurred or became evident after their recent stroke (i.e. in the past three months to two years) were eligible for this study. A CRF research nurse (Audrey Kuchnowski or Liz Fraser) helped to check if the patient had adequate capacity in cognition and verbal communication to take part in this study (this would identify a few patients who were not eligible for the study. For those patients, I would explain why this intervention was not suitable for them and thanks for their participation so far). Only if both the CRF nurse and I agreed that the patient was eligible for the study, I invited the patient to take part in the intervention stage.

After the patient gave the written consent (Appendix 6) for participating the intervention stage, I assigned a unique participant number (from S001 to S012) to him/her. This participant number was used in all questionnaires for clinical outcomes (including baseline assessment and all post-treatment assessments), to allow for anonymised assessment of outcomes by researchers. I conducted the baseline assessment for the participant using four questionnaires: a case definition of PSF, the FAS, the NEADL, and the SIS (these questionnaires have been introduced in detail in Chapter 3). In case the participant had uncertainty in giving the answer to any item of the questionnaires, I gave explanations or examples to help them understand the

question. The result of the PHQ-9 that the participant completed during the survey stage was used as the result of the baseline assessment for mood.

4.2.4.2 Intervention stage

Setting

This single-arm feasibility study was conducted at a single site at the Department of Clinical Psychology of Astley Ainslie Hospital, a rehabilitation hospital in Edinburgh. The project team reimbursed participants their expenses on travelling between home and hospital (e.g. bus tickets, parking fees, taxi fees, or petroleum).

Intervention programme

The intervention programme has been introduced in detail in Chapter 3. In brief, the intervention was delivered by the a clinical psychologist (KA) to each participant individually, which consisted of six face-to-face treatment sessions over a period of 12 weeks, followed by one telephone-delivered review session one month later. At the first treatment session, the dates and time for the subsequent treatment sessions were agreed between the participant and the therapist and logged into an Outline of Sessions (see Appendix 7), of which the participant and the therapist each kept a copy as a reminder of the appointment. Participants were required to inform the project team by telephone if they could not attend the appointment, of which this process was co-ordinated by the administrative secretary (Maureen Harding) of the Department of Geriatric Medicine of Royal Infirmary of Edinburgh (where my office was based).

Each treatment session had a therapeutic theme (as covered by each session in the Participant Manual), from the general introduction of this intervention and education about PSF to specific strategies to challenge participants' behaviours and thoughts:

- Session 1: Introduction and fatigue education
- Session 2: Goal setting and activity planning
- Session 3: Progress assessment and goal modification

- Session 4: Cognitive restructuring
- Session 5: Dealing with blocks and setbacks
- Session 6: Overview and future planning

Immediately after the final treatment session (i.e. Session 6), the therapist gave a set of five questionnaires to the participant to complete at home, which included the four questionnaires used for baseline assessment plus the PHQ-9. One month after Session 6, I mailed the same set of five questionnaires to each participant. Together with the questionnaires, I provided a stamped addressed envelope for the participant to return the questionnaires to me. After receiving the completed questionnaires, I sent a copy of all questionnaires to the therapist (KA) and worked with her on a written report of the individual result for each participant.

One week after sending out the report of the individual result of one-month assessment to the participant, I contacted the participant by telephone to check if s/he had received the report and to negotiate a date and time for the review session. The review session was delivered by the therapist over the telephone to each participant, which was about 30 minutes on average. The main aim of the review session was to consolidate the learned skills and to reinforce the improvement. During the review session, the therapist discussed with the participant his/her progress in overcoming fatigue and plans for making further improvement.

Intervention manuals

The structure and content of the intervention manuals have been introduced in Chapter 3. The Participant Manual was distributed to each participant in the format of small leaflets, each of which outlined the content that would be discussed in the forthcoming session. I gave the leaflet for the first session to each participant at the consenting meeting. For the subsequent sessions, the leaflet was given by the therapist by the end of the previous session. A matching Therapist Manual was used by the therapist, which provided detailed content of each session and instructions for the therapist to follow.

4.2.5 Outcome measures

4.2.5.1 Feasibility outcomes

Data collection

Feasibility data were collected throughout the study process, from both the participants and the therapist and including both quantitative and qualitative data.

Outcome measures and data analysis

Recruitment

I recorded the numbers of patients eligible at each stage of recruitment and reasons for ineligibility.

Acceptability of intervention programme

Acceptability of the intervention to participants was determined by participants' attendance, feedback questionnaires, and a feedback meeting. Attendance to each session and reasons for rescheduling or non-attending were recorded. I recorded the number of dropouts and reasons for withdrawal. Through the feedback questionnaires and the feedback meeting I asked both general and specific questions to participants about their opinions on the acceptability of the intervention programme and the study design.

Feasibility of clinical outcome assessment

I recorded the number of participants completing and returning questionnaires on time at each assessment, as well as reasons for delayed completing or non-returning. I also recorded items of each questionnaire that participants did not complete or did not give an adequate answer.

Participant feedback

After all participants (those who retained in the study) completed their review sessions, they were invited to a focus group feedback meeting. At this meeting, they

were asked to complete an anonymised, semi-structured feedback questionnaire, which contained 14 questions assessing the usefulness of the intervention strategies, adequacy of the intervention content, arrangement of intervention sessions, acceptability of outcome questionnaires, and arrangement of follow-up assessments (see Appendix 8). I also discussed with participants their opinions on the acceptability of delivering this intervention by stroke nurses, through telephone, or online. Participants who were unable to attend the focus group were invited to give feedback over the telephone.

Therapist feedback

After completing all treatment and review sessions, the therapist provided a written report regarding a) adequacy of the intervention programme, b) feasibility of the delivery process, c) suggestions to improve this intervention, and d) feasibility of delivering the intervention by stroke nurses.

4.2.5.2 Clinical outcomes

Data collection

With the participants' consent, I accessed their demographic and clinical information in the NHS TRAK system, which included age, sex, incident or recurrent stroke, time since the last stroke onset, psychological history, and cardiopulmonary comorbidities.

Baseline assessment of clinical outcomes was conducted by me with each participant at the meeting for recruitment (T0). Three post-treatment assessments (T1: immediately after Session 6; T2: one month later; and T3: three months later) were conducted by postal questionnaires and completed by the participant at home.

Clinical outcome measures

- A case definition of post-stroke fatigue (Lynch et al., 2007)
- Fatigue Assessment Scale (FAS) (Michielsen et al., 2004)

- Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001)
- Nottingham Extended Activities of Daily Living (NEADL) (Nouri and Lincoln, 1987)
- Stroke Impact Scale 3.0 (SIS, 9 subscales) (Duncan et al., 2003)

Data analysis

Data analyses were performed in IBM SPSS (version 21). For the comparisons between participants who completed all sessions and those who dropped out, the independent t-test was used for continuous variables and the Fisher's exact test for dichotomous variables with a significance level of 5% (2-tailed). For participants who completed all treatment and review sessions, results of each outcome before-and-after treatment were compared using the paired t-test for continuous outcomes and the McNemar test for dichotomous outcomes.

Considering the correction for multiple comparisons (13 measures and 3 post-treatment assessments), the critical level of significance would drop from 0.05 to 0.001 (2-tailed). However, there might be interactions between some measures (for example the case definition and the FAS, and the PHQ-9 and the emotional subscale of SIS) and the results of three post-treatment assessments were not independent of each other, thus the appropriate adjusted critical significance level might be somewhere between 0.001 and 0.05, but the exact value is unknown. Therefore, I reported the exact *p* value and 95% CI of the difference in each outcome measure for each comparison.

Section 4.3 Results

Figure 4.3 is the flowchart of this feasibility study.

Phase 2 (July 2014 to April 2015)

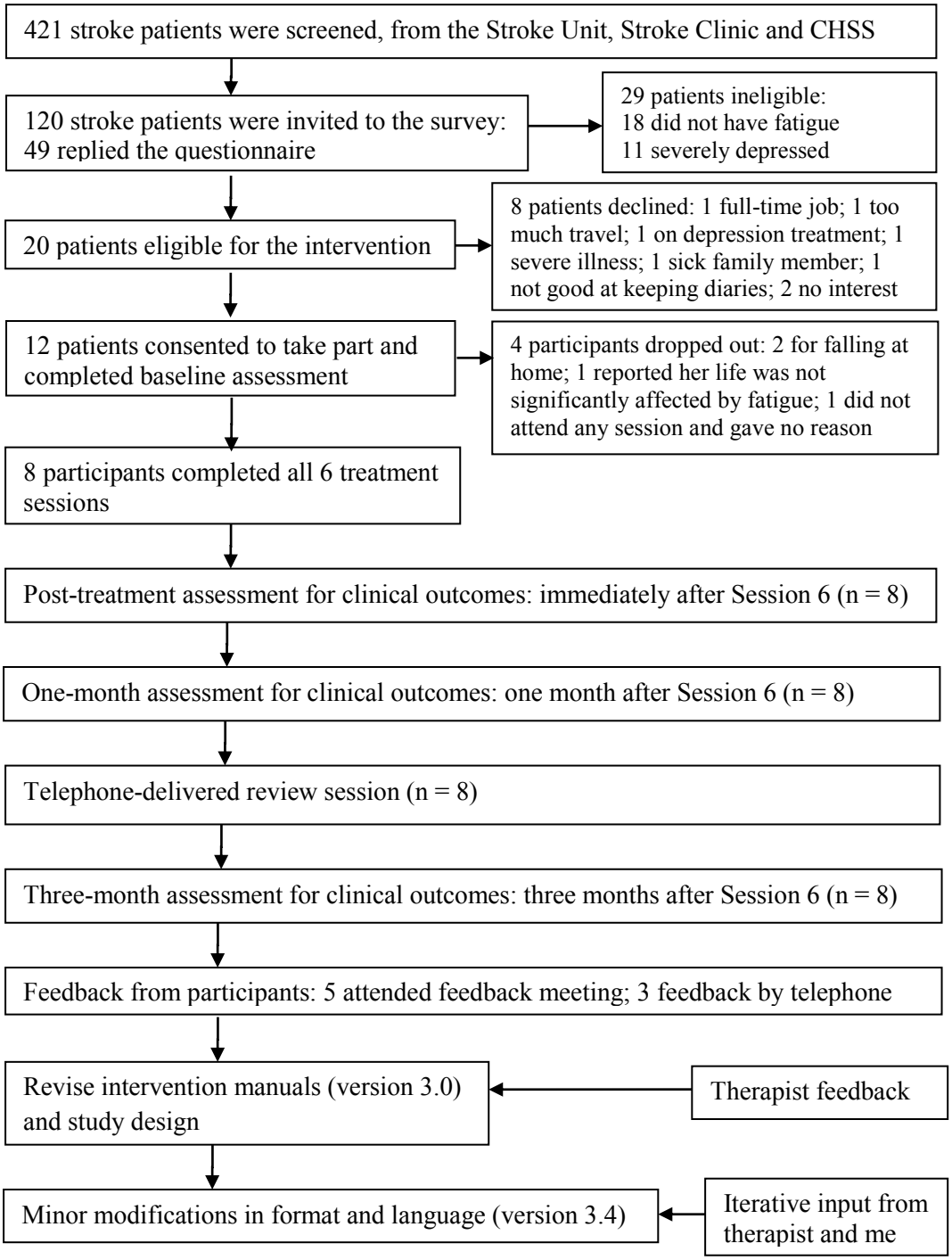

Figure 4.3 Flowchart of the feasibility study for a psychological intervention for post-stroke fatigue.

4.3.1 Recruitment

The recruitment was started in July 2014, when 341 patients from the Stroke Unit and 80 patients from the Stroke Clinic (who had their stroke in the past two years) were screened. Of these patients, 116 patients (66 from the Stroke Unit and 50 from the Stroke Clinic) were invited to complete the survey for post-stroke fatigue and depression. The other 305 patients were excluded for the following reasons: not stroke but transient ischaemic attack (TIA) or other mimic conditions, medically unstable, homebound or in nursing home, in other research studies, deceased, or living out of the Lothian area. The CHSS stroke nurses normally visited about 15 stroke patients each week, and in total they referred four potentially eligible patients to me. However, the total number of patients screened by these CHSS stroke nurses is unknown. The recruitment was finished in October 2014, when the pre-specified sample size of 12 participants was achieved.

In summary, from July 2014 to October 2014, we approached 120 stroke patients with the intention of securing the engagement of 12 eligible participants (Table 4.2). 49 stroke patients (41%) completed and returned the survey questionnaire, of whom 31 (63%) reported fatigue and the other 18 did not. Of the 31 fatigued patients, 11 patients (35%) had a total PHQ-9 score of 15 or more (indicating at least moderately severe depression) thus were excluded; the remaining 20 patients were eligible for the intervention stage, i.e. having self-reported fatigue but not severely depressed.

Table 4.2 Numbers of patients at each stage of recruitment

No. of patients	Stroke Clinic	Stroke Unit	CHSS	Total
Initial screening	80	341	Unknown	421
Invited to the survey	50	66	4	120
Replied to the survey	23	24	2	49
Eligible for the intervention	12	7	1	20
Consented to the intervention	7	5	0	12

Of the 20 patients who were eligible for the intervention stage, eight declined to take part during my telephone invitation. Their reasons for not participating included a) full-time job (n=1), b) too much travel from home to hospital (n=1), c) currently on a therapy for depression (n=1), d) severely ill in bed (n=1), e) sick family member (n=1), f) not good at keeping diaries (n=1), and g) simply no interest (n=2). The other twelve patients agreed to take part in the intervention stage and attended the consenting meeting with me at the Clinical Research Facility (CRF) of Royal Infirmary of Edinburgh. None of them were excluded by the CRF nurse and myself at this stage (i.e. they all had adequate capacity in cognition and verbal communication) and all gave the written consent to take part in this feasibility study.

4.3.2 Participant characteristics

Of the 12 participants, five were women and seven were men, and they had a mean age of 63 years (SD = 13, range 47 to 85 years). Eight participants had had their first-ever stroke and the other four participants had had a recurrent stroke in the previous two years, and all were ischaemic stroke. The mean time from the onset of the recent stroke to recruitment was 16 months (SD = 6, range 5 to 23 months). Five participants had cardiopulmonary comorbidities, two participants had psychological conditions, and the other five participants did not have any cardiopulmonary or psychological comorbidities. For the two participants with current psychological

conditions, either the therapist or I talked to their GPs or clinical psychologists before recruiting the participants to the study.

4.3.3 Feasibility outcomes

Attendance and retention

Four participants (33%) dropped out: one participant did not attend any session and gave no reasons, another participant withdrew after the first session as she reported her life was not significantly affected by fatigue and this intervention was not suitable for her, and the other two participants withdrew because they had fallen and therefore were unable to attend sessions in hospital (one had attended one session and the other had attended two sessions).

The other eight participants (67%) completed all six treatment sessions as well as the review session. Of these participants, seven participants attended all face-to-face treatment sessions as planned and the other participant had one session rearranged due to his busy schedule during the Christmas season. For the telephone-delivered review sessions, only one participant attended the session on the agreed date and time, whilst the other seven participants rescheduled their sessions due to their delay of completing one-month assessment questionnaires (n = 2) or forgetting about the appointment for the review session (n = 5).

Questionnaires for clinical outcomes

Completion of questionnaires

The baseline assessment was completed by 12 participants at the meeting for signing the consent form. Some patients asked questions about items that they thought were irrelevant to them, for example, items relating to driving and gardening in the NEADL for patients who did not drive or those who did not have a garden, and also the item relating to religious activities in the SIS for patients who did not have religious beliefs. For these questions, I explained to the patient that according the scale guidance these items should be marked as ‘not at all’ or ‘none of the time’.

The subsequent assessments were completed by the eight participants who had completed all the treatment sessions, by postal questionnaires. Most participants gave consistent and adequate answers to the questions, whilst one participant gave some obviously different answers from his answers at baseline assessment. Those questions included two questions in the FAS and three questions in the mood subscale of the SIS, in each case the answers were scored in the opposite direction (i.e. higher scores representing more or less fatigue) as compared with other questions in the same questionnaire. I contacted this participant by telephone and clarified with him the answers to these questions.

Timing of returning postal questionnaires

For the post-treatment assessment, five participants completed and returned questionnaires in time (i.e. within one week after the final treatment session), one participant returned in the second week (i.e. delayed for one week), another participant in the third week (i.e. delayed for two weeks), and the other participant in the fourth week (i.e. delayed for three weeks, around the time for one-month assessment). For this last participant, I did not send questionnaires to him for one-month assessment; instead, I used his results of post-treatment assessment as the results of both the post-treatment assessment and the one-month assessment for data analysis.

I sent questionnaires to the other seven participants for the one-month assessment, of whom five participants returned the completed questionnaires by mail within one week, another participant returned by mail in the second week, and the other participant completed the questionnaires by telephone in the second week.

For the three-month assessment, six participants returned the completed questionnaires by mail within one week and the other two participants completed the questionnaires in the third week by telephone.

Participant feedback

Five participants attended the feedback meeting and the other three participants provided their feedback by telephone.

Usefulness of intervention

Of eight participants who completed all sessions, seven (87.5%) rated the intervention 'very useful' or 'somewhat useful' in improving their fatigue (Table 4.3). Three participants reported that they had not used the strategies for sleep regulating or thought challenging, as they considered that these problems were not relevant to them. For the strategy for sleep regulating, the rating of usefulness varied among participants who had used it. Regarding the other strategies, each was rated as 'very useful' by more than 70% of the participants (Table 4.3). In addition, one participant said that the survey for post-stroke fatigue was useful, as the identification of fatigue enabled him to recognise it as a problem and thus take action working against it. One participant thought that this intervention was targeting his mood but he did not have any depression problems, thus he rated this intervention was 'not useful at all' in general, including the strategies for regulating sleep and for the review session. Though interestingly his fatigue score improved.

Table 4.3 Participants' rating of the usefulness of the intervention in improving their post-stroke fatigue

Intervention strategies	Participants who used the strategy	Numbers of participants			
		Not useful at all	A little useful	Somewhat useful	Very useful
General rating of intervention	8	1 (12.5%)	0	2 (25.0%)	5 (62.5%)
Fatigue education	8	0	0	1 (12.5%)	7 (87.5%)
Activity and sleep diaries	8	0	1 (12.5%)	1 (12.5%)	6 (75.0%)
Planning activities	8	0	2 (25.0%)	0	6 (75.0%)
Regulating sleep	5	1 (20.0%)	1 (20.0%)	1 (20.0%)	2 (40.0%)
Challenging thoughts	5	0	0	1 (20.0%)	4 (80.0%)
Overcoming blocks	7	0	0	2 (28.6%)	5 (71.4%)
Review session	8	1 (12.5%)	1 (12.5%)	0	6 (75.0%)

Difficulty in completing home tasks

Most participants (60% or more) rated all home tasks as being 'not difficult' or 'a little difficult' (Table 4.4). Some participants found that keeping diaries, increasing daily activity, and regulating sleep were difficult. Nevertheless, they commented that despite the difficulties, they were able to make changes in daily life to overcome fatigue by completing these tasks.

Table 4.4 Participants' rating of the difficulty in completing home tasks

Home tasks	Participants who used the task	Numbers of participants			
		Not difficult at all	A little difficult	Somewhat difficult	Very difficult
Keeping diaries	8	4 (50.0%)	1 (12.5%)	3 (37.5%)	0
Making plans	8	5 (62.5%)	2 (25.0%)	1 (12.5%)	0
Increasing activities	8	4 (50.0%)	1 (12.5%)	3 (37.5%)	0
Challenging thoughts	5	2 (40.0%)	3 (60.0%)	0	0
Regulating sleep	5	3 (60.0%)	0	0	2 (40.0%)

Session arrangement

All eight participants were satisfied with the arrangement of six treatment sessions over a period of 12 weeks. Five participants rated the content of all sessions as being 'of the right amount', whilst two participants thought Session 1 was 'too much' and another participant thought Session 6 was 'too little'.

Feedback on follow-up assessments

One participant rated the three-month follow-up and three assessments after treatment 'too many' (this was the participant who rated this intervention as 'not useful at all'). The other seven participants stated that three assessments over three months after treatment were acceptable in terms of the amount and the length of interval. Two participants also suggested having a longer follow-up assessment so that it could act as an incentive for them to continue making progress.

Feedback on questionnaires for clinical outcomes

Most participants stated that the questionnaires were easy to complete. But two participants indicated ‘a little difficulty’ in completing the SIS, in terms of its length (60 items in total). One of these participant also commented that there were some duplicating items between different questionnaires, for example the SIS and the NEADL, which he felt ‘annoying’.

Plans of delivering the intervention by stroke nurses

Some participants had concerns about our future plans for nursing staff to deliver psychological interventions, regarding their lack of psychological expertise. Nevertheless, after I explained that nursing therapists would be specifically trained for this intervention and supervised by experienced psychologists, these participants agreed that the nurse-delivery approach would be acceptable.

Preferences for delivery in person, by telephone, or online

All participants suggested that treatment sessions should be delivered face to face. They felt that they would be taken more seriously when meeting the therapist in person, and this would result in them being more committed in the sessions. Based on their experience of telephone-delivered review sessions, they had difficulty in attending such appointment and were easily distracted by their environment during the session. Participants suggested that they would not wish to undertake a therapy online, because they would not take information on the internet seriously.

They commented that ‘in face-to-face session, you feel like being treated as a person’, ‘it is awkward to receive a therapy over telephone’, ‘when talking over telephone, it is easily distracted by your kids around’, ‘I would not take things on the internet seriously’ and ‘It is hardly to lie to a therapist in person; but if over telephone, probably; and if online, very likely’.

Therapist feedback

The intervention manual

The therapist, who was a clinical psychologist with rich experience in delivering CBT and working with stroke patients, commented that this intervention 'has been carefully designed on the basis of standard CBT literature' and 'the chapters have been clearly laid out'. However, she suggested a more even distribution of materials between sessions, because there was too much information in Session 1 and insufficient materials in Session 6 for some participants. This feedback was consistent with feedback from some participants.

Sleep/Activity diaries

A Sleep Diary and an Activity Diary were used in this study, to record details of sleep patterns, physical activities and extent of social interaction. The therapist suggested that these diaries were too arduous for the participant to complete every day. She suggested these diaries to be used only following the initial session and for the final session as an overall assessment of improvement during the intervention, rather than as a daily monitoring.

Review session over telephone

The therapist suggested that the telephone-delivered review session could have been improved if questionnaires for one-month assessment had been timeously returned and mutually appropriate arrangements had been made for telephone calls. However, seven out of eight participants had their review sessions rearranged due to the delay of returning one-month assessment questionnaires or participants' forgetting about the appointment. Delivering the review session person-to-person might be a better delivery approach, because this may be an incentive for participants to return the questionnaires in time and also participants may be more likely to be committed to the review session when meeting the therapist in person.

Potential challenges for delivery by stroke nurses

The therapist suggested that as the CBT model of PSF presented thoughts and emotions in a conceptual way, which would be unfamiliar for both inexperienced therapist and patients. People are usually aware of their emotions in the first instance before attempting to analyse their thoughts that actually precede the emotions. Thus it is important to acknowledge this to both the therapist and patients. For inexperienced nursing staff, it would require rehearsal and repetition to familiarise them with the CBT. For example, the specialist training for nursing staff should be provided by an experienced CBT therapist, which include introduction of basic CBT principles, familiarisation with both the Therapist Manual and the Participant Manual, and practicing administration of the intervention between nursing staff.

4.3.4 Clinical outcomes

Baseline characteristics

Clinical characteristics of participants (n = 12) who completed baseline assessment are summarised in Table 4.5. Those who dropped out had more women and poorer physical strength than participants who completed all sessions. There was no difference between these two groups in other demographic or baseline clinical outcomes.

Of the eight participants who completed all sessions, five fulfilled the case definition of PSF at baseline, whilst the other three did not fulfil it as their fatigue did not present every day or did not occupy most of their daytime. The two participants with psychological conditions at recruitment were under relevant treatment and their psychological conditions were stable (with a total PHQ-9 score less than 15). All eight participants were very independent in daily activities, with a total score of the NEADL ranging from 20 to 22 (out of a maximal possible score of 22); and the lost scores were mainly due to that the participant did not drive or not have a garden. Participants' self-rating of recovery from stroke at baseline ranged from 50% to 98%.

Table 4.5 Clinical characteristics of participants at recruitment (n = 12)

Baseline characteristics	Participants completing all sessions (n = 8)	Participants dropping out (n = 4)	*p* values
Female/Male	1/7	4/0	0.01*
Mean age (years)	62.0 (SD = 14.7)	64.5 (SD = 8.8)	0.76
First/Recurrent stroke	6/2	2/2	0.55
Mean time since recent stroke (months)	16.3 (SD = 5.1)	14.8 (SD = 7.5)	0.69
Fulfilling case definition of post-stroke fatigue	5 (62.5%)	3 (75.0%)	1.00
Fatigue Assessment Scale	26.5 (SD = 8.0)	24.5 (SD = 5.2)	0.66
Patient Health Questionnaire-9	7.6 (SD = 4.3)	6.3 (SD = 3.0)	0.59
Nottingham Extended Activities of Daily Living	20.8 (SD = 0.9)	18.0 (SD = 2.6)	0.12
SIS General Recovery	74.8 (SD = 16.7)	80.0 (SD = 8.2)	0.57
SIS Physical Strength	89.1 (SD = 9.9)	73.4 (SD = 10.7)	0.03*
SIS Memory and Thinking	75.4 (SD = 21.3)	77.7 (SD = 22.7)	0.88
SIS Emotion	66.0 (SD = 26.1)	81.9 (SD = 13.9)	0.20
SIS Communication	80.4 (SD = 23.3)	93.8 (SD = 7.9)	0.18
SIS Daily Activities	93.4 (SD = 6.54)	90.0 (SD = 4.1)	0.37
SIS Mobility	87.5 (SD = 15.1)	86.8 (SD = 11.4)	0.94
SIS Hand Function	93.8 (SD = 9.5)	81.3 (SD = 17.0)	0.13
SIS Social Activity	67.8 (SD = 24.5)	59.4 (SD = 35.1)	0.63

*p value < 0.05. SIS: Stroke Impact Scale.

Intervention effects on clinical outcomes

Table 4.6 presents clinical outcomes at each assessment and the difference between baseline assessment and each of the subsequent assessment.

Table 4.6 Clinical outcomes at baseline and three assessments after treatment (n = 8)

Outcome measures	Baseline mean (SD)	Post-treatment assessment		One-month assessment		Three-month assessment	
		Mean (SD)	Mean difference (95% CI)**; p values	Mean (SD)	Mean difference (95% CI)**; p values	Mean (SD)	Mean difference (95% CI)**; p values
PSF case definition	62.5%	25.0%	*p*=0.25	25.0%	*p*=0.25	12.5%	*p*=0.13
FAS	26.5 (8.0)	21.8 (7.4)	4.8 (-2.1, 11.6); *p*=0.15	19.5 (8.4)	7.0 (-0.8, 14.8); *p*=0.07	17.3 (8.6)	**9.3 (1.4, 17.1); *p*=0.03***
PHQ-9	7.6 (4.4)	4.8 (4.9)	2.9 (-0.002, 5.8); *p*=0.05	4.5 (5.1)	**3.1 (0.2, 6.1); *p*=0.04***	5.0 (6.3)	2.6 (-0.7, 5.9); *p*=0.10
NEADL	20.8 (0.9)	20.5 (1.2)	0.3 (-0.3, 0.8); *p*=0.35	20.9 (1.1)	-0.1 (-1.0, 0.7); *p*=0.73	21.0 (1.1)	-0.3 (-1.0, 0.5); *p*=0.45
SIS General Recovery	74.8 (16.7)	84.1 (12.6)	-9.4 (-18.8, 0.1); *p*=0.05	84.6 (15.7)	-9.9 (-20.1, 0.4); *p*=0.06	88.6 (15.2)	**-13.9 (-25.8, -2.0); *p*=0.03***
SIS Physical Strength	89.1 (9.9)	87.5 (13.8)	1.6 (-10.8, 14.0); *p*=0.78	85.9 (19.7)	3.1 (-13.6, 20.0); *p*=0.67	89.8 (12.5)	-0.8 (-14.0, 12.4); *p*=0.90
SIS Memory and Thinking	75.5 (21.3)	79.9 (23.3)	-4.5 (-10.2, 1.2); *p*=0.11	82.0 (24.4)	-6.6 (-15.3, 2.2); *p*=0.12	87.1 (18.0)	**-11.6 (-19.2, -4.0); *p*=0.009***
SIS Emotion	66.0 (26.1)	76.0 (27.0)	-10.1 (-24.1, 3.9); *p*=0.13	78.8 (22.8)	-12.8 (-27.5, 1.8); *p*=0.08	84.4 (18.8)	**-18.4 (-30.6, -6.2); *p*=0.009***
SIS Communication	80.4 (23.3)	85.7 (23.0)	-5.4 (-16.3, 5.6); *p*=0.29	87.5 (21.9)	-7.1 (-18.2, 3.9); *p*=0.17	87.5 (17.9)	-7.1 (-15.9, 1.6); *p*=0.09
SIS Daily Activities	93.4 (6.5)	92.5 (10.2)	0.9 (-4.4, 6.3); *p*=0.69	92.8 (8.3)	0.6 (-4.7, 5.9); *p*=0.79	95.9 (5.3)	-2.5 (-5.5, 0.5); *p*=0.09
SIS Mobility	87.5 (15.1)	91.0 (14.1)	**-3.5 (-5.5, -1.4); *p*=0.005***	91.3 (15.0)	**-3.8 (-6.8, -0.8); *p*=0.02***	91.3 (14.0)	**-3.8 (-7.1, -0.6); *p*=0.03***
SIS Hand Function	93.8 (9.5)	93.8 (11.6)	0.0 (-4.5, 4.5); *p*=1.00	92.5 (11.0)	1.3 (-2.5, 5.0); *p*=0.45	95.6 (8.6)	-1.9 (-9.6, 5.8); *p*=0.58
SIS Social Activity	67.9 (24.6)	86.3 (14.5)	**-18.5 (-29.4, -7.6); *p*=0.005***	82.8 (24.3)	**-15.0 (-26.7, -3.2); *p*=0.02***	82.4 (19.9)	**-14.6 (-23.3, -5.8); *p*=0.006***

**p* value < 0.05. **Mean of the difference in scores or proportions between the baseline assessment and the assessment after treatment, i.e. the result of baseline assessment minus the result of post-treatment assessment. FAS: Fatigue Assessment Scale; PHQ-9: Patient Health Questionnaire-9; NEADL: Nottingham Extended Activities of Daily Living; SIS: Stroke Impact Scale. Of FAS and PHQ-9, higher scores indicate worse outcomes and the positive value of MD indicates improvement; of NEADL and SIS subscales, higher scores indicate better outcomes and the negative value of MD indicates improvement.

Presence of clinically significant fatigue

Numbers of participants fulfilling the case definition of PSF decreased from five (62.5%) at T0 to two (25.0%) at T1, and further decreased to one (12.5%) at T3, although this decrease in proportions was not statistically significant (Table 4.6).

Fatigue Assessment Scale (FAS)

Means scores of FAS decreased over time across four assessments (Figure 4.4). The decrease was most evident between T0 and T1 (by a mean score of 4.8 points, p = 0.15), and continued between T1 and T2 (by a further 2.2 points, p = 0.05) and between T2 and T3 (by a further 2.3 points, p = 0.11). Overall, the FAS score decreased significantly from baseline to the three-month assessment (by a mean score of 9.3 points, Table 4.6).

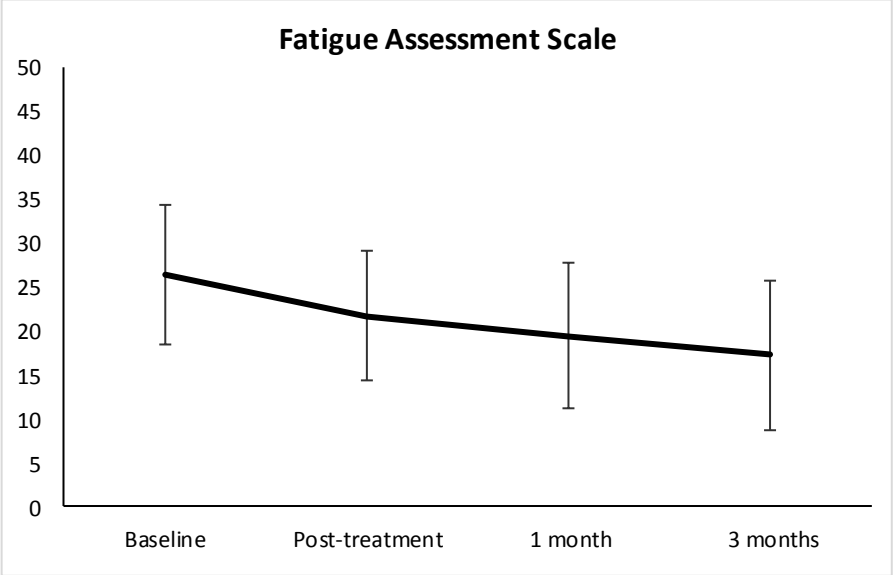

Figure 4.4 Scores of the Fatigue Assessment Scale (FAS) at baseline and at three assessments after treatment. The horizontal axis is the time of assessment. The vertical axis is the FAS scores. Error bars represent the 95% confidence interval of the mean FAS scores at each assessment.

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 scores decreased from T0 to T1 ($p = 0.05$) and maintained stable at follow up (Figure 4.5). There was no significant difference between T1 and T2 ($p = 0.17$) or between T2 and T3 ($p = 0.61$).

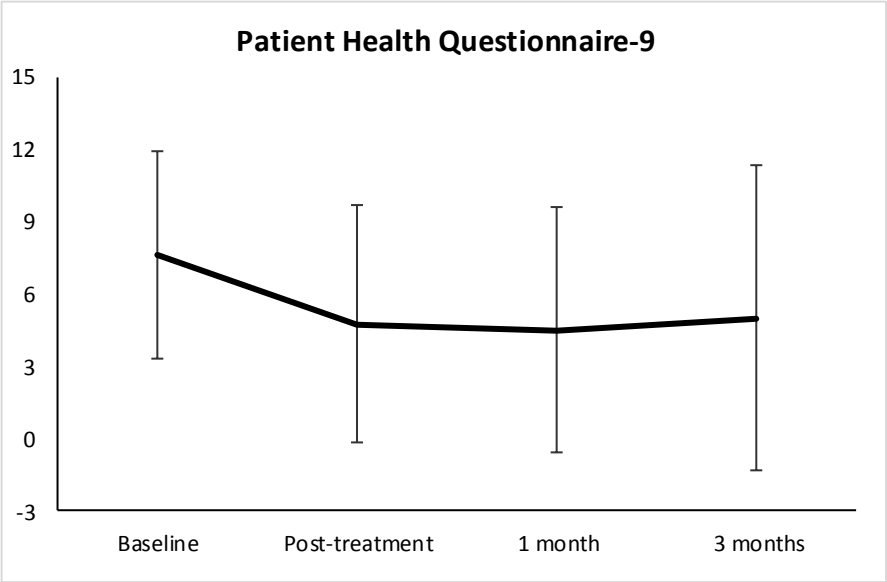

Figure 4.5 Scores of the Patient Health Quesitonnaire-9 (PHQ-9) at baseline and at three assessments after treatment. The horizontal axis is the time of assessment. The vertical axis is the PHQ-9 scores. Error bars represent the 95% confidence interval of the mean PHQ-9 scores at each assessment.

Nottingham Extended Activities of Daily Living (NEADL)

All participants had good independence in activities of daily living, with a mean score of NEADL of 20.8 (SD = 0.9, out of a possible maximal score of 22 for full independence) at T0. The level of independence was stable over time (Figure 4.6) and there was no significant difference in NEADL scores between T0 and any of the follow-up assessments (Table 4.6). Also there was no difference between T1 and T2 (p = 0.20), or between T2 and T3 (p = 0.35).

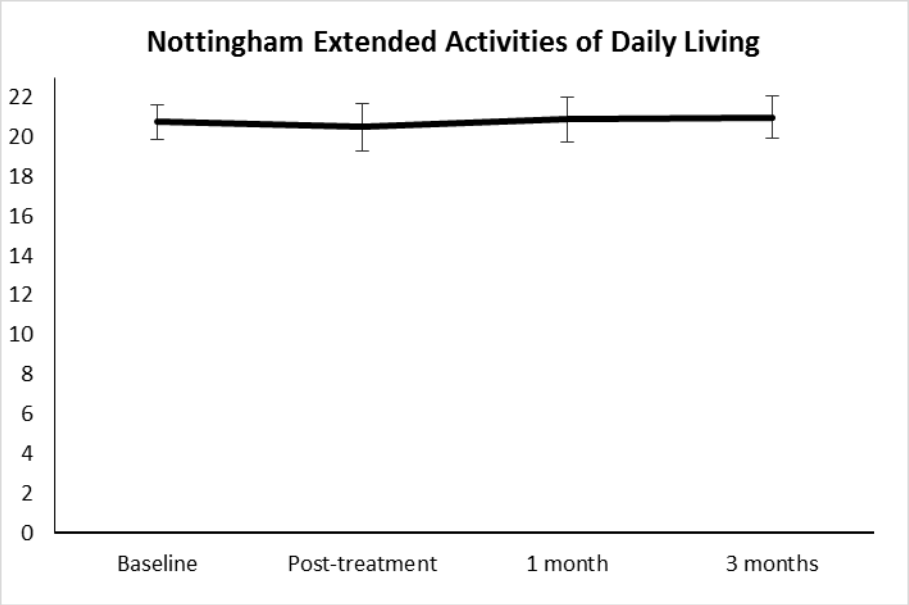

Figure 4.6 Scores of the Nottingham Extended Activities of Daily Living (NEADL) at baseline and at three assessments after treatment. The horizontal axis is the time of assessment. The vertical axis is the NEADL scores. Error bars represent the 95% confidence interval of the mean NEADL scores at each assessment.

Stroke Impact Scale (SIS) 3.0

Self-rating on recovery

For participants' self-rating of their recovery from stroke (Figure 4.7), there was a marginally significant increase of scores from baseline to immediately post-treatment ($p = 0.05$), a relatively stable status from immediately after treatment to one-month assessment ($p = 0.82$), and a marginally significant increase from one-month to three-month assessments ($p = 0.05$). Overall, the self-rating of recovery was improved significantly from baseline to three-month assessment (Table 4.6).

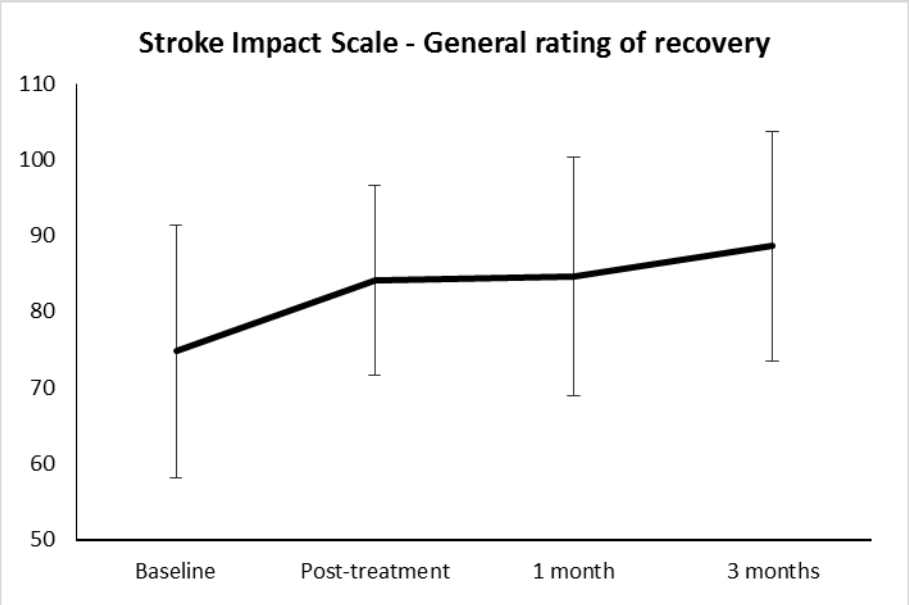

Figure 4.7 Scores of the general recovery by the Stroke Impact Scale (SIS-recovery) at baseline and at three assessments after treatment. The horizontal axis is the time of assessment. The vertical axis is the SIS-recovery scores. Error bars represent the 95% confidence interval of the mean SIS-recovery scores at each assessment.

Other subscales of SIS

Scores of eight subscales of SIS are summarised in Table 4.6 and illustrated in Figure 4.8. The most evident improvement was in the self-reported of participation in social activity, of which the score improved significantly from baseline to immediately

post-treatment ($p = 0.005$); this improvement was stable afterwards, with no significant difference between post-treatment and one-month assessments ($p = 0.40$) or between one-month and three-month assessments ($p = 0.93$).

Significant improvement from baseline to three-month assessments was also present in self-reported mobility, memory and thinking, and emotion (Table 4.6). The mobility scores improved significantly from baseline to post-treatment ($p = 0.005$) and kept stable between post-treatment and one-month assessments ($p = 0.69$) and between one-month and three-month assessments ($p = 1.00$). For both the memory and thinking subscale and emotion subscale, scores increased over time but did not reach a significant level until at three-month assessment (Table 4.6).

For the other four subscales (i.e. physical strength, communication, daily activities, and hand function), there was no significant difference between baseline scores and those at any follow-up assessment (Table 4.6, Figure 4.8).

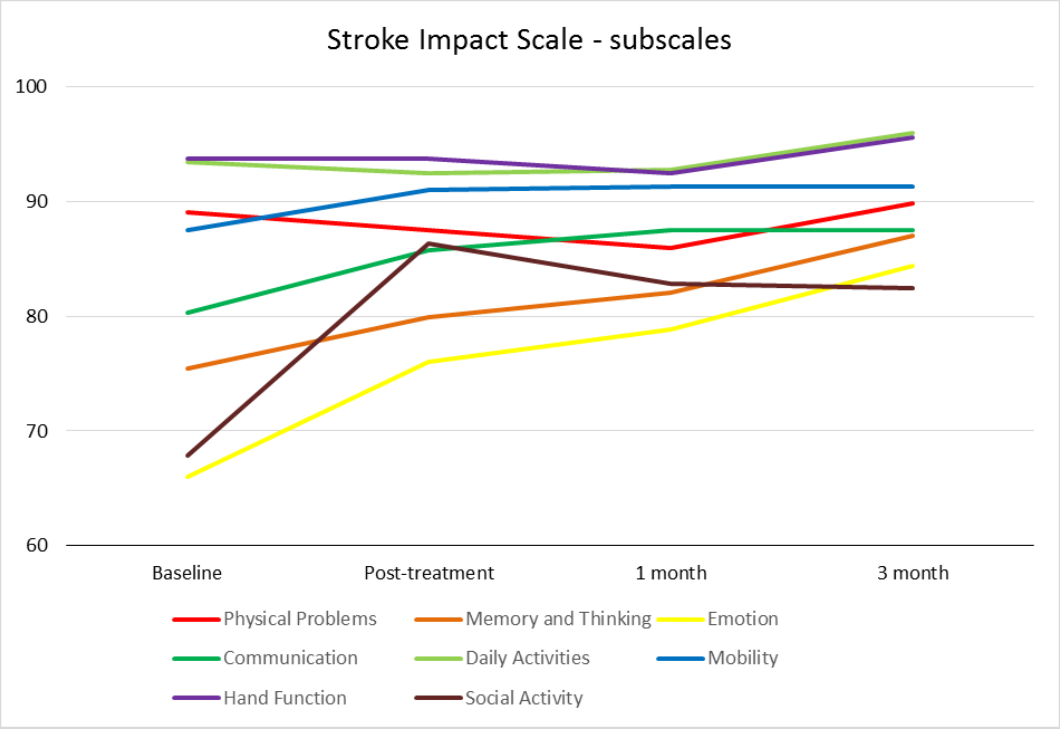

Figure 4.8 Scores of eight subscales of the Stroke Impact Scale (SIS) at baseline and three assessments after treatment. The horizontal axis is the time of assessment. The vertical axis is the mean score of each subscale of SIS.

Section 4.4 Discussion

This chapter has described a feasibility study to test the acceptability and feasibility of a psychological intervention for the treatment of PSF. The intervention was well received by the stroke patients in terms of the adherence to the intervention programme. Also most participants rated this intervention very useful in helping them overcome PSF. According to the feedback from participants and therapist, a number of changes could be incorporated to improve the study design and intervention programme, as discussed in this section.

4.4.1 Feasibility of study design

Recruitment

The recruitment process was feasible in the local health system in the Lothian area of Scotland with a recruitment rate of 10% of initially approached stroke patients. About 41% of the invited patients replied to the survey questionnaires for post-stroke fatigue and depression; and 63% of those who replied had fatigue. To ensure a good response rate to the survey, I had used the strategies reported previously to be effective in increasing response rates of postal questionnaires, for example using short and colour printed questionnaires and providing stamped return envelops (Edwards et al., 2002). However, the response rate in the current study was lower than that in previous studies. In a Norwegian study, which mailed the FSS to patients who were discharged from the Stroke Unit at least six months previously, 58% of patients returned the questionnaire and 42% of those who replied had PSF (Naess et al., 2012). A Dutch study sent postal questionnaires to community patients who had stroke more than one year ago, asking whether fatigue was their main complaint (yes/no), 65% of patients returned the questionnaire and 50% of them indicated that fatigue was their main complaint (van der Werf et al., 2001).

One possible reason for the lower response rate in the current study is that the target population was different from other studies. For example, the Norwegian study had used a wider inclusion criteria than the current study, which included patients with

either stroke or TIA (Naess et al., 2012). Another possible explanation is that the previous studies were purely surveys for fatigue, whilst in the current study I had provided information for patients that if the result of the survey indicated that they had fatigue I would further invite them to take part in an intervention study. This might require more initiative for the patients to take part in the current study, that is, patients who were more interested in PSF (e.g. they perceived fatigue as a problem for them) were more likely to take part in the current study. This may explain our lower response rate but a higher proportion of responding patients had PSF.

The outpatient Stroke Clinic is an important resource of potential participants. In the current study, 14% of stroke patients approached from the Stroke Clinic were recruited, compared with 8% approached from the Stroke Unit and 0% from the CHSS. Compared to patients discharged from the Stroke Unit, those from the Stroke Clinic usually have less severe stroke. It is possible that patients with less severe stroke are more likely to take part in the research study for fatigue, as for these patients fatigue could be a prominent problem whilst for patients with more severe stroke fatigue is a less severe problem for them as compared to other disabling complications. This hypothesis may be partly supported by the findings that all our participants had good independence in daily activities at recruitment. This was similar in another pilot trial for the treatment of PSF, where the mean score of the baseline Barthel Index of all participants was 92.5 (out of a maximal possible score of 100, indicating full independence) (Clarke et al., 2012).

Attrition and reasons for withdrawal

The dropout rate (n = 4, 33%) was higher than expected. In a previous longitudinal study on PSF in the same general population, 13% of the consenting participants did not attend any assessment and another 18% withdrew after the one-month assessment (Duncan et al., 2015). In a trial for PSF in the Netherlands, 16% of the randomised participants discontinued the treatment for various reasons (Zedlitz et al., 2012).

In the current study, one participant withdrew after attending the first session as she reported that she had coped well with her fatigue, so that she did not need an

intervention. To screen for patients with PSF, I had adapted a single question 'do you feel tired all the time or get tired very quickly since your stroke' from the GM-SAT (Rothwell et al., 2013) and provided a simple answer of 'yes' or 'no'. Learning from this participant, in future we may need to ask an additional question to identify those who have fatigue and also would like extra help for their fatigue. For example, it may be better to expand the answers to 'yes and I would like additional help and support', 'yes but I am receiving enough help and support', or 'no', which are the original answers developed in the GM-SAT for this question (Rothwell et al., 2013). Another two participants withdrew due to the falling at home thus were unable to travel to hospital. I offered to deliver the sessions to them on the telephone, but both participants declined as they thought it would be too difficult to continue a research study when their mobility impaired. Falling is common in stroke patients. In a study following 108 stroke patients for six months after their discharge from hospital, 73% of patients had least one falling during this period (Forster and Young, 1995). Another study reported that the incidence of falling in stroke patients was more than twice of the incidence in age and sex matched people (Jørgensen et al., 2002). Stroke patients are usually elder people and vulnerable to many other medical conditions, which may affect their attendance in research studies. The final participant withdrew without attending any session and did not give any reason.

Although a case definition had been specifically designed for PSF, our project decided not to use it to screen for PSF. Instead, we used a simple screening question for PSF, with an aim to include a broader range of patients as long as they perceived fatigue as a problem for them. Of the eight participants who completed all their treatment sessions, three did not fulfil this case definition at recruitment, because their fatigue did not present every day or did not occupy most of their daytime. This suggests that the case definition may be too strict to be used as a screening question. Therefore, I would suggest using the simple question rather than the case definition to screen for PSF in future studies.

Attendance and delivery modes

Participants had very good adherence to attending face-to-face treatment sessions, given the dates and time had been agreed in advance between the participant and the therapist at the initial session. But for the telephone-delivered review session, some participants gave different excuses to delay the session or simply forgot the appointment. This is in contrary to a previous study, which reported that patients with depression had better adherence to the telephone-delivered psychotherapy than to the face-to-face approach (Mohr et al., 2012). In the current study, the face-to-face meetings with the therapist were greatly appreciated by the participants, and they expressed unfavourable opinions about the potential for online or telephone-delivery approaches. Similarly, in a feasibility study that delivered a mindfulness-based intervention for mental fatigue in patients with traumatic brain injury (n = 16) or stroke (n = 18), seven out of 34 participants (20%) did not accept to attend the internet-based intervention (Johansson et al., 2015). Thus, although online psychotherapies have been frequently used for patients with mental conditions (Fischer et al., 2015, Rooksby et al., 2015), its acceptability to stroke patients is unclear and the low acceptance may affect patients' adherence to the intervention.

When discussing our plan of delivering this intervention by stroke nurses, participants were concerned about the expertise of the nursing staff in delivering psychological interventions. Adequate training and supervision will be needed for nurses to deliver psychological interventions. A study of psychotherapy for chronic fatigue syndrome reported no therapist effect (between clinical psychologists and specialist nurses) on the fatigue outcome (Cella et al., 2011). Strategies used in this study of chronic fatigue syndrome to minimise the therapist effect included the manualised therapy, standardised training, and supervision by experienced psychotherapists (Cella et al., 2011). One thing that should be pointed out is that in the above study of therapist effect, the specialist nurses had completed a postgraduate diploma in cognitive behavioural psychotherapy (Cella et al., 2011), which is not practical to be provided for nurses in routine stroke care. However, the psychotherapist (TC) in our project team, who was also an investigator in the above

study on therapist effect, suggested that a short-term training with a few sessions of introduction and practice would be sufficient to train nurses to deliver brief psychological interventions.

Follow-up assessment for outcome measures

The completion of post-treatment assessment was delayed in a number of participants, and some of them returned the questionnaires around the time for one-month assessment. There is not much difference to be expected between the two assessments. Thus, in future it may be better to conduct one instead of two assessments between the final treatment session and the review session. That is, after the final treatment session, participants will be given the questionnaires to complete at home and then return to the therapist by post before they attend the review session. This arrangement may have some advantages over the current arrangement. Firstly, this will give the participant one month's time to complete one set of questionnaires rather than two sets, of which the latter had been hardly achieved by some participants in the current study. Secondly, this will allow participants have some time to reflect on their participation in the study. Finally, the review session will be an incentive to encourage participants to return questionnaires, as the discussion during the review session will be based on the result of these questionnaires.

As some participants suggested a longer follow-up than the current three months and also because PSF is a chronic problem, in future we would consider extend the three-month follow-up to six months or even longer after the end of treatment.

4.4.2 Improvement of clinical outcomes

I analysed data of the eight participants who completed all their treatment sessions and found significant improvement in fatigue severity, mood, self-reported mobility and participation in social activity from baseline to three months after the end of treatment. I had considered also including data of the four participants who dropped out in the data analysis, i.e. using their baseline data as the post-treatment results. Thus I consulted a medical statistician (Niall Anderson), who suggested that I should

not include the dropout data. This is because for the current feasibility study with a small sample size of 12 participants, the dropout of four participants took up a significant proportion (33%) of the whole sample size. If these dropouts were included in the analysis, this would inevitably comprise the reported improvement.

It is relevant to note that only one participate dropped out because of the intervention itself (she felt that she did not actually need the intervention), whilst for the other three participants their dropouts were not directly related to the current intervention (one did not attend any session and the other two withdrew because they had fallen at home and could therefore not attend further sessions). Also the current feasibility study did not aim to investigate the intervention efficacy on PSF. Therefore, I did not include the data of the dropped out participants in the analysis. The efficacy of the intervention should be investigated in future trials with the randomised controlled design and larger sample sizes. Also, an intention-to-treat analysis will need to be used to control for the attrition bias.

4.4.3 Plans for future adaptation of the intervention manuals

Revision of intervention manuals

According to the feedback from participants and therapist, I revised the intervention manuals for future use. Please see Appendix 9 for the final version of the Participant Manual (version 3.4) and Appendix 10 for the corresponding Therapist Manual (version 3.2).

Session arrangement

In a future trial, some information from the participant manual in Session 1 will be removed and be given to the participant to read at home prior to attending the initial treatment session. Also Session 6 will be combined with Session 5, as this last session does not provide any new skills but just a review of previous sessions. These changes will ensure a more even distribution of content between sessions. The Therapist Manual will be revised with the corresponding changes in the Participant Manual.

Treatment strategies

The strategies that were most useful to participants included the education about PSF and using diaries to record and plan for activities. These strategies will be retained as the main strategies in the revised Participant Manual.

For other strategies, including regulating sleep patterns, challenging unhelpful thoughts, sharing fatigue experience with others, and overcoming 'blocks', some participants reported that they did not use them as they did not have these problems. Thus the implementation of these strategies should be individualised for each participant. The revised manuals will still contain information of these strategies, but only participants who have relevant problems will be recommended to use relevant strategies.

Section 4.5 Conclusions

This psychological intervention was well received by stroke patients and the clinical psychologist, and the study process of recruitment, intervention delivery, and follow up was generally feasible in the local health system. Although the statistical power of this study was limited, there were statistically significant improvements in several aspects of life including fatigue severity. Based on these promising results, an exploratory randomised controlled trial would be a useful next stage for the intervention development, to further pilot other issues of the study design such as the nurse-delivery approach and the randomised controlled design.

CHAPTER V: Interventions for Post-stroke Fatigue – an Updated Systematic Review

Section 5.1 Introduction

In previous chapters, I described the theoretical (Chapter 2), modelling (Chapter 3) and part of the piloting (Chapter 4) stages of developing a psychological intervention for PSF. The MRC framework suggests that these three early stages of the intervention development should be considered as part of a larger iterative activity rather than as sequential stages (Campbell et al., 2007). Thus, I have updated the evidence and refined the intervention with input from three interactive strands: literature review, expert opinions from stroke clinicians and psychotherapists, and user input from stroke patients.

This framework also suggests that the results of intervention development and evaluation should be presented in the context of an updated systematic review of similar interventions (Craig et al., 2008b). A previous Cochrane review of interventions for PSF (published in 2009) concluded that there was insufficient evidence to inform the treatment of PSF (McGeough et al., 2009). Based on this review and the knowledge that psychological interventions are effective in reducing fatigue in conditions other than stroke, I developed the current psychological intervention for PSF. While developing this intervention, I became aware that several new interventions had been tested for PSF since 2009. Therefore, I decided to update this Cochrane review, in the hope of providing some new evidence that could be included in future studies.

I did not conduct this updated review before developing the current psychological intervention, because there would have then been insufficient time for me to develop and deliver the intervention within my three-year PhD study period. Also the intervention development is an iterative process and this thesis only covers the early development stages, thus the intervention needs to be refined by data from other subsequent studies before testing in a larger definitive trial. Therefore, this updated

review did not only focus on psychological interventions but reviewed any intervention that had been tested to treat or prevent fatigue in stroke patients, in order to identify any evidence that could inform the development of novel interventions for PSF in the future.

Updating a systematic review is to search for new evidence to incorporate into a previously completed systematic review, using the originally formulated protocol that may be modified or extended (Moher and Tsertsvadze, 2006). Thus I used the same protocol for the evidence search and study selection as used in the previous review. The previous review was only able to include three trials that tested different interventions and reported diverse outcome measures, making it difficult to perform summary statistical analysis. Over the last decade, more researchers and clinicians became interested in PSF, thus it was anticipated that this updated review would identify more studies to allow for statistical analyses. Therefore, I modified the protocol to provide methods for statistical analysis and the modification had been discussed with and agreed by all review authors before the updated search was conducted (for details of the differences between the previous protocol in 2008 and the current review, please see Appendices for this thesis, Appendix 1.3 the full publication of this updated Cochrane review, pages 101-102). The current review was updated by trials identified by searches in May 2014 and published in the Cochrane Database of Systematic Reviews 2015, Issue 7 (Wu et al., 2015a).

Section 5.2 Abstract

Background

Post-stroke fatigue (PSF) is a common and distressing problem after stroke. The best ways to prevent or treat PSF are uncertain. Several different interventions can be argued to have a rational basis. The aim of this review was to determine whether there was any evidence that any intervention reduces the fatigue severity or the proportion of stroke patients with fatigue, or both; and to determine the effect of intervention on health-related quality of life, disability, dependency and death, and whether such intervention is cost effective.

Methods

The search was up-to-date in May 2014. We searched the Cochrane Stroke Group Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, AMED, PsycINFO, Digital Dissertations, British Nursing Index, PEDro and PsycBITE. We also searched four ongoing trials registries, scanned reference lists, performed citation tracking of included trials and contacted experts.

Two review authors independently scrutinised all titles and abstracts and excluded obviously irrelevant studies. We obtained the full texts for potentially relevant studies and three review authors independently applied the inclusion criteria. We included randomised controlled trials (RCTs) that compared an intervention with a control, or compared different interventions for PSF.

Two review authors independently extracted data and assessed risk of bias for each included trial. The primary outcomes were severity of fatigue, or proportion of patients with fatigue after treatment. We performed separate analyses for trials primarily investigating the intervention efficacy in treating PSF, trials primarily investigating the intervention efficacy in preventing PSF, and trials primarily investigating the intervention efficacy on symptoms other than fatigue in stroke patients but reported fatigue as an outcome. We pooled results from trials that had a

control arm. For trials that compared different potentially active interventions without a control arm, we performed analyses for individual trials without pooling.

We calculated standardised mean difference (SMD) as the effect size for continuous outcomes and risk ratio (RR) for dichotomous outcomes. We pooled the results using a random-effects model and assessed heterogeneity using the I^2 statistic. We performed separate subgroup analyses for pharmacological and non-pharmacological interventions. We also performed sensitivity analyses to assess the influence of methodological quality on effect sizes.

Results

We retrieved 12,490 citations, obtained full texts for 58 studies and included 12 trials (three from the 2008 search and nine from the 2014 search) with 703 patients. Eight trials were specifically designed to treat PSF, and each tested a different intervention. Of these eight trials, six trials with seven comparisons provided data suitable for meta-analysis (five pharmacological interventions: fluoxetine, enerion, (-)-OSU6162, citicoline and a combination of Chinese herbs; and two non-pharmacological interventions: a fatigue education programme and a mindfulness-based stress reduction programme). The fatigue severity was lower in the intervention groups than in the control groups (244 patients, pooled SMD = -1.07, 95% confidence interval (95% CI) -1.93 to -0.21), with significant heterogeneity between trials (I^2 = 87%, degrees of freedom (df) = 6, $p < 0.0001$). The beneficial effect was not seen in trials that had used adequate allocation concealment (two trials, 89 patients, SMD = -0.38, 95% CI -0.80 to 0.04) or trials that had used adequate blinding of outcome assessors (four trials, 198 patients, SMD = -1.10, 95% CI -2.31 to 0.11). No trial primarily investigated the efficacy of any intervention in preventing PSF. Four trials (248 patients) were primarily designed to treat symptoms after stroke other than fatigue, but reported PSF as an outcome. They tested antidepressants, tirilazad mesylate, continuous positive airway pressure (CPAP) for sleep apnoea, and a self-management programme for stroke recovery; but none of them showed any benefit on PSF.

Conclusions

There was insufficient evidence on the efficacy of any intervention to treat or prevent fatigue after stroke. Trials to date have been small and heterogeneous, and some have had a high risk of bias. Some of the interventions described were feasible in people with stroke, but their efficacy should be investigated in RCTs with a more robust study design and adequate sample size.

Section 5.3 Background

In Chapters 1 and 2 I have provided the background and rationale for this Cochrane review. In brief, fatigue is common and persistent and is a priority for research in stroke patients. Its aetiologies and mechanisms are not well understood. A myriad of biological, psychosocial, and behavioural factors might be associated with PSF (Wu et al., 2015b).

Since PSF may have several causative or maintaining factors (Wu et al., 2015b), there are a number of potential interventions, in combination or alone, that may be helpful. Possible interventions include pharmacological interventions (e.g. antidepressants, wakefulness stimulants), psychological interventions (e.g. CBT, educational programme), and physical training (e.g. graded physical training, aerobic exercise). Nevertheless, due to our lack of knowledge of the exact aetiologies or mechanisms of PSF, it is unclear which approach may be effective.

Therefore, we performed this systematic review using broad inclusion criteria with the aim of identifying any intervention that might prevent or improve PSF (even if the intervention was not primarily designed to manage PSF). The objectives of this review were to determine whether, among stroke patients, any intervention reduces the proportion or severity of fatigue, or both; and to determine the effect of intervention on health-related quality of life, disability, dependency, and death; and whether such intervention is cost effective.

Section 5.4 Methods

5.4.1 Search strategies

With the help of the Cochrane Stroke Group Co-ordinators (Hazel Fraser and Brenda Thomas), we performed updated searches of the following electronic databases and trial registers from the previous searches in 2008 to May 2014: Cochrane Stroke Trial Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, AMED, PsycINFO, ProQuest Dissertation and Theses Database, British Nursing Index, PEDro (www.pedro.fhs.usyd.edu.au), PsycBITE (www.psycbite.com), ISRCTN (www.isrcn.com), Trials Central (www.trialscentral.org), Stroke Trials Registry (www.strokecenter.org/trials), and Health Service Research Projects in Progress (wwwcf.nlm.nih.gov/hsr_project/home_proj.cfm). (For details of the searches performed in 2008, please see the previous review (McGeough et al., 2009))

In order to further identify the published, unpublished and ongoing trials, we checked the reference lists of the included trials, used the Web of Science Cited Reference Search for forward tracking of included trials, and contacted relevant researchers in the field of PSF. We searched for trials in all languages and arranged translation of relevant papers published in languages other than English.

5.4.2 Study selection

5.4.2.1 Selection process

I scrutinised all titles and abstracts retrieved from the electronic searches (published between February 2008 and May 2014) for relevance. Four other review authors (Ho-Yan Chun, HYC; Eileen Cowey, EC; Mansur Kutlubaev, MK; Gillian Mead, GM) scrutinised these titles and abstracts independently from me: HYC screened studies from MEDLINE, EMBASE, PsycINFO, AMED, CINAHL, CENTRAL, ProQuest Dissertations and Theses Database, PEDrom and British Nursing Index; EC screened studies from PsycBITE, ISRCTN, Stroke Trials Registry and Health

Service Research Projects in Progress; MK screened studies from Trials Central; and GM screened studies from the Cochrane Stroke Trial Register. We excluded obviously irrelevant citations and obtained full references for potentially relevant studies. I together with two other review authors (HYC and MK) each independently read all full texts and determined whether the study fulfilled the inclusion criteria. We resolved any discrepancies about whether or not a study fulfilled the inclusion criteria through discussion.

5.4.2.2 Inclusion criteria

Types of studies

We included randomised controlled trials (RCTs) in patients with a clinical diagnosis of stroke, where the interventions were used to treat or prevent PSF. This included three groups of trials:

- Trials primarily intended to treat PSF: the aim of the intervention was to treat fatigue (as stated by the trial investigators), which required patients to have fatigue at recruitment.
- Trials primarily intended to prevent PSF: the aim of the intervention was to prevent fatigue (as stated by the trial investigators) in stroke patients who did not have fatigue at recruitment.
- Trials not primarily intended to treat or prevent PSF but which reported fatigue as an outcome: the aim of the intervention was to improve health status or other symptoms after stroke, and fatigue was pre-specified as an outcome. These trials usually did not specify whether the patients had to have fatigue at recruitment or not.

We excluded trials that used fatigue as a measure to assess whether the intervention was tolerable in patients (i.e. whether the intervention had induced intolerable tiredness during treatment) rather than a measure to assess the therapeutic effect. For trials using a cross-over design, we only included data from the first phase, that is,

before crossing over the treatment. We included trials irrespective of their publication status and publication language.

Participants

We included adult patients (aged 18 years or over), both men and women, with a clinical diagnosis of stroke. We included all pathological subtypes of stroke, including ischaemic stroke, haemorrhagic stroke, and subarachnoid haemorrhage. We included any methods of diagnosis or assessment of PSF, but it was not necessary for patients to have fatigue at recruitment. For trials reporting mixed populations of patients (e.g. a group of patients with either stroke or brain injury), we included them only if more than 75% of the patients had had a stroke, or if separate data for the stroke patients were reported by or were later obtained from trial investigators.

Interventions

We included any pharmacological interventions and non-pharmacological interventions, in combination or alone. We included trials that attempted to evaluate the following comparisons:

- A comparison between an intervention and a control (where the control was either placebo, usual medical care, attention control, or wait-list).
- A comparison between two or more different interventions, with or without a control.
- A comparison between different doses or intensity of the same type of intervention, with or without a control.

Outcome measures

The primary outcome was fatigue at the end of treatment, measured as either the proportion of patients with fatigue or the mean severity of fatigue, or both. Examples of possible outcome measures included, but were not limited to: the Fatigue Severity Scale (FSS) (Krupp et al., 1989), the Visual Analogue Scale for fatigue severity, and

the energy/fatigue scale from the Medical Outcomes Study (i.e. the vitality subscale of the Short Form-36, SF-36).

If a trial had used a number of different tools to assess fatigue, we included the main outcome measure as specified by trial investigators. For instances where trial investigators had not specified the main one, we specified our main outcome measure in order of preference based on the following criteria:

a) A measure of fatigue specifically designed for stroke patients (e.g. the case definition of post-stroke fatigue);

b) A generic measure of fatigue that has been tested in stroke patients (e.g. the Fatigue Assessment Scale, FAS);

c) A generic measure for fatigue that has not been previously tested in stroke patients.

If the scales were in the same category according to the above criteria, we specified the main outcome measure from most commonly used scales (e.g. FSS) to less commonly used scales in the publications identified in this review.

Our pre-specified secondary outcomes included health-related quality of life (e.g. SF-36), disability (e.g. modified Rankin scale), dependence (e.g. Barthel Index score), death, and cost effectiveness.

5.4.3 Data extraction and analysis

The second review author (HYC) and I independently extracted data from the included trials and recorded the information on a data extraction form. Another review author (MK) extracted the data for one trial published in Russian. We collected information about the study setting, the methodological design (randomisation; allocation concealment; blinding of patients, researchers and outcome assessors; and intention-to-treat analysis), the numbers of patients at recruitment and at the end of the study, the characteristics of patients (age, sex, time since stroke onset, pathological subtypes, and severity of stroke), the treatment and

control interventions (type of intervention, dose/intensity, frequency and duration), the primary and secondary outcome measures (methods and time of assessment), the criteria and assessment methods of fatigue at baseline and follow-up, and the results of each assessment. We contacted trial investigators to request for additional information that we thought relevant but which had not been reported in the publication.

5.4.3.1 Assessment of risk of bias

Two review authors (HYC and I) independently documented the methodological quality of the included trials for the following quality criteria: allocation concealment, blinding of outcome assessors, and intention-to-treat analysis. This was done by another review author (MK) for the trial published in Russian. We used the Cochrane criteria and the 'Risk of bias' tool to assess the methodological quality (Higgins and Green, 2011).

5.4.3.2 Measures of treatment effect

I calculated standardised mean differences (SMDs) and relevant 95% confidence intervals (CIs) for continuous outcomes (i.e. fatigue scores) and risk ratios (RRs) and relevant 95% CI for dichotomous outcomes (i.e. presence or absence of fatigue). If there were fatigue scales where the score decreases as fatigue increases, I multiplied scores of these scales by -1. For trials reporting both dichotomous and continuous outcomes of fatigue, I collected data for both types of measures.

5.4.3.3 Assessment of heterogeneity

I assessed heterogeneity between trials and between pre-specified subgroups, using the statistic with Chi^2 distribution with k – 1 degrees of freedom (df; where k was the number of trials or number of subgroups) to determine the statistical significance of heterogeneity. I quantified heterogeneity using the I^2 statistic, which describes the proportion of total variance across trials that is attributed to heterogeneity.

5.4.3.4 Assessment of reporting bias

I had intended to explore publication bias using a funnel plot. However, this was not done because, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2011), "tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis". In the current review, there were only six trials in the meta-analysis.

5.4.3.5 Data synthesis

I performed separate analyses for trials primarily intended to treat PSF, for trials primarily intended to prevent PSF, and for trials not primarily targeting PSF but other symptoms after stroke, because the key characteristic of their patients (i.e. whether they had fatigue at recruitment) was different.

Trials primarily intended to treat post-stroke fatigue

I performed separate analyses for trials that compared the intervention(s) with a control (where placebo, usual medical care, attention control or wait-list was used as control) and for trials that compared different potentially active interventions without a control.

For trials with a control arm, I performed separate analyses for continuous outcomes and for dichotomous outcomes of fatigue. For either type of outcome, where data were suitable, I performed the meta-analysis using a random-effects model in Review Manager 5 (RevMan, 2014). If a trial assessed outcomes at multiple time points (e.g. immediately after treatment and at six-month follow-up), I performed separate analyses for outcomes assessed at each time points.

For trials without a control arm, I did not perform the meta-analysis because no two trials compared a same pair of interventions; instead, I calculated individual mean difference (MD) or RR for each trial, which would indicate the comparative efficacy of one intervention over the other. Here I used MD rather than SMD for continuous outcomes because SMD was used for the pooling of results from trials using different

scales for the same outcome, but for individual trials MD was preferable because it was more interpretable.

Trials primarily intended to prevent post-stroke fatigue

I had intended to perform the same analyses for this group of trials as I did for the trials primarily intended to treat PSF, but no trials were eligible for inclusion in this group.

Trials not primarily intended to treat or prevent post-stroke fatigue

I had intended to perform the same analyses for this group of trials as I did for the trials primarily intended to treat PSF. However, the data were too diverse across trials to be pooled, as they were different in all four aspects of the studied populations, treatment interventions, control interventions, and outcome measures (i.e. PICO). Therefore, I calculated the MD or RR for each trial and reported them individually.

Subgroup analysis

I had intended to perform the subgroup analysis for different types of interventions. However, trials in the meta-analysis each had tested a different intervention. Thus, I could only broadly categorise these interventions into 'pharmacological interventions' and 'non-pharmacological interventions' and performed a subgroup analysis to investigate whether one group of interventions was superior to the other. I did not perform other pre-specified subgroup analyses, i.e. for the source of patients, time since stroke, and amount of treatment. This was because these subgroups were pre-specified to investigate the contribution of these clinical characteristics to heterogeneity under the same type of intervention (e.g. antidepressants, CBT, or physical exercise), but trials included in the meta-analysis had each used a different intervention, thus, I could not perform further subgroup analyses under the individual type of interventions.

Sensitivity analysis

I explored methodological heterogeneity by sensitivity analyses for allocation concealment (with analysis limited to the trials with adequate allocation concealment), blinding of outcome assessors (with analysis limited to the trials with blinding of outcome assessors), and intention-to-treat analysis (with analysis limited to the trials with intention-to-treat analysis). I performed post-hoc sensitivity analyses a) by excluding one trial in which the baseline fatigue scores were not comparable between groups, and b) by excluding one comparison that was a visual outlier in the forest plot. For each sensitivity analysis, I compared the pooled effect size with the summary effect size of all included trials, using a Z-test (Borenstein et al., 2009).

Section 5.5 Results

5.5.1 Results of search

Figure 5.1 summarises the process for electronic searches and study selection in the previous and current reviews.

For the current review, we identified 6839 unique citations from electronic databases and 909 records from ongoing trials registers. We obtained full texts for 29 published studies and relevant information for nine ongoing trials. We included nine new trials (of which two were ongoing trials in the 2008 review) and nine new ongoing trials that met the inclusion criteria. Together with the three trials identified in the 2008 search (McGeough et al., 2009), we included 12 completed trials (Brown et al., 2013, Choi-Kwon et al., 2007, Clarke et al., 2012, Guo et al., 2012, Gurak and Parfenov, 2005, Johansson et al., 2012a, Johansson et al., 2012b, Karaiskos et al., 2012, Lorig et al., 2001, Ogden et al., 1998, Zedlitz et al., 2012, Zhou et al., 2010) and nine ongoing trials (Hackett, 2013, Chuang, 2013, Laska et al., 2014, Mead, 2012, Liu, 2012, MacKay-Lyons, 2012, Michael, 2008, Overgaard and Poulsen, 2012, Vanroy, 2010).

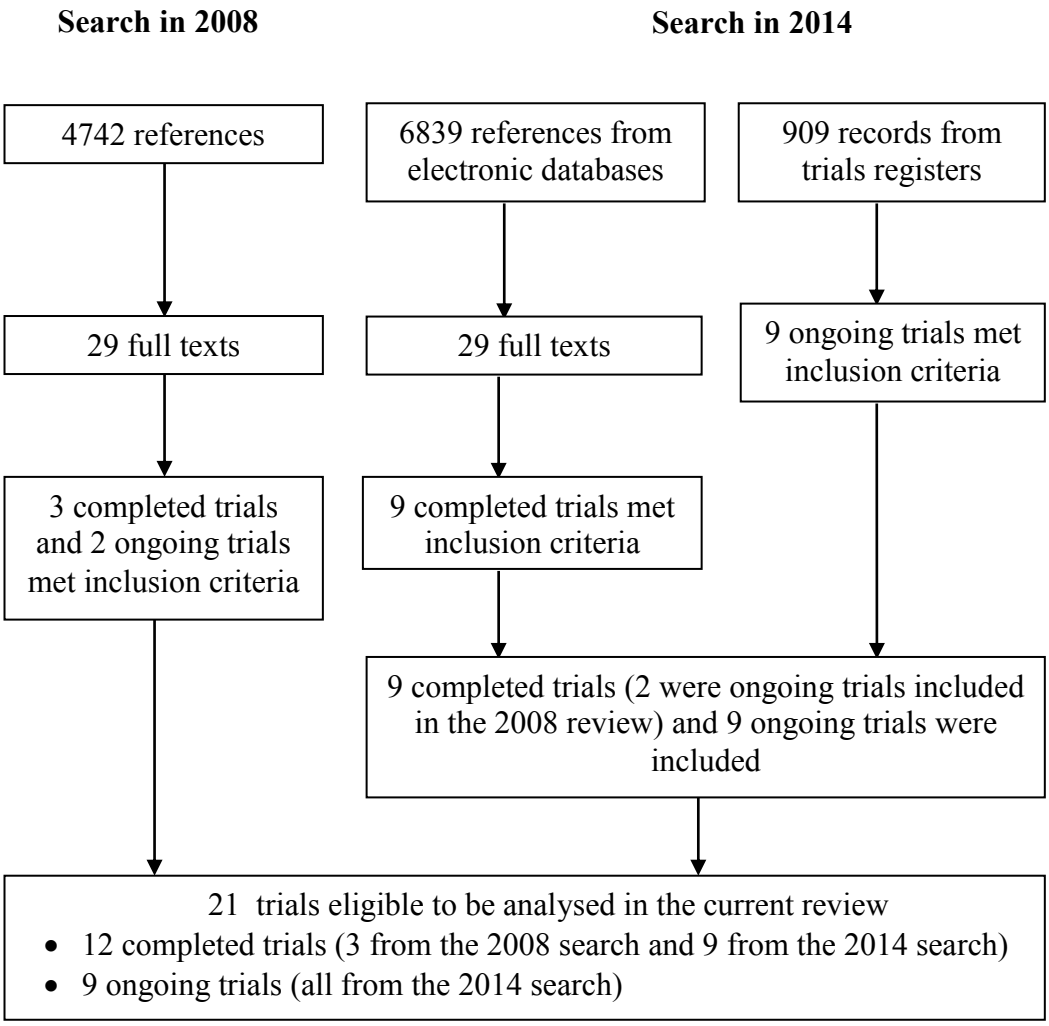

Figure 5.1 Flowchart of electronic search and study selection for a systematic review of interventions for post-stroke fatigue.

5.5.1.1 Included studies

Completed trials

Among the 12 included trials (703 patients), eight trials (455 patients) were primarily intended to treat PSF (Choi-Kwon et al., 2007, Clarke et al., 2012, Guo et al., 2012, Gurak and Parfenov, 2005, Johansson et al., 2012a, Johansson et al., 2012b, Zedlitz et al., 2012, Zhou et al., 2010), no trial was primarily intended to prevent fatigue after stroke, and the other four trials (248 patients) did not primarily target PSF but other symptoms after stroke, but reported fatigue as an outcome (Brown et al., 2013, Karaiskos et al., 2012, Lorig et al., 2001, Ogden et al., 1998).

Trials primarily intended to treat post-stroke fatigue

Characteristics of the study design of each individual trials is presented in Table 5.1 and summarised in the text below.

Participant characteristics: all eight trials (455 patients) recruited adult patients of both sexes with the male proportion ranging from 33% (Gurak and Parfenov, 2005) to 80% (Choi-Kwon et al., 2007) and the mean age ranging from 50 years (Johansson et al., 2012b) to 72 years (Clarke et al., 2012), except for one trial, which recruited mixed populations of patients with stroke (16 patients) or traumatic brain injury (10 patients) but did not separately report these demographics for the subgroup of stroke patients (Johansson et al., 2012a). Five trials recruited patients with ischaemic stroke and haemorrhagic stroke, and the other three trials recruited only patients with ischaemic stroke. Six trials recruited community-dwelling patients, one trial recruited inpatients, and one trial recruited both inpatients and outpatients. Three trials recruited patients who were at least three months after stroke onset, one trial more than four months after stroke, two trials more than one year after stroke, one trial within six months of stroke, and one trial with patients at a mean of six months and no more than three years after stroke.

Definition of post-stroke fatigue: different diagnostic criteria of fatigue were used at recruitment, which included the self-reported experience of fatigue by patients (Choi-

Kwon et al., 2007), a mean score of the FSS of 4 or more (Clarke et al., 2012), the Traditional Chinese Medicine (TCM) diagnostic criteria for Qi-deficiency (i.e. "fatigue" in Chinese culture) (Guo et al., 2012), a score of the Multidimensional Fatigue Inventory-20 (MFI-20, cut-off score not reported) (Gurak and Parfenov, 2005), a total score of the Mental Fatigue Scale (MFS) of 10 or more (Johansson et al., 2012a, Johansson et al., 2012b), a total score of the Checklist Individual Strength-fatigue subscale of 40 or more (Zedlitz et al., 2012), and a total score of the energy subscale of the Stroke Specific Quality of Life (SSQOL-energy) of 12 or less (Zhou et al., 2010).

Treatment and control interventions: four trials investigated pharmacological interventions and the other four trials investigated non-pharmacological interventions. Six trials used placebo, usual medical care, attention control or wait-list as the control and the other two studies compared different potentially active interventions.

Outcome assessment: all eight trials assessed fatigue outcomes immediately after the end of treatment: eight trials reported fatigue scores in each group (continuous outcomes of fatigue); two trials also reported the numbers/proportions of stroke patients with PSF (dichotomous outcomes of fatigue). In addition, four trials assessed the presence or severity of fatigue at a later follow-up point.

Table 5.1 Summary of trials primarily intended to treat post-stroke fatigue: participants, treatment and control interventions, and outcomes (PICO)

Studies	Participant characteristics	Numbers of participants	Treatment interventions	Control interventions	Outcomes at the end of treatment	Follow-up assessments
Pharmacological interventions						
Choi-Kwon 2007 (Choi-Kwon et al., 2007)	Community-dwelling patients; At least 3 months after ischaemic or haemorrhagic stroke	Recruitment: n=83 End of treatment: n=78 Completion of follow-up: n=78	Fluoxetine (a selective serotonin reuptake inhibitor, 20 mg, daily, 3 months)	Placebo (20 mg, daily, 3 months)	FSS scores; Proportion of participants with fatigue	FSS scores, at 3 months after end of treatment
Guo 2012 (Guo et al., 2012)	Inpatients; Within 6 months after ischaemic stroke	Recruitment: n=90 End of treatment: n=90	Group 1: oral Chinese herbs (100 mL, twice daily, 4 weeks) plus intravenous Chinese herbs (250 mL, daily, 14 days) Group 2: placebo oral Chinese herbs (100 mL, twice daily, 4 weeks) plus intravenous citicoline (500 mg/250 mL, daily, 14 days)	Placebo oral Chinese herbs (100 mL, twice daily, 4 weeks) plus intravenous saline (250 mL, daily, 14 days)	FSS scores	Not applicable
Gurak 2005 (Gurak and Parfenov, 2005)	Community-dwelling patients; At least 3 months after ischaemic stroke	Recruitment: n=30 End of treatment: n=30	Enerion (a synthetic derivative of vitamin B1, 200 mg, twice daily, 30 days) plus standard outpatient rehabilitation	Standard outpatient rehabilitation	Scores of the General Fatigue subscale of MFI-20	Not applicable
Johansson 2012a (Johansson et al., 2012b)	Community-dwelling patients; At least 12 months after ischaemic or haemorrhagic stroke	Recruitment: n=6 End of treatment: n=6	(-)-OSU6162 (a monoaminergic stabiliser, 15 to 45 mg, twice daily, 4 weeks)	Placebo (15 to 45 mg, twice daily, 4 weeks)	MFS scores	Not applicable

Table 5.1 Summary of trials primarily intended to treat post-stroke fatigue: participants, treatment and control interventions, and outcomes (PICO) *(continued)*

Non-pharmacological interventions						
Clarke 2012 (Clarke et al., 2012)	Community-dwelling patients; 3 to 18 months after ischaemic or haemorrhagic stroke; Having PSF (assessed by FSS)	Recruitment: n=19 End of treatment: n=16	Fatigue Group Education therapy (6 weekly group sessions, 60 minutes for each session)	General Group Education therapy (6 weekly group sessions, 60 minutes for each session)	FSS scores	FSS scores at 3 months after the end of treatment
Johansson 2012b (Johansson et al., 2012a)	Community-dwelling patients; At least 12 months after ischaemic or haemorrhagic stroke	Recruitment: n=unknown End of treatment: n=16	Mindfulness-based stress reduction therapy (8 weekly group sessions, 2.5 hours for each session plus 45 minutes home practice for 6 days a week)	Wait-list	MFS scores	Not applicable
Zedlitz 2012 (Zedlitz et al., 2012)	Community-dwelling patients; At least 4 months after ischaemic or haemorrhagic stroke;	Recruitment: n=83 End of treatment: n=73 Completion of follow-up: n=68	Group 1: cognitive behavioural therapy (12 weekly cognitive treatment sessions, 2 hours for each session) Group 2: cognitive behavioural therapy plus graded activity training (treadmill walking and strength training for 2 hours, twice a week, 12 weeks)	None	CIS-f and SOL-f scores	CIS-f and SOL-f scores at 6 months after the end of treatment
Zhou 2010 (Zhou et al., 2010)	Inpatients and outpatients; Within 3 years after ischaemic stroke	Recruitment: n=128 End of treatment: n=128 Completion of follow-up: n=128	Group 1: electro-acupuncture (30 minutes per day, 10 days as 1 cycle, for 3 cycles with 2-day intervals between cycles) plus cupping at back (10 minutes, once every 2 days, 5 weeks) Group 2: sertraline (50 mg, daily, 5 weeks) plus compound aminobutyric acid and vitamin E capsules (2 capsules, 3 times per day, 5 weeks) and magnesium gluconate solution (100 mg/10 mL, magnesium 58.6 mg, 3 times per day, 5 weeks)	None	SSQOL-energy scores; Proportion of participants with PSF	Proportion of participants with PSF at 2 months after the end of treatment

CIS-f: Checklist Individual Strength – fatigue subscale; FSS: Fatigue Severity Scale; MFI-20: Multidimensional Fatigue Inventory – 20; MFS: Mental Fatigue Scale; n: number of participants; PSF: post-stroke fatigue; RCT: randomised controlled trial; SOL-f: Self-observation List – fatigue subscale; SSQOL-energy: Energy subscale of Stroke-specific Quality of Life; TCM: Traditional Chinese Medicine.

Trials primarily intended to prevent post-stroke fatigue

We identified no trial primarily intended to prevent PSF.

Trials not primarily intended to treat or prevent post-stroke fatigue

Four trials (248 patients) did not primarily target PSF but primarily intended to investigate the efficacy of interventions on treating other symptoms after stroke. These trials reported fatigue as a secondary outcome.

Brown *et al*. (Brown et al., 2013) assessed the feasibility of a continuous positive airway pressure (CPAP) therapy for sleep apnoea in patients with ischaemic stroke. Thirty-two stroke patients who had a positive result on the test for sleep apnoea were randomised to either the active CPAP group or the sham CPAP group, where patients were given an active or sham device for the CPAP for home use, respectively. Nineteen patients completed the three-month treatment. The primary outcome was the self-reported usage of the device by patients. Fatigue was measured by the FSS as a secondary outcome at the end of the three-month treatment. I calculated the MD for post-treatment fatigue scores between the active and the sham CPAP groups.

Lorig *et al*. (Lorig et al., 2001) evaluated a Chronic Disease Self-management Programme (CDSMP) on health status, healthcare utilisation, and self-efficacy outcomes in patients with stroke, heart disease, lung disease, or arthritis. In total, 1140 community-dwelling patients were recruited, of which 125 had stroke. Of these 125 stroke patients, 67 were allocated to the treatment group and 58 to the wait-list control group. Patients in the treatment group were immediately offered a manual of programme content and received seven consecutive weekly sessions (peer-taught sessions, 2.5 hours for each session). Participants in the wait-list group were offered the manual and the intervention six months after randomisation. Primary outcomes were health behaviours, health status, and health service utilisation. Fatigue was measured using the energy/fatigue scale from the long-form Medical Outcomes Study as a secondary outcome. Outcomes were collected at baseline, six months, one year, and two years after randomisation. The trial investigators did not report results

separately for the different diseases, but they provided unpublished data for the subgroup of 125 stroke patients at six-month follow-up. However, the investigators did not provide data of post-treatment scores but only the changes of scores from baseline to after treatment. I calculated the MD for the changes of scores between the treatment group and the wait-list group.

Ogden *et al*. (Ogden et al., 1998) assessed the efficacy of tirilazad mesylate (a hypothesised neuroprotective agent) on recovery following subarachnoid haemorrhage. Thirty-one women were randomised to receive either tirilazad mesylate (150 mg/100 mL) or placebo (100 mL) for 10 consecutive days after the onset of subarachnoid haemorrhage. Eighteen women were interviewed three months later and were asked whether they had experienced fatigue that was much worse than prior to their subarachnoid haemorrhage. If patients answered 'yes' then the interviewer explored this with further questioning and patients were asked to provide specific examples. Patients' responses to questioning were analysed as a 'yes' or 'no' to debilitating fatigue based on the subjective opinion of the interviewer. I calculated the RR for the risk of patients having fatigue after treatment between the tirilazad group and the placebo group.

Karaiskos *et al*. (Karaiskos et al., 2012) investigated the efficacy of three antidepressants for treating depression in patients with ischaemic or haemorrhagic stroke. Sixty patients with a clinical diagnosis of depression after stroke were randomised to one of three groups for anti-depressive treatment (20 patients in each group): duloxetine (60 to 120 mg/day, for three months), citalopram (20 to 40 mg/day, for three months), or sertraline (50 to 200 mg/day, for three months). The primary aim of this trial was to investigate the effects of these antidepressants on depression and anxiety. Fatigue was measured using the FSS as a secondary outcome at one month, two months, and three months after the start of treatment. I calculated the MDs for the FSS at the end of three-month treatment between the duloxetine group and the citalopram group, between the duloxetine group and the sertraline group, and between the citalopram group and the sertraline group.

Ongoing trials

The two ongoing trials (Brown et al., 2013, Zedlitz et al., 2012) identified in the previous review (McGeough et al., 2009) were completed and published by the time of current search in 2014 and are discussed in the previous section for 'completed trials'. We identified a further nine ongoing trials in the current search.

Three trials are primarily intended to treat PSF. Chuang *et al*. (Chuang, 2013) (estimated enrolment: 160 patients) is investigating the efficacy of a combined therapy of functional electrical stimulation and graded treadmill training (one hour daily, three days per week for four weeks) versus conventional rehabilitation on fatigue and shoulder pain after stroke. The inclusion criteria require patients to be at least six months after stroke and have both hemiplegic shoulder pain and PSF within the past seven days before assessment. The primary outcome is a vertical numerical rating scale with a face rating scale for fatigue and pain at the end of treatment. Liu *et al*. (Liu, 2012) (90 patients) is investigating the efficacy of astragalus membranaceus (a Chinese herb, 2.8 g three time per day, treatment duration unknown) versus placebo (2.8 g three time per day, treatment duration unknown) on PSF. The inclusion criteria require patients to be at least three months after stroke and have fatigue based on a screening scale (methods unknown). The primary outcome is the Brief Fatigue Inventory at two years after treatment. Overgaard *et al*. (Overgaard and Poulsen, 2012) is investigating efficacy of modafinil (a wakefulness promoting agent, 400 mg once daily for three months) versus placebo (400 mg once daily for three months) on PSF. The inclusion criteria require patients to be within 14 days of stroke onset and have fatigue according to the MFI-20. The primary outcome is the total score of MFI-20 at the end of the three-month treatment period.

Three trials are investigating the efficacy of physical training on functional outcomes of stroke, where fatigue is measured as a secondary outcome. MacKay-Lyons *et al*. (MacKay-Lyons, 2012) (20 patients) is investigating the efficacy of aerobic exercise or cognitive training, or both, on cognition after stroke. Patients who are at least six months after stroke are randomised to one of the four arms for a six-week treatment: aerobic training group, cognitive training group, aerobic plus cognitive training

group, and control group. Fatigue is assessed using the FSS at ten-week follow-up. Michael *et al*. (Michael, 2008) (54 patients) is investigating the efficacy of adaptive physical activity (APA) on physical fitness and quality of life of stroke patients. Patients who are at least six months after stroke and with residual hemiparetic gait deficits are randomised to one of the three arms for a six-month treatment: APA group, APA plus progressive treadmill walking group, and home exercise group. Fatigue is assessed by psychosocial questionnaires as a secondary outcome at baseline, three months, six months, and nine months after the beginning of the treatment. Vanroy *et al*. (Vanroy, 2010) (50 patients) is investigating the efficacy of aerobic exercise on aerobic capacity and daily functioning in stroke patients. Patients who are within six weeks after stroke onset are randomised to either an aerobic exercise group or a passive mobilisation group for a 12-week treatment. Fatigue is assessed at baseline, after 12 weeks' treatment, six months, one year, and two years after baseline (assessment methods unknown). This trial has been completed but is not yet published.

Three parallel trials are investigating the efficacy of fluoxetine on recovery of stroke and assess fatigue as a secondary outcome: FOCUS trial (estimated enrolment: 3000 patients) (Mead, 2012), AFFINITY trial (1600 patients) (Hackett, 2013), and EFFECTS trial (1500 patients) (Laska et al., 2014). These three trials share the same core protocol, which are recruiting patients who are between two and 15 days after stroke onset and randomise them to either the fluoxetine group (20 mg daily, orally, for six months) or the placebo group (20 mg daily, orally, for six months). The primary outcome is the modified Rankin Scale at six months after recruitment. Fatigue is a secondary outcome assessed by the vitality subscale of SF-36 at six months and 12 months after recruitment.

5.5.1.2 Excluded studies

In the search in 2008, we excluded two trials because one had non fatigue-related outcomes (Allison and Dennett, 2007), and in the other fatigue was not a measure for therapeutic effect (Underwood et al., 2006). We identified nine trials but excluded them after full-text screening: three ongoing trials were specifically targeting PSF but

were excluded because they had only a single treatment group without a control arm (Feys and Maris, 2013, Kirkevold, 2012, Wu, 2014), of which the feasibility study described in this thesis was included in this group; two trials measured fatigue as to assess whether patients were too tired after using the intervention rather than to test the therapeutic effect on fatigue (Cruz, 2013, Lin, 2013); two trials did not use randomisation (Kim, 2012, Sianni, 2008); one trial compared patients with multiple sclerosis with patients with stroke but did not have a control group for stroke patients (Brioschi et al., 2009); and one trial recruited mixed populations of patients but did not report data for the subgroup of stroke patients and we could not obtain these data from trial investigators (Robinson et al., 2003).

5.5.2 Risk of bias in included studies

Figures 5.2 and 5.3 summarise the risk of bias of all included trials, irrespective of whether they were primarily intended to treat or prevent PSF. In the text below, I separately summarise the risk of bias of the eight trials primarily intended to treat PSF and that of the four trials not primarily intended to treat or prevent PSF.

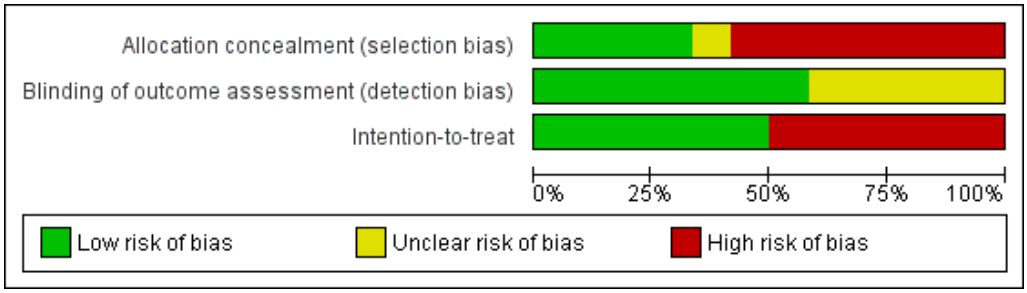

Figure 5.2 Review authors' judgements about each risk of bias item presented as percentages across all included studies.

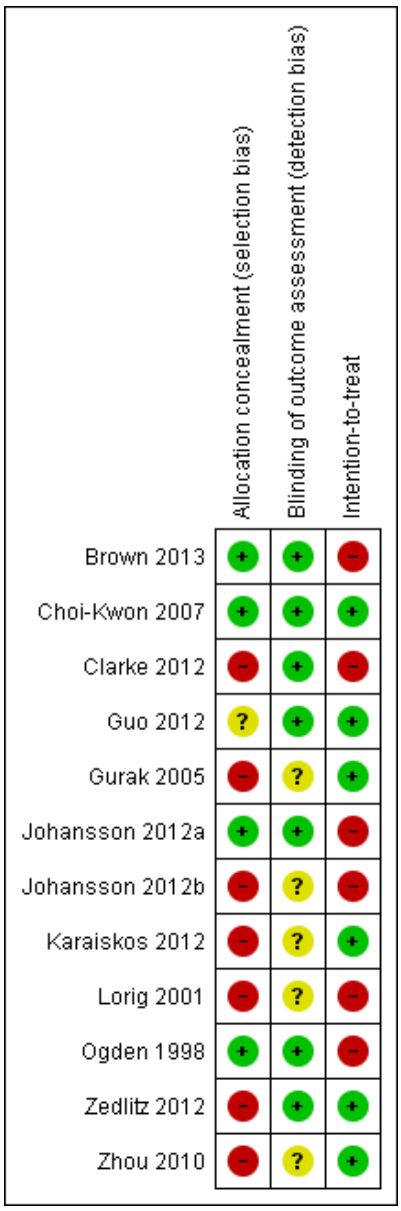

Figure 5.3 Review authors' judgements about each risk of bias item for each included study.

5.5.2.1 Selection bias (allocation concealment)

Of the eight trials primarily intended to treat PSF, two trials used the placebo with identical appearance of the tested drug and a 'double-blind' procedure and thus had a low risk of selection bias (Choi-Kwon et al., 2007, Johansson et al., 2012b), one trial reported the use of 'placebo' but did not report details of allocation concealment thus its risk of bias was unclear (Guo et al., 2012), and the other five trials had a high risk of bias because they did not use adequate allocation concealment (Clarke et al., 2012, Gurak and Parfenov, 2005, Johansson et al., 2012a, Zedlitz et al., 2012, Zhou et al., 2010).

Of the four trials not primarily intended to treat or prevent PSF, two trials had a low risk of selection bias (Brown et al., 2013, Ogden et al., 1998), and the other two trials had a high risk of selection bias (Karaiskos et al., 2012, Lorig et al., 2001).

5.5.2.2 Detection bias (blinding of outcome assessors)

Of the eight trials primarily intended to treat PSF, five trials used adequate strategies to blind the outcome assessors and thus had a low risk of detection bias (Choi-Kwon et al., 2007, Clarke et al., 2012, Guo et al., 2012, Johansson et al., 2012b, Zedlitz et al., 2012), and the other three trials did not report sufficient information to permit this judgement thus the risk was unclear (Gurak and Parfenov, 2005, Johansson et al., 2012a, Zhou et al., 2010).

Of the four trials not primarily intended to treat or prevent PSF, two trials had a low risk of detection bias (Brown et al., 2013, Ogden et al., 1998), and the risk in other two trials was unclear (Karaiskos et al., 2012, Lorig et al., 2001).

5.5.2.3 Attrition bias (Intention-to-treat analysis)

Of the eight trials primarily intended to treat PSF, two trials performed intention-to-treat analysis (low risk) (Choi-Kwon et al., 2007, Zedlitz et al., 2012), three trials had the same numbers of patients at the end of trials as that at randomisation (low risk) (Guo et al., 2012, Gurak and Parfenov, 2005, Zhou et al., 2010), and the other three

trials had drop-outs and used the available-case analysis (high risk) (Clarke et al., 2012, Johansson et al., 2012a, Johansson et al., 2012b).

Of the four trials not primarily intended to treat or prevent PSF, one trial had the same number of patients at the end of trial as that at randomisation (low risk) (Karaiskos et al., 2012), and the other three trials had drop-outs and used the available-case analysis (high risk) (Brown et al., 2013, Lorig et al., 2001, Ogden et al., 1998).

5.5.3 Effect of interventions

5.5.3.1 Trials primarily intended to treat post-stroke fatigue

Eight trials (455 patients) were primarily intended to treat PSF, of which six trials compared the interventions(s) with control (where the control was placebo, usual medical care, attention control or wait-list) (Choi-Kwon et al., 2007, Clarke et al., 2012, Guo et al., 2012, Gurak and Parfenov, 2005, Johansson et al., 2012a, Johansson et al., 2012b), and the other two trials compared different potentially active interventions without a control arm (Zedlitz et al., 2012, Zhou et al., 2010) (details of interventions see Table 5.1).

5.5.3.1.1 Trials with a control arm (interventions versus control)

Of the six trials (244 patients) that had a control arm (Choi-Kwon et al., 2007, Clarke et al., 2012, Guo et al., 2012, Gurak and Parfenov, 2005, Johansson et al., 2012a, Johansson et al., 2012b), one trial compared two potentially active interventions with a control (Guo et al., 2012). For this trial, I divided the number of patients in the control group to two equal-size groups so that there were two comparisons each with a treatment group and a control group. Thus, there were seven comparisons with 244 patients.

Continuous outcomes

Summary meta-analysis

All of these six trials (seven comparisons with 244 patients) reported continuous measures of fatigue after treatment. Fatigue severity was lower in the intervention group compared with the control group (pooled SMD = -1.07, 95% CI -1.93 to -0.21), with significant heterogeneity between trials (I^2 = 87%, df = 6, p < 0.0001 for heterogeneity; Figure 5.4).

Study ID	Number of participants	Treatment interventions	Standardised Mean Difference (95% confidence interval)	Forest plot
Outcomes at the end of treatment				
Guo 2012a	45	Citicoline	-0.21 (-0.83, 0.41)	
Johansson 2012a	6	(-)-OSU6162	-0.27 (-1.99, 1.44)	
Choi-Kwon 2007	83	Fluoxetine	-0.38 (-0.82, 0.05)	
Gurak 2005	30	Enerion	-1.07 (-1.85, -0.30)	
Guo 2012b	45	Chinese herbs	-4.35 (-5.48, -3.22)	
Subtotal	**209**	**Pharmacological interventions**	**-1.23 (-2.40, -0.06)**	
	Heterogeneity: $Chi^2 = 45.84$, df = 4 ($p < 0.00001$); $I^2 = 91\%$			
Clarke 2012	19	Fatigue Group Education	-0.43 (-1.35, 0.50)	
Johansson 2012b	83	Mindfulness-based Stress Reduction	-1.01 (-2.08, 0.06)	
Subtotal	**35**	**Non-pharmacological interventions**	**-0.68 (-1.37, 0.02)**	
	Heterogeneity: $Chi^2 = 0.66$, df = 1 ($p = 0.42$); $I^2 = 0\%$			
Total	**244**	**All interventions**	**-1.07 (-1.93, -0.21)**	
	Heterogeneity: $Chi^2 = 46.52$, df = 6 ($p < 0.0001$); $I^2 = 87\%$			
	Test for subgroup differences: $Chi^2 = 0.64$, df = 1 ($p = 0.42$); $I^2 = 0\%$			
Outcomes at three months after the end of treatment				
Clarke 2012	19	Fatigue Group Education	-0.10 (-1.09, 0.89)	
Choi-Kwon 2007	83	Fluoxetine	-0.37 (-0.81, 0.06)	

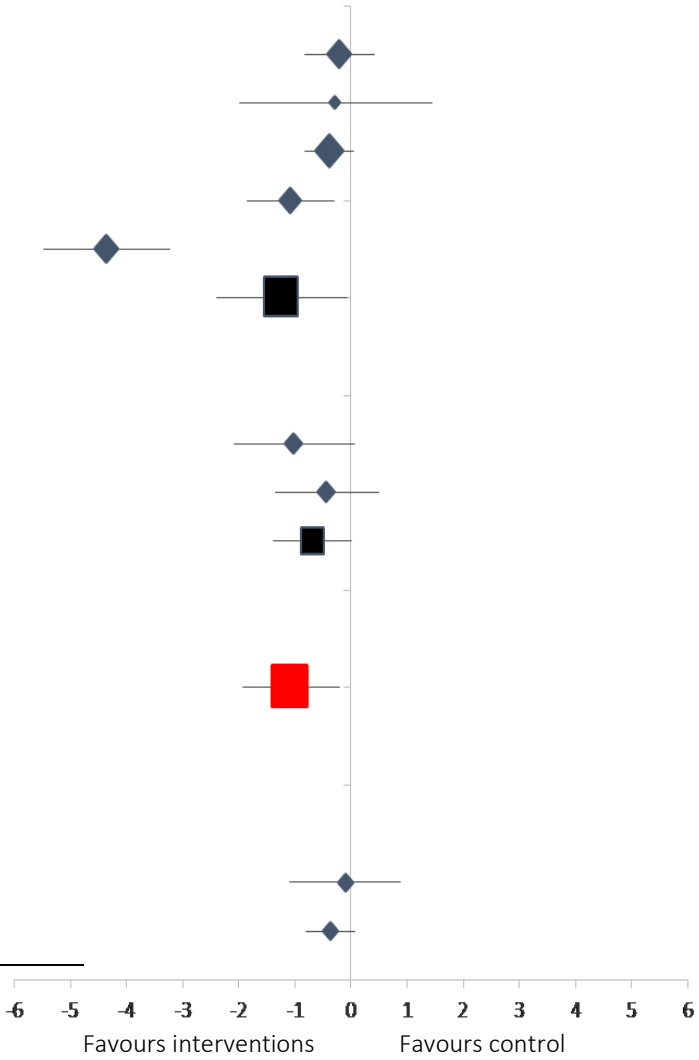

Figure 5.4 Forest plot for continuous outcomes of trials primarily intended to treat fatigue.

Subgroup analysis

There was no significant heterogeneity between the subgroup of pharmacological interventions and the subgroup of non-pharmacological interventions (Figure 5.4). Pharmacological interventions showed a marginally significant effect on reducing PSF (five comparisons, 209 patients), whilst non-pharmacological interventions showed no statistically significant effect (two comparisons, 35 patients) (Figure 5.4).

Sensitivity analysis

Two trials (two comparisons, 89 patients) reported adequate strategies for allocation concealment (Choi-Kwon et al., 2007, Johansson et al., 2012b), of which interventions showed no significant effect on PSF (pooled SMD = -0.38, 95% CI -0.80 to 0.04; with no significant heterogeneity: $I^2 = 0\%$, df = 1, $p = 0.90$).

Four trials (five comparisons, 198 patients) reported the use of adequate strategies for blinding the outcome assessors (Choi-Kwon et al., 2007, Clarke et al., 2012, Guo et al., 2012, Johansson et al., 2012b), of which interventions showed no significant effect on PSF (pooled SMD = -1.10, 95% CI -2.31 to 0.11; with significant heterogeneity: $I^2 = 91\%$, df = 4, $p < 0.00001$).

Three trials (four comparisons, 203 patients) used intention-to-treat analysis or had no patient lost to follow-up (Choi-Kwon et al., 2007, Guo et al., 2012, Gurak and Parfenov, 2005), of which interventions showed a beneficial effect over the control (pooled SMD = -1.41, 95% CI -2.73 to -0.09; with significant heterogeneity: $I^2 = 93\%$, df = 3, $p < 0.00001$). This pooled SMD was not significantly different ($p = 0.67$) from the summary SMD of all seven comparisons (pooled SMD = -1.07, 95% CI -1.93 to -0.21).

Fatigue scores at baseline in one trial were significantly higher in the control group than the treatment group (Choi-Kwon et al., 2007), so I performed a post-hoc sensitivity analysis by excluding this trial. The pooled SMD of the remaining five trials (six comparisons, 161 patients) was -1.22 (95% CI -2.34 to -0.09; with significant heterogeneity: $I^2 = 88\%$, df = 5, $p < 0.00001$), which was not significantly

different (p = 0.84) from the summary SMD of all seven comparisons (pooled SMD = -1.07, 95% CI -1.93 to -0.21).

One included comparison (Guo et al., 2012), a combination of oral and intravenous Chinese herbs versus placebo Chinese herbs (SMD = -4.35, 95% CI -5.48 to -3.22), appeared as an outlier in the forest plot (Figure 5.4). After excluding this comparison (45 patients), the pooled SMD of the remaining six comparisons (199 patients) was -0.49 (95% CI -0.78 to -0.20; with no significant heterogeneity: I^2 = 0%, df = 5, p = 0.52), which was not significantly different (p = 0.21) from the summary SMD of all seven comparisons (pooled SMD = -1.07, 95% CI -1.93 to -0.21).

Outcomes at three-month follow-up

Two trials that assessed fatigue at three months after the end of treatment. I calculated the SMDs for each trial, which indicate that neither intervention had a significant effect on fatigue at three-month follow-up (Figure 5.4).

Dichotomous outcomes

Of the six trials (seven comparisons) that compared the intervention with the control, only one trial (83 patients) reported the number/proportion of patients with PSF after treatment (dichotomous outcomes of fatigue) (Choi-Kwon et al., 2007). There was no significant difference in proportions of patients with PSF between the fluoxetine group and the placebo group at baseline (100% versus 100%), at the end of treatment (82% versus 93%, RR = 0.89, 95% CI 0.75 to 1.05), or at three months after the end of treatment (85% versus 93%, RR = 0.91, 95% CI 0.78 to 1.07).

5.5.3.1.2 Trials without a control arm (comparison between different interventions)

Two trials compared different potentially active interventions without a control arm. Because these two pairs of comparisons were different (also because they reported different types of outcomes), we did not perform a meta-analysis, but calculated individual MD or RR for each trial.

Zedlitz *et al*. (Zedlitz et al., 2012) (83 patients) reported the continuous outcomes of fatigue after treatment. Fatigue scores were not significantly different between the Cognitive and Graded Activity Training (COGRAT) group and the cognitive therapy group either at the end of treatment (for CIS-f: MD = 0.80, 95% CI -3.63 to 5.23; for SOL-f: MD = -0.30, 95% CI -1.35 to 0.75) or at six months after the end of treatment (for CIS-f: MD = -2.00, 95% CI -6.74 to 2.74; for SOL-f: MD = -0.50, 95% CI -1.64 to 0.64).

Zhou *et al*. (Zhou et al., 2010) (128 patients) reported both continuous outcomes and dichotomous outcomes of fatigue after treatment. Trial investigators reported that scores of SSQOL-energy after treatment were significantly higher (indicating better outcome) in the electro-acupuncture plus cupping (a traditional Chinese therapy in which heated glass cups are applied to the skin along the back of the body) group than the medication group ($p < 0.05$). These scores were presented graphically but raw data were not reported and we could not obtain these data from trial investigators, thus I did not calculate an MD for this trial. Twenty-two patients in the electro-acupuncture plus cupping group and 41 patients in the medication group had PSF at the end of treatment (34% versus 64%, RR = 0.54, 95% CI 0.37 to 0.79), and 30 patients in the electro-acupuncture plus cupping group and 52 patients in the medication group had PSF at two months after the end of treatment (47% versus 81%, RR = 0.58, 95% CI 0.43 to 0.77).

5.5.3.1.3 Secondary outcomes

Three trials assessed health-related quality of life (Clarke et al., 2012, Guo et al., 2012, Zedlitz et al., 2012), and one trial assessed disability and dependence (Clarke et al., 2012). No trial reported death or cost-effectiveness. Here I present the results of these outcomes as reported by the trial investigators.

Clarke *et al*. (Clarke et al., 2012) reported a significant improvement in the social functioning subscale of the SF-36 for both groups ($p = 0.03$) but there was no difference between groups ($p = 0.20$). There was no significant change from baseline to post-treatment assessment in other subscales of the SF-36, the Barthel Index, or

the modified Rankin Scale, and none of the changes were significantly different between groups.

Guo *et al*. (Guo et al., 2012) reported that the total score of the SSQOL after treatment was significantly higher in the TCM (a combination of Chinese herbs) group than that in the citicoline group ($p < 0.01$) and the placebo group ($p < 0.01$).

Zedlitz *et al*. (Zedlitz et al., 2012) reported a significant reduction of scores of the Stroke-adapted Sickness Impact Profile – 30 from baseline to post-treatment assessment ($p = 0.002$), but this change was not significant between groups ($p > 0.1$).

5.5.3.2 Trials primarily intended to prevent post-stroke fatigue

We identified no trial that was primarily intended to prevent PSF.

5.5.3.3 Trials not primarily intended to treat or prevent post-stroke fatigue

We identified four trials that were not primarily intended to treat or prevent PSF. Three trials reported continuous outcomes and one reported dichotomous outcomes of fatigue after treatment. I did not pool results from these trials because they had substantial differences in the studied populations, treatment and control interventions, and outcome measures. Instead, I calculated effect sizes for each of these trials and present the individual results in Table 5.2. In summary, none of these interventions showed any benefit on reducing fatigue in stroke patients.

Table 5.2 Summary of trials not primarily targeting post-stroke fatigue: participants, treatment and control interventions, and outcomes (PICO)

Studies	Participants	Interventions	Measures of fatigue and results (reported by trial investigators)	Effect size on fatigue (calculated by review authors[1])	Comments
Continuous outcomes					
Brown 2013	Recruitment: n=32 Completion of treatment: n=19	Treatment: active CPAP Control: sham CPAP Duration: 3 months	Scores of FSS at the end of treatment Active CPAP: mean score 3.11, SD 1.30 Sham CPAP: mean score 2.66, SD 1.69	MD 0.45, 95% CI -0.59 to 1.49	Trial investigators only provided data for the 19 participants who completed the trial. They found no between-group difference of scores of either sleep apnoea (Epworth Sleepiness Scale) or fatigue after treatment
Lorig 2001	Recruitment: m=125 Completion of treatment: n=104	Treatment: CDSMP Control: wait-list Duration: 7 weeks	Changes of scores of energy/fatigue scale from the long form Medical Outcomes Study CDSMP: mean decrease of energy score 0.087, SD 0.988 Wait-list: mean decrease of energy score 0.246, SD 0.600	MD -0.16, 95% -0.44 to 0.12	Higher energy score indicates lower fatigue severity; decrease of energy score indicates increase of fatigue severity; the greater decrease of energy score indicates the greater increase of fatigue severity
Karaiskos 2012	Recruitment: n=60 Completion of treatment: n=60	Group 1: duloxetine Group 2: citalopram Group 3: sertraline No control Duration: 3 months	Scores of FSS at the end of treatment Duloxetine: mean score 3.7, SD 1.1 Citalopram: mean score 3.9, SD 1.3 Sertraline: mean score 4.0, SD 1.4	Duloxetine versus citalopram: MD -0.20, 95% CI -0.95 to 0.55 Duloxetine versus sertraline: MD -0.30, 95% CI -1.08 to 0.48 Citalopram versus sertraline: MD -0.10, 95% CI -0.94 to 0.74	Trial investigators found significant improvement of depression and anxiety after treatment in each of the three groups, but no significant change of fatigue scores during the treatment in any group
Dichotomous outcomes					
Ogden 1998	Recruitment: n=31 Completion of treatment: n=18	Treatment: tirilazad mesylate Control: placebo Duration: 3 months	Self-report of debilitating fatigue by participants Tirilazad: 4 participants Control: 9 participants	RR 0.42, 95% CI 0.16 to 1.07	Trial investigators only provided data for the 18 participants who completed the trial. They found no between-group difference in either Glasgow Outcome Scale scores or cognitive impairment, but concentration, sustained attention, psychomotor speed, and debilitating fatigue were worse in placebo group

CDSMP: Chronic Disease Self-management Programme; CI: confidence interval; CPAP: continuous positive airway pressure; MD: mean difference; RR: risk ratio; SD: standard deviation. [1] I calculated the effect size using the intention-to-treat analysis: based on the number of participants and their grouping at recruitment.

Section 5.6 Discussion

5.6.1 Summary of main results

We included 12 completed trials (703 patients) and identified nine ongoing trials meeting our inclusion criteria. Of the 12 completed trials, eight trials were primarily intended to treat PSF, none was primarily intended to prevent PSF, and the other four trials did not primarily target PSF but reported fatigue as an outcome.

Of the eight trials primarily intended to treat PSF, four trials investigated pharmacological interventions and the other four investigated non-pharmacological interventions. The wide range of different interventions identified in the current review reflect the uncertainty and complexity of the aetiologies and mechanisms of PSF. Meta-analysis indicated that the overall effect of these interventions on treating PSF was statistically significant. However, the identified trials were small and heterogeneous, and the benefit was not seen in trials with low risks of methodological bias. Of the four trials not primarily intended to treat or prevent PSF, none showed an effect on reducing fatigue in stroke patients. In summary, there are insufficient data to draw any firm conclusions about whether or not these interventions were effective, either to treat or prevent PSF.

Antidepressants and other psychostimulants

Our previous systematic review found that PSF was associated with depressive symptoms and this association existed even in stroke patients who did not meet criteria for depression (Wu et al., 2014b). In addition, a small study found that PSF was associated with serotonin synthesis (Ormstad et al., 2014). Thus, it is plausible that treatment for depression may reduce PSF. Potential efficacy of psychostimulants in the management of PSF was shown in non-randomised trials (Brioschi et al., 2009). However, RCTs identified in the current review found no beneficial effects of any antidepressants (Choi-Kwon et al., 2007, Karaiskos et al., 2012), or other psychostimulants (Johansson et al., 2012b), on PSF. It is important to note that these trials were small, thus may lack of power to detect the effect. A number of larger

trials are ongoing, which may provide further evidence on the efficacy of psychostimulants on PSF (Hackett, 2013, Laska et al., 2014, Mead, 2012, Overgaard and Poulsen, 2012).

Psychological interventions

Although PSF is associated with depressive symptoms and neuroendocrine changes, RCTs to date provided no evidence on the efficacy of psychostimulants. One possible explanation is that PSF is a complex phenomenon influenced by a mixture of biological, physical, psychological, and behavioural factors and there are interactions between these factors (Wu et al., 2015b). Psychological interventions (e.g. CBT) targeting patients' perceptions and behaviours are effective in treating fatigue in conditions other than stroke, such as cancer (Armes et al., 2007) and chronic fatigue syndrome (White et al., 2011). Furthermore, the psychological profile of patients with PSF is comparable to that of patients with other chronic conditions (Zedlitz et al., 2011). Therefore, psychological interventions effective for fatigue in other conditions are promising interventions to treat fatigue in stroke patients. However, the existing studies, including the feasibility study described in this thesis (Wu, 2014), have only informed the feasibility of psychological interventions for PSF in stroke patients, but their efficacy on PSF is unknown due to the limitations of study design in these trials (Clarke et al., 2012, Johansson et al., 2012a, Lorig et al., 2001, Zedlitz et al., 2012). The current psychological intervention described in this thesis was excluded in this Cochrane review, because it was still at an early development stage, where a single-arm feasibility study could not provide information of its efficacy on PSF. Future studies are expected to investigate the efficacy of psychological interventions specially designed for PSF in RCTs with adequate sample sizes and controlled with usual medical care.

Physical training

Small studies found that PSF was associated with reduced physical fitness (Lewis et al., 2011) and lower levels of physical activity (Duncan et al., 2015). Furthermore, one study found that PSF was related to the reduced excitability of the motor cortex

(Kuppuswamy et al., 2015). Physical training after stroke may improve physical fitness and stimulate cortical excitability, which may help to reduce fatigue. In the current review, we identified one trial that reported that CBT plus graded activity training was more effective in reducing PSF than CBT alone (Zedlitz et al., 2012). However, from this trial we do not know whether the reduction of fatigue was a result of the physical training alone or a combination effect of physical training and CBT. This question may be answered by some ongoing trials that compare physical training, cognitive training, or both, with a sham or usual medical care control (Chuang, 2013, MacKay-Lyons, 2012, Michael, 2008, Vanroy, 2010), which have fatigue as an outcome.

Other interventions

Traditional Chinese therapies (including medicine and physical therapy) showed promising effects on PSF, but the components of each therapy were complicated and the study quality was poor (Guo et al., 2012, Zhou et al., 2010). Some other interventions showed efficacy on PSF in single small trials, for example enerion (a synthetic derivative of vitamin B1) (Gurak and Parfenov, 2005) and tirilazad mesylate (a hypothesised neuroprotective agent) (Ogden et al., 1998). These were small trials and the efficacy of these drugs should be investigated in future RCTs with an adequate sample size and a robust study design. The CPAP, with was designed for sleep apnoea after stroke, was of no benefit on reducing either fatigue or sleep apnoea (Brown et al., 2013). This trial was very small and had significant drop-outs. In addition, we do not know if other interventions, if effective for sleep disorders, are helpful to reduce PSF.

5.6.2 Quality of the evidence

There was considerable heterogeneity in the study design of the included trials. Firstly, the heterogeneity might be attributed to the different interventions used in different trials. Although we stratified heterogeneity by grouping trials into pharmacological interventions and non-pharmacological interventions, significant heterogeneity remained within the subgroup of pharmacological interventions, where

no two trials used a same type of drug. This means each type of intervention has only been evaluated in one trial, which limits the generalisability of the findings. Secondly, heterogeneity might also be attributed to the differences in patient characteristics, with many different criteria used for diagnosis of fatigue and also the time window from stroke onset to randomisation ranging from within first few months to several years after stroke. Given different factors may contribute to fatigue at different stages of its natural history (Wu et al., 2015b), the efficacy of a specific intervention may be different for patients with different characteristics.

Another important aspect of study design is the sample size required to detect a clinically significant therapeutic effect. Of the 12 included trials, only six trials (50%) had a sample size of over 50 patients, and the largest sample was 128 patients. The other six trials each had no more than 30 patients who completed the trial and were primarily aimed to test the feasibility of the interventions rather than to investigate efficacy. In addition, none of these 12 trials reported how the sample size was determined. The small sample size might have limited the power to detect the clinically significant effect.

In summary, the included trials were small and heterogeneous, and some of them had a high risk of bias. It is difficult to interpret the significance of outcomes when there is inadequate concealment of allocation, non-blind assessment, or significant drop-outs in several of the included trials. Although the interventions showed an overall significant effect on treating PSF, the sensitivity analyses indicated that, in trials with a low risk of bias, this effect was no longer significant. In summary, there was no robust evidence to inform the prevention or treatment of PSF. The efficacy of interventions should be investigated in future RCTs with a more robust design.

5.6.3 Potential bias in the review process

The inclusion criteria of this review were deliberately broad with an aim to inform future research. We sought to include trials that fatigue was a secondary as well as a primary outcome and the patients in the included trials did not necessarily have fatigue at baseline to be eligible for inclusion, because identifying strategies to

prevent (as well as treat) fatigue is important. However, the identification of all relevant trials might have been confounded by a number of factors. We did not search any non-English databases, thus we only had access to trials that published their abstracts in English. In addition, for trials measuring fatigue as a secondary outcome, trial investigators might not have reported the results of fatigue in the abstract or coded it as a keyword identifiable for electronic searches. Furthermore, some trials had used scales that part of the scale is the valid tool for assessing PSF (e.g. SF-36 vitality subscale); for these trials, if fatigue was not a specific target of the intervention, 'fatigue' or its synonyms might not appear in the report, thus we could not identify such trials. To minimise the risk of missing relevant studies, we used extensive search strategies and contacted experts in the field for relevant studies. We would appreciate if other researchers who have noticed any relevant studies missing from this review could inform us, so that we can update our review.

5.6.4 Agreement and disagreement with other studies or reviews

As far as we know, there are no other systematic review of interventions for PSF. Our review identified a mixture of pharmacological and non-pharmacological interventions. Non-pharmacological interventions identified in our review were similar to those identified in a Cochrane Overview of reviews of interventions for fatigue in adults with advanced progressive illness (e.g. cancer, motor neuron diseases, and chronic pulmonary diseases), which include aerobic exercise, physical training, education programmes, and psychological interventions (Payne et al., 2012). However, in the Cochrane Overview, the pharmacological interventions (e.g. amantadine and carnitine) were different from the pharmacological interventions identified in our review (e.g. antidepressants and neuroendocrine regulators). A possible explanation is that the choice of drugs might be relevant or specific to fundamental diseases. Furthermore, we found that psychological interventions or physical training, or both, for fatigue were feasible in stroke patients, although their efficacy on PSF should be further investigated. This is consistent with a systematic review of interventions for chronic fatigue syndrome, where the review authors

concluded that CBT and graded exercise therapy were promising treatment strategies for fatigue (Whiting et al., 2001).

Section 5.7 Conclusions

There was insufficient evidence on the efficacy of any intervention for the treatment or prevention of PSF. The identified interventions included antidepressants and psychostimulants, psychological interventions, physical training, traditional Chinese herbs, and vitamin B supplementation. Although some interventions showed a significant benefit for PSF, they had been tested in small trials which had some methodological limitations. Therefore, larger randomised trials are needed to confirm whether these interventions are really effective. Other interventions showed no evidence of efficacy, but this does not mean that these interventions are useless. This is because all the trials were very small and heterogeneous, and some have had a high risk of bias. Given the high prevalence and distressing consequences of fatigue following stroke, more research is urgently needed to identify effective interventions for PSF.

CHAPTER VI: Thesis Discussion

Section 6.1 Summary of my thesis

The purpose of this thesis was to develop a psychological intervention for the treatment of PSF. This section is a summary of the work that I have done for the intervention development, which was based on the theoretical phase, modelling phase and part of the piloting phase of the MRC framework for developing and evaluating complex interventions (Craig et al., 2008a). In the following sections, I will discuss the clinical implications of the current work and directions for future research.

The first stage of this thesis was to identify the evidence to justify the choice of a psychological intervention for PSF and to determine its therapeutic components (Chapter 2). I systematically reviewed the literature on natural history of PSF, which suggested that fatigue is common at an early stage after stroke and often persist to the chronic stage. This justified the need for interventions for PSF. In addition, longitudinal studies indicated that PSF is often a persistent problem but if it does resolve naturally, this tends to occur in the first few months after stroke. These findings imply that the chronic stage (e.g. three months after stroke onset) is the best timing for implementing interventions for PSF, as at this stage we will be able to distinguish persistent fatigue from a transitory phenomenon. The mechanisms of PSF are elusive and our understanding is mainly based on cross-sectional associations rather than causal relationships. To identify potential targets for treatment, I conducted a systematic review to investigate clinical factors associated with PSF. Drawing on the literature, I proposed a conceptual model for understanding PSF. This model illustrates a temporal process of the development of ongoing fatigue, which involves a mixture of biological, psychological, behavioural and environmental factors that predispose, trigger, or perpetuate fatigue at different stages in relation to stroke onset. There is limited evidence regarding the predisposing factors and triggers of PSF, whilst co-existing psychological and behavioural factors are commonly reported in observational studies of PSF. Some of

these factors have bidirectional associations with PSF and are usually modifiable, which include depressive symptoms, anxiety, lower self-efficacy, and reduced physical activity. Interventions targeting these associations may help to reduce PSF. Other comorbidities (e.g. sleeping problems and pain) and some medications (e.g. antidepressants and anti-hypertensive drugs), which are commonly used in stroke patients, may also cause fatigue, thus should be considered in patients with PSF.

The second stage was to develop treatment rationale of the intervention (Chapter 3). As there was insufficient evidence to recommend any treatment for PSF, I learnt from interventions for fatigue in conditions other than stroke. The psychological and behavioural factors that I identified as being associated with PSF can be addressed by CBT, a type of psychological interventions. Individual-based CBT is effective in treating cancer-related fatigue and chronic fatigue syndrome (which share some psychosocial characteristics with PSF). The premise of CBT is that changing unhelpful thoughts and behaviours would affect how people feel physically and emotionally. In the situation of PSF, a hypothesis is that fatigue is perpetuated by a vicious cycle of fatigue, physical deconditioning and reduced physical activity, and this cycle may be reinforced by distressed mood and low self-efficacy. The cognitive approach of CBT to improve patients' self-efficacy for taking physical activity and the behavioural approach to directly promote physical activity may break this vicious cycle and thus improve fatigue (symptoms) and mood (emotional feelings). As a complex intervention, this intervention also included strategies to improve sleep and to identify other possible causes of fatigue (e.g. pain and some medications).

The next stage was to develop the intervention programme (Chapter 3). By adapting from a nurse-delivered intervention programme for cancer-related fatigue and a self-management programme for chronic fatigue syndrome, I developed the intervention in collaboration with stroke clinicians, clinical psychologists, and a psychotherapist, all of whom had both clinical and research experience with stroke patients. The psychotherapist had expertise in managing chronic fatigue in conditions other than stroke. I also incorporated input from service users (i.e. stroke patients and their caregivers) by focus groups and individual consultations. The current intervention

consisted of six face-to-face treatment sessions at two-week intervals over a period of 12 weeks, followed by a telephone-delivered review session one month later. The key aim of the intervention was to encourage participants to gradually increase their physical activity, by strategies such as planning and recording daily activities and challenging their negative thoughts. Also for participants with sleeping problems, the intervention provided information of sleep hygiene and a sleep diary to facilitate reconstruction of sleep patterns.

The fourth stage was to model the intervention process and to pilot the trial procedures (Chapter 4). I used a multi-stage process to determine the eligibility of participants, which included screening their clinical records, contacting their GPs, survey questionnaires for fatigue and depression, and telephone conversations and face-to-face meetings with potential participants. I recruited 12 participants over a period of four months from a single NHS site (i.e. in the NHS Lothian, from a Stroke Unit, an outpatient Stroke Clinic, and the community stroke service). The intervention was delivered by a clinical psychologist (i.e. the therapist) who had expertise in delivering CBT and more than ten years' experience of working with stroke patients. The recruitment was feasible in the local health system in the Lothian area, Scotland. Participants were satisfied with the format and contents of the intervention and reported that it was helpful in improving their fatigue. In response to the feedback from the participants and the therapist, I refined the intervention programme by combining sessions 5 and 6 into a single session and simplifying some contents of the Participant Manual for future studies. Also I would suggest that, in future trials for this intervention, it is better to deliver the review session in person rather than by telephone and have a longer follow-up period than the current three months. The final version of the Participant Manual (version 3.4, Appendix 9) and the Therapist Manual (version 3.2, Appendix 10) are provided in the Appendices of this thesis for future use.

A Cochrane review of interventions for PSF, published in 2009, concluded that there was insufficient evidence to inform the treatment of PSF. Based on this review and the knowledge that psychological interventions are effective in reducing fatigue in

conditions other than stroke, I developed the current psychological intervention for PSF. Whilst reviewing the literature on PSF and conducting the feasibility study of this intervention, I became aware that several new interventions had been tested for PSF since 2009. So I updated this Cochrane review (Chapter 5), in the hope of providing some new evidence on the management of PSF that could be included in future studies. I identified 12 trials, of which each tested a different intervention for PSF. These included antidepressants and other psychostimulants, psychological interventions, physical training, traditional Chinese medicine, and vitamin supplementation. There was insufficient evidence to recommend the use of any specific intervention for the management of PSF. However, this does not mean that the identified interventions are ineffective. The frequent lack of significant effects that I observed in the existing studies could arise from the small sample sizes, the limitations in study design, and the diversity of interventions. More research is needed to address the methodological issues and provide further evidence for the management of PSF. The diversity of existing interventions reflects the multidimensional nature of PSF, which involves interactions of various biological, psychological, behavioural and environmental factors. The current psychological intervention was excluded from this review because of its single-arm design, but it is one of the promising interventions for PSF worth being investigated in future studies.

In summary, this thesis has presented a phased and evidence-based process of developing a psychological intervention for PSF. The intervention was developed based on the current theories about the mechanisms of PSF and was refined by iterative input from stroke clinicians, psychological therapists, and stroke patients. After the intervention was approved by the ethics committee, it was tested in a small group of stroke patients and further refined by incorporating feedback from the participants and the therapist. Given that the intervention had multiple therapeutic targets, the expected improvement was not only in fatigue but also mood and physical activity, which was reflected in the clinical results of the current feasibility study. Therefore, this is a complex intervention not only in its multiple therapeutic components but also in multidisciplinary personnel it had involved and multiple expected outcomes.

This is also a brief psychological intervention as it was a short-term intervention programme over 12 weeks and did not require the therapist to have complex psychological skills. The programme was developed based on a nurse-delivered programme for cancer-related fatigue and a self-management programme for chronic fatigue syndrome. In the current study the intervention was delivered by a clinical psychologist in order to test whether this intervention was comparable to psychological interventions normally used in clinical practice and if it was acceptable to the therapist from the perspective of a clinical psychologist. The therapist was required to strictly adhere to the intervention manual and to avoid using any additional psychological skills. The intervention was designed to be ultimately delivered by stroke nurses so that it would be affordable in the NHS. The feasibility of the nurse-delivery of this intervention will be tested in future studies.

A limitation of this study was that I did not have recordings or direct observation of the intervention delivery during sessions, as the therapist reported uncomfortable to be recorded or observed. To ensure that key therapeutic components be delivered to the participant, I had provided a checklist of key therapeutic components of each session for the therapist to read before the session and to complete after the session (i.e. the therapist was asked to tick the component if she had delivered it during the session). The therapist reported in the checklist for each participant that all key therapeutic components had been delivered. However, this checklist was unable to reflect the therapy enthusiasm of the therapist, which is important for psychological interventions that are delivered through interactions between the therapist and the participant. Also the adherence reported in this checklist might have been biased as it was reported by the therapist rather than be observed by a third person. In addition, although inter-therapist diversity is not a concern for this single-site study, in future multi-centre trials it is important to record and supervise the intervention delivery processes, in order to ensure the core element of intervention has been delivered in the same pattern by all therapists across sites.

Section 6.2 Implications for clinical practice

Although currently there is insufficient evidence to recommend the use of any specific intervention for the treatment or prevention of PSF, findings from this thesis contribute towards a growing knowledge of PSF to inform its clinical management.

In Chapter 2, I have systematically reviewed the literature and proposed a model for PSF (Wu et al., 2015b). In qualitative studies exploring patients' views of PSF, one of the major concerns of the patients was that they felt unprepared for, and uneducated about their fatigue (Flinn and Stube, 2010, White et al., 2012). In general stroke care, there is evidence that providing information about stroke improves patients and carers' knowledge of stroke and reduces patients' depression scores, although the best way to provide information is unclear (Forster et al., 2012). As fatigue is a common problem and is often present immediately after stroke, information about the potential of PSF and its impact on daily lives need to be provided for stroke patients and their families at an early stage after stroke (e.g. during acute stroke hospitalisation) as part of the general information about stroke. Knowing that PSF is a legitimate symptom and being prepared for it, patients may be less distressed when PSF occurs and be less anxious to seek validation for their symptoms. Currently in the Lothian area, the health service routinely provides stroke patients with an information pack for stroke education, which includes a leaflet about 'coping with tiredness'. In future, this leaflet may be improved by introducing PSF as a specific problem after stroke and providing information about possible impacts of PSF on daily lives.

PSF tends to be a persistent problem but if it does resolve naturally, this tends to occur in the first few months after stroke, which may reflect the influence of stroke recovery or lifestyle changes during hospitalisation. In clinical practice, persistent fatigue is probably more important to identify than a transitory fatigue. Given that fatigue is so common after stroke, arguably clinicians should screen for it. Clinicians may be more interested in screening PSF in medically stable patients and in the chronic stage (i.e. three or six months after stroke onset, probably during the routine follow-up of stroke patients) rather than in the acute phase of stroke, in order to

distinguish persistent fatigue from a transitory phenomenon. One of our participants commented that the screening questionnaire for PSF was very useful, because it helped him to identify fatigue as a problem thus he could take action to work against it. In the current study, we used a single question from the GM-SAT to screen for PSF, as it is a brief and feasible tool in stroke patients. In future studies, we will need to investigate the sensitivity and specificity of this single fatigue question in identifying clinically significant fatigue in stroke patients as against the standard criteria for PSF (e.g. the case definition of PSF).

However, if any patients report PSF at an early stage (e.g. within three months after stroke onset), clinicians need to provide further fatigue education to help patients understand and manage their fatigue. Patients who report PSF should be educated about potential mechanisms of PSF. The key message is that the persistent presence of PSF is associated with many different factors after stroke and some of these factors, such as low mood and reduced physical activity, are manageable and reversible. If these associated factors are properly identified and treated, it may help to reduce PSF. In the current feasibility study, seven out of eight participants rated the fatigue education as 'very useful' in helping them overcome fatigue and the other one rated it as 'somewhat useful'. Based on the fatigue education, patients will be encouraged to keep physically active in their daily life. Although the best way to promote physical activity in stroke patients is still uncertain, being active in daily living may be an easy starting point. Other medical issues that could cause fatigue, such as depression, pain, sleep disorders and medication, should be screened for and managed in fatigued patients.

Although the power of this small study was limited (n = 8), the decrease of fatigue scores from baseline to three months after treatment (mean FAS scores decreased by 9 points out of a possible range from 10 to 50) was statistically significant. But it is important to note that there was no control group in the current study, so we cannot exclude the possibility that fatigue scores might have fallen spontaneously. I recruited patients who were at least three months after their stroke onset, with a mean time of 16 months (range 5 to 23 months). Previous longitudinal studies reported no

significant change of fatigue scores over time in the chronic stage after stroke (as discussed in Chapter 2). For example, in a longitudinal study recruiting stroke patients from the same sources of the current study (i.e. from the Stroke Unit and outpatient Stroke Clinics in Lothian), the majority of patients (51%) did not have a change in the FAS scores by more than 4 points from six months to 12 months after their stroke, and in the remaining patients who had the FAS scores changed by more than 4 points, half of them had a decrease and the other half had an increase (Duncan et al., 2014). This suggests that the participants attending the current study were more likely to experience a reduction in their fatigue than the general stroke population. However, the stroke populations were not identical in these two studies, that is, the current study only recruited patients who answered 'yes' to the fatigue screening question but the previous longitudinal study did not require patients to have fatigue to be recruited. Therefore, the efficacy of this intervention on PSF should be investigated in well-designed RCTs, where these non-interventional factors will be controlled for.

In the current study, participants' self-reporting of fatigue severity, mood, mobility, and participation in social activities seemed to improve immediately after the end of treatment and this improvement was sustained to the three-month follow-up. Whether the intervention has long-lasting changes to behaviours should be investigated in future RCTs. Follow-up is necessary to determine the stability of improvements over a period of time. In addition, some of our participants reported that knowing about the upcoming assessment was the motivation for them to keep working on this intervention, and they suggested using a longer follow-up than the current three months. Therefore, I would suggest using a longer follow-up (e.g. six months or longer) in future trials for this intervention. Also to ensure the continued improvement over time, a review session may be provided during the follow-up, for example, in the middle between the end of treatment and the end of follow-up, just as the one provided at one month after the end of treatment in the current feasibility study.

Section 6.3 Implications for research and future directions

Research of PSF is still in its infancy but there is increasing interest in this area. Taking my systematic review of psychological associations of PSF as an example, I identified 31 studies that had investigated the association between PSF and depression, which were published before October 2012 and the earliest one was published in 1999 (i.e. 2.2 papers per year on average) (Wu et al., 2014b). Through a recent updated search, I identified 11 new studies published between October 2012 and August 2015 (3.7 papers per year on average). The increasing number of research studies indicates an increase of interest in PSF by researchers and clinicians. Although our current knowledge of PSF is mainly about its psychological and behavioural factors, some researchers have started to explore its biological mechanisms such as inflammation (Becker et al., 2015), neuroendocrine (Ormstad et al., 2014) and cortical excitability (Kuppuswamy et al., 2015). However, these are single small studies, of which the results should be confirmed in future studies. Also in my Cochrane review of interventions for PSF, although the existing 12 trials provided insufficient evidence to inform the clinical management of PSF, there are nine ongoing RCTs which may provide new evidence in the near future (Wu et al., 2015a). The current psychological intervention is a potential treatment for PSF, but whether it is effective on PSF should be investigated in future trials.

RCTs are the gold standard for determining intervention efficacy and effectiveness. However, evaluations are often undermined by problems of acceptability, compliance, delivery of the intervention, recruitment and retention, or smaller-than-expected effect sizes (Craig et al., 2008a). Therefore, the MRC framework suggests that a series of pilot studies are required to estimate these uncertainties and to refine the study design, before embarking on a definitive RCT (Craig et al., 2008a). The current feasibility study was the initial stage of piloting, which tested acceptability of intervention procedures, estimated the likely rates of recruitment and retention of participants. The results showed that the intervention was well accepted to both stroke patients and the clinical psychologist, and the procedures for recruitment, intervention delivery and follow up were feasible in the local health system.

According to the MRC framework, the next step will be an exploratory RCT to further test the feasibility of the intervention and issues of study design that had not been investigated in the current study, for example, testing a randomised controlled design (Craig et al., 2008b). In this section, I will discuss issues to be considered for planning a future exploratory RCT (a grant application for this future study is in progress), which include optimal intervention, choice of control, outcome evaluation, determining sample size, and improving recruitment. I will also discuss whether this intervention could be adapted to a wider population of stroke patients with fatigue, low mood, or anxiety symptoms, as these symptoms often coexist in stroke patients and in the general population interventions to treat these symptoms are similar.

Optimal intervention

At this early development stage in this thesis, the intervention was delivered by a clinical psychologist (KA) to test whether the intervention was comparable to psychological interventions normally used in clinical practice and whether the intervention was acceptable to the therapist from the perspective of a clinical psychologist. However, one could argue that the psychologist-delivered approach is not practical in the NHS, because of the shortage of trained psychologists in stroke care (Bowen et al., 2005). Therefore, at the commencement of this study, our project team decided that this intervention should be designed to be suitable for nurse delivery in the longer term, so that it could be affordable in the NHS.

To ensure that the current intervention does not require the therapist to have complex psychological expertise, we adapted it from a nurse-delivered psychological intervention for cancer-related fatigue (Armes et al., 2007) and a self-management psychological intervention for chronic fatigue syndrome (Burgess and Chalder, 2005). In addition, the psychotherapist (TC) in the project team had been involved in the above two studies for non-stroke fatigue and several other nurse-led psychological interventions (Kennedy et al., 2006, Maissi et al., 2011, Reme et al., 2011), who provided advice in developing this brief psychological intervention in the current study. Furthermore, the therapist (KA) was required to strictly adhere to the intervention manuals without using any additional psychological skills. By the end of

this feasibility study, we had refined the intervention manuals according to the feedback from the participants and therapist, and are now seeking to have these manuals published. To move forward to the next stage of the development of this intervention, we will conduct an exploratory trial to test if the nurse-delivery approach is acceptable to the patients and nursing therapists, and whether it is feasible and affordable in the NHS.

To ensure that the nursing therapists correctly understand the intervention and adhere to the manuals, they will receive the specialist training in CBT prior to delivering the intervention to the patient. The training will be provided by experienced CBT therapists, starting with one or two introduction sessions to introduce basic CBT principles and the intervention manuals, followed by practical sessions for nursing staff to rehearse the administration of the intervention with one another. Based on the experience of the psychotherapist (TC) and the clinical psychologist (KA) in working with and training nursing staff, this short-term specialist training will allow the nurses to acquire essential skills for delivering a CBT. During the intervention delivery, the experienced CBT therapists will also provide supervision to nursing therapists on a monthly basis. This 'light touch' supervision would allow the intervention to be deliverable in routine stroke care.

PSF is a common and chronic problem. Therefore, after short-term, intensive, specialist care by stroke physicians, clinical psychologists, or stroke nurses, more cost-effective health service is needed to provide patients with long-term care. If this intervention shows to be feasible to be delivered by stroke nurses who do not have psychological background, delivery by community health service (e.g. by general practitioners, physiotherapists or occupational therapists) will be tested in future so that the intervention can be generalised to a wider range of stroke patients and for longer term. Furthermore, given the chronic nature of PSF, patients and their families take the primary roles in health care. Thus 'expert patients', i.e. patients who have been benefit from this intervention, and their families who have been involved in the intervention are possible therapists to deliver the intervention to peer patients in future.

Although some previous trials for PSF used group-based psychological interventions (Clarke et al., 2012, Zedlitz et al., 2012), in the current study we used an individual-based approach. CBT is a complex intervention, which may work best if individualised and tailored to local context (Craig et al., 2013). The individual-based approach would allow the intervention to be flexible and individualised; for example, for patients who do not have sleep problems, the strategies for sleep hygiene will not be introduced to them. Also, participants in the same group will be expected to progress at the same pace during the study, which would be difficult to achieve because participants may have different main complaints and their ability of learning may be different. In addition, in the NHS Lothian, stroke nurses routinely visit community-dwelling stroke patients at home, which would provide the occasion for individual delivery; whilst group-based interventions will require participants to travel to the same venue, which may increase the burden to participants as well as the travelling cost. Therefore, in the next stage, we will test the feasibility of delivering this CBT by stroke nurses on a one-to-one basis to patients with PSF.

Choice of control group for a future trial

The current study did not have a control group, which is an essential part of RCTs to ensure the internal validity of the treatment effect. In RCTs, the efficacy or effectiveness of an experimental intervention is determined relative to a control condition. There are three commonly used control conditions for psychological interventions: a) strategies that are defined by and under the control of investigators, b) strategies that are provided in routine clinical care and are not in the control of investigators, and c) no treatment (Mohr et al., 2009).

An example of the investigator-defined control is used in a previous RCT that compared two potentially active interventions, CBT alone and CBT plus graded activity training, for the treatment of PSF (Zedlitz et al., 2012). This study reported that the combination therapy was better than CBT alone, but whether CBT or graded exercise training alone was effective on PSF is unclear. Another pilot RCT used a stroke group education therapy as the control for a fatigue group psychoeducation therapy for PSF (Clarke et al., 2012). This type of control is known as the ‘attention

control', which aims to provide participants in the control group with additional 'attention' (e.g. contact with the project team and interaction with the therapist) as comparable to the 'attention' provided for participants in the treatment group. Some researchers suggest using the attention control to balance the 'placebo effect' that could be caused by factors such as additional care and attention given to participants (Lindquist et al., 2007). However, for psychological interventions, this type of control is not analogous to the placebo control in drug trials. This is because the interaction with therapists is an integral part of the intervention that is not provided in routine care, and that participants' motivation and emotions thought to be affected by the 'placebo effect' are managed through the interaction with therapists. Psychological interventions are complex interventions that we cannot really tell which part of the interaction with therapists is therapeutic and which is not. Thus I would suggest not using the attention control in future trials for the current psychological intervention, because it may contain some active therapeutic components and it would also increase the cost of a future trial.

For the current intervention, we are interested in whether any intervention as a whole offers an improvement over current clinical practice. In clinical practice there is no specific treatment for PSF, thus routine medical care for stroke patients means no treatment for PSF. Therefore, routine medical care is the optimal control for the current intervention. To standardise the routine care provided for each participant (i.e. the standardised routine medical care), we will provide information for education about PSF and general advice to encourage participants to increase their level of activity, but without providing any cognitive restructuring approaches.

However, we should be aware that when using (standardised) routine medical care as control, it is difficult to blind participants and therapists to the allocation. Some researchers stated that participants' awareness that they are not receiving treatment would have negative effects on outcomes (Walach et al., 2008). Because the clinical outcomes in this study were all measured by the self-report questionnaires by the participants, bias from the non-blinding of participants needs to be considered when interpreting the results.

Outcome evaluation

This intervention was aimed to improve patients' feelings and emotions in the situation of PSF, by challenging their thoughts and behaviours. Thus the expected outcomes were the improvement in fatigue and mood. In addition, health-related quality of different domains of life after stroke was assessed. In the current study, postal questionnaires (FAS, PSF case definition, PHQ-9 and SIS) were used to measure these clinical outcomes. Most of our participants returned questionnaires in time; for those who had difficulty in returning the questionnaire, completing questionnaires over telephone was a feasible alternative. These scales will be used in future trials for this intervention. The preliminary data obtained in the current study showed that for some measures the beneficial effect was sustained to three months after the end of treatment. Also fatigue is a chronic problem that is not expected to be solved by a 'quick fix', so the optimal follow-up period needs to be six months or longer (as discussed in the previous section).

Fatigue will be the primary outcome because the current intervention was specifically designed to reduce PSF. We measured both the presence (using a case definition specially designed for PSF) and severity (using the FAS) of PSF. A previous study conducted a meta-analytic comparison between continuous and dichotomous outcomes in studies of psychotherapy for depression, reporting that the two types of outcomes resulted in comparable pooled effect sizes (Cuijpers et al., 2010). However, other researchers suggested that of small RCTs (50 participants or less), studies that reported continuous outcomes had a significant higher mean power than those that reported dichotomous outcomes (Bhandari et al., 2002). Given the low rate of recruitment in the current study (12 participants recruited from 421 initially screened stroke patients), I would expect a small sample size for future studies thus will use fatigue severity as the primary outcome.

One of the key strategies of this intervention was to promote physical activity in daily living, thus the participation in daily activities was assessed by the NEADL. The lack of effect on this measure as well as on the Daily Activities subscale of the SIS might be due to the high-functioning sample in this study, of whom the mean

NEADL score at baseline was 20.8 (SD = 0.9, out of a possible maximal score of 22, indicating full independence). Some researchers suggested that this lack of effect was common in trials of exercise after stroke, as current measures of disability were not sufficiently sensitive for high-functioning stroke patients (Saunders, 2009). In addition, some participants in the current study pointed out that some items in the NEADL were duplicated with the Daily Activities subscale of the SIS. Therefore, I suggest not using the NEADL in future trials for this intervention, as it is does not sensitive enough to provide information of the efficacy on daily activities but adds burdens to participants.

In addition, although not assessed in the current study, in future studies I would suggest assessing participants' illness beliefs and coping behaviours prior to and after the intervention programme. This will help us to better understand if this intervention has taken the effect through a cognitive behavioural approach.

Sample size

A major reason for conducting an exploratory trial (a further pilot study) in the future is to obtain data for sample size calculation for the definitive trial (Lancaster et al., 2004). The essential components required for sample size calculations include the alpha for type I error, the beta for type II error (or, the power=1-beta), variance of the primary outcome measure, and the minimal clinically important difference (MCID) (Noordzij et al., 2010). The alpha and the power are usually pre-specified by researchers, where an alpha at 0.05 means that the researcher expects a <5% change of drawing a false-positive conclusion and a power at 0.9 means that the researcher desires a 90% probability of correctly rejecting null hypothesis. The sample size calculation is based on using the population variance of the primary outcome, which is estimated by means of the sample standard deviation (SD, in case of a continuous outcome, e.g. the FAS).

If using the FAS as the primary outcome, a change of four points or more has been considered to represent a clinically relevant change in fatigue status in patients with sarcoidosis (de Kleijn et al., 2011); however, the MCID of the FAS has not been

established in stroke patients. Therefore, future exploratory studies are needed to provide some preliminary data on the difference between the groups, to help researchers determine a difference that is biologically plausible and clinically relevant in the studied population (Noordzij et al., 2010). Estimates of clinical important difference or effect size based on small samples will be positively biased (i.e. too large) (Hertzog, 2008). Hertzog *et al*. suggested that studies with a total sample size between 30 and 40 could give bias-corrected estimates for medium to large effect sizes, but for small effect sizes even a sample size of 80 would be insufficient (Hertzog, 2008).

The sample size of the exploratory trial is important because it also influences the accuracy of the variance estimate. For example, the standard deviation in a small sample tends to be negatively biased, thus if used to estimate population variance for sample size calculation it is likely to result in an underpowered study (Hertzog, 2008). Kieser *et al*. suggested that pilot RCTs with sample sizes between 30 and 50 in total would be sufficient to derive a later definitive trial with a sample size between 150 and 400 with 80% power (Kieser and Wassmer, 1996). This was based on Browne's theory that using the upper limit of the 100 (1-γ)% confidence interval of the estimate of population variance for the sample size calculation would guarantee a planned power with at least 100 (1-γ)% probability (i.e. 80% in Kieser's simulation) (Browne, 1995).

The 4-point difference on the FAS was used as a clinically significant difference of fatigue severity in an observational study for PSF (Duncan et al., 2014), in which the mean FAS score was 24.24 and SD was 8.06 (unpublished, obtained by personal communication). If these findings are consistent with future exploratory trials, when using a difference of four points as the MCID of the FAS for the current intervention, future definitive RCTs for intervention efficacy would require a minimal sample size of 86 participants in each group (total n = 172) to provide a power of 0.9 to detect this MCID at a critical significance level of 0.05 (Florey, 1993). As discussed in the previous paragraph, an exploratory trial with a sample size of 50 will be sufficient to

provide accurate estimates to derive a later definitive trial with a sample size of 172 with adequate power.

In summary, considering practical issues in the recruitment and to control for biases in estimating effect sizes and variance, a total sample size of 50 or more may be sufficient for the next stage exploratory RCTs to provide accurate estimates for future definitive trials.

Improving recruitment

We approached 120 stroke patients and recruited 12 participants from a single NHS site (NHS Lothian) over a period of four months. To recruit an adequate sample size for a definitive RCT (which would require a few hundred of participants or even more), we will need to involve multiple recruiting centres in the future. In the current study, we only retrospectively screened for patients who had had a stroke between the past three months to two years, from a single site, due to the limited recruiting time. If the recruitment period could be longer (e.g. six months or one year), we could also recruit participants prospectively; for example, we could identify potential participants while they are in hospital and consent them for subsequent fatigue screening, and then send them screening questionnaires at three months after their stroke. In a previous RCT investigating strategies to improve medication adherence in stroke patients, which used this two-stage prospective recruitment, the researchers identified potential participants at their discharge from the stroke clinic or stroke unit and sent postal questionnaires to 407 participants when they were at three months after stroke. Of these, 355 (87%) of them completed and returned questionnaires (O'Carroll et al., 2013). This response rate is more than twice of that in the current study (41%). Thus, consenting patients at discharge and contacting them at three months to screen for fatigue may improve the recruitment for this intervention in future trials. A central randomisation system would be needed to provide randomisation and allocation for all participating centres. This could be an online randomisation system or a telephone-served system. The feasibility of this central randomisation system will need to be tested in the exploratory RCT.

Adapting to a wider population with fatigue, low mood, and anxiety symptoms after stroke?

My systematic reviews have revealed significant associations between fatigue, depression and anxiety in stroke patients. Also in clinical practice, we have observed that fatigue, low mood, and anxiety symptoms often coexist in stroke patients, even in those who do not meet clinical criteria for depression or anxiety. Given the psychological profile of patients with PSF, a generic intervention targeting an 'emotional syndrome' of these three symptoms but tailored towards the prominent symptom might be a reasonable approach in future studies.

Although the current intervention was specifically designed to treat PSF, participants also showed improvement in mood from baseline to post-treatment and the improvement was maintained to three-month follow-up. This is not surprising because symptoms of fatigue, depression and anxiety often coexist in stroke patients and share some common associations such as sleep disorders and reduced physical activity (as discussed in Chapter 2). Also CBT is widely used in clinical practice to manage emotional conditions, including depression and anxiety (Chambless and Ollendick, 2001). This suggests that it might be possible to adapt the current fatigue intervention to address a wider range of conditions after stroke, which may include fatigue, low mood, and anxiety symptoms. Patients with clinical depression or clinical anxiety would not be included, because these are generally separate conditions from fatigue and patients with these conditions will require more specific psychological interventions. Patients with low mood or emotional distress that do not meet the criteria for depression or anxiety usually do not receive psychological care in the local health system, for whom the current intervention may provide a novel approach to address these problems.

This does not mean that we can simply apply this fatigue intervention to patients with low mood or emotional distress. The psychotherapist (TC) in our project team suggested that, based on her experience, the therapeutic effects on fatigue and mood would be 'diluted' if the intervention is targeting both conditions simultaneously.

Therefore, more studies are needed to explore the mechanisms of low mood and emotional distress in stroke patients, and investigate their similarities and differences with PSF. If their psychosocial properties are comparable to PSF, we may be able to adapt the current fatigue intervention for these conditions but should incorporate symptom-specific contents (e.g. for fatigue the intervention was focused on physical activity, but for low mood the intervention may need to focus on thoughts and emotions).

Section 6.4 Conclusions

The current study has presented an evidence-based process of developing a psychological intervention for PSF. The systematic review of natural history of PSF indicated that fatigue is common immediately after stroke and often persists over time, which justified the necessity of an intervention for PSF. A psychological intervention was proposed for treating PSF based on the clinical observation that PSF often coexists with low mood and reduced physical activity. To identify therapeutic targets for this psychological intervention, I systematically reviewed observational studies of PSF and found that PSF was associated with depressed mood, anxiety, lower self-efficacy, reduced physical activity, and sleep disorders. Based on psychological interventions for fatigue in conditions other than stroke, these psychological and behavioural factors that I have identified as being associated with PSF could be managed by a cognitive behavioural approach. Therefore, I developed a manualised CBT for PSF by adapting from a nurse-delivered intervention programme for cancer-related fatigue and a self-management programme for chronic fatigue syndrome (both of which share some psychosocial characteristics with PSF).

The development process involved a multidisciplinary group of stroke-related health professionals and service users, considering both theoretical issues and practical issues in stroke care and clinical psychology. I modelled this intervention programme and tested the feasibility of recruitment, delivery process and follow-up procedures in a group of 12 patients with PSF, where the intervention was delivered by a clinical psychologist (i.e. the therapist). The intervention was well-received by the patients with PSF, and procedures of recruitment, intervention delivery and follow up were feasible in the local health system. I refined the intervention according to the feedback from both the participants and the therapist. The preliminary results showed improvement in self-reported fatigue severity, mood, mobility, and participation in social activity from baseline to three months after the end of treatment.

This is the initial stage of the development of this psychological intervention. The success of this feasibility study suggests that an exploratory trial with the randomised controlled design would be a useful next step for the intervention development.

Firstly, in the current study the intervention was delivered by a clinical psychologist but clinical psychologists are not commonly involved in routine stroke care, thus we need to test whether delivering this intervention by stroke nurses, which may be a more practical approach, is acceptable and feasible in the NHS. Secondly, the current study was a single-arm pilot study based on a single NHS site, which provided no information about the feasibility of recruitment from multiple centres and of the randomised controlled design. These issues of the trial design will be tested in the future exploratory trial. Finally, the future exploratory trial will provide data to inform the sample size calculation for definitive trials.

Although there is little information about the intervention efficacy, findings from this thesis contribute to a growing knowledge of PSF that could inform the clinical management of PSF. Fatigue is a common problem and often present immediately after stroke, thus information should be provided early after stroke to patients and their families as part of the general information about stroke, to prepare them for the potential PSF. Ideally, patients should be screened for PSF in the chronic phase (e.g. three months after stroke), in order to distinguish persistent fatigue from a transitory phenomenon. Fatigued patients should be provided information about potential mechanisms of PSF and reassured that their fatigue is often reversible if factors perpetuating their fatigue, such as distressed mood, lower self-efficacy, reduced physical activity, and sleeping problems, are properly identified and treated.

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