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Anxiety after Stroke

Intervention Design and a Randomised Controlled Trial

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Declaration

I declare that this thesis was written by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification except as specified.

Parts of this work have been published in scientific journals, on which I am first author. This thesis contains extracts from the following:

- 'A systematic review of anxiety interventions in stroke and acquired brain injury: efficacy and trial design', published in the January 2018 issue of Journal of Psychosomatic Research (Chun, Whiteley, Dennis, Mead, Carson, 2018)
- 'Anxiety after stroke: the importance of subtyping', published in the February 2018 issue of Stroke (Chun, Whiteley, Dennis, Mead, Carson, 2018)
- 'TASK: the feasibility phase of a novel web-enabled trial, a trial protocol', published in the August 2018 issue of Pilot and Feasibility Studies (Chun, Carson, Dennis, Mead, Whiteley, 2018)
- 'Anxiety after stroke, time for an intervention', a leading opinion article, published in the June 2015 issue of International Journal of Stroke (Chun, Whiteley, Carson, Dennis, Mead, 2015).

My supervisors provided comments on versions of my accepted and published work. I made editorial changes of these publications for inclusion in this thesis. The publications can be found in the appendices.

Acknowledgements

I would like to express my gratitude to my magnificent team of supervisors, Professor Alan Carson, Dr Will Whiteley, Professor Martin Dennis, and Professor Gillian Mead for their guidance, insightful wisdom, and constructive critique throughout my fellowship. Ever since I attended the Edinburgh Stroke Winter School in 2014, they have been constantly instilling confidence in me, creating opportunities for me to learn, develop, and widen my horizons as an academic. From them I learnt the principles of high quality clinical research methodology. Their vast experience and vision inspired me to find innovative solutions to design efficient clinical trials. I wish to thank Professor Alan Carson for the training in neuropsychiatry, which enabled me to gain invaluable insights into the anxiety issues experienced by stroke patients. This experience provided the ingredients for my anxiety intervention.

I thank my parents for an upbringing that has taught me, from an early age, the importance of solid hard work, perseverance, and self-discipline. These qualities gave me the most rewarding experiences in the past three years. I was fortunate to be able to find emotional support from all those around me, including my family, friends, and colleagues. The generosity of the research participants in giving up their time to help other people was a constant reminder of my purpose and duty as a clinical researcher—to improve patient outcomes.

Finally, I would like to thank the Stroke Association for supporting my pre-doctoral research training through the Princess Margaret Research Development Fellowship and the Chief Scientist Office of Scotland for funding my clinical academic fellowship and the research contained in this thesis.

Ho-Yan Yvonne Chun

Abstract

Introduction

Anxiety is common and potentially debilitating after stroke. There is no reliable evidence to guide treatment. Barriers exist in accessing psychological care after stroke. Little is known about anxiety subtypes and what provokes anxiety in people after stroke. Treatment approaches effective in non-stroke populations may not be feasible or generalisable to stroke patients.

Aims

The first aim is to develop an intervention for treating anxiety after stroke and evaluate its feasibility in patients. The second aim is to test the feasibility of a randomised controlled trial (RCT) to evaluate the intervention's effectiveness.

Methods

I used a range of clinical research methodologies: i) a systematic review to summarise the design of anxiety interventions in stroke and acquired brain injury and their efficacy; ii) a prospective cohort study to investigate the frequency of anxiety subtypes, anxiety-provoking stimuli, factors associated with anxiety, and clinical outcomes associated with anxiety after stroke; iii) a study of diagnostic validity and reliability of two anxiety measures, iv) complex intervention development using a systematic approach; v) a feasibility RCT—Treating Anxiety after StroKe (TASK RCT)

Results

My anxiety intervention was practical to deliver and acceptable to patients. The TASK RCT procedures were feasible at a small scale. This thesis will inform further refinements of the intervention and trial procedures in preparation for the large scale definitive TASK RCT.

Lay Summary

There are 1.2 million stroke survivors in the UK. About a quarter of them have anxiety. This is when anxiety or fear becomes excessive or out-of-proportion, affecting the person's ability to carry on with their life normally. At present, we do not have an effective treatment to offer these patients. Many people are suffering and are unable to access any psychological support.

The research

Using existing scientific findings, patient interviews, and questionnaires, I aimed to design a new treatment for anxiety after stroke. I tested this new treatment in a fair scientific experiment—a clinical trial in a small group of patients. My research assessed whether the treatment was acceptable and practical to deliver in patients, and whether the trial methods could be used in the future at a much larger scale.

Outcomes and expected benefits

I successfully designed a new anxiety treatment, delivered via the Internet and telephone. The small group of participants found this new treatment acceptable and practical. They also found it acceptable and practical to participate in a clinical trial just by using the Internet and telephone.

Equipped with these research findings, I will improve the design of the anxiety treatment and the clinical trial procedures. I will need to repeat this experiment in a much larger scale for many more patients across the country. Only a large-scale clinical trial will tell us if this treatment really is beneficial to stroke patients. If beneficial, we will be able to extend this treatment to everyone experiencing anxiety after stroke across the National Health Service.

Thesis Synopsis

My thesis follows the programme of research which I conducted sequentially in the past three years, leading to the development of my anxiety intervention—TASK, an acronym for Treating Anxiety after StroKe. I designed and conducted a streamlined randomised controlled trial (RCT) equipped with technology-enabled procedures to evaluate the TASK intervention.

In Chapter 1, I provide the background knowledge which my work for this thesis is based on. My original research begins in Chapter 2 with a systematic review of RCTs of anxiety treatments in acquired brain injury in order to provide learning points to help me optimise intervention and trial design. Chapter 3 reports my prospective cohort study, which aims to generate new knowledge about anxiety subtypes after stroke and identify common anxiety-provoking situations. These findings inform the content of my TASK intervention. Chapter 4 reports a study of diagnostic validity and reliability of two anxiety measures, the tools for measuring anxiety in my TASK RCT. Chapter 5 describes the TASK intervention development using a systematic, logical, and evidence-based methodology. A summary of key existing scientific evidence, my research findings, and additional stakeholder activities is presented, with all the processes and outcomes of my final TASK intervention modelled in a logic diagram. Chapter 6 reports the TASK RCT, the feasibility phase of a streamlined web-enabled trial. This trial evaluates the feasibility of i) novel trial procedures and ii) the TASK intervention. This trial represents my first step in designing scalable procedures to enable a centralised large-scale RCT to be conducted remotely and efficiently in the future. Chapter 7 is a general discussion of all the work I carried out for this thesis and its wider implications for the future.

Abbreviations

6SQuID	Six essential Steps in Quality Intervention Development
ABI	Acquired brain injury
ACTH	Adrenocorticotrophin
AUC	Area under curve
BAI	Beck anxiety inventory
CBT	Cognitive behavioural therapy
CENTRAL	Cochrane Central Register of Controlled Trials
CHSS	Chest Heart and Stroke Scotland
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CONSORT	Consolidated Standards of Reporting Trials
CRH	Corticotrophin-releasing hormone
CT	Computerised tomography
DASS	Depression Anxiety Stress Scales
DSM	Diagnostic Statistical Manual
EQ5D5L	EuroQoL-5D5L health-related quality of life measure
EQUATOR	Enhancing the QUAlity and Transparency of health Research network
FQ	Fear Questionnaire
GAD	Generalised anxiety disorder
HADS-A	Hospital Anxiety and Depression Scale-anxiety subscale
HAMA	Hamilton Anxiety Rating Scale
HPA	Hypothalamo-pituitary axis
ICD-10	International Classification of Diseases -10
ICH	Intracerebral haemorrhage
IQR	Interquartile range
LACS	Lacunar Stroke
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NaSSA	Noradrenergic and specific serotonergic antidepressant
NHS	National Health Service
NIHSS	National Institute of Health Stroke Scale
NPV	Negative predictive value
OCD	Obsessive compulsive disorder
OCSP	Oxfordshire Community Stroke Project
OR	Odds ratio
PACS	Partial anterior circulation stroke
POCS	Posterior circulation stroke
PPV	Positive predictive value

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PTSD	Post-traumatic stress disorder
RCT	Randomised controlled trial
REDCap	Research Electronic Data Capture
ROC	Receiver operator characteristic
SAH	Subarachnoid haemorrhage
SAS	Zung Self-rating Anxiety Scale
SCID	Structured Clinical Interview for DSM disorders
SD	Standard deviation
SMD	Standardised mean difference
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STAI	State-Trait Anxiety Inventory
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TACS	Total anterior circulation stroke
TASK	Treating Anxiety after StroKe
TBI	Traumatic brain injury
TCA	Tricyclic antidepressants
TIA	Transient ischaemic attack
TIDieR	Template for Intervention Description and Replication
T-MOCA	Telephone Montreal Cognitive Assessment
UK	United Kingdom
WSAS	Work and Social Adjustment scale

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Chapter 1

Introduction: Stroke, Transient Ischaemic Attack, and Anxiety

Publication status and acknowledgement of contribution

This chapter contains extracts from my submitted manuscript for a book chapter, entitled 'Neuropsychiatry of stroke and transient ischaemic attack', which is currently undergoing editorial review. I wrote the final submitted version of this book chapter and the sections included in this thesis chapter with comments from my supervisors.

This chapter contains extracts from my published and accepted manuscripts:

i) Systematic review of anxiety treatments in acquired brain injury and stroke (Appendix A)

ii) Anxiety after stroke: the importance of subtyping (Appendix B)

I wrote the initial draft, subsequent and final versions of all published and accepted manuscripts following comments from my supervisors.

1.1 Stroke and transient ischaemic attack

Stroke is defined as *'a clinical syndrome characterised by an acute loss of focal cerebral function with symptoms lasting more than 24 hours or leading to death, and which is thought to be due to either spontaneous haemorrhage into the brain substance (haemorrhagic stroke) or inadequate cerebral blood supply to a part of the brain (ischaemic stroke) as a result of low blood flow, thrombosis or embolism associated with diseases of the blood vessels (arteries or veins), heart or blood'* (1).

A transient ischaemic attack (TIA), often referred to as a 'mini-stroke', is '*an acute loss of focal cerebral function or ocular function with symptoms lasting less than 24 hours, thought to be due to inadequate cerebral or ocular blood supply as a result of low blood flow, thrombosis or embolism'(2)*.

In practice, TIA and stroke are clinically indistinguishable within the first few hours of symptom onset and should therefore be considered as an 'acute stroke syndrome'(1).

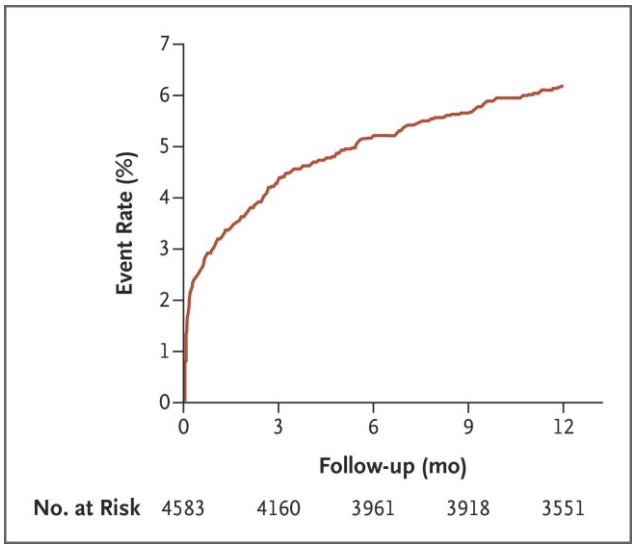
1.1.1 Epidemiology

Stroke is a sudden, potentially fatal and disabling illness. It is one of the leading causes of death and disability both globally and in the United Kingdom (UK). In the UK, stroke affects around 150, 000 people a year(3). A quarter of strokes are fatal within a year, and over a third of stroke survivors are living with severe disability(3). While primarily a disease affecting older people (over 65s), about one in four strokes occurs in those under the age of 65(4). Hypertension, atrial fibrillation, carotid artery stenosis, diabetes and smoking are the main modifiable risk factors for stroke and TIA.

Stroke represents a significant health and economic burden to the UK. Stroke costs the UK £9 billion a year including expenditure on health and social care (49%), informal care (27%), loss of productivity (15%), and benefit payments (9%)(5). In a survey of 500 young stroke survivors (aged 25-59), nearly 70% reported they were unable to return to work following a stroke(6).

About 20% of ischaemic strokes are preceded by a TIA(7). Although its symptoms are only temporary, TIA carries a high risk of stroke, with the greatest risk being in the first few hours to days after TIA onset(8). This elevated risk of stroke begins to level off three months following symptom onset (Figure 1) and over the first 3 years to an annual risk of 2% thereafter(9). However, the risk of major vascular events for the subsequent 10 to 15 years remains high, with an annual risk of 3% for myocardial infarction (MI) or death from coronary heart disease(10).

Figure 1. Cumulative incidence of the composite outcome (stroke, acute coronary syndrome, or death from cardiovascular causes)(11)



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1.1.2 Aetiology of stroke

Approximately 85% of strokes are ischaemic, 10% are intracerebral haemorrhage (ICH), and 5% are subarachnoid haemorrhage(12). Ischaemic stroke and TIA share the same underlying pathophysiological mechanisms: i) large vessel-to-vessel thromboembolism originating from atheromatous large vessels such as the carotid arteries and aortic arch (50%); ii) cardioembolism frequently related to atrial fibrillation (20%) or other cardiac conditions e.g. infective endocarditis, prosthetic heart valve, atrial myxoma, and iii) small vessel disease (lacunar strokes) (25%) related to hypertension and diabetes(1). Giant cell arteritis e.g. temporal arteritis can give rise to a thromboembolic stroke and is suspected in the elderly presenting with a headache, monocular blurred vision and raised inflammatory markers. Rarer causes are carotid or vertebral artery dissection, paradoxical embolism through a patent foremen ovale, recreational drug use, inflammatory vascular disorders, hereditary disorders, and cerebral venous thrombosis.

Primary ICH most commonly occurs due to small vessel disease. In elderly, a lobar ICH suggests underlying cerebral amyloid angiopathy. ICH can occur secondary to an underlying vascular abnormality e.g. intracranial aneurysm, arteriovenous malformation, cavernoma, brain tumour or septic emboli. Subarachnoid haemorrhage can occur secondary to rupture of an intracranial aneurysm or vascular malformation.

1.1.3 Diagnosis and investigations

Symptoms of a stroke usually occur abruptly and reach maximum severity rapidly at onset. Stroke syndromes present with a wide array of symptoms depending on the site of the vascular lesion. The Oxfordshire Community Stroke

Project (OCSP) classification is used widely in the UK. It broadly classifies stroke syndromes into those arising from the anterior circulation i.e. carotid territory and its branches e.g. middle cerebral artery, and those from the posterior circulation i.e. vertebrobasilar territory (Table 1).

Table 1. The OCSP classification of stroke syndromes (1)

Total Anterior Circulation Syndrome (TACS)	*1) Motor:* Hemiplegia and/ or facial weakness or severe hemiparesis +/- hemisensory deficit *2) Higher cerebral:* Dysphasia (dominant hemisphere) Visuospatial deficit or neglect (non-dominant hemisphere) *3) Visual field:* Homonymous hemianopia
Partial Anterior Circulation Syndrome (PACS)	Two of *1) 2) 3)*
Lacunar Syndrome (LACS)	*Pure motor stroke* Unilateral weakness must involve at least two out of three areas of the face, whole arm and leg *Pure sensory stroke* *Ataxic hemiparesis* *Sensorimotor stroke* *N.B. no visual field defect, no impairment in higher cerebral function*
Posterior Circulation Syndrome (POCS)	*Any of the following:* Ipsilateral cranial nerve (III-XII) palsy with contralateral motor and/or sensory deficit Bilateral motor and/ or sensory deficit Disorder of conjugate eye movement Cerebellar dysfunction Isolated hemianopia or cortical blindness

The National Institute of Health Stroke Scale (NIHSS) is a 15-item neurological examination which enables rapid standardised neurological

assessment and scoring of stroke severity and is used widely in acute stroke practice and research(13). Routine investigations include a 12-lead electrocardiogram to exclude persistent atrial fibrillation, routine blood tests including lipid profile, brain and carotid artery imaging. Further cerebral angiographic imaging and cardiac investigations e.g. bubble echocardiogram, 24 hour electrocardiogram are sometimes requested when clinically indicated.

1.1.4 Management

Hyperacute stroke management focuses on the timely delivery of evidence-based interventions to revascularize the blocked artery within the first few hours of onset of an ischaemic stroke e.g. intravenous thrombolysis in the first 4.5 hours(14), mechanical thrombectomy for up to 6 hours, or up to 24 hours with demonstrable mismatch on imaging sequences(15). All stroke patients requiring hospitalisation are admitted to an acute stroke unit equipped to provide organised stroke unit care, delivered by a multidisciplinary team of stroke physicians, nurses and therapists specialised in looking after stroke patients. This model of care reduces mortality and disability after stroke(16).

The modified Rankin scale (mRS) is a measure of stroke outcome and is widely used in clinical practice and as a primary outcome in clinical trials evaluating effectiveness of stroke interventions. An mRS of 0-2 denotes functional independence or a non-disabling stroke, whereas an mRS of 3-5 represents outcome with increasing functional dependence and a poor outcome(17). A simplified mRS questionnaire employing a simple algorithm has been shown to provide a valid and reliable determination of mRS score in-person or over the telephone(18).

Secondary prevention

Ischaemic stroke and TIA broadly share the same risk factors and pathogenesis. While short-term prognosis and hyperacute treatment differ, the two diagnoses share the same long-term secondary prevention approach: antiplatelet therapy, cholesterol-lowering with statins, antihypertensives, oral anticoagulation for atrial fibrillation, diabetic management, and lifestyle modifications e.g. smoking cessation, weight loss, exercise.

Owing to the very high risk of stroke within the first few days of a TIA, all suspected TIAs are started on antiplatelet therapy by their general practitioner or emergency physician, followed by specialist assessment in emergency TIA clinics within four days of referral.

Life after stroke

Stroke is a life-changing illness that potentially threatens the individual's survival, independence, and ability to participate in occupational and social activities. In National Health Service (NHS) Lothian, there are no formal 'life after stroke' services other than a period of stroke rehabilitation for those with marked deficits and functional impairments. Charity-employed community stroke nurses provide visits to stroke patients at home after their discharge from the stroke unit. Patients attending clinics, including TIAs and minor strokes are discharged to primary care with no formal follow-up.

Neuropsychiatric complications are common post-stroke but are underappreciated in clinical settings(19). These include anxiety, depression, cognitive impairment, fatigue, apathy, and emotional lability. Post-stroke psychiatric co-morbidities are associated with a decreased likelihood of returning to work, poorer quality of life, and long-term disability(20, 21). Post-stroke

neuropsychiatric complications often overlap and are difficult to assess in the presence of aphasia or cognitive impairment. At present, there is no reliable evidence to guide treatments for any of these complications.

1.2 What is anxiety?

Definitions

Anxiety refers to a universal emotional state that we, as people, all experience. We use the two words, fear and anxiety interchangeably in our day-to-day life to denote this common emotional experience. Though related, the two words have distinguishable meanings. The Oxford dictionary defines fear as '*an unpleasant emotion caused by the threat of danger, pain, or harm',* and anxiety, as *'a feeling of worry, nervousness, or unease about something with an uncertain outcome'(22).* The former refers to an unpleasant emotion in response to a tangible and acute threat while the latter describes a similar response to something that is diffuse and indeterminate. Delineating the terminology becomes relevant when discussing the scientific study of fear and anxiety—their physiological changes, neurocircuitry and behavioural models.

This section covers the key relevant scientific knowledge of adaptive fear and anxiety, followed by their maladaptive counterparts—anxiety disorders, their clinical assessment and management. Throughout my thesis, I use the words fear and anxiety interchangeably to reflect the day-to-day language used by clinicians and patients. Where it is applicable, I make a clear reference to their distinctive definitions.

1.2.1 Adaptive anxiety

Anxiety is ubiquitous across animal species and is *'a group of adaptive functions by which an organism senses, evaluates and responds to cues of danger in its external (or internal) environment'(23).* Anxiety has evolutionary origins, granting organisms a way to survive by adapting to changing circumstances. In the face of dangers or threats, people and animals experience an unpleasant state—anxiety. The feeling is so unpleasant that we are compelled to behave in a certain way. These behavioural reactions may be learnt or innate, and can occur with or without our conscious control. All serve to reduce the dangers we are facing. Consider the three examples below:

> Example 1: A person avoids walking down a quiet dark alley after a night out due to concerns about personal safety and the knowledge that a recent crime has taken place in that same location.
>
> Example 2: A person walks down the same alley in order to get to his friend's house. He speeds up his pace on hearing a sudden loud noise behind him.
>
> Example 3: A person abruptly becomes motionless as he discovers himself being held at knifepoint by a robber.

Similar behavioural reactions are also evident in other animals, and are conventionally classified into the 'approach/ avoid' and the 'escape/ freezing' behavioural models. In animal experiments, the 'approach/ avoid' is a model of anxiety to intangible threat, while 'escape/ freezing' is a model of fear in response to an actual danger.

To illustrate the evolutionary origin of the fear response to an actual threat, imagine a newly hatched marine iguana, chased by a group of racer snakes on the Galapagos archipelago (or see it for yourself on BBC's Planet

Earth II's YouTube video: www.youtube.com/watch?v=B3OjfK0t1XM). By remaining motionless, the baby iguana stays undetected under the motion-sensitive vision of the otherwise blind natural predators. When the opportunity arose to escape for survival, the iguana ran for its life and miraculously made it to safer grounds. Freezing in the face of a seemingly inescapable danger, and escaping for a chance of survival are both universal fear responses. To mount such behavioural responses, a multitude of physiological changes has to occur.

1.2.2 Physiological changes

Charles Darwin (1809-1882), an English biologist, described a man's fear in his book, *'The Expression of the Emotions in Man and Animals'* in 1871,

> *"The frightened man at first stands like a statue motionless and breathless or crouches down as if instinctively to escape observation. The heart beats quickly and violently, so that it palpitates or knocks against the ribs; skin instantly becomes pale… we see in the marvellous and inexplicable manner in which perspiration immediately exudes from it. This exudation is all the more remarkable, as the surface is then cold……The hairs on the skin stand erect and the superficial muscles shiver. The breathing is hurried……the salivary glands act imperfectly; the mouth becomes dry and is often opened and shut. One of the best marked symptoms is the trembling of all the muscles of the body, often first seen in the lips. The voice becomes husky or indistinct, or may altogether fail."(24)*

These are the salient features that follow the activation of the autonomic nervous system, which we now know as the fight-or-flight response, a term coined by the American physiologist Walter Bradford Cannon (1871-1945) in 1915(25). The

fight-or-flight response is mediated via a series of neuroendocrine processes beginning in the amygdala, a structure within the medial temporal lobe. The amygdala activates the locus coeruleus in the pons and the hypothalamus. The locus coeruleus projects directly and activates the adrenoceptors in the preganglionic sympathetic neurons in the spinal cord. Release of acetylcholine by the preganglionic neurons at the ganglia trigger the release of noradrenaline from the postganglionic neurons that innervate various effector organs, resulting in a series of physiological changes that prepare our body for quite literally, fight or flight (Table 2). The adrenal medulla is directly stimulated by the sympathetic nervous system to release adrenaline and noradrenaline. These catecholamines exert the fight-or-flight responses by increasing glucose metabolism, cardiac output, and blood flow to the skeletal muscles.

Table 2. Fight or flight responses—activation of the sympathetic nervous system

Effector organ	**Physiological changes**
Eye	Pupils dilatation, retraction of eyelid
Lacrimal & salivary glands	Decreased secretion
Heart	Increase in heart rate, contractility
Lungs	Bronchodilation and decreased secretions
Upper GI tract	Decreased gastrointestinal motility; contraction of sphincters
Adrenal gland (directly stimulated by pre-ganglionic neuron)	Release of catecholamines (adrenaline, noradrenaline)
Skin	Piloerection—hairs become erect
	Increased secretion in sweat glands (palms, plantars)
Blood vessels	Vasoconstriction of skin vasculature Vasodilatation of blood vessels in skeletal muscles
Intestine	Reduced intestinal motility
Bladder	Inhibition of micturition

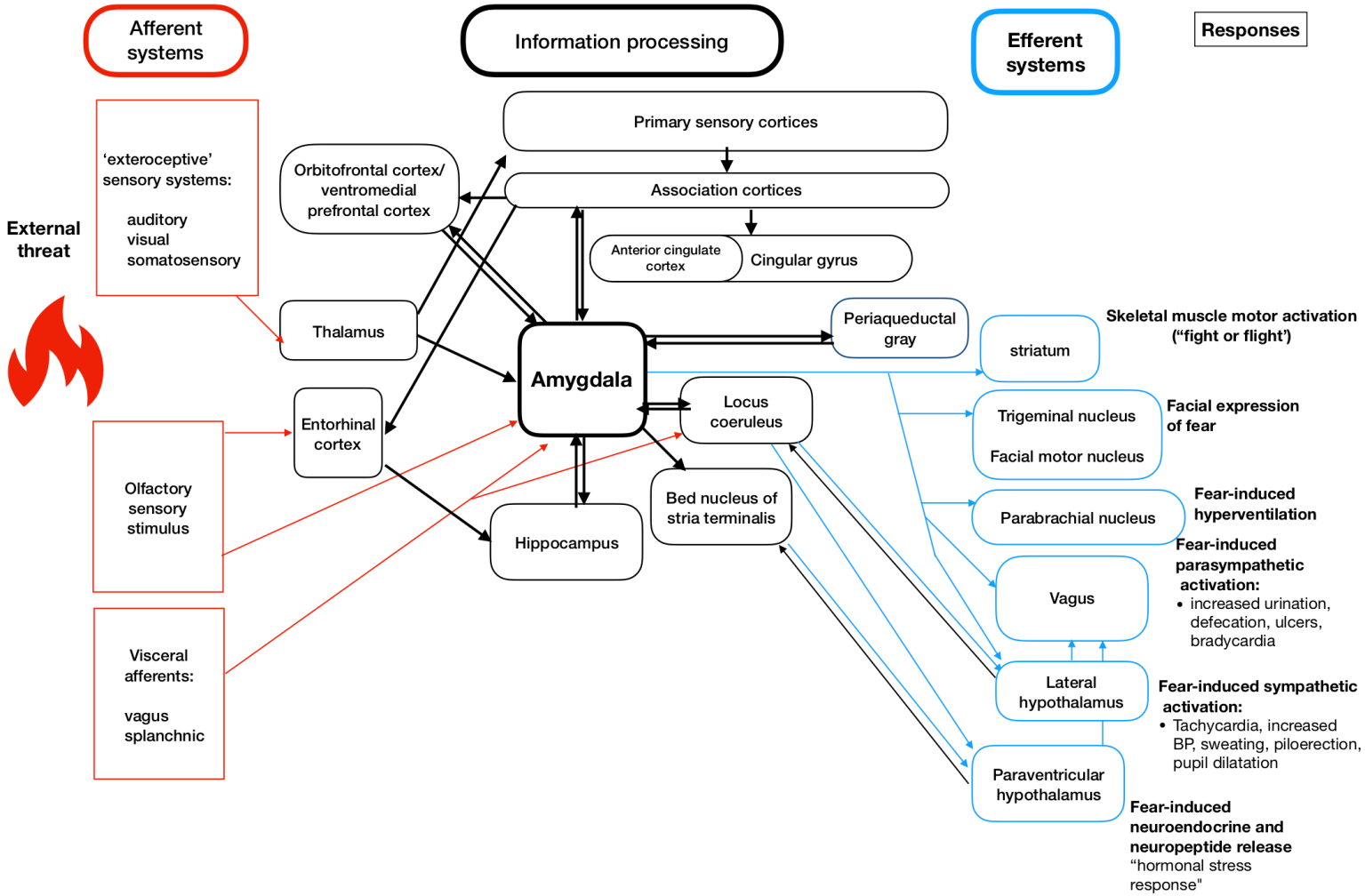
Simultaneously, the hypothalamus activates the pituitary gland to release adreno-corticotrophic hormone (ACTH) into the circulation, stimulating the adrenal cortex to release cortisol, which is loosely termed as a stress hormone. Cortisol increases glucose availability by converting fats and protein into glucose(26).

Perceiving a danger, or even just anticipating one, i.e. a psychological stimulus, can trigger the fight-or-flight response, as can physical insults to our body e.g. trauma, hypothermia, hypotension, hypoglycaemia, hypoxia, pain. All of these are imminent threats to our survival.

1.2.3 Neurocircuitry

In response to a threatening stimulus, our brain has to produce a fear response in its entirety, simultaneously giving rise to the behavioural and physiological responses, as well as the subjective experience of the emotion that we know as fear. The neurocircuitry of fear involves numerous structures including the amygdala, hippocampus, prefrontal cortex, cingulate gyrus, hypothalamus, and other areas. Charney et al. conceptualised the neurocircuitry of fear as three components(27): i) the afferent structures for receiving sensory input, ii) the structures for stimulus processing, and iii) the efferent structures for sending signals to the effector organs that ultimately give rise to the behavioural, physiological, and emotional responses (Figure 2). Afferent signals arising from our sensory organs are relayed to the primary sensory cortices via the thalamus, with the exception of olfactory signals, which go directly to the entorhinal cortex. From the primary sensory cortices, information enters the adjacent sensory association cortices, then onto a complex network of structures for information processing where amygdala is central to mediating the efferent output (Figure 2).

Figure 2. Neurocircuitry of fear and anxiety, adapted from Charney et al.(27)



In addition to this three-component model, LeDoux et al. adds a 'two systems framework' in fear processing, in which there is one system that involves primarily the cortical structures, resulting in the generation of conscious feelings (the cognitive circuit) while another system is responsible for the physiological and behavioural responses i.e. the more 'basic' and 'primitive' reactions that occur mainly unconsciously, involving mostly the subcortical areas, also known as the defensive survival circuit(28).

The amygdala

Amygdala ('almond' in Latin) is an almond-shaped structure located in the medial temporal lobe. It consists of at least 13 nuclei with complex interconnections(29). Once sensory information of an immediate threat is relayed to the amygdala, the lateral nucleus of the amygdala sends signals to the central nucleus, which in turn triggers the behavioural and physiological responses of fear e.g. freezing, rise in heart rate and blood pressure, release of stress hormones. Observations in both animal and human studies demonstrated the role of the central nucleus of amygdala in mediating the autonomic and somatic changes observed in fear whereas the bed nucleus of stria terminalis is thought to be involved in the behavioural expression of anxiety to intangible threat(30).

The hypothalamus

The hypothalamus, a structure lying below the thalamus in the diencephalon, is made up of nuclei responsible for regulating a range of physiological functions related to survival—drinking, feeding, thermoregulation, and sleep. The hypothalamus is concerned with homeostasis—maintaining a constant internal environment by effecting appropriate responses in the presence

of internal and/ or external stimuli e.g. a surge in blood pressure, a drop in ambient light(26). Besides mediating the fight-or-flight response via the sympatho-medullary pathway, it is also responsible for mediating the response via the hypothalamo-pituitary-adrenal (HPA) axis. Hypothalamus releases cortocotrophin-releasing hormone (CRH) and vasopressin that triggers the pituitary gland to release ACTH into the blood. Adrenal cortex then releases cortisol upon activation by ACTH(26).

Neurotransmitters and neuropeptides.

Communication between the various brain regions and effector organs require neurotransmitters and neuropeptides. Noradrenaline, dopamine, serotonin (5-hydroxytryptamine), gamma-amino-butyric-acid, vasopressin, CRH, and ACTH are some of the key neurotransmitters and neuropeptides implicated in fear and anxiety(27).

Anxiety to intangible threat

Anxiety in response to intangible, potential, and anticipated threats(31) is more difficult to study in the laboratory as conditions that provoke this kind of anxiety in humans are not as easily reproduced as the discrete stimuli that provoke fear in animal models (e.g. electric shocks). Furthermore, human cognition is more complex. Animal models of anxiety to uncertain threat have relied on observing animals' innate exploratory or social behaviours e.g. exploration of an open field or elevated maze in mice, parental separation and variable foraging availability in non-human primates(23). In spite of these limitations, it was evident that adverse rearing conditions led to prolonged activation of the HPA and elevated sympathetic arousal in animals(32)

1.3 Maladaptive anxiety—phobic and generalised anxiety

Anxiety can become maladaptive. This is when fear or anxiety becomes excessive, pervasive or out-of-proportion to the danger posed by a situation. When anxiety is maladaptive to the extent that it interferes with the person's occupational or social functioning, it may be considered an anxiety disorder. Anxiety is not a single unitary disorder. It can be broadly divided into two clinical subtypes—phobic and generalised, mirroring the division between adaptive fear (in response to well-defined danger) and adaptive anxiety (in response to intangible threat).

Phobic and generalised anxiety

Phobic anxiety is characterized by a disproportionate fear of well-defined situations or stimuli(33). Exposure to the feared situation triggers unpleasant anxiety symptoms, accompanied by marked avoidant behaviour of that feared situation—the hallmark of phobic anxiety(33). Whilst avoidant behaviour may relieve anxiety in the short-term it can become disabling if the behaviour becomes consolidated through conditioning e.g. becoming housebound in agoraphobia as a result of learning to associate 'danger' with 'leaving house'. By contrast, generalised anxiety disorder (GAD) is diffuse and unremitting, characterized by persistent and multiple worries e.g. finances, health, and an inability to stop worrying(33).

1.3.1 Diagnostic criteria and assessment

Clinicians make a clinical diagnosis of an anxiety disorder based on widely accepted standardised classification systems. Commonly used systems include the American Psychiatric Association's Diagnostic Statistical Manual of Mental

disorders (DSM) and the International Classification of Diseases (ICD-10). The DSM's latest version, the DSM-V, was published in 2013(33). Its accompanying validated research tool, the Structured Clinical Interview for DSM disorders (SCID-DSM-V) became available in 2015. At the time of planning my research methods for this thesis in 2014, the SCID was available only for the preceding version, the DSM-IV-TR(34). This version was widely used and regarded as the 'gold-standard' in psychiatry research. Hence, it was selected to be the diagnostic tool of choice in my research for this thesis. Table 3 shows the current DSM-V diagnostic criteria for GAD, agoraphobia, social phobia and specific phobia. I have highlighted the key changes made since the update from DSM-IV-TR.

Of particular relevance to my thesis, all phobic disorders (agoraphobia, social phobia and specific phobia) had the criterion '*the person recognises that the fear is excessive or unreasonable'* removed and replaced by the new criterion '*The fear or anxiety is out of proportion to the actual danger posed by the phobic situations and to the sociocultural context'*. Agoraphobia can be diagnosed irrespective of the presence of panic disorder in the update. I adopted both of these changes when conducting the SCID interviews for this thesis.

Table 3. DSM-V criteria for anxiety disorders and key changes from DSM-IV-TR

DSM-V	Key changes since DSM-IV-TR
Generalised anxiety disorder A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance) B. The individual finds it difficult to control the worry C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months): 1) restlessness or feeling keyed up or on edge; 2) being easily fatigued; 3) difficulty concentrating or mind going blank; 4) irritability; 5) muscle tension; 6) sleep disturbance D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning E. The disturbance is not attributable to the physiological effects of a substance or another medical condition e.g. hyperthyroidism The disturbance is not better explained by another mental disorder e.g. panic disorder, social anxiety disorder, obsessive compulsive disorder, separation anxiety disorder, PTSD, anorexia nervosa, somatic symptom disorder, body dysmorphic disorder, illness anxiety disorder, or the content of delusional believes in schizophrenia or delusional disorder	*Illness anxiety disorder*—worry about illness, concern about pain, and bodily preoccupations was not a diagnosis before the update.
Agoraphobia A. Marked fear or anxiety about two (or more) of the following five situations: 1. Using public transportation; 2. Being in open spaces; 3. Being in enclosed spaces; 4. Standing in line or being in a crowd; 5. Being outside of the home alone B. The individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of developing panic-like symptoms or other incapacitating or embarrassing symptom C. The agoraphobic situations almost always provoke fear or anxiety	New criterion E Removal of the diagnoses: *panic disorder with agoraphobia*, and *agoraphobia without history of panic disorder*

Table 3 continued	In the update, agoraphobia can be diagnosed irrespective of the presence of panic disorder—this is the diagnostic approach used in my methodology
D. The agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety	
E. The fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context	
F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more.	Minor changes to wording
G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning	
H. If another medical condition is present, the fear, anxiety, or avoidance is clearly excessive	
I. The fear, anxiety, or avoidance is not better explained by the symptom of another mental disorder .g. specific phobia, social anxiety disorder, OCD, body dysmorphic disorder, PTSD, separation anxiety disorder	
Specific phobia	
A. Marked fear or anxiety about a specific object or situation	
B. The phobic object or situation almost always provokes immediate fear of anxiety	Removal of the diagnostic criterion, 'the person recognises that the fear is excessive or unreasonable'
C. The phobic object or situation is actively avoided or endured with intense fear or anxiety	
D. The fear or anxiety is out of proportion not the actual danger posed by the specific object or situation and to the social cultural context	
E. The fear, anxiety , or avoidance is persistent, typically lasting for 6 months or more	New criterion E
F. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning	Minor changes in wording
G. The disturbance is not better explained by the symptoms of another mental disorder, including agoraphobia, obsessive-compulsive disorder, posttraumatic stress disorder, separation anxiety disorder, or social anxiety disorder	

Social phobia (or social anxiety disorder)

A. Marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g. having a conversation, meeting unfamiliar people), being observed (e.g. eating or drinking), and performing in front of others (e.g. giving a speech)	Diagnostic features remain the same with changes in wording for criteria A and B.
B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e. will be humiliating or embarrassing; will lead to rejection nor offend others)	Removal of the diagnostic criterion, 'the person recognises that the fear is excessive or unreasonable'
C. The social situations almost always provoke fear or anxiety	
Table 3 continued	New criterion E
D. The social situations are avoided or endured with intense fear or anxiety	
E. The fear or anxiety is out of proportion not the actual threat posed by the social situation and to the sociocultural context	
F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 months of more	
G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning	
H. The fear, anxiety, or avoidance is not attributable to the physiological effects of a substance or another medical condition	
I. The fear, anxiety, or avoidance is not better explained by symptoms of another mental disorder	
J. If another medical condition is present, the fear, anxiety, or avoidance is clearly unrelated or is excessive	

Panic disorder

A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes and during which time four or more of the following symptoms occur	Minor changes in wording only

- Palpitations, sweating; trembling; sensations of shortness of breath; feelings of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy; unsteady/ light headed/ faint; chills/ heat sensations; paraesthesia; derealisation/depersonalisation; fear of losing control/ going crazy; fear of dying

B. At least one of the attack has been followed by 1 month (or more) of one or both of the following:
   - Persistent concern about additional panic attacks or their consequences
   - A significant maladaptive change in behaviour related to the attacks e.g. behaviours designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations
C. The disturbance is not attributable to the physiological effects of a substance or another medical condition
D. The disturbance is not better explained by another mental disorder e.g. social phobia, specific phobia, OCD, PTSD, separation disorder

In the DSM-IV-TR and its accompanying SCID, post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) were classified as anxiety disorders. Since the update, these two disorders have been re-classified—PTSD in the category of 'Trauma- and stressor-related disorders' and OCD in the category of 'Obsessive-compulsive and related disorders'.

1.3.2 Epidemiology of anxiety disorders

The Adult Psychiatric Morbidity Survey in England, a population-based cross-sectional survey commissioned by NHS Digital, gave the following estimates for anxiety disorders in 2014 (Table 4) (35). This survey used the Clinical Interview Schedule–Revised Score (36) and the PTSD checklist for diagnosis of anxiety disorders(37). GAD was the commonest anxiety disorder in adults while phobias were uncommon.

Table 4. Prevalence estimates of anxiety disorders in England in 2014(35)

Anxiety disorder	Age group							
	16-24	25-34	35-44	45-54	55-64	65-74	75+	All
	%	%	%	%	%	%	%	%
GAD	6.3	6.1	6.9	7.3	6.4	4.0	2.5	5.9
Phobias	3.3	3.3	3.0	2.7	2.3	0.6	0.5	2.4
Panic disorder	1.2	0.5	0.3	0.5	0.5	0.7	0.6	0.6
OCD	1.8	1.4	1.6	1.6	1.5	0.3	0.3	1.3
PTSD	8.0	5.4	4.6	4.5	3.7	1.6	0.6	4.4

Risk factors

The study of anxiety and its pathological forms supports a multifactorial aetiology of clinical anxiety disorders—the complex interplay of biological (genetic, physiological), psychological, and social or environmental factors. The Adult Psychiatric Morbidity Survey in England found that common mental disorders—GAD, phobias, panic disorder, OCD, and depression were more prevalent in black women, people below the age of 60 and living alone, women

living in large households, the unemployed, and people receiving benefits and smokers(35). Co-morbidity was high amongst anxiety disorders, and between anxiety disorders and mood disorders including depression.

1.3.3 Fear conditioning and exposure therapy

Fear can be acquired and extinguished via 'classical conditioning', also known as 'learning by association'. Ivan Pavlov in the late nineteenth century discovered that dogs learnt by classical conditioning. By repeatedly pairing the ringing of a bell (a neutral stimulus) with food (a natural stimulus of salivation), his dogs became conditioned to salivate on hearing the bell, even in the absence of food(38). In 1920, John Watson and Rosalie Raynor demonstrated that a nine-month old infant known as Little Albert, could be conditioned to exhibit fear to a previously neutral stimulus (a white fluffy rat) by repeatedly presenting Albert the rat with a naturally aversive stimulus—a loud hammering sound(39). Their experiments also demonstrated that a phobic fear could generalise across a range of similar situations—Little Albert's fear of the fluffy rat extended to other similarly fluffy objects, including a fur coat and a Santa Claus mask(39). Shortly following this, Mary Cover Jones, another American psychologist went on to apply the same principles of classical conditioning in a child named Little Peter, who had a phobia of rabbits. By repeatedly presenting him a rabbit together with his favourite candy while gradually bringing the animal closer to him(40), Little Peter's phobia of rabbits was extinguished.

Classical conditioning, complemented by operant conditioning(41, 42), in which reward leads to positive reinforcement of a behaviour, are learning behavioural theories fundamental to exposure therapy—a behavioural therapy. Systematic desensitization or graduated hierarchical exposure, is the current form

of exposure therapy developed by Joseph Wolpe(43). Phobic individuals confront their defined feared situation in gradual hierarchical steps. Through conditioning and habituation, the unpleasant feelings of anxiety associated with that situation gradually diminish. By encouraging the individual to confront their feared situation, exposure therapy breaks the vicious cycle of maladaptive escape and avoidant behaviours. These maladaptive behaviours, if not treated, are reinforced by the pleasant sense of relief and comfort that escape or avoidance brings. Exposure therapy, usually delivered as part of cognitive behavioural therapy (CBT), is an effective treatment for phobic disorders in the non-stroke populations(44, 45) and yet has never been evaluated in stroke patients with anxiety(46).

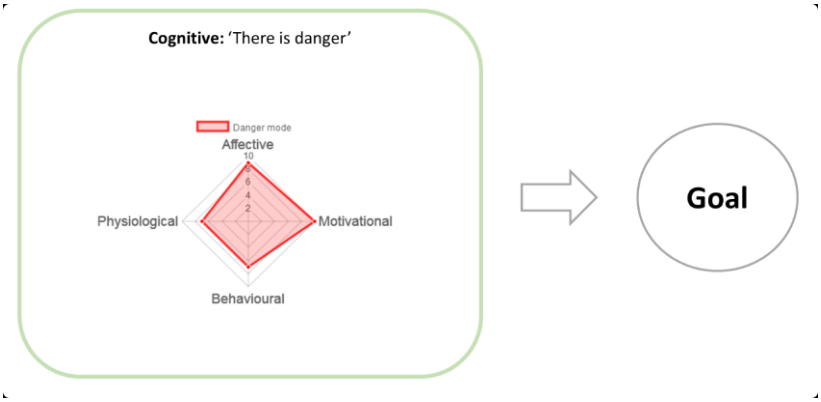
1.3.4 Cognitive model and cognitive therapy

In the cognitive model established by Aaron Beck in the 1960s, an individual's feelings of anxiety arise from maladaptive thoughts—misconception, distortions (overgeneralization, exaggeration), and faulty assumptions about himself and/or his world. Cognitive therapy guides the individual to recognise these maladaptive thoughts, and helps him appraise them objectively by testing the validity of these thoughts with rules of evidence, logic or alternative explanation in a process known as cognitive restructuring(47).

Aaron Beck described the integration of multiple components in the cognitive model: modes, schemas, and systems, which gave rise to the cognitive-affective-behavioural response in a given situation(48). For example, a dangerous situation orientates us to respond in a 'danger' mode. This mode refers to the response arising from the synchronous activity of a network of basic systems: the cognitive ('there is danger'), affective (rapidly increasing levels of anxiety),

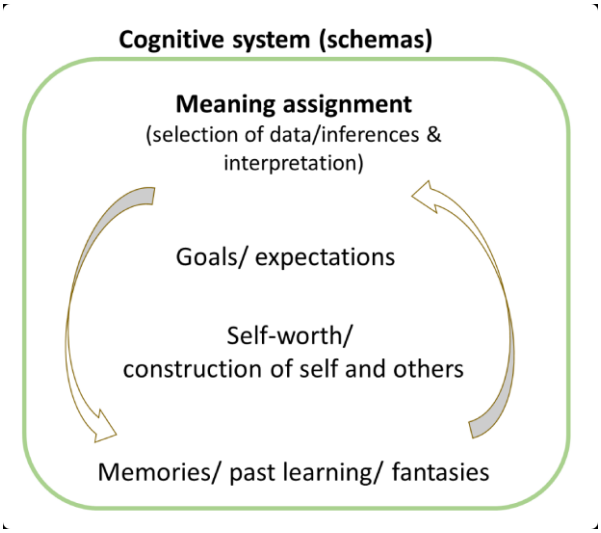
motivational (an intense impulse to flee), behavioural (the action of fleeing), and physiological (chest, palpitations, and dizziness) systems. These basic systems result in a coordinated goal-directed strategy(48) (Figure 3).

Figure 3. A synchronous response of cognitive, affective, motivational, physiological and behavioural response



The basic cognitive system is responsible for information processing and assignment of meanings, based on a series of schemas (Figure 4). Memories, past learning, and fantasies mould a person's perception of himself and other people, and goals and expectations(48). Based on these schemas, inferences are made and situation is interpreted often out of the person's awareness.

Figure 4. Cognitive schemas in the basic cognitive system



A superimposing conscious control system—also known as meta-cognition or ‘thinking about thinking’ exerts control over the basic systems and can override them (Figure 5a). For example, a person with a fear of spider enters the ‘danger mode’ on seeing a spider. The conscious control system applies logic, corrects the ‘automatic’ thinking patterns from the basic cognitive system, pays less attention to unpleasant thoughts or memories, inhibits the impulse to flee, and forces the person to pick up and release the spider using a glass jar (Figure 5b) (48).

Figure 5a) A superimposing conscious control system exerts control over the basic systems in the cognitive-affective-behavioural response

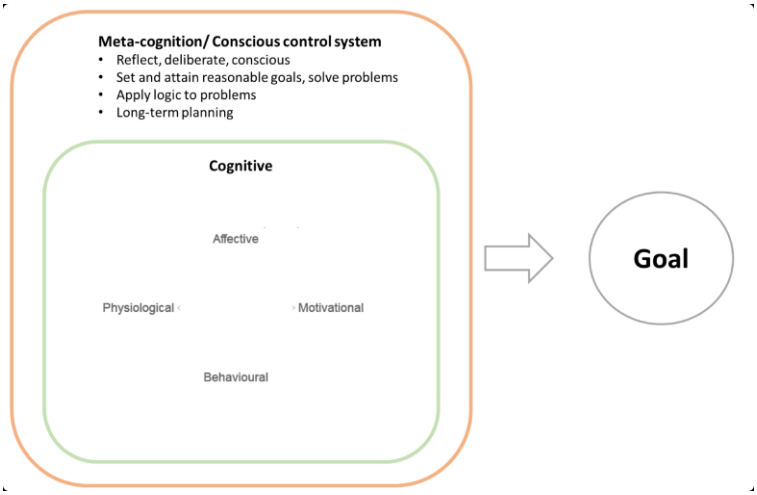
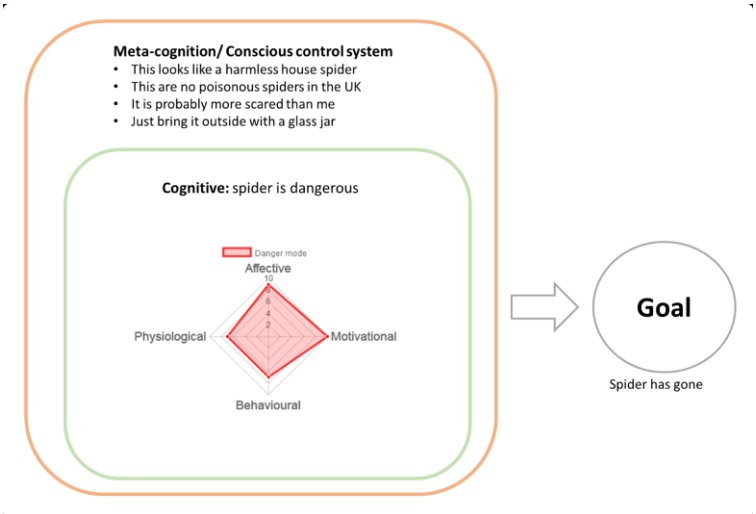
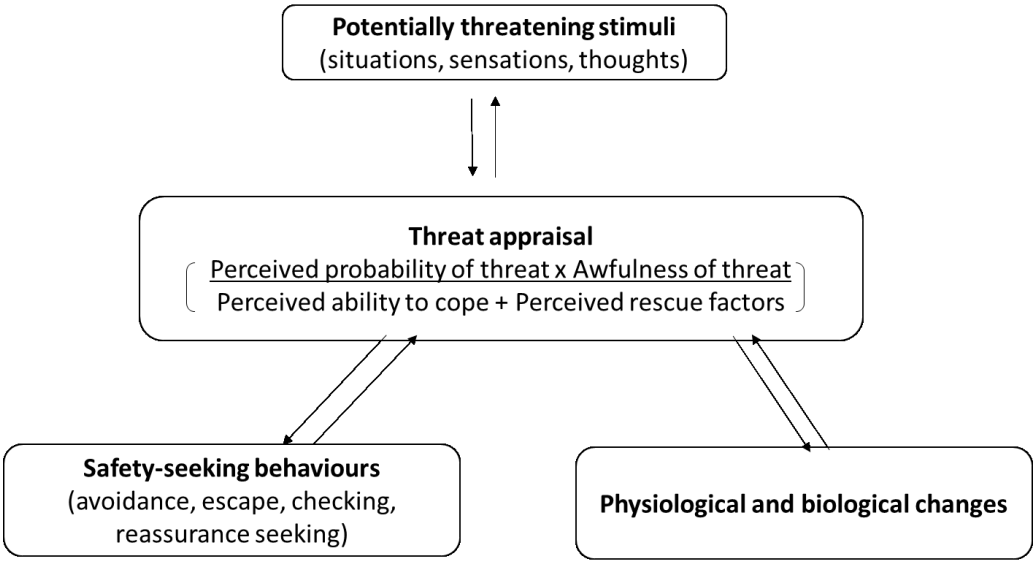


Figure 5b) in a person with spider phobia



In a person with anxiety, the cognitive system selectively pays attention (selective attention) to certain stimuli associated with the perceived danger(48). The more he notices the stimuli, the more heightened the anxiety feelings (physiological and biological), and the more attention he pays to these stimuli and feelings (Figure 6). This leads to and reinforces the incorrect interpretation that these stimuli are associated with increased danger. Avoidance of these stimuli reinforces the belief that danger subsides once the stimuli are removed.

Figure 6. The cognitive-affective-behavioural model for perpetuating and the maintenance of anxiety(48)



To understand the cognitive patterns underlying anxiety after stroke, I will need to explore the stimuli of anxiety, the core beliefs (e.g. perceived threat) held by anxious and non-anxious stroke patients, and their 'safety-seeking' behaviours. Once these have been identified, I will be able to design a way to help anxious stroke patients identify where their thinking has become trapped and guide them to discover alternative ways of looking at their situation in a more helpful way.

1.3.5 Evidence-based treatments for anxiety disorders

Systematic reviews and meta-analyses provide the evidence base for a range of therapies for adult anxiety disorders(44): exposure therapies for phobic disorders (45), medications for GAD e.g. selective serotonin reuptake inhibitors (SSRI), short-term benzodiazepines, and CBT techniques e.g. cognitive restructuring, problem solving(49-51). More recent systematic reviews suggest that guided self-help CBT interventions are more efficacious than self-help only (bibliotherapy or computerised)(52, 53). Guided internet-based CBT is superior to waitlist control and as efficacious as face-to-face CBT in treating anxiety disorders or depression in general adults (54, 55).

1.4 Anxiety after stroke and transient ischaemic attack

Stroke is a life-changing illness that potentially threatens the individual's survival, independence, and ability to participate in occupational and social activities. Patients with disabling strokes face uncertainties surrounding the likelihood of recovery and prognosis, while patients with non-disabling strokes or TIAs are warned of an ongoing threat of a recurrence, or worse, that of a severely debilitating stroke. Anxiety disorders may present in the acute setting, during rehabilitation or become apparent only after discharge(56).

1.4.1 Epidemiology

Anxiety is common, affecting around a quarter of stroke(56), and nearly a third of TIA(57). It can hamper stroke rehabilitation effort and prevent patients from returning to their usual activities. Patients with a 'probable anxiety disorder' at 3 months had a poorer quality of life at 1, 3 and 5 years post-stroke after adjusting for age, sex and stroke severity(58). Anxiety symptoms can persist for

up to 10 years(58). There are consistent associations between post-stroke anxiety and pre-stroke depression and early anxiety after stroke(59).

1.4.2 Assessing anxiety after stroke

The Hospital anxiety and depression scale is the most commonly used anxiety screening tool in stroke(60). However, it was not developed with stroke patients in mind. It does not distinguish anxiety subtypes, and has no utility in aphasia or cognitive impairment. Currently, there is no universal consensus as to how anxiety is best assessed in clinical trials or practice in stroke. Conducting semi-structured psychiatric interviews is time-consuming and requires specially-trained personnel, making it impractical in clinical trials.

1.4.3 Treatments for anxiety after stroke

The most recent Cochrane update of interventions for anxiety after stroke included only 3 trials (n=196). These studies were limited by small sample size and inadequate description of their methods and controls, and so are insufficient as a guide for treatment(61). Despite earlier observations that phobic anxiety might be present after stroke(62-64), intervention studies have treated anxiety post-stroke as one unitary phenomenon and evaluated general approaches such as relaxation and antidepressants(61), which are unlikely to be effective in phobic anxiety. It remains uncertain as to whether what works for general adults with anxiety will also work in anxiety after stroke and TIA. Stroke survivors may have specific fears amounting to specific phobias that need defining; patients may not tolerate psychological treatments; efficacy of therapy may be dependent on considerable effort and other factors such as fatigue and cognitive impairment.

1.5 Aims of my thesis

The aims of my thesis are to develop an intervention for anxiety after stroke and TIA, provide some information on its acceptability and ease of delivery and test the feasibility of a design of a randomised controlled trial (RCT) to test the effectiveness of the intervention.

Chapter 2

A Systematic Review and Meta-analysis of Anxiety Interventions in Stroke and Acquired Brain Injury: Efficacy and Trial Design

Publication status and acknowledgement of contribution

This chapter has been published in the January 2018 issue of the Journal of Psychosomatic Research (Appendix A).

I designed the protocol for this review, performed searches, screened abstracts, extracted data, performed quality assessment and data analysis. Dr Richard Newman (RN) was the second reviewer who independently screened abstracts, extracted data and performed quality assessment. The trial search information specialists at the Cochrane Stroke Research Group supplied the search strategies for this systematic review.

I wrote the initial draft, subsequent and final versions of all published and accepted manuscripts following comments from my supervisors. I made minor editorial changes to the published version in this chapter and added Section 2.4.5, ‘Summary of key points for this chapter’.

2.1 Introduction

There is little RCT evidence to guide treatment for anxiety after stroke. RCTs of anxiety intervention in stroke have not yielded any definitive evidence in a recent Cochrane review—only three trials (2 pharmacological, 1 relaxation CD) with 196 participants were included(61). These studies had high risk of bias and were of small sample size. Aware of the lack of RCT evidence in anxiety after stroke I aimed to review systematically the wider evidence base encompassing both stroke and traumatic brain injury (TBI). To date, there is no evidence to suggest that the pathophysiological mechanism underlying anxiety disorders differs from one acquired brain injury (ABI) condition to another. It may be reasonable to extrapolate from one ABI to the other as both TBI and stroke conditions have abrupt onset, result in varying degrees of brain damage, and transient or long-term neurological and neuropsychiatric impairments. The last systematic review of anxiety interventions in TBI in 2007 included three studies, providing some evidence for CBT in acute stress disorder and in improving generalised anxiety symptomology but these studies had small sample sizes and were done in mild TBI only(65).

Summarizing the key considerations in intervention and trial design (anxiety subtype targeted, setting and timing of intervention and outcome measure), and the sources of potential bias will guide the design of my TASK intervention and optimise the quality of the feasibility RCT.

Aims

To evaluate the efficacy of anxiety treatments and to summarize key aspects of trial design, I aimed to perform a systematic review of RCTs of

interventions for anxiety disorders in ABI conditions including stroke—ischaemic, haemorrhagic or subarachnoid haemorrhage (SAH), and TBI.

2.2 Methods

I followed a pre-defined protocol in conducting this systematic review and reported my review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist(66).

2.2.1 Searches and information sources

I searched electronically for RCTs on Medline (1946-18/8/17), Embase (1980-17/8/17), PsychInfo (1940-17/8/17), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (inception-16/10/17), the Cochrane Stroke Register (16/10/17), and the Cochrane Central Register of Controlled Trials (CENTRAL) (inception-16/10/17) using search strategies supplied by the trials search co-ordinator of the Cochrane Stroke Group. I reviewed the reference list of key systematic reviews to date to identify additional titles(65, 67). I contacted authors of eligible titles that were trial protocols, conference abstracts or trial register entries for published or unpublished primary data.

Search strategies

Database: Embase

Search dates: 1980 - 17.8.2017

1. cerebrovascular disease/ or exp basal ganglion haemorrhage/ or exp brain hematoma/ or exp brain haemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp cerebrovascular malformation/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke patient/ or stroke unit/
2. (stroke$ or post stroke or poststroke or post-stroke or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or SAH).tw.

3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.
5. hemiparesis/ or hemiplegia/ or paresis/ or exp aphasia/ or dysphasia/ or exp neurologic gait disorder/
6. (hempar$ or hemipleg$ or paresis or paretic or aphasi$ or dysphasi$).tw.
7. brain injury/ or acquired brain injury/ or brain concussion/ or brain contusion/ or brain damage/ or brain stem injury/ or cerebellum injury/ or diffuse axonal injury/ or postconcussion syndrome/ or traumatic brain injury/ or brain hypoxia/ or head injury/
8. ((brain or cerebr$) adj5 (injur$ or hypoxi$ or damage$ or concussion or trauma$)).tw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. anxiety/
11. exp anxiety disorder/
12. exp anxiolytic agent/
13. (anxiety or anxieties or anxious or agoraphobi$ or phobi$ or panic disorder$ or panic attack$ or (obsess$ adj3 compuls$) or post?traumatic stress$ or PTSD).tw.
14. (feel$ adj5 (apprehens$ or dread or disaster$ or fear$ or worry or worried or terror)).tw.
15. beck anxiety inventory/ or hamilton anxiety scale/ or "hospital anxiety and depression scale"/ or self-rating anxiety scale/ or state trait anxiety inventory/
16. 10 or 11 or 12 or 13 or 14 or 15
17. Randomised Controlled Trial/ or "randomised controlled trial (topic)"/
18. Randomisation/
19. Controlled clinical trial/ or "controlled clinical trial (topic)"/
20. control group/ or controlled study/
21. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
22. Crossover Procedure/
23. Double Blind Procedure/
24. Single Blind Procedure/ or triple blind procedure/
25. placebo/ or placebo effect/
26. (random$ or RCT or RCTs).tw.
27. (controlled adj5 (trial$ or stud$)).tw.
28. (clinical$ adj5 trial$).tw.
29. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
30. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
31. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
32. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
33. (cross-over or cross over or crossover).tw.
34. (placebo$ or sham).tw.

35. trial.ti.
36. (assign$ or allocat$).tw.
37. controls.tw.
38. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 9 and 16 and 38
40. limit 39 to human

Database: Ovid Medline® In-process & other non-indexed citations and Ovid

Medline ®

Search dates: 1946 - 18.8.2017

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebrovascular trauma/ or exp intracranial arterial diseases/ or exp intracranial arteriovenous malformations/ or exp "intracranial embolism and thrombosis"/ or exp intracranial haemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/ or exp hypoxia, brain/
2. (stroke$ or post stroke or poststroke or post-stroke or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or SAH).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.
5. exp hemiplegia/ or exp paresis/ or exp aphasia/ or exp gait disorders, neurologic/
6. (hempar$ or hemipleg$ or paresis or paretic or aphasi$ or dysphasi$).tw.
7. exp brain damage, chronic/ or brain injuries/ or exp brain concussion/ or exp brain haemorrhage, traumatic/ or brain injury, chronic/ or diffuse axonal injury/
8. craniocerebral trauma/ or exp head injuries, closed/ or exp intracranial haemorrhage, traumatic/
9. ((brain or cerebr$) adj5 (injur$ or hypoxi$ or damage$ or concussion or trauma$)).tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. anxiety/
12. anxiety disorders/ or agoraphobia/ or obsessive-compulsive disorder/ or panic disorder/ or phobic disorders/ or exp stress disorders, traumatic/
13. exp Anti-Anxiety Agents/
14. (anxiety or anxieties or anxious or agoraphobi$ or phobi$ or panic disorder$ or panic attack$ or (obsess$ adj3 compuls$) or post?traumatic stress$ or PTSD).tw.
15. (feel$ adj5 (apprehens$ or dread or disaster$ or fear$ or worry or worried)).tw.
16. manifest anxiety scale/
17. 11 or 12 or 13 or 14 or 15 or 16

18. Randomised Controlled Trials as Topic/
19. random allocation/
20. Controlled Clinical Trials as Topic/
21. control groups/
22. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
23. double-blind method/
24. single-blind method/
25. Placebos/
26. placebo effect/
27. cross-over studies/
28. randomised controlled trial.pt.
29. controlled clinical trial.pt.
30. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
31. (random$ or RCT or RCTs).tw.
32. (controlled adj5 (trial$ or stud$)).tw.
33. (clinical$ adj5 trial$).tw.
34. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
35. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
36. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
37. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
38. (cross-over or cross over or crossover).tw.
39. (placebo$ or sham).tw.
40. trial.ti.
41. (assign$ or allocat$).tw.
42. controls.tw.
43. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. 10 and 17 and 43
45. limit 44 to humans

Database: PsychINFO

Search dates: 1940 -17/8/17

1. cerebrovascular disorders/ or cerebral haemorrhage/ or exp cerebral ischemia/ or cerebrovascular accidents/ or subarachnoid haemorrhage/
2. (stroke$ or post stroke or poststroke or post-stroke or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or SAH).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.

5. hemiparesis/ or hemiplegia/ or exp aphasia/
6. (hempar$ or hemipleg$ or paresis or paretic or aphasi$ or dysphasi$).tw.
7. traumatic brain injury/ or brain damage/ or brain concussion/ or exp head injuries/
8. ((brain or cerebr$) adj5 (injur$ or hypoxi$ or damage$ or concussion or trauma$)).tw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp anxiety/
11. exp anxiety disorders/
12. anxiety management/
13. state trait anxiety inventory/ or taylor manifest anxiety scale/
14. (anxiety or anxieties or anxious or agoraphobi$ or phobi$ or panic disorder$ or panic attack$ or (obsess$ adj3 compuls$) or post?traumatic stress$ or PTSD).tw.
15. (feel$ adj5 (apprehens$ or dread or disaster$ or fear$ or worry or worried or terror)).tw.
16. 10 or 11 or 12 or 13 or 14 or 15
17. clinical trials/ or treatment effectiveness evaluation/ or placebo/
18. (random$ or RCT or RCTs).tw.
19. (controlled adj5 (trial$ or stud$)).tw.
20. (clinical$ adj5 trial$).tw.
21. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
22. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
23. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
24. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
25. (cross-over or cross over or crossover).tw.
26. (placebo$ or sham).tw.
27. trial.ti.
28. (assign$ or allocat$).tw.
29. controls.tw.
30. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 9 and 16 and 30
32. limit 31 to human
33. limit 32 to yr="1940 -Current"

Database: Cochrane Central Register of Controlled Trials (CENTRAL)

Search dates: Inception to 16.10.17

#1 [mh ^"cerebrovascular disorders"] or [mh "basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh "carotid artery diseases"] or [mh "cerebrovascular trauma"] or [mh "intracranial arterial diseases"] or [mh " intracranial arteriovenous malformations"] or [mh "intracranial embolism and thrombosis"] or [mh "intracranial haemorrhages"] or [mh ^stroke] or [mh "brain infarction"] or [mh ^"stroke, lacunar"] or [mh ^"vasospasm, intracranial"] or [mh ^"vertebral artery dissection"] or [mh "hypoxia, brain"]
#2 (stroke* or poststroke or "post-stroke" or apoplex* or cerebral next vasc* or cerebrovasc* or cva or SAH):ti,ab

#3 ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or "anterior circulation" or "basilar artery" or "vertebral artery") near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab
#4 ((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal next gangli* or putaminal or putamen or "posterior fossa" or hemispher* or subarachnoid) near/5 (haemorrhage* or haemorrhage* or haematoma* or hematoma* or bleed*)):ti,ab
#5 [mh ^hemiplegia] or [mh paresis] or [mh aphasia] or [mh "gait disorders, neurologic"]
#6 (hempar* or hemipleg* or paresis or paretic or aphasi* or dysphasi*):ti,ab
#7 [mh "brain damage, chronic"] or [mh ^"brain injuries"] or [mh "brain concussion"] or [mh "brain haemorrhage, traumatic"] or [mh ^"brain injury, chronic"] or [mh ^"diffuse axonal injury"]
#8 [mh ^"craniocerebral trauma"] or [mh "head injuries, closed"] or [mh "intracranial haemorrhage, traumatic"]
#9 ((brain or cerebr*) near/5 (injur* or hypoxi* or damage* or concussion or trauma*)):ti,ab
#10 (68-#9)
#11. [mh ^anxiety]
#12. [mh ^"anxiety disorders"] or [mh ^agoraphobia] or [mh ^"obsessive-compulsive disorder"] or [mh ^"panic disorder"] or [mh ^"phobic disorders"] or [mh "stress disorders, traumatic"]
#13. [mh "Anti-Anxiety Agents"]
#14. (anxiety or anxieties or anxious or agoraphobi* or phobi* or panic next disorder* or panic next attack* or (obsess* near/3 compuls*) or post next traumatic next stress* or PTSD):ti,ab
#15. (feel* near/5 (apprehens* or dread or disaster* or fear* or worry or worried)):ti,ab
#16. [mh ^"manifest anxiety scale"]
#17. {or #11-#16}
#18. #10 and #17

Database: EBSCO Health CINAHL Plus

Search dates: Inception to 16.10.17

#S1. (MH "Anxiety+") OR (MH "Anxiety Disorders+")
#S2. (MH "Stroke") OR (MH "Stroke Patients")
#S3. (MH "Brain Injuries+") OR (MH "Right Hemisphere Injuries") OR (MH "Left Hemisphere Injuries")
#S4. S1 AND S2 AND S3

2.2.2 Eligibility criteria

I included RCTs that evaluated interventions designed to target anxiety symptoms/ anxiety disorder as a primary outcome, with any comparator group (placebo, usual care, waitlist control, active comparator). I included RCTs that recruited participants aged 18 or over with ABI conditions: ischaemic or haemorrhagic stroke; SAH, confirmed by brain imaging with or without a lumbar puncture; moderate-to-severe TBI as defined according to the Scottish Intercollegiate Guidelines Network(69). I excluded mild TBI, a clinical group that was difficult to diagnose reliably(70). Where studies were carried out in a mixed sample, I included only those that recruited over 70% of stroke/SAH/ moderate-to-severe TBI. I excluded trials that recruited exclusively military veterans. No language restrictions were applied.

2.2.3 Data extraction and analysis

RN and I screened titles and abstracts independently and excluded ineligible titles. We assessed full text for eligibility and resolved discrepancies through discussion. A neuropsychiatrist was consulted if a consensus could not be reached. RN and I extracted data independently using an electronic data extraction form. I collated the final data. I assessed studies that were only available in Chinese. I recorded characteristics of the study population: ABI diagnosis, age, sex, exclusion of specific deficit, baseline anxiety level, and intervention type (e.g. psychotherapy, pharmacotherapy, other).

Quality assessment

I reported the level of bias across six domains of study design for the included studies: (A) random sequence generation, (B) allocation concealment, (C) blinding of participants and personnel, (D) blinding of outcome assessment

(E) incomplete outcome data, and (F) selective reporting. I categorised the level of bias into 'low', 'high' or 'unclear' and recorded justification for the judgement for each domain in accordance with the Cochrane Risk of Bias Tool (http://methods.cochrane.org/bias/assessing-risk-bias-included-studies).

Efficacy of intervention

I estimated effect size for each comparison by calculating the standardised mean difference (SMD) with 95% confidence intervals (CI) using the mean and standard deviation (SD) of the post-intervention anxiety severity. I carried out meta-analysis for studies of the same intervention type using inverse variance and random-effects models. All analysis was performed using the Cochrane Review Manager (RevMan) Version 5.3(71). Where data were not reported in study publication I contacted the corresponding authors for further information.

Key study characteristics and potential bias in trial design

I summarized the key study characteristics: anxiety type targeted, the setting and timing of intervention, outcome measures, the type of comparator, and ways that could have introduced or minimised potential bias in study design.

2.3 Results

The electronic searches yielded 8218 titles after removal of duplicates (Figure 7). Of the 59 full text articles reviewed, 14 eligible studies with 928 participants were included. Sample size ranged from 17 to 206. Four studies were in Chinese(72-75). No clear evidence of publication bias on the funnel plot (Figure 8)

Figure 7. PRISMA diagram for reporting study inclusion in systematic review

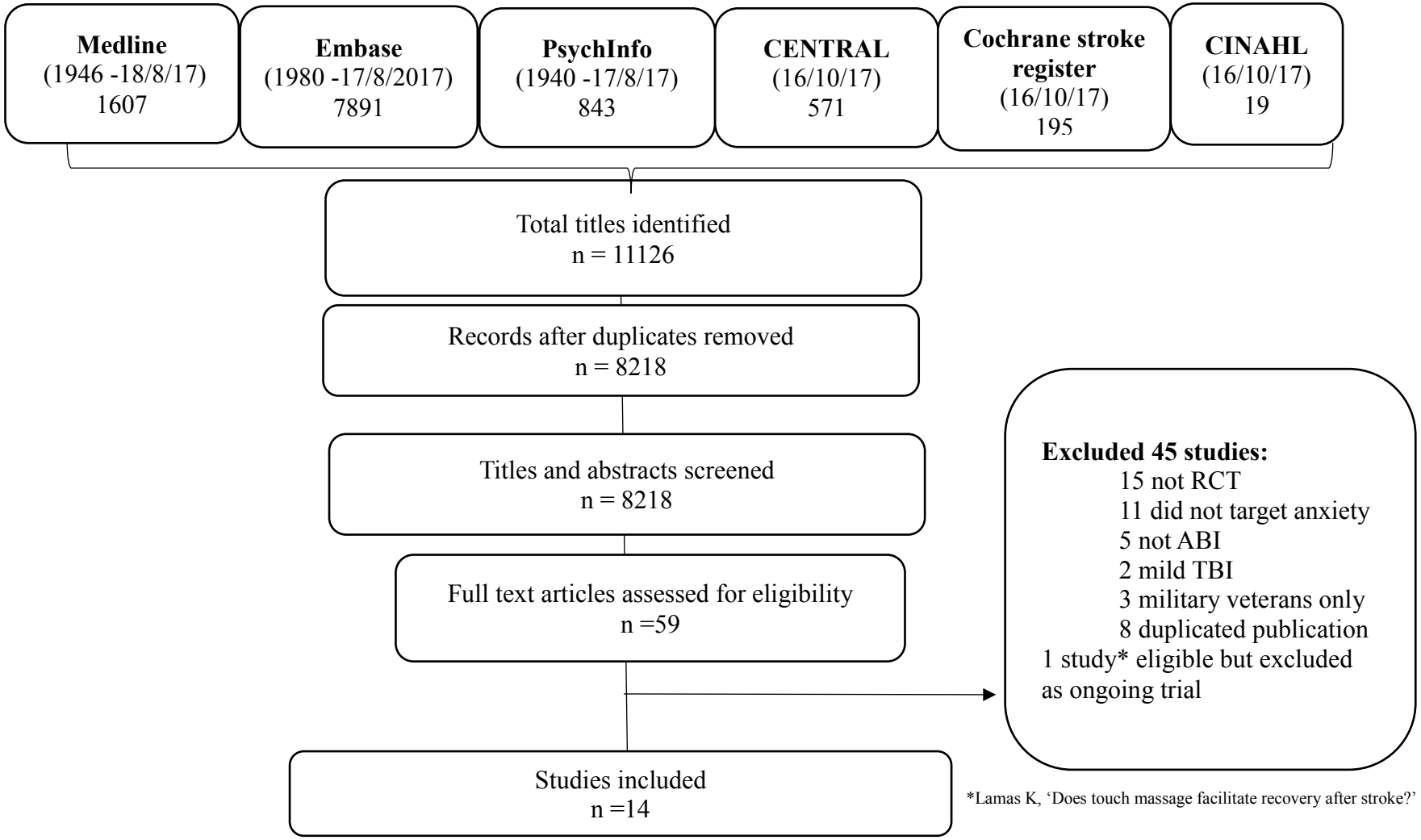
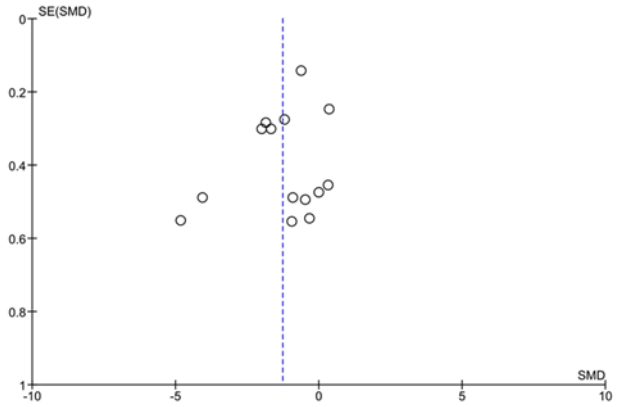


Figure 8. Funnel plot of included studies in the systematic review



2.3.1 Characteristics of study population

Table 5 summarizes the characteristics of the study population in the 14 included studies. 12 studies recruited stroke patients only (ischaemic and primary haemorrhage)(72-83), one study recruited stroke and moderate-to-severe TBI(84), and one study recruited moderate-to-severe TBI only(85). No study recruited patients with SAH. The mean age ranged from 48 to 72 years in studies of stroke patients only, and from 35 to 58 years in the two studies that included TBI patients. More men than women were recruited in all included studies. 12 studies excluded patients with communication difficulties due to aphasia or cognitive impairment(72-74, 76-82, 84, 85); one yoga exercise intervention excluded participants who were unable to ambulate independently(77).

Seven studies required participants to have a baseline diagnosis of anxiety disorder or 'emotional distress' either made on standardised diagnostic criteria e.g. DSM-IV-TR, or by meeting a defined cut-off on a rating scale(72, 73, 79, 82-85). Six studies did not specify a baseline anxiety level for inclusion (74-

78, 80). One study of a preventative intervention excluded the diagnosis of GAD on DSM-IV-TR at baseline(80).

2.3.2 Methods for assessing anxiety

Studies used different anxiety rating scales at baseline and outcome assessment: Hamilton Anxiety Rating Scale (HAMA) in five studies (72, 73, 75, 81, 83), Hospital Anxiety and Depression Scale-anxiety subscale (HADS-A) in three studies (79, 80, 85); State-Trait Anxiety Inventory (STAI) in three studies (76-78); Depression Anxiety Stress Scales (DASS) in one study(84); Zung Self-rating Anxiety Scale (SAS) in one study(74); Beck Anxiety Inventory (BAI) in one study(82).

2.3.3 Study quality assessment

None of the 14 studies scored 'low' risk of bias across all six domains (A-F) of study design (Figure 9). Three studies scored 'low' risk across five domains (80, 81, 85). Two studies scored 'low' risk across four domains(82, 84). One studies scored 'low' risk across three domains(77). Eight studies scored 'low' risk on fewer than three of the six domains(72-76, 78, 79, 83), including six studies that scored 'high' risk or 'unclear' risk across all six domains(72-76, 83).

2.3.4 Efficacy of intervention

The 14 included studies provided 19 comparisons: eight psychotherapy(74, 80-82, 84, 85), five pharmacotherapy(72, 73, 75, 81), one combined pharmacotherapy and psychotherapy(72), two exercise(76, 77), and three other interventions(78, 79, 83). I carried out meta-analyses for psychotherapy and pharmacotherapy studies (Figure 9).

Table 5. Characteristics of study population in included studies (n= 14)

Study by year	**ABI**	**Anxiety type targeted**	**Eligible time since injury**	**Setting**	**Exclusion of specific deficit** e.g. speech	**Sample size**	**Type of intervention (I) and control (C), number randomized (n)** ***'description'***		**Age Mean (SD)**		**Female %**		**Baseline anxiety level** measure: mean (SD)	**Time of intervention since injury** mean (SD)	
							I	**C**	**I**	**C**	**I**	**C**		**I**	**C**
Zhang 2001 (74)	stroke	unspecified	not specified	Setting not given, China	NA	206	Psychotherapy (n=103) *'One weekly sessions, each lasting 20-30 minutes, for 5-6 weeks, delivered by trained researcher using in-house manual'*	Usual care (n=103) *'Usual care'*	NA	NA	NA	NA	SAS I) 34(8) C) 31 (8)	NA	NA
Ye 2004 (73)	stroke	'mixed anxiety and depression'	not specified	Neurology inpatient, China	Impairment of comprehension	90	1) Paroxetine (n=31) *'20mg daily for 12 weeks'* 2) Imipramine (n=32) *'incremental regime of 50-150mg daily for 12 weeks '*	Routine care (n=30) 'Routine care: for 12 weeks'	1) 58.04 (8.28) 2) 56.9 (11.36)	59.21 (9.52)	1) 26 2) 37	43	HAMA 1) 18.2 (4.6) 2) 18.9 (4.4) C) 17.9 (2.24) Required diagnosis of mixed anxiety and depression on CCMD	NA	NA
Wang 2005 (72)	stroke	'mixed anxiety and depression'	'acute' stroke	Neurology inpatient, China	Aphasia; severe cognitive impairment	81	1) paroxetine (n=27) *'20mg daily for 6 weeks'* 2) paroxetine + psychotherapy (n=27) *'Paroxetine 20mg daily + weekly psychotherapy session lasting 30-60 minutes, delivered by psychiatrist for 6 weeks'*	Routine care (n=27) *'routine stroke care'*	1) 62.4 (6.1) 2) 64.0 (5.3)	63.2 (5.7)	1) 48 2) 48	48	HAMA 1) 14.0 (2.8) 2) 13.9 (2.9) C) 13.8 (2.8) Required diagnosis of mixed anxiety and depression on CCMD	1) 21.7 days (4.9) 2) 22.0 days (4.7)	21.4 days (5.0)
Zhang 2005 (75)	stroke	unspecified	not specified	Neurology inpatient, China	NA	94	Buspirone butylbromide (n=47) *'A 2-week course of buspirone butylbromide (first week 20-30mg/day, second week 40-60mg per day)'*	Routine care (n=47) *'Routine care'*	57.8 (6.4)	59.2 (5.8)	36	38	HAMA I) 22.7 (5.2) C) 22.5 (4.3)	NA	NA
Wu 2008 (87)	stroke	'post-stroke neurosis'	not specified	Outpatient, China	Aphasia; cognitive impairment	67	acupuncture (n=34) *'acupuncture once a day for 2 courses with 15 times as one course'*	alprazolam (n=33) *'0.4-0.8mg 3 times a day for 4 weeks'*	48-72	49-70	44	48	HAMA I) 22.31 (3.1) C) 22.3 (3.2) Required diagnosis of post-stroke neurosis on ICD-10	Range: 15-53 days	Range: 15-61 days

Table 5 continued

Study by year	**ABI**	**Anxiety type targeted**	**Eligible time since injury**	**Setting**	**Exclusion of specific deficit** e.g. speech	**Sample size**	**Type of intervention (I) and control (C), number randomized (n)** *'description'*		**Age Mean (SD)**		**Female %**		**Baseline anxiety Level** measure: mean (SD)	**Time of intervention since injury in sample** mean (SD)	
							I	**C**	**I**	**C**	**I**	**C**		**I**	**C**
Aidar 2012 (76)	ischaemic stroke	unspecified	>=1 year	Community, Portugal	Aphasia	29	Resistance exercise training (n=14) *'4 familiarization sessions + 3 pre-treatment sessions + 12 treatment sessions delivered 3 times a week, focused on walking & strength training.* *Duration: each session lasted 45-60minutes with minimum 48-hour rest between sessions.'*	Usual care (n=15) *'continue normal daily activities'*	51.7 (8.0)	52.5 (7.7)	45	31	STAI (data not available)	NA	NA
Chan 2012 (88)	stroke	unspecified	>=6 months	Community, Australia	Unable to follow 2-stage commands; unable to ambulate for 10m or more	17	*Yoga and exercise (YEX) (n=9)* *'90-minute group yoga class once per week for 6 weeks plus 24 individual 40-minute home practice sessions + Exercise (EX)'*	Exercise only (EX) (n=8) *'50-minute exercise class, once per week for 6 weeks'*	67.1 (15.4)	71.7 (12.7)	13	17	STAI-state I) 36.8 (11.6) 2) 37 (5.8)	6.4 years (3.0)	11.2 years (5.8)
Hsieh 2012 (85)	moderate-to-severe TBI	unspecified	not specified	Community, Australia	Language impairment	27	1) Motivational interviewing (MI) + Cognitive Behavioural Therapy (CBT) (n=9) *'3 weekly MI sessions + 9 weekly CBT sessions'* 2) Non-directional counselling (NDC) + CBT (n=10) *'3 weekly NDC sessions + 9 weekly CBT sessions'* *Both delivered by clinical psychologist or clinical neuropsychologist*	Usual care and waitlist (n=8) *'offered CBT after waitlist period'*	1) 41.8 (15.2) 2) 36.4 (14.1)	35.6 (9.8)	1) 22 2) 30	13	HADS-A 1) 11.9 (3.3) 2) 13.0 (5.0) C) 11.8 (4.3) DSM-IV TR anxiety disorder or adjustment issues required	1) 37.2 months (45.4) 2) 50.4 months (89.7)	23.0 months (18.5)

Table 5 continued

Study by year of publication	**ABI**	**Anxiety type targeted**	**Eligible time since injury**	**Setting**	**Exclusion of specific deficit** e.g. speech	**Sample size**	**Type of intervention (I) and control (C), number randomized (n)** ***'description'***		**Age Mean (SD)**		**Female %**		**Baseline anxiety level** measure: mean (SD)	**Time of intervention since injury in sample** mean (SD)	
							I	**C**	**I**	**C**	**I**	**C**		**I**	**C**
Mikami 2014 (81)	stroke	Generalized anxiety disorder (GAD)	within 3 months	Community, USA	Severe comprehension deficits	149	1) Escitalopram (n=47) *'5 or 10mg per day for 12 months'* 2) Problem solving therapy (PST) (n=53) *'manual-based, 6 treatment sessions (weeks 1, 2, 3, 4, 6 and 10), plus 6 reinforcement sessions (Months 4, 5, 6, 8, 10 and 12)'*	Placebo (n=49) *'Placebo pills'*	1) 61.5 (13.7) 2) 68.3 (10.4)	64.8 (13.5)	1) 36 2) 45	33	HAMA 1) 7.1 (5.6) 2) 8.3 (5.4) C) 6.8 (4.4) Excluded DSM-IV TR GAD diagnosis	NA	NA
Hoffman n 2015 (80)	stroke	unspecified	not specified	Stroke unit inpatient & community, Australia	communication difficulties/ cognitive impairment	33	1) Coping skills (n=11) *'cognitive and behavioural exercises, delivered by clinical psychologist'* 2) Self-management (n=12) *' Information provision and activities to learn problem solving skills, delivered by occupational therapist'*	Usual care (n=10) *'multidisciplinary care on stroke unit'* *Both interventions 1) and 2) consist of 8 one-hour face-to-face sessions, with first 2 sessions delivered pre-discharge, and remaining sessions at patient's home*	1) 63.6 (13.0) 2) 60.8 (11.7)	57.0 (14.2)	1)36 2) 25	40	HADS-A 1) 5.3 (2.9) 2) 5.7 (0.5) C) 8.4 (3.1)	NA	NA

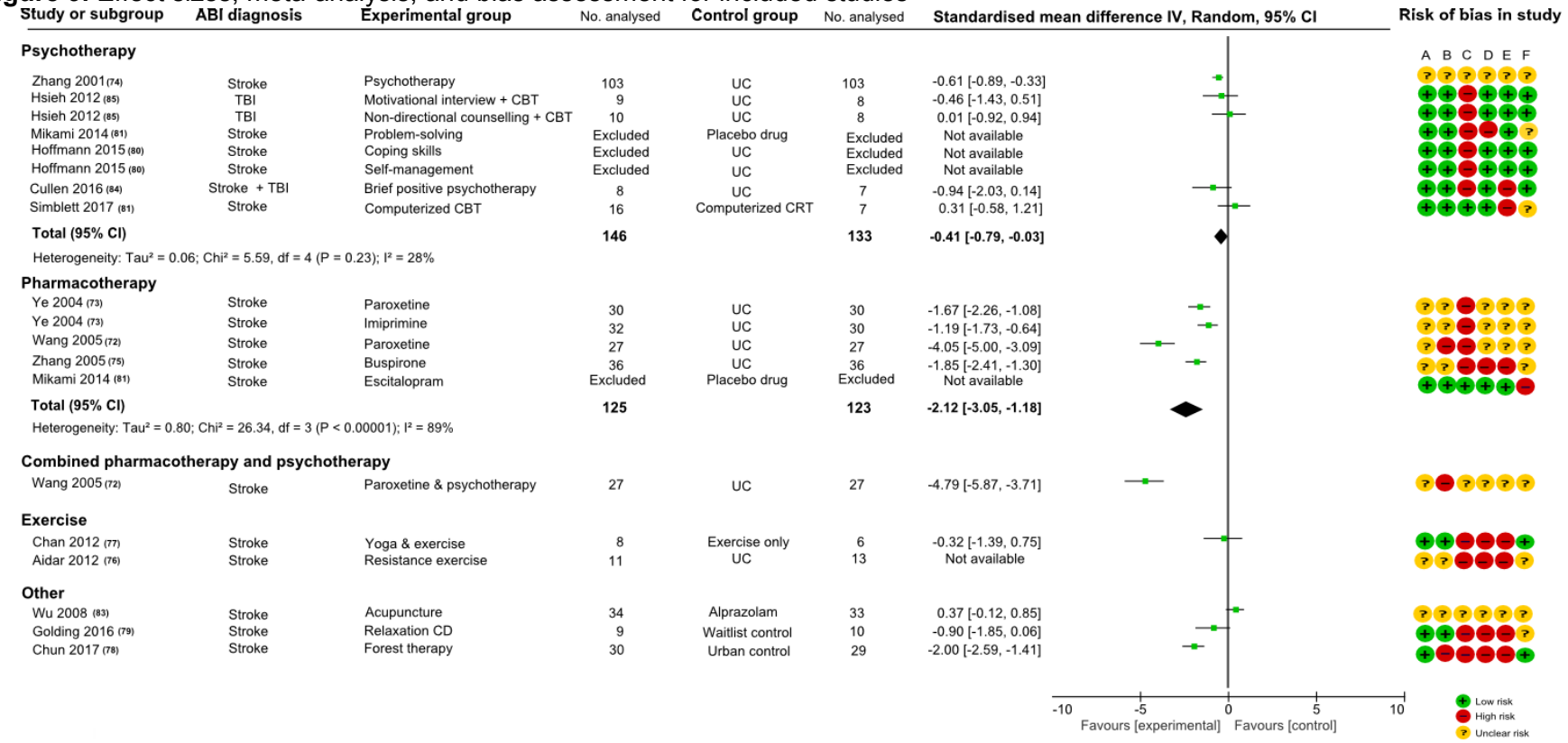
Study by year	**ABI**	**Anxiety type targeted**	**Eligible time since injury**	**Setting**	**Exclusion of specific deficit** e.g. speech	**Sample size**	**Type of intervention (I) and control (C), number randomized (n)** ***'description'***		**Age Mean (SD)**		**Female %**		**Baseline anxiety level** measure: mean (SD)	**Time of intervention since injury in sample mean (SD)**	
							I	**C**	**I**	**C**	**I**	**C**		**I**	**C**
Cullen 2016 (84)	stroke; moderate-severe TBI	'emotional distress—anxiety and/ or depression'	3-36 months	Outpatient clinic, UK	Significant communication impairments	27	Brief positive psychotherapy (n=14) *'One-to-one weekly sessions with psychologist for 8 weeks—Psychoeducation about ABI and positive psychology (Week 1), therapeutic exercises and homework (Weeks 2-7), midpoint review at (Week4), final review and plan for maintenance (Week 8)'*	Usual care (n=13) *'Within clinical service'*	median 54.0 (IQR 46.0-59.0)	median 58.0 (IQR 56.0-68.0)	36	39	DASS-21 anxiety I) 17.6 (9.7) C) 21.1 (9.4) Had to score moderate-to-above on at least depression or anxiety subscale on DASS-21	median: 5.8 months (IQR 3.5-8.2)	median: 5.6 months (IQR 3.1-8.4)
Golding 2016(79)	stroke	unspecified	Not specified	Community, UK	Unable to complete telephone questionnaire	21	I: relaxation CD *'self-help autogenic relaxation CD, five times per week for a month with diarly sheets; each session 20-minute in length, instructions on body awareness'*	Waitlist	67.8 (7.5)	62.4 (8.4)	40	50	HADS-A I) 10.9 (3.4) C) 10.5 (3.5) Had to score at least 6 on HADS-A	118 months (101)	70 months (70)
Chun 2017(78)	stroke	unspecified	At least 1 year after stroke onset	Community, Korea	Severe cognitive or communication impairment	59	I: Forest therapy *'4-day and 3-night program at recreational forest area, consisting of 1) promoting positive emotion through mediation, 2) experiencing the forest through all five sense and 3) walking in the forest'*	Urban group *'stay in a hotel, with similar mediation and walking activities in the urban area'*	62.1 (8.3)	59.5 (9.7)	37	28	STAI I) 38.1 (11.0) C) 34.3 (12.1)	140 months (90)	153 months (84)
Simblett 2017 (89)	stroke	'emotional distress—anxiety and/or depression'	within 5 years	Community, UK	Impairment of comprehension; visual or auditory problem that would interfere participation and could not be corrected	28	Computerised cognitive behavioural therapy (cCBT) (n=19) *'An 8-module online course--'Beating the Blues', one module per week for 8 consecutive weeks'*	Computerised Cognitive remediation therapy (cCRT) (n=9) *' An 8-module online course-'ForamenRehab', one module per week for 8 consecutive weeks'*	62.1 (11.4)	64.6 (8.1)	47	11	BAI I) 11.2 (7.6) C) 8.3 (6.2) Required 'emotional distress': BDI >13 or BAI >7	Median: 1.19 years (IQR 0.5-1.1)	Median: 0.89 years (IQR 0.6-4.1)

Table 5 continued

											Both the intervention and active control are delivered via computer, facilitated by a researcher via telephone/email/face-to-face

I indicates intervention; C, control; n, number; SD, standard deviation; IQR, interquartile range; NA, data not available; DASS, Depression Anxiety Stress Scales; DSM-IV, Diagnostic Statistical Manual of Mental Disorders, fourth edition; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; CCMD, Chinese Classification of Mental Disorders, third version; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Rating Scale for Depression; SAS, Zung Self-Rating Anxiety Scale. STAI, State Trait Anxiety Inventory

Figure 9. Effect sizes, meta-analysis, and bias assessment for included studies



ABI, acquired brain injury; IV, inverse variance; CI, confidence intervals; UC, usual care; TBI, traumatic brain injury; CBT, cognitive behavioural therapy; CRT, cognitive remediation therapy. Risk of bias: (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Incomplete outcome data (attrition bias); (F) Selective reporting (reporting bias)

Psychotherapy

Six studies provided eight comparisons of psychotherapy interventions, the contents of each are summarized in Table 5. Data were not available for three comparisons after contacting study authors. Meta-analysis of the five comparisons showed an overall positive effect favouring psychotherapy intervention over control (SMD: -0.41 [95%CI -0.79, -0.03]). I^2 statistic of 28% suggests a low-to-moderate level of heterogeneity across studies (Figure 9). The only study that demonstrated an effect favouring *'psychotherapy'* over usual care(74) received 'unclear' risk of bias across all six domains of study design. The remaining four neutral comparisons (one '*brief positive psychotherapy*' versus usual care(84), one *'motivational interviewing & CBT'* versus usual care(85); one *'non-directional counselling & CBT'* versus usual care(85), one *'computerised CBT'* versus computerised cognitive remediation therapy(82)) received 'low' risk of bias across at least three domains of study design; all had small sample sizes. One comparison not included in my analysis reported that group receiving placebo was four times more likely to develop GAD compared to 'problem-solving' therapy (adjusted hazard ratio: 4.00 [95%CI 1.84, 8.70])(21). The other two comparisons not included in my analysis reported a non-statistically significant reduction in adjusted mean HADS-anxiety score with psychotherapy: 'coping skills' versus usual care (-0.5, [95%CI -2.0, 1]); 'self-management' versus usual care (-0.6, [95%CI -2.0, 0.8]) (20).

Pharmacotherapy

Four studies provided five comparisons of pharmacotherapy versus control, data were not available in one comparison after contacting study author(81). Meta-analysis of these four comparisons showed an overall effect

favouring pharmacotherapy intervention over control (SMD: -2.12 [95%CI -3.05, -1.18]). I^2 statistic of 89% suggests a high level of heterogeneity across studies. Two of these comparisons were between paroxetine, an SSRI and usual care (72, 73). One comparison was between imipramine, a tricyclic antidepressant (TCA) and usual care(73). One study compared buspirone, an azapirone anxiolytic with usual care (75). All four comparisons were from three studies which scored 'high' risk or 'unclear' risk of bias across all domains of study design. The study without available data for analysis reported that group receiving placebo was four times more likely to develop GAD compared to escitalopram (adjusted hazard ratio: 4.95 [95%CI 1.54-15.93])(81).

Combined pharmacotherapy and psychotherapy

One comparison of combined paroxetine and psychotherapy with usual care demonstrated a large effect favouring combined therapy (SMD -4.79 [95%CI -5.87, -3.71])(72). This study scored 'unclear' and 'high' risk of bias across all six domains of study design.

Exercise intervention

Two studies evaluated exercise interventions, One study compared yoga and exercise with exercise only and showed a neutral effect(77). One study on resistance exercise reported lower state anxiety favouring resistance exercise over usual care but data were unavailable for calculating SMD after contacting the study author(76). Both studies had small sample sizes. The yoga study scored 'low' risk of bias across three domains of study design and the study on resistance exercise scored 'high' and 'unclear' risk of bias across all six domains.

Other therapies

One study compared acupuncture with alprazolam (83), one study compared relaxation CD with waitlist control(79). Both of these studies were neutral. The study of acupuncture scored 'unclear' risk of bias across all six domains, and the study of relaxation CD scored 'high' risk of bias across more than three domains of study design. One study compared forest therapy with urban control and demonstrated an effect favouring forest therapy (SMD: -2.00 [-2.59, -1.41]). This study scored 'high' risk of bias on four domains of study design. All three studies had small sample sizes.

2.3.5 Characteristics of study design

Anxiety subtype targeted

One study specified GAD as the target of its interventions (escitalopram; problem solving therapy)(81). No study targeted phobic disorder. Two studies of pharmacotherapy (SSRI, TCA), and combined pharmacotherapy (SSRI) and psychotherapy specified a diagnosis of 'mixed anxiety and depression' as an inclusion criterion and had positive results (72, 73). Two studies of psychotherapy (brief positive psychotherapy; computerised CBT) targeted 'emotional distress'—anxiety and/or depression and were neutral (82, 84). One study of acupuncture and alprazolam targeted 'post-stroke neurosis' which is now a defunct diagnosis(83). The remaining eight studies targeted 'anxiety' without subtyping(74-80, 85), three of them were positive(74, 75, 78).

Setting of intervention

Seven studies were carried out in the community(76-79, 81, 82, 85), three studies in an inpatient setting(72, 73, 75), two in outpatient clinic(83, 84), and one

commenced in an inpatient setting then continued in the community(80). One study did not report setting of the intervention (74). Only one community-based study was positive (78). All three inpatient studies and the study with unknown setting were positive.

Timing of intervention since injury

Seven studies specified time since injury as an inclusion criterion: 'acute stroke'(72); within 3 months(81); between 3-36 months(84); anytime within 5 years(82); at least 6 months(77); at least one year(76, 78). The actual time of intervention since injury in the studied sample ranged from 15 days to 13 years. Of the five positive studies, three did not report timing of intervention since injury in studied samples, one study reported intervention at 21 days from injury(72), and one reported intervention at 140-150 months (11-13 years)(78).

Timing of outcome measures

Eight studies measured anxiety outcome at the end of the intervention(72, 73, 75-78, 83, 85). Other studies measured primary outcome at various time points post-intervention: 2 weeks; 8 weeks; 12 weeks; 12 months. Four of the five positive studies measured primary outcome at the end of intervention(72, 73, 75, 78) and one measured at two weeks post-intervention(74).

Comparator

'Usual care' was the most commonly used control condition. Four studies used an active comparator(77, 78, 82, 83) and one study used a placebo control(81). Four of the five positive studies used 'usual care' as control conditions(72-75) and one used an active control(78).

2.3.6 Summary of sources of potential bias in study design

A) Random sequence generation

Studies scoring 'unclear' risk of bias in this domain only reported that patients were randomly allocated but did not give detail on how, and by whom the randomisation sequence was generated. Studies scoring 'low' risk reported the type of randomisation carried out e.g. computerised randomisation, stratified randomisation with blocking, random number generator, and by whom the randomisation was performed e.g. person external to the study/ independent of the study

B) Allocation concealment

Studies scoring 'high' risk of bias did not report how allocation sequence was concelaed. Studies scoring 'low' risk reported methods that would prevent the study team from knowing the allocation in advance e.g. allocation informed via mailed letters by external person who carried out randomisation, study personnel were blinded to randomisation block length with randomisation performed externally, use of opaque/ sealed envelopes pre-filled by person independent of the study.

C) Blinding of participants and personnel

Most studies scored 'high' risk in this domain as blinding of participants was rarely attempted. The most common comparator group was 'usual care'. I considered participant blinding sufficient in the study that used computerised CRT as a comparator of computerised CBT, and the study that used placebo as a comparator of escitalopram.

D) Blinding of outcome assessment

Studies scoring 'high' risk reported outcome assessment being performed by the same study personnel that delivered the interventions. Studies that scored 'low' risk reported methods to blind outcome assessment e.g. a second research assistant performed outcome assessment using a standard script to prevent unblinding, use of self-rated questionnaires and data entry by blinded assessor.

E) Incomplete outcome data

All studies scoring 'high' risk lost follow-up data (attrition ranged from 2 – 22%) and did not perform intention-to-treat analysis. Reasons for attrition were: personal reasons, additional health concerns/ injury unrelated to intervention, improved mood, other commitments, lack of time, found it distressing to talk about difficulties, wish to discontinue involvement.

F) Selective reporting

I examined the published trial protocol, if available, for each included study to detect whether selective reporting was present. One study scoring 'high' risk reported results on anxiety from the same study in an earlier publication that evaluated the intervention for depression prevention.

2.4 Discussion

2.4.1 Key findings

My findings suggest efficacy of psychotherapy and pharmacotherapy interventions in the treatment of anxiety after ABI. The positive effect sizes were driven entirely by studies of low quality. These findings alone are not definitive evidence to guide treatment of anxiety after stroke.

2.4.2 Limitations and strengths of this review

Limitations

Data for calculating SMDs were missing in four comparisons despite contacting corresponding authors. I included one mixed ABI (strokes in >85% of intervention and control groups), and one TBI-only samples. Almost all studies excluded patients who had communication impairments e.g. dysphasia, cognitive impairment, and varied in settings, timing since injury, timing of outcome measures, limiting the generalisability of my findings.

Strengths

Compared to previous systematic reviews in stroke and TBI (65, 67) I opted to include studies from a broader ABI population encompassing stroke (ischaemic, primary haemorrhage, SAH) and moderate-to-severe TBI, and included a wider continuum of baseline anxiety levels (i.e. not limited to patients with a baseline anxiety diagnosis). This approach led to more studies to be included in my review, and enabled meta-analysis of the same type of anxiety interventions for the first time. Furthermore, I found studies that were better reported and of better quality which were excluded in the previous reviews. This enabled a summary of key aspects of trial design and measures to minimise bias in order to help guide trialists, including myself, in designing high quality RCTs in the future.

2.4.3 Implications for intervention design

Anxiety subtype targeted

Studies have targeted ‘mixed anxiety and depression’, ‘emotional distress (anxiety and/or depressive symptoms)’, or ‘anxiety’. Only one study specified the prevention of GAD as the target of intervention. No studies targeted phobic

disorder. Phobic disorders e.g. agoraphobia may be more common after stroke(56).

Intervention design should reflect the treatment approaches known to be effective at treating these anxiety subtypes in non-stroke populations. Anxiety with a phobic element invariably requires some form of behavioural therapy with exposure work, while generalised anxiety is treated with other CBT techniques e.g. cognitive restructuring, problem solving, and/or medications e.g. SSRI. Although the content of psychotherapy interventions varied across the included studies, the majority of interventions consisted of some form of, or a combination of psychoeducation, skills learning e.g. problem solving, positive psychology, therapeutic exercises, and CBT. Interventions for anxiety after stroke should encompass components that aim to address the symptomology of both phobic and generalised anxiety subtypes. A variety of anxiety rating scales were used to assess primary outcome in the included studies. These are validated for generalised anxiety and none for the phobic subtype. The choice of outcome measures should reflect both types of anxiety symptomology given that phobic disorder may also be common after stroke.

Setting and timing of intervention, and timing of outcome measures

Most of the positive studies were carried out in an inpatient setting and measured primary outcome immediately post-intervention. This approach does not address the consistent finding from other studies that anxiety continues to be frequent at six-months or more post-stroke(56) and cannot generalise to patients who have returned to living in the community. An anxiety intervention should aim to relieve anxiety and its debilitating impact on stroke patients in the long-term. Determining the best time of outcome measure should be based on this goal and

be balanced against the feasibility of study procedures to ensure completion of long-term follow-up. My supervisors and I felt it reasonable to measure outcome at the end of the intervention and then after a period with no treatment to see whether any benefits would be sustained.

2.4.4 Implications for trial design

Most of the positive studies in this review were poorly reported across all aspects of study design on the Cochrane bias assessment tool. All trialists should adhere to standardised reporting guidelines e.g. Consolidated Standards of Reporting Trials (CONSORT) checklist on RCTs, and the TiDier (Template for Intervention Description and Replication) checklist when evaluating complex interventions, both of which can be found on the EQUATOR (Enhancing the QUAlity and Transparency of health Research network) website: http://www.equator-network.org/reporting-guidelines/consort/.

Participant blinding and control conditions

Most of the included studies did not attempt participant blinding. 'Usual care' was the commonest comparator in this review and in four out of the five positive studies. The description of what constituted 'usual care' was minimal across the included studies. 'Usual care' and waitlist controls have been shown to exaggerate effect size in meta-analyses of trials evaluating psychotherapy(90). A recently published transparent decision framework helps guide trialists select the appropriate type of control based on several factors: participants' interests (expected benefit, or harm or worsening of symptoms induced by the control condition), the researchers' interests (available resources, maximizing validity of findings), and trial purpose (e.g. phase 2, phase 4) (91). Placebo is the gold-

standard comparator for pharmacotherapy intervention. In a trial of psychotherapy or other non-pharmacological intervention, an active comparator or another established treatment that is known to be effective and widely available in the 'real world' would be more appropriate as a control in phase 3 or phase 4 (pragmatic/ real world) trials(91).

Other measures to minimise bias

Some included studies provided examples of good practice in minimizing bias in other domains: external personnel to randomise patient; allocation concealment to ensure study personnel could not foresee allocation while recruiting; use of outcome assessors blinded to allocation; use of standard script at telephone follow-up to prevent unblinding; use of self-completed outcome measures; data input by blinded external assessor; reporting missing data and methods for handling missing data; intention-to-treat analysis; publishing protocol on trial registries.

Studies should also provide detailed description of the experimental intervention and control condition to ensure standardised procedures are given to all participants of each arm e.g. use of manuals. Adherence to the allocated treatment and any deviation from standardised procedures should be recorded and reported.

2.4.5 Summary of key points from this chapter

- There is low quality evidence to suggest psychotherapy and pharmacotherapy may be effective interventions in the treatment of anxiety after stroke
- The evidence is from underpowered studies that carried high risk of bias.

- Trials have not distinguished between different anxiety subtypes, and have not tailored the treatment to specific type
- Large-scale well-designed definitive trials are needed to establish whether pharmacotherapy or psychotherapy works
- Compared to pharmacological interventions, psychological or behavioural interventions pose unique challenges in trial methodology, both in its execution and in bias minimisation
- My review highlighted the key strengths and weaknesses of existing anxiety intervention and trial design. These findings will help me design the TASK intervention to be clinically relevant and feasible, as well as ensuring that I take measures to minimise bias in the TASK RCT design.

Chapter 3

Anxiety after stroke: the importance of subtyping—a prospective cohort study

Publication status and acknowledgement of contribution

This chapter has been published in the February 2018 issue of Stroke (Appendix B). I designed and wrote the protocol and ethics application for this study with input from my supervisors. I carried out all study procedures including recruitment, data collection, and data analysis. I received assistance from the Scottish Stroke Research Network in participant recruitment to this study at the Royal Infirmary of Edinburgh. Professor Alan Carson provided training in the use of SCID, supervised all my SCID interviews, and provided final confirmation of all psychiatric diagnoses made in this study. Dr William Whiteley provided guidance in my data analysis, statistics, and data visualisation.

I wrote the initial draft, subsequent and final versions of all published and accepted manuscripts following comments from my supervisors. I made minor editorial changes to the published version in this chapter and added Section 3.5, 'Implications for my anxiety intervention design'.

3.1 Introduction

Anxiety is common, affecting around a quarter of stroke(56), and nearly a third of transient ischaemic attack(TIA)(57). It can hamper stroke rehabilitation effort and prevent patients from returning to their usual activities. Despite earlier observations that phobic anxiety might be present after stroke(62-64), intervention studies have treated anxiety post-stroke as one unitary phenomenon and evaluated general approaches such as relaxation and antidepressants(67), which are unlikely to be effective in phobic anxiety. Clinical trials have not yielded any definitive evidence to guide treatment for anxiety after stroke(67). It is well recognised in non-stroke populations that phobic and generalised anxiety disorders need different treatment approaches.

Phobic and generalised anxiety

Phobic anxiety is characterized by a disproportionate fear of well-defined situations or stimuli(33). Exposure to the feared situation triggers unpleasant anxiety symptoms, accompanied by marked avoidant behaviour of that feared situation: the hallmark of phobic anxiety(33). Whilst avoidant behaviour may relieve anxiety in the short-term it can become disabling if the behaviour becomes consolidated through conditioning e.g. becoming housebound in agoraphobia as a result of learning to associate ‘danger’ with ‘leaving house’. Treatment of phobic disorders requires systematic, repeated, hierarchical exposure to the specific anxiety-provoking stimulus(45). By contrast, GAD is diffuse and unremitting, characterized by persistent and multiple worries e.g. finances, health, and an inability to stop worrying(33). SSRI, benzodiazepines (in short term only), and/ or other CBT techniques e.g. cognitive restructuring, problem solving are effective at treating GAD(49, 50).

Aims

To determine the target for anxiety treatment after stroke, I need to know the proportions of anxiety subtypes; if phobic, the specific stimuli; the factors associated with anxiety; the impact of anxiety on functional outcomes and quality of life. I aim to report i) the frequency of phobic disorder and GAD at three months after stroke and TIA, ii) avoidant behaviour of specific anxiety-provoking situations, iii) the predictors of anxiety and, iv) the associations with dependence, quality of life, and social participation.

3.2 Methods

3.2.1 Sampling and recruitment

Prospective recruitment

I screened consecutive eligible patients admitted to the acute stroke unit and TIA clinics in NHS Lothian—the sole provider of stroke and TIA services for the city of Edinburgh, Midlothian and East Lothian regions in Scotland, between 9th September, 2015 and 28th June, 2016. I included participants who (i) were aged 18 or over, (ii) had a new clinical diagnosis of stroke, 'definite', or 'probable TIA', (iii) had mental capacity to give informed consent, and (iv) were able to communicate in English on the telephone. I excluded patients with subarachnoid haemorrhage, subdural and extradural hematoma, ocular TIA, patients at terminal stage of life, or who were difficult to follow-up–no fixed abode, current illicit or alcohol dependence

Definitions of stroke and TIA

I used clinical diagnosis of stroke or TIA made by consultant stroke clinicians according to the following: *stroke*—the sudden loss of focal cerebral function, lasting 24 hours or longer, thought to be caused by an inadequate blood supply to part of the brain (ischaemic stroke), or spontaneous haemorrhage into the brain substance (primary intracerebral haemorrhagic), where brain imaging was normal or showed evidence of recent ischemia or haemorrhage(1); *TIA*—a clinical time-based definition of symptoms lasting fewer than 24 hours; TIA was 'definite' when a diagnosis of TIA was the only one considered for the symptoms, and 'probable' when a TIA was the most likely of a number of differential diagnoses.

3.2.2 Baseline characteristics

I used hospital electronic health records to gather data on age, sex, diagnosis on discharge, vascular territory of stroke/TIA, and the NIHSS score, a measure of neurological impairment on admission(92). I assigned an NIHSS of zero to all TIAs. I recorded whether the participants lived alone pre-stroke or TIA, had a past history of stroke or ischaemic heart disease, and past diagnosis of anxiety or depression by checking the electronic heath records first, then confirmed at the time of interview.

3.2.3 Assessment of anxiety and other neuropsychiatric disorders

At three months, I performed a semi-structured psychiatric interview using the telephone version of the SCID for DSM-IV-TR(34). The SCID for DSM-IV-TR

has fair to excellent inter-rater agreement for diagnosing both anxiety disorders and depression between experienced and newly trained clinicians(93), and between its telephone and face-to-face versions(94). The following conditions were screened using the relevant SCID modules: panic disorder, agoraphobia, social phobia, specific phobia, GAD, OCD, PTSD, minor and major depressive episodes. All SCID diagnoses were made according to the SCID coding system and after confirmation with AC at weekly meetings. Participants who were unable to talk on the telephone had face-to-face interviews at home or at an outpatient clinic. I measured cognition with the telephone Montreal Cognitive Assessment (T-MoCA)(95). The T-MOCA is a brief screening tool for mild cognitive impairment with feasibility and validity in a stroke and TIA sample(95). It has a total score of 22 and differs from the standard MoCA by omitting the visuospatial, executive and naming items.

3.2.4 Modified Fear Questionnaire to assess avoidant behaviour

One week before the SCID interview, I sent the participant a modified Fear Questionnaire (FQ) (Table 6) for completion by post or online. The original FQ consists of an agoraphobic subscale (5-item), a social phobia subscale (5-item), and a blood/injury phobia subscale (5-item)(96). Each item denotes a situation, and is rated according to the level of avoidance from zero (would not avoid it) to eight (always avoid it). I replaced the blood/injury items with six other specific situations that my supervisors and I encountered in our clinical practice—*i) physical exertion, ii) having sex, iii) being alone at home*, and '*any of your normal day-to-day activities for fear of having iv) a headache, v) another stroke, or vi) a fall'*. During the interview, I also recorded positive responses to a list of 11

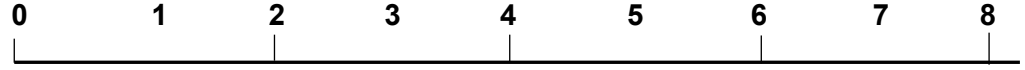
pre-defined anxiety-provoking stimuli (Table 7), similar to the ones on the modified FQ. Professor Alan Carson and I derived these additional anxiety-provoking stimuli from the shared clinical experience of our multidisciplinary stroke team in neuropsychiatry and post-acute stroke settings.

Table 6. Modified FQ

How much would you avoid each of the situations below because of fear or other unpleasant feelings?

Choose a number from the scale below
Write the number you choose in the space opposite each situation

Please enter '0' if the situation never arises, and you are not avoiding it for fear or other unpleasant feelings



Would not avoid it	**Slightly avoid it**	**Definitely avoid it**	**Markedly avoid it**	**Always avoid it**

	Situation	**Number from 0-8**
1.	Eating or drinking with other people	_____
2.	Being alone at home	_____
3.	Any of your normal day-to-day activities for fear of having another stroke or 'mini-stroke'	_____
4.	Travelling alone or by bus	_____
5.	Walking alone in busy streets	_____
6.	Being watched or stared at	_____
7.	Going into crowded shops	_____
8.	Talking to people in authority	_____

9.	Any of your normal day-today activities for fear of having a fall	_____
10.	Being criticised	_____
11.	Going alone far from home	_____
12.	Physically exerting yourself	_____
13.	Speaking or acting to an audience	_____
14.	Large open spaces	_____
15.	Having sex	_____
16.	Any of your normal day-to-day activities for fear of having a headache	_____

3.2.5 Factors associated with anxiety disorder at three months after stroke/TIA

I pre-specified age, sex, living alone pre-stroke/TIA, and a past diagnosis of anxiety or depression as potential factors associated with having anxiety disorder at three months after stroke/TIA.

3.2.6 Measures of dependence, quality of life and social participation

Measures of dependence, quality of life and social participation were completed at the time of SCID with the simplified mRS questionnaire(18) (Table 8) and its scoring algorithm (Figure 10), the EuroQoL-5D5L (EQ5D-5L)(97) (Table 9), and the Work and Social Adjustment scale (WSAS)(98) (Table 10).

Table 7. Eleven pre-specified questions on anxiety-provoking situations or stimuli during SCID interview

Agoraphobia-related situations	
Have you felt nervous, anxious or uncomfortable…	1) travelling more than a certain distance from home 2) going out of the house alone 3) going into a crowded place like a busy store, cinema, restaurant 4) using public transport e.g. travelling on buses or trains 5) standing in a queue
Social situations	
6) Was there anything that you have been afraid to do or felt uncomfortable doing in front of other people, like speaking, eating, or writing?	
Other specific situations/ stimuli	
Does any of these make you feel anxious, nervous or uncomfortable?	7) physical exertion 8) being alone at home
	9) having headaches 10) having another stroke
Have you been worrying about	11) falling

Table 8. Simplified mRS

Please tick Yes or No for each of the following questions	**Yes**	**No**
Could you live alone without any help from another person? (This means being able to bathe, use the toilet, shop, prepare or get meals, and manage finances		
Can you do everything that you were doing right before your stroke, even if slower and not as much?		
Are you completely back to the way you were right before your stroke?		
Can you walk from one room to another without help from another person?		
Can you sit up in bed without any help?		

Figure 10. The simplified mRS scoring algorithm

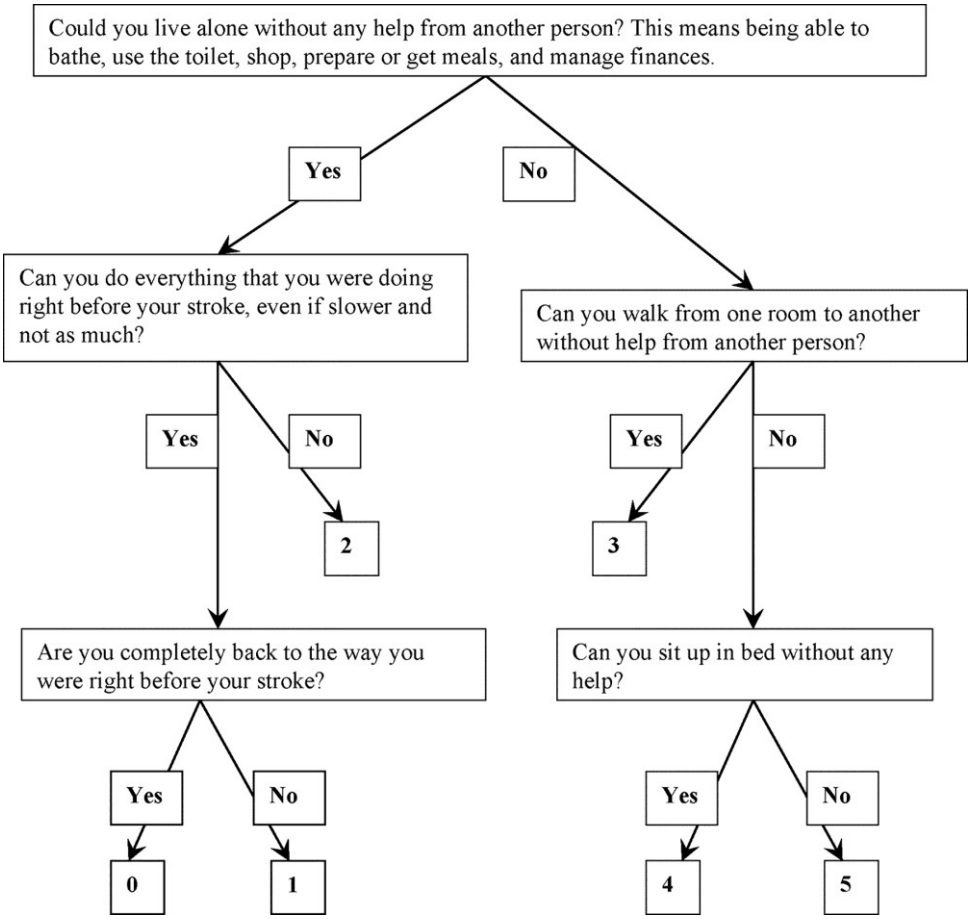


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Table 9. EuroQoL-5D5L questionnaire (sample version)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Table 9 continued

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

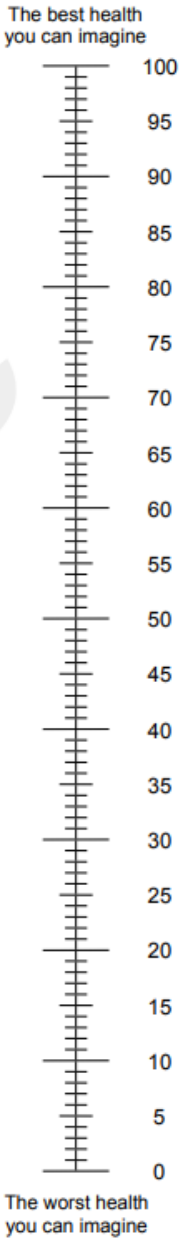


Table 10. Work and social adjustment scale

If you are retired or choose not to work for reason unrelated to your problem, tick ☐

Not at all **slightly** **definitely** **markedly** **very severely**

Score 0-8

Because of my (problem) my **ability to work** is impaired '0' means 'not at all impaired' and '8' means very severely impaired to the point I can't work

Because of my (problem) my **home management** (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired.

Because of my (problem) my **social leisure activities** (with other people e.g. parties, bars, clubs, outings, visits, dating, home entertaining) are impaired

Because of my (problem), my **private leisure activities** (done alone, e.g. reading, gardening, collecting, sewing, walking alone) are impaired)

Because of my (problem), my ability to form and maintain **close relationship**s with others, including those I live with, is impaired

Total WSAS score ☐

3.2.7 Statistical analyses and sample size calculation

I used descriptive statistics to summarize data, confidence intervals for proportions, and univariable and multivariable logistic regression to calculate unadjusted and adjusted odds ratios (OR) for associations. Group differences

were assessed using univariable logistic regression, t-, and Mann-Whitney tests as appropriate to data type. Only returned FQs were analyzed for avoidant behaviour. All items on the online questionnaire must be scored to permit submission, preventing any unscored items. Any unscored item on a returned postal questionnaire was given the most conservative interpretation and imputed zero, assuming that the item was irrelevant or did not elicit any anxiety symptoms. I carried out all statistical analyses using STATA14(99). I aimed for a target sample size of approximately 200 to achieve a desired precision of +/- 0.05 around an estimated frequency of post-stroke anxiety of 0.20.

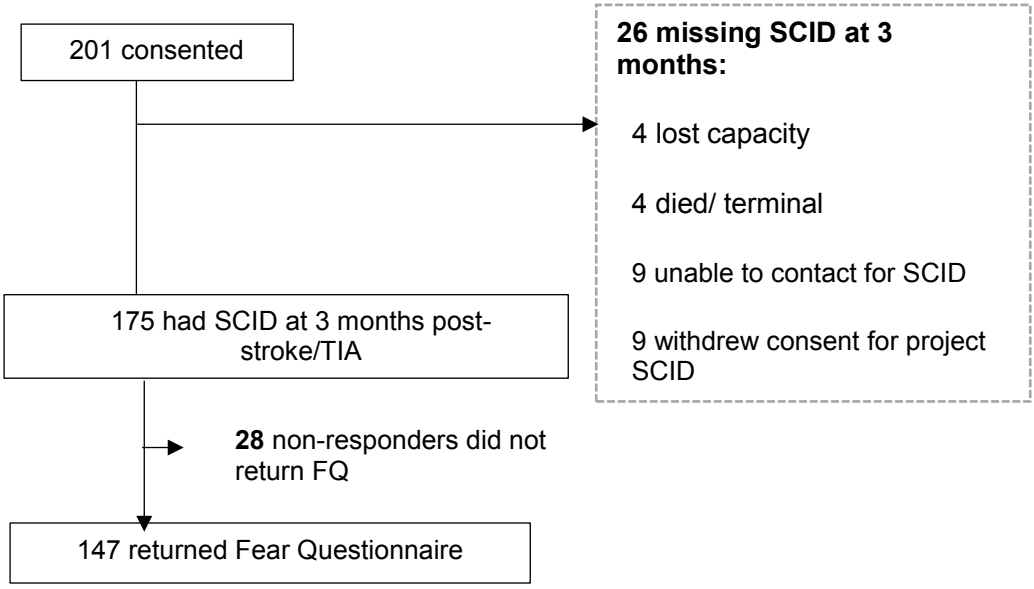
3.2.8 Reporting standards and ethics approval

I reported the study in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. I obtained a favourable opinion from the South East Scotland Research Ethics Committee (15/SS/0087) on 1/9/2015. All participants gave written informed consent.

3.3 Results

I recruited 201 participants between 9/9/15 and 28/6/16. 26/201 participants did not have SCID at three months—three had died, one was on palliation for terminal cancer, four had lost mental capacity, nine withdrew consent for SCID, and nine were not contactable (Figure 11).

Figure 11. Flow diagram of recruitment and follow-up of my prospective cohort



Participants lost to follow-up were more likely to live alone (losses: 15/26, 58%; analysed: 60/175, 34%, p=0.024), otherwise they were similar to those who were analysed (Table 11).

Table 11. Baseline characteristics of prospective cohort analysed (n = 175) and lost to SCID follow-up (n = 26)

		Prospective analysed		**Loss to SCID follow-up**		**chi square** (or other specified)
		All	**%**		**%**	
Number (n)		**175**		**26**		
Age	mean	69·6		72·2		p=0·276 (unpaired t-test)
	SD	11·6		11·2		
	median	71·4		75·7		
	IQR	61·6-78·2		64·5-82·4		
Age group						
Below 65		40	23%	7	27%	
65-75		44	25%	6	23%	
Above 75		91	52%	13	50%	
Sex						
Female		70	40%	9	35%	p=0·597
Male		105	60%	17	65%	
Diagnosis						
Ischaemic		109	62%	17	65%	p=0.201
Primary intracerebral haemorrhage		5	3%	2	8%	
TIA (probable or definite)		61	35%	7	27%	
Severity of stroke						
NIHSS	median	0		1		
	IQR	0-2		0-3		
Hemisphere						
Left anterior circulation		82	47%	14	54%	p=0·226
Right anterior circulation		53	30%	10	38%	
Posterior		35	20%	2	8%	
Unknown		5	3%	0	0%	
Pre-stroke/TIA Status						
Lived alone before stroke	Yes	60	34%	15	58%	**p=0·024**
	No	115	66%	11	42%	
Independent before stroke	Yes	169	97%	26	100%	
	No	6	3%	0	0%	
Post-stroke/TIA status						
Orientated speech	Yes	170	97%	25	96%	p=0.790
	No	5	3%	1	4%	

Table 11 continued		**Prospective analysed**		**Loss to SCID follow-up**		**chi square** (or other specified)
		All	**%**		**%**	
Able to lift arms	Yes	168	96%	26	100%	
	No	7	4%	0	0%	
Able to walk	Yes	168	96%	25	96%	p=0·970
	No	7	4%	1	4%	
Past diagnosis of depression or anxiety disorder						
Depression only		30	17%	2	8%	p=0·111
Anxiety only		11	6%	0	0%	
Both depression and anxiety disorder		11	6%	0	0%	
No past diagnosis of anxiety or depression		123	70%	24	92%	

In the analysed sample (Table 12), 175 participants (mean age [SD]: 70 [12]; women: 70/175, 40%) had SCID at three months post-stroke/TIA. The majority had ischaemic stroke, a third had TIA, and few had primary ICH (ischaemic stroke: 109/175, 62%; TIA: 61/175, 35%; primary ICH: 5/175, 3%). I recruited similar numbers from the acute stroke unit and TIA clinic (acute stroke unit: 80/175, 46%; TIA clinics: 95/175, 54%). My sample therefore consisted of patients with mild stroke and TIA (NIHSS median [IQR]: 0 [0-2]). Nearly all participants were interviewed by telephone (telephone: 168/175, 96%; face to face: 7/175, 4%).

Table 12. Baseline characteristics of prospective cohort, by anxiety disorder at 3 months (n = 175)

	Prospective Cohort		SCID Diagnosis				Univariable Logistic Regression		
	All		Any Anxiety Disorder		No Anxiety Disorder				Likelihood
No. of Patients	175		38	22%	137	78%	OR	95% CI	Ratio Test
Demographics									
Age, y; mean (SD)	69.6	(11.6)	64.2	(12.3)	71.0	(10.9)			
Age group, y									
<65	62	35%	23	61%	39	28%	1		*P*=0.001*
65–75	55	31%	6	16%	49	36%	0.21	0.08–0.56	
>75	58	33%	9	24%	49	36%	0.31	0.13–0.75	
Sex									
Women	70	40%	18	47%	52	38%	1.47	0.71–3.04	*P*=0.298
Men	105	60%	20	53%	85	62%	1		
Recruitment setting									
Clinic	95	54%	21	55%	74	54%	1		*P*=0.891
Acute stroke unit	80	46%	17	45%	63	46%	1.05	0.51–2.17	
Diagnosis									
Ischemic stroke	109	62%	24	63%	85	62%	1		*P*=0.140
Primary intracerebral hemorrhage	5	3%	3	8%	2	1%	5.31	0.84–33.6	
TIA (probable or definite)	61	35%	11	29%	50	36%	0.78	0.35–1.72	
Hemisphere of stroke/TIA symptoms									
Left anterior circulation	82	47%	17	45%	65	47%	1		*P*=0.662
Right anterior circulation	53	30%	13	34%	40	29%	1.24	0.55–2.83	
Posterior circulation	35	20%	6	16%	29	21%	0.79	0.28–2.21	
Uncertain	5	3%	2	5%	3	2%	2.55	0.03–16.49	
Neurological impairment (NIHSS)									
Median (IQR)	0	(0–2)	0	(0–2)	0	(0–2)			
TIA	61	35%	11	29%	50	36%	1		*P*=0.575
Stroke, NIHSS									
0	30	17%	9	24%	21	15%	1.95	0.70–5.39	
1–4	71	41%	16	42%	55	40%	1.32	0.56–3.11	
>4	13	7%	2	5%	11	8%	0.83	0.16–4.27	
Prestroke status									
Lived alone before stroke/TIA									
Yes	60	34%	15	39%	45	33%	1.33	0.64–2.80	*P*=0.450
No	115	66%	23	61%	92	67%	1		
Independent before stroke/TIA									
Yes	169	97%	37	97%	132	96%	1.4	0.16–12.37	*P*=0.753
No	6	3%	1	3%	5	4%	1		
Past diagnosis of depression or anxiety disorder									
None	123	70%	15	39%	108	79%	1		*P*<0.001*
Depression only	30	17%	10	26%	20	15%	3.6	1.42–9.14	
Anxiety only	11	6%	6	16%	5	4%	8.64	2.35–31.83	
Both depression and anxiety	11	6%	7	18%	4	3%	12.6	3.29–48.21	

Table 12 continued

	Prospective Cohort		SCID Diagnosis				Univariable Logistic Regression		
	All		Any Anxiety Disorder		No Anxiety Disorder				
No. of Patients	175		38	22%	137	78%	OR	95% CI	Likelihood Ratio Test
History of stroke									
Yes	22	13%	7	18%	15	11%	1.84	0.69–4.89	*P*=0.237
No	153	87%	31	82%	122	89%	1		
History of ischemic heart disease									
Yes	30	17%	8	21%	22	16%	1.39	0.56–3.44	*P*=0.479
No	145	82%	30	79%	115	84%	1		

CI indicates confidence interval; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCID, Structured Clinical Interview for Diagnostic Statistical Manual-IV-Text Revision; and TIA, transient ischemic attack.
*$P<0.05$.

3.3.1 Frequency of anxiety disorders and psychiatric co-morbidity at three months after stroke or TIA

A fifth of my sample had at least one anxiety disorder at three months after stroke/TIA (38/175, 22% [95%CI 16-29]). Phobic disorder was the most frequent anxiety subtype ('phobic disorder only': 18/175, 10%; 'both phobic disorder and GAD': 13/175, 7%; 'GAD only': 7/175, 4%) (Figure 12a, Table 13). PTSD appeared as a co-morbidity in 'phobic disorder only' cases (6/18), 'GAD only' cases (1/7), and 'both phobic disorder and GAD' cases (4/13) (Table 13). Half of all people with anxiety disorder also had a minor or major depressive episode (20/38, 53%) (Figure 12b). I found no difference in cognitive function between patients with anxiety disorder and those without (tMoCA median, IQR: [anxiety disorder] 18, 16-21; [no anxiety disorder] 19, 17-20, p=0.692). Of the TIA patients, 18% (11/61) had an anxiety disorder, 10% (6/61) had 'phobic disorder only', 3% (2/61) had 'both phobic disorder and GAD', and 5% (3/61) had 'GAD only'.

Figure 12. (a) Number of cases (sample frequency) of phobic disorder and GAD, (b) comorbid depression at 3 months (n=175).

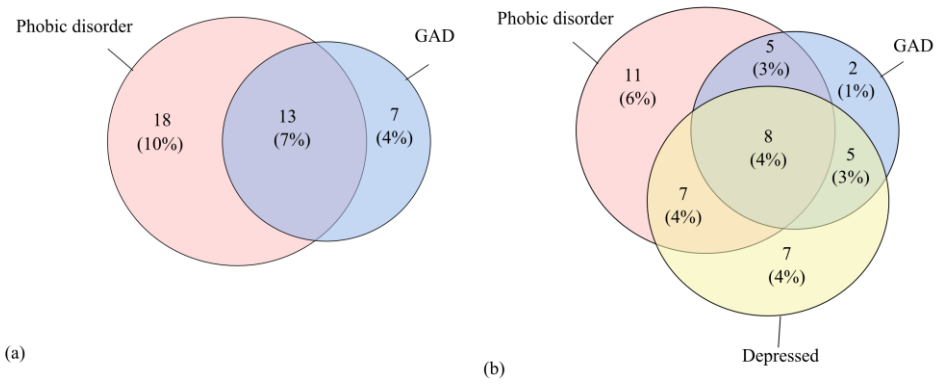


Table 13. Sample frequencies of SCID-diagnosed phobic disorder, GAD and psychiatric co-morbidity (n = 175)

SCID Diagnosis	Total (n=175)	Sample Frequency, %	95% Confidence Intervals
Any anxiety disorder	38	22	16–29
Phobic disorder only	18	10	6–16
Comorbidity			
Panic disorder	5	3	1–7
PTSD	6	3	1–7
OCD	0	0	0–2
Depressive episode (minor+major)	7	4	2–8
GAD only	7	4	2–8
Comorbidity			
Panic disorder	2	1	0–4
PTSD	1	0.5	0–3
OCD	0	0	0–2
Depressive episode (minor+major)	5	3	1–7
Both phobic disorder and GAD	13	7	4–12
Comorbidity			
Panic disorder	7	4	2–8
PTSD	4	2	1–6
OCD	2	1	0–4
Depressive episode (minor+major)	8	5	2–9
All depressed (minor or major depressive)	27	15	11–22
Depressed with an anxiety disorder	20	11	7–17
Depressed without anxiety disorder	7	4	2–8
Not depressed	148	85	79–90

GAD indicates generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, Post-traumatic stress disorder; and SCID, Structured Clinical Interview for Diagnostic Statistical Manual-IV-Text Revision.

3.3.2 Avoidant behaviour and anxiety-provoking situations

84% (147/175) returned completed FQ for analysis. Non-responders were younger than the FQ sample analysed (mean age: [non-responders] 64.8 +/-14.9; [FQ analysed] 70.5 +/-10.6, p=0.017) but did not differ statistically in other characteristics (Table 14). Participants with an anxiety disorder at three months reported significantly higher level of avoidant behaviour across all situations on the FQ compared to participants without (Figure 13).

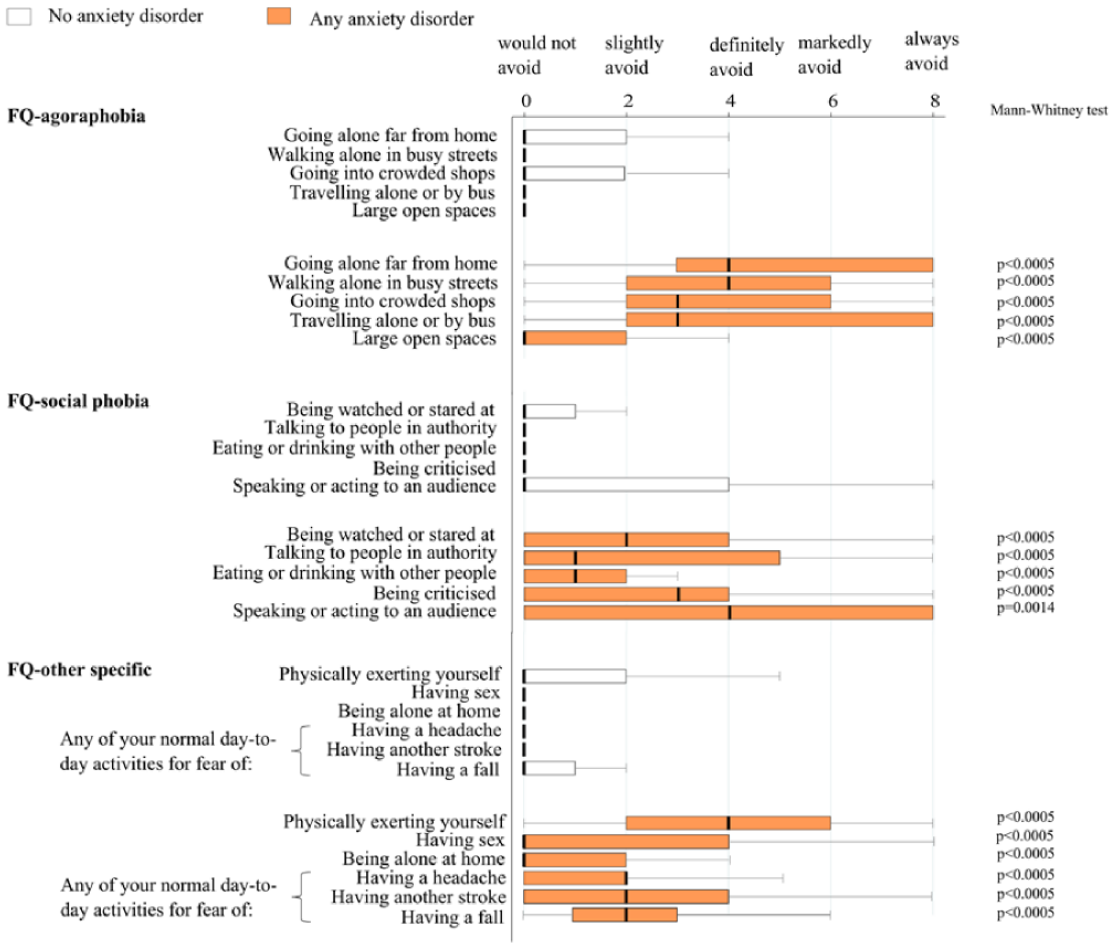
Table 14. Baseline characteristics of sample with modified FQ data (n=147) and non-responders (n = 28) in prospective cohort

Number of patients (%)		**FQ data analysed**		**missing FQ data**		chi-square (or other specified)
		n=147	**%**	**n=28**	**%**	
Age	mean	70.5		64.8		**p=0.017** (unpaired t-test)
	SD	10.6		14.9		
	median	72.0		63.5		
	IQR	63.3-78.3		56.0-77.0		
Sex						
Female		59	40%	11	39%	p=0.933
Male		88	60%	17	61%	
Diagnosis						
Ischaemic		88	60%	21	75%	
Primary intracerebral haemorrhage		4	3%	1	4%	p=0.243
TIA (probable or definite)		55	37%	6	21%	
Neurological impairment						
NIHSS	median	0		1		
	IQR	0-2		0-3		
Hemisphere						
Left anterior circulation		67	46%	15	54%	
Right anterior circulation		45	31%	8	29%	p= 0.803
Posterior		31	21%	4	14%	
Unknown		4	3%	1	4%	

Table 14 continued

Number of patients (%)		FQ data analysed n=147	%	missing FQ data n=28	%	chi-square (or other specified)
Pre-stroke/TIA Status						
Lived alone before stroke	Yes	48	33%	12	43%	p=0.304
	No	99	67%	16	57%	
Independent before stroke	Yes	143	97%	26	93%	p=0.287
	No	4	3%	2	7%	
Post-stroke/TIA status						
Orientated speech	Yes	144	98%	26	93%	p=0.191
	No	3	2%	2	7%	
Able to lift arms	Yes	141	96%	27	96%	p=0.898
	No	6	4%	1	4%	
Able to walk	Yes	141	96%	27	96%	p=0.898
	No	6	4%	1	4%	
Past diagnosis of depression or anxiety disorder						
Depression only		24	16%	6	21%	
Anxiety only		10	7%	1	4%	
Both depression and anxiety disorder		9	6%	2	7%	p=0.837
No past diagnosis of anxiety or depression		104	71%	19	68%	
Diagnosis of any anxiety disorder on SCID	Yes	29	20%	9	32%	p=0.160
	No	118	80%	19	68%	

Figure 13. Avoidant behaviour in agoraphobic, social and other specific situations (n= 147)



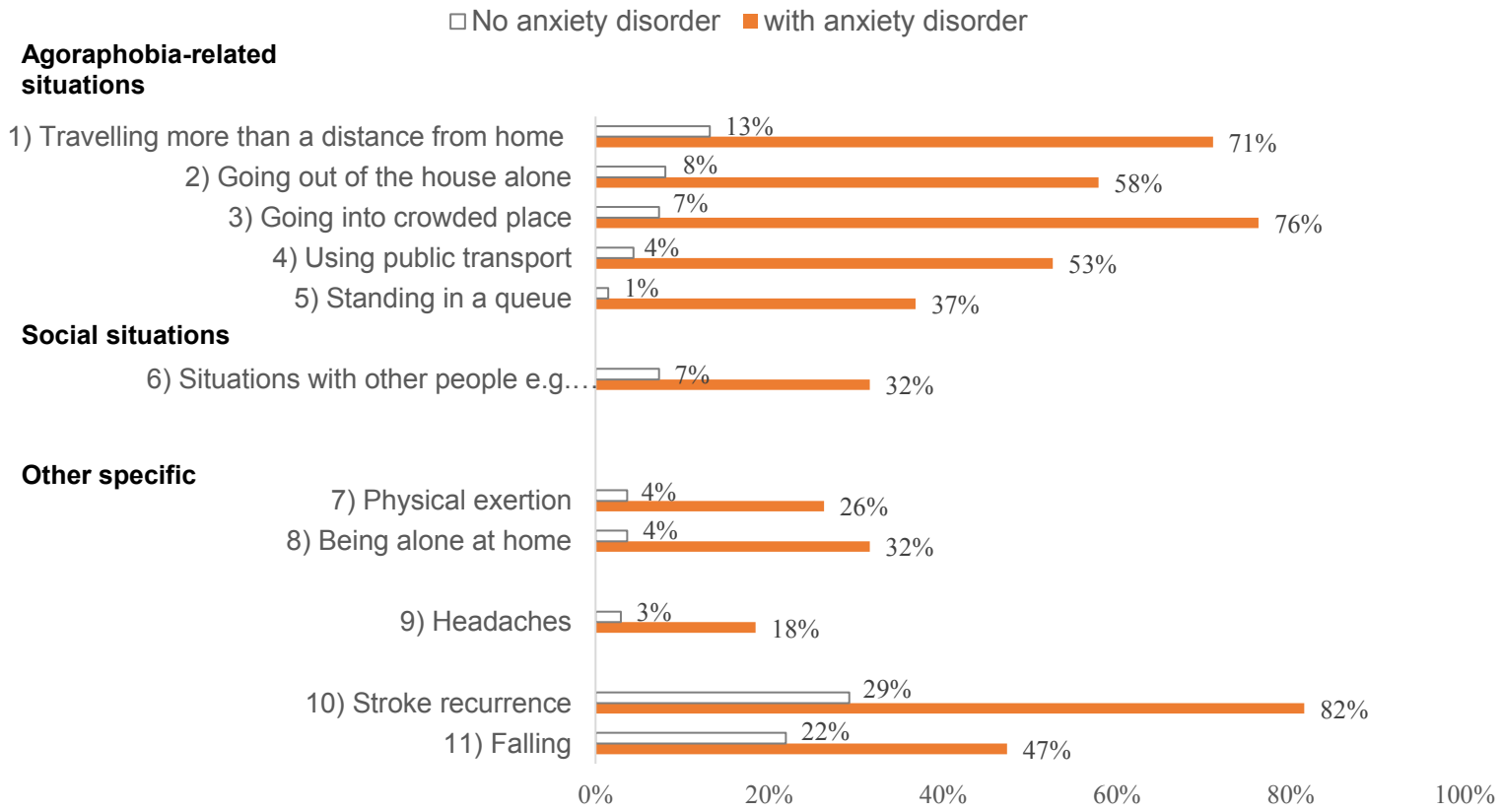
Thick lines represent median; boxes represent interquartile range; whiskers represent range. FQ indicates Fear Questionnaire.

Similarly, during SCID, positive responses to all of the 11 pre-defined situations were more common in participants with anxiety disorder compared to those without (Figure 14). The fear of stroke recurrence had the most positive responses in those with anxiety disorder (31/38, 82%) and in those without (40/137, 29%). I listed any additional anxiety-provoking situations reported by participants during SCID (Table 15).

Table 15. Other anxiety-provoking situations reported during SCID

	Has anxiety disorder	**No anxiety disorder**
Anxiety-provoking situation/ stimuli/ thought	People watching me,/ looking at me/ judging me	Mobility concerns when out alone due to weakness and poor balance
	Incontinence	Not recovering from physical impairment e.g. weakness, handwriting
	Being in the shower when alone at home	Not being able to return to usual activities/ responsibilities e.g. looking after spouse, returning to occupation
	Being alone while looking after somebody e.g. grandchildren	Worry about getting dementia
	Driving	Embarrassed about not being able to use fork in a restaurant
	Any funny or odd feeling makes me think it is going to be a stroke	Any funny or odd feeling make me think it is going to be a stroke

Figure 14. Positive responses to the eleven pre-specified questions on anxiety-provoking situations during SCID



3.3.3 Associations with dependence, health-related quality of life, and social participation at three months

Despite similar baseline neurological impairment (NIHSS 0-4: [anxiety disorder] 95% vs [no anxiety disorder] 92%, p=0.575), participants with anxiety disorder were more dependent (mRS3-5: [anxiety disorder] 55% vs [no anxiety disorder] 29%, p<0.0005), reported more problems across all health-related quality of life domains on the EQ-5D5L (Figure 15), and more restriction in social participation (median WSAS, IQR: [anxiety disorder] 19.5, 10-27; [no anxiety disorder] 0, 0-5, p<0.001).

3.3.4 Factors associated with anxiety at 3 months after stroke/TIA

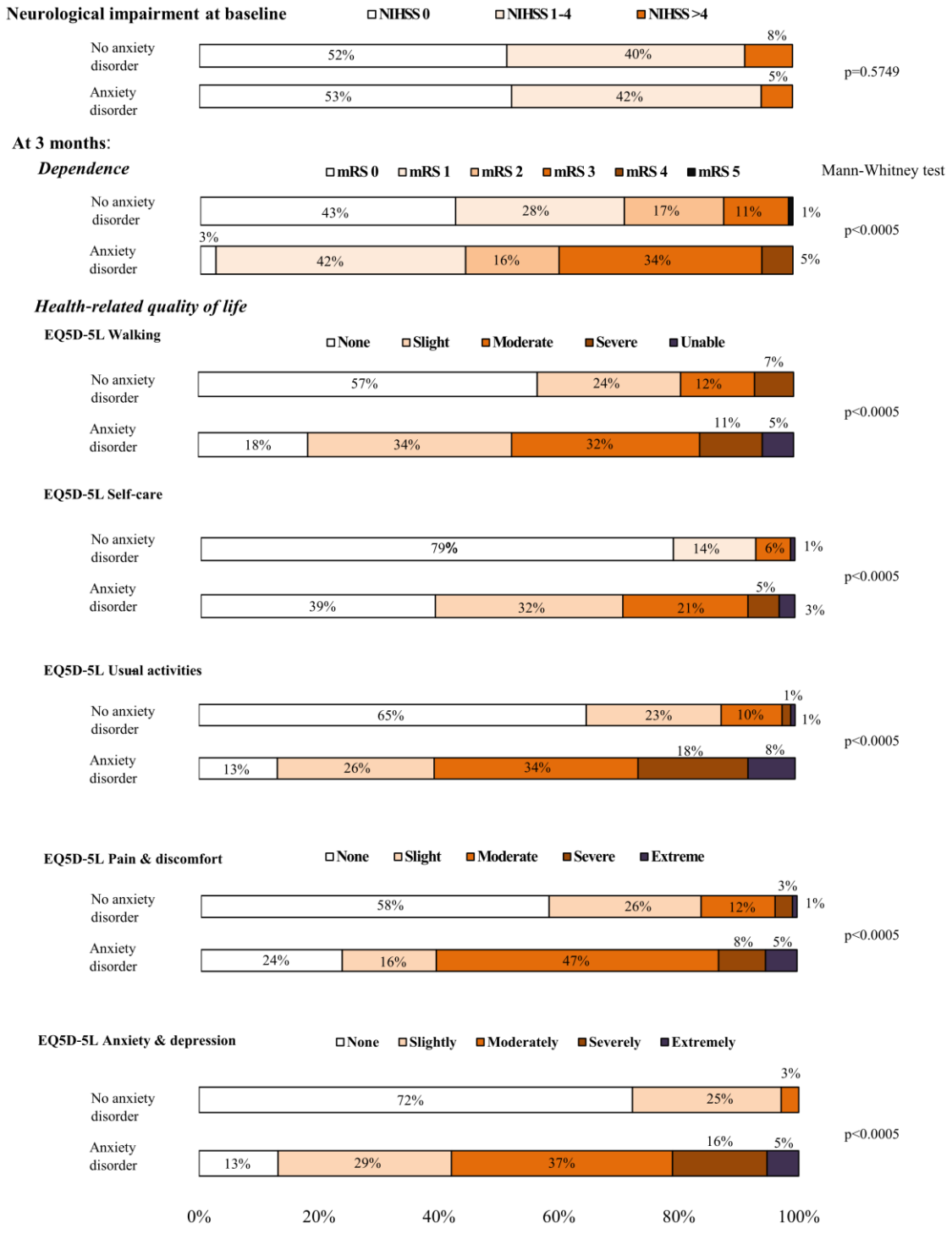
The odds of having an anxiety disorder at 3 months after stroke or TIA decreased by a third per decade increase in age (adjusted odds ratio (OR) 0.64, 95%CI 0.45-0.91), and increased four-fold when there was a past diagnosis of anxiety or depression (adjusted OR 4.38, 95%CI 1.94-9.89) (Table 16). Sex or living alone pre-stroke/TIA was not statistically associated with anxiety disorder at three months.

Table 16. Unadjusted and adjusted ORs of pre-defined predictors for the outcome of any anxiety disorder at 3 months post-stroke/TIA (n=175)

	Outcome variable: Any anxiety disorder at 3 months post-stroke/TIA				
Independent variable	Unadjusted OR (95% CI)	Multivariable Logistic Regression Adjusted OR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
Age, y (per decade increase)	0.60 (0.44–0.83)	0.67 (0.47–0.94)	0.65 (0.46–0.92)	0.65 (0.46–0.92)	0.64 (0.45–0.91)
Past diagnosis of anxiety or depression	5.71 (2.65–12.32)	4.85 (2.21–10.66)	4.51 (2.01–10.12)	4.66 (2.10–10.31)	4.38 (1.94–9.89)
Being a woman	1.47 (0.71–3.04)		1.37 (0.61–6.14)		1.33 (0.58–3.07)
Living alone prestroke/TIA	1.33 (0.64–2.80)			1.31 (0.89–3.08)	1.29 (0.56–2.99)
Likelihood ratio test comparing models with model 1			*P*=0.4526	*P*=0.4873	*P*=0.6294

CI indicates confidence interval; OR, odds ratio; and TIA, transient ischemic attack.

Figure 15. Baseline NIHSS, mRS and EuroQol-5D-5L domains, by anxiety disorder at 3 months post-stroke/TIA (n=175).



3.4 Discussion

3.4.1 Key findings

In my sample of stroke and TIA patients, a fifth had an anxiety disorder diagnosed at psychiatric interview at three months. I found phobic disorder to be the predominant anxiety subtype after stroke or TIA. Anxious patients reported more avoidance in agoraphobia-related, social and other specific situations or stimuli—physical exertion, having sex, being alone at home, activities related to fear of having a headache, another stroke, or a fall. PTSD was more common than I had anticipated. Younger age and having a past history of anxiety or depression increased the likelihood of developing anxiety post-stroke/TIA. Despite having a similar level of neurological impairment at baseline, participants with anxiety disorder were more dependent, had poorer health-related quality of life, and were more restricted in social participation at three months after stroke or TIA compared to those without anxiety disorder.

3.4.2 Potential bias in our methodology

As the interviewer, I was a stroke clinician who received training in performing the SCID. I minimised any variability in diagnosis by having all final diagnoses discussed and confirmed with AC, a consultant neuropsychiatrist, at weekly meetings. A systematic review of studies assessing the agreement between diagnostic telephone and face-to-face psychiatric interviews found good agreement (kappa 0.69-0.84) between the two versions in psychiatric populations(100), supporting the use of telephone SCID for anxiety disorders and depression. However, there are no such comparability data in stroke. The use of telephone SCID in our study could have influenced the accuracy of the 'true

estimates' of our SCID diagnoses. SCID diagnosis was made based on formal diagnostic criteria and coding system, taking into account detailed narrative of the patient's experience. Temporary distress experienced by the participant at the time of SCID, if any, was unlikely to influence the final diagnosis. My final sample size of 175 fell short of the 200 I intended to recruit. This impacted slightly on the precision of the frequency estimate for 'any anxiety disorder', from +/- 0.05 to +/- 0.06.

I noted a high proportion of previous anxiety or depression in our sample. Case ascertainment relied on participants' recollection of any past diagnosis made throughout their lifetime. This method could have led to overestimates and was not sufficiently reliable to inform us to what extent the participant suffered from anxiety prior to their stroke, or if they had 'trait' anxiety. Case ascertainment from primary care records would provide a more reliable estimate.

I had losses of follow-up in the prospective cohort. More people lived alone in the losses compared to those who underwent SCID. This could have led to underestimates of anxiety disorder and depression, as living alone was associated with a higher psychiatric morbidity in the general population(101). I lost FQ data through non-responders and they were younger compared to the FQ sample analysed. While over a quarter of participants completed the FQ online as their preferred method, I did not test the agreement between the two versions. Our population was at the milder end of the stroke spectrum.

3.4.3 Interpretation

My frequency estimate falls within the range of frequencies reported in a recent meta-analysis of anxiety post-stroke: 18-25%(56). I found phobic disorder to be the predominant anxiety subtype post-stroke/TIA, and quantified for the first

time, the avoidant behaviour of specific anxiety-provoking situations in people with anxiety post-stroke/TIA. My study is the first to have assessed the frequency of anxiety subtypes using diagnostic interview in TIA patients(102). Similar to my main analysis, phobic disorder was the most frequent anxiety subtype post-TIA. My frequency estimate of anxiety disorder post-TIA is similar to that reported using a rating scale cut-off for 'definite anxiety' in a regional stroke registry(57).

Earlier studies suggested phobic anxiety might be present after stroke(62-64), yet clinical trials of anxiety intervention did not translate this finding, treating anxiety post-stroke as one unitary phenomenon. Thus far, only general approaches such as relaxation and antidepressants have been evaluated in stroke(67), which are unlikely to be effective in patients with predominantly phobic anxiety. My findings suggest the need to evaluate exposure techniques—an approach known to be effective in phobic disorder in non-stroke populations(45), but one that has never been evaluated in stroke. I identified the specific situations/ stimuli avoided in our anxious participants which could be potential targets for psychotherapy e.g. CBT.

Fear of stroke recurrence

The fear of stroke recurrence was the most commonly reported anxiety-provoking stimulus in my participants, with or without anxiety disorder. In my interviews, I found this anxious anticipation—the experience of anxiety by thinking about an event in the future, to have led to differential behaviours in our participants. In some, this anticipatory anxiety brought about a desire for better health and increased positive health behaviours, e.g. complying with medications and doctor's advice on lifestyle, giving up smoking. In others, this anticipatory anxiety became disproportionate, and perpetuated maladaptive avoidant

behaviours of specific situations e.g. travelling alone, crowds, physical exertion, social gatherings. The fear of stroke recurrence, accompanied by a sense of complete loss of control in a public place appeared to underlie the agoraphobia in my participants. These maladaptive thinking patterns and avoidant behaviours are potential targets for cognitive restructuring and exposure therapy in a CBT intervention. In exposure therapy, phobic patients confront their specific feared situation in a graduated hierarchical fashion, until the unpleasant anxiety feelings diminish. The individual's realization that catastrophe has not occurred despite confronting his/her feared situation e.g. taking the bus, can be used to help challenge a maladaptive belief e.g. *'I'm going to have a stroke if I travel on the bus'.*

Psychiatric co-morbidity

Psychiatric co-morbidity was common in my sample and their symptoms should be considered in the treatment of anxiety post-stroke/TIA. Few studies have estimated the frequency of clinical diagnosis of PTSD post-stroke/TIA(103). Frequency of PTSD was estimated in my study using the SCID in which the patient's stroke or TIA was considered a significant stressful event that met the entry criterion for PTSD. This method could have inflated the frequency of PTSD observed. Furthermore, it is arguable whether PTSD diagnostic criteria are appropriate at all for use in stroke patients given how common the diagnosis of stroke/TIA is, and at only three months after the event, it would be difficult to ascertain whether the patient is suffering from PTSD or emotional distress from an ongoing stressor. Like phobic and generalised anxiety, PTSD has specific treatment strategies in non-stroke populations—trauma-focused CBT and eye movement reprocessing(104, 105). These now need to be tested in stroke. My

finding on PTSD adds weight to my general thesis that treating anxiety as a unitary condition after stroke will lessen the likelihood of finding effective treatments. In PTSD, individuals persistently re-experience the traumatic event in the form of distressing flashbacks, intrusive thoughts and nightmares(33). In my cases of PTSD, emotional distress was provoked by bodily sensations or situations that reminded the individuals of their index event e.g. headaches, odd sensation in affected limb, meeting people who were likely to enquire about the index event. Panic disorder was nested within my phobic and GAD cases. It refers to a tendency to have panic attacks—the most extreme and unpleasant form of anxiety state with marked autonomic symptoms and the feeling of 'impending catastrophe'. Panic disorder is usually managed with CBT, and/ or medications. Consistent with the literature(56, 106), concurrent depression was common amongst anxiety cases, reaffirming the need to manage depression in those with anxiety post-stroke. My frequency estimate of post-stroke depression was half of what was usually reported(107). This is probably because our sample consisted of mainly mild stroke and TIA patients, and that stroke severity and physical disability are the most consistent predictors for post-stroke depression(108).

Factors associated with anxiety post-stroke/TIA

The likelihood of developing anxiety after stroke or TIA increased in younger people and in those with a history of anxiety or depression, consistent with anxiety in the general population. The observed relationship between age and anxiety in both stroke and non-stroke populations could be a cohort effect in which generational factors rather than age alone might be implicated. For

example, stoicism might be a characteristic of people born in the 40s while younger people might have less resilience and more anxiety as a generation.

In contrast to the general population, men were as likely as women to develop anxiety post-stroke/TIA. I found no statistical significant association between lesion location and anxiety post-stroke/TIA.

Associations with dependence, quality of life and social participation

My study findings on dependence, quality of life and social participation challenge the pervasive view amongst stroke clinicians that these patients are not disabled by their seemingly 'minor' cerebrovascular event. Anxiety disorders, PTSD and depression can be profoundly disabling and need to be considered as important outcomes in stroke and TIA.

Implications for future research

The lack of evidence-based anxiety interventions is a barrier to improving outcomes in patients with anxiety post-stroke/TIA. Trialists must recognise the need for different treatment approaches for phobic and generalised anxiety. Given the predominance of phobic disorder post-stroke/TIA, exposure therapy needs to be evaluated in a clinical trial in this population. Individually tailored CBT is feasible in clinical trial setting of post-stroke depression(109, 110) and may be similarly applied in anxiety post-stroke/TIA.

3.4.4 Generalisability

My sample is different from the population of patients with stroke, in that all the participants could communicate by telephone, hence in general had mild deficits. Based on the Scottish Stroke Care Audit registry data, I would expect

around a fifth of the NHS Lothian stroke population to have communication difficulties. Furthermore, competing research studies were recruiting patients with more severe deficits at the same time as this study's recruitment. I recruited half of my sample from clinic where patients tended to have mild or resolution of neurological symptoms. I therefore consider my sample as representative of the mild stroke and TIA population with limited generalisability to severe stroke, or those who have significant communication difficulties. The tMOCA scores in my sample are consistent with findings in a similar sample of stroke and TIA patients(95), and suggest the presence of mild cognitive impairment, a known manifestation of mild stroke and TIA(111).

3.5 Implications for my anxiety intervention design

In designing the content of my TASK intervention, I will consider adapting exposure therapy for treating phobic anxiety and cognitive therapy techniques such as cognitive restructuring and problem solving for generalised anxiety. Phobic disorder, regardless of the focus of the phobia e.g. agoraphobia, social phobia, fear of physical exertion, should be treated with graduated hierarchical exposure therapy. My TASK intervention will aim to teach participants to apply exposure therapy techniques to confront their feared situations, whatever these might be. Considering how common agoraphobia appeared in my sample, I will include content specifically relating to the treatment of agoraphobia in my intervention.

Fear of stroke recurrence was the commonest anxiety-provoking thought. It appeared to be what perpetuated much of the observed avoidant behaviour in my anxious participants. It was of course reasonable for people to fear a life-threatening and potentially disabling health event such as stroke. Why then did

some participants go on to have an overwhelming fear that dominated their daily life, restricting their activities, when others managed to live life as usual despite being aware of a risk of stroke recurrence? Based on my interviews, it appeared that participants with anxiety disorder, whether phobic or generalised, had a grossly distorted view of their risk of stroke recurrence. Consequently, these participants feared having a debilitating stroke on a regular basis. When asked to quantify their own stroke risk, the anxious participants reported perceiving their daily stroke risk to be as high as 50% to 80%. No wonder they were anxious!

'Your risk of having another stroke is higher than the general population now that you have had a TIA or stroke' is what we, as stroke clinicians tend to convey to our patients in order to emphasise the urgency for clinic assessment and secondary prevention. This is an anxiety-increasing message which serves to 'stress' patients into engaging in healthy behaviours. This stress, however, could lead to anxious patients becoming pre-occupied with their risk of stroke recurrence in a maladaptive way. The Yerkes-Dodson law demonstrated that performance e.g. memory, task performance is related to arousal or stress in an inverted U-shaped curve(112). Someone who is not aroused at all does not perform a task well. By increasing his arousal or stress, his performance improves up to a point. Once an optimal level of performance is reached, further increase in stress leads to a decline in performance. This relationship might explain why some patients may require an anxiety-reducing message in their health interests while others may need an anxiety-increasing message. In choosing the health 'message' stroke clinicians must balance increasing anxiety unduly while not falsely reassuring patients.

Most clinicians, including myself, generally refrain from the use of quantified long-term stroke risk derived from population-based observational studies (2 to 5 % annual stroke risk) when speaking to patients. Exactly why we do not wish to give this information to our patients is unclear. In my experience, non-specialist clinicians may not be familiar with the research evidence, some clinicians are not sure if patients would find this information meaningful, and others worry about patients misinterpreting the given risk, which may fuel further anxiety. Evidence suggests that primary care and hospital physicians overestimate the risk of stroke recurrence following a TIA(113). It is possible that clinicians are contributing to the development of anxiety post-stroke/TIA by unintentionally encouraging a distorted view of stroke risk amongst patients.

Participants without anxiety disorder seemed able to convince themselves that they had done everything they could to minimise their future stroke risk e.g. taking medications, living a healthy lifestyle. They were able to carry on with their daily life without thinking too much about their risk of recurrence.

In my TASK intervention, I plan to take anxious participants through a checklist of all the steps they could take to minimise their stroke risk including smoking cessation, adhering to medications, being physically active, taking medications etc.

My anecdotal experience suggested that anxious stroke/TIA patients found great relief from hearing me say 'the *majority of people do not go on to have another stroke after their TIA or minor stroke'*. I found all anxious patients to be pleasantly surprised, often breathing a great sigh of relief, after learning that their long-term risk of stroke recurrence per year was as low as 2 - 5%, not 50 - 80%. Perhaps clinicians should now feel more relaxed at providing a quantified stroke risk so that our patients can go home with a more realistic view of their risk

of stroke recurrence in the long term. In my TASK intervention, I plan to incorporate my findings and experience to help anxious patients correct their distorted view of stroke risk by educating them with a realistic risk, and offering them the reassuring and evidence-based advice that *'the majority of people do not go on to have another stroke after their TIA or minor stroke'*.

Some of my anxious participants reported that headaches or other physical sensations such as stabbing pain, the odd tingle, and dizziness could provoke anxiety as they often associated these symptoms with having another stroke. In some cases, these symptoms could lead to repeated admissions to the emergency department and repeated brain imaging. Residual deficits from the initial stroke, common post-stroke phenomena e.g. hyperaesthesia over the affected side, headaches, and anxiety could all give rise to, or accentuate bodily symptoms. Most of the recurrent symptoms these participants reported were not typical of an acute stroke. In my TASK intervention, I aim to include educational content on the somatic symptoms that commonly occur, but are not dangerous post-stroke.

Chapter 4

Diagnostic Accuracy and Reliability of Two Anxiety Measures

Publication status and contribution

I am currently preparing this chapter for submission for a peer review publication.

I designed and conducted this study as part of the the observational study in Chapter 3. I recruited additional participants by retrospective postal invitations for this study. I designed the methods with input from my supervisors and performed all study procedures including data collection and analyses. Professor Alan Carson provided training and supervision of my SCID interviews. He confirmed all psychiatric diagnoses made in this study. Francesca Wright, a final year medical student assisted with data entry in this study. Dr Will Whiteley and Dr Cat Graham (statistician), provided guidance on my statistical analysis plan, data analysis and data visualisation.

I wrote this chapter with comments from my supervisors.

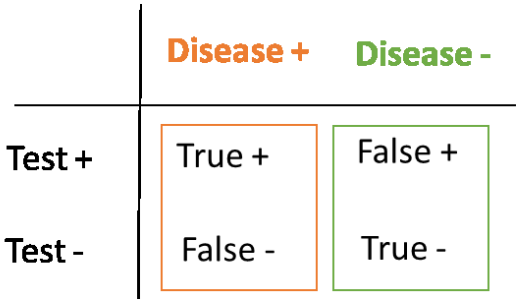
4.1 Introduction

I demonstrated in Chapter 3 that phobic disorder was frequent and could occur in the absence of GAD after stroke and TIA. Based on my systematic review in Chapter 2 and findings from a recent systematic review of anxiety screening tools in stroke(60), I found that only generalised anxiety measures had been used and validated in stroke. An anxiety questionnaire that enquires about generalised anxiety symptomology only may not detect phobic anxiety if it does not enquire about specific phobic situations or maladaptive avoidance. While the use of SCID is considered a 'gold-standard' tool for diagnosing anxiety disorders in research, its use requires specialist training and is too time-consuming to be feasible in a clinical trial setting. Brief self-completed anxiety measures offer feasible alternatives for use in an RCT. In my TASK RCT, I will need valid, reliable and feasible measures for both phobic disorder and GAD.

Validity and reliability of an anxiety measure

Validity and reliability represent the quality of a measurement scale. Validity is defined as the extent to which a test measures what it is intended to measure(114). Criterion validity refers to whether scores on an index test agree with a 'gold standard' measurement of the same construct(114). One way of measuring criterion validity of an index test is to assess its diagnostic accuracy, or sensitivity and specificity, against 'gold-standard' diagnosis of the disease.

Figure 16. Contingency table for index test result and disease status



Sensitivity is the probability of having a positive test given that the individual has the disease (Figure 16). Specificity refers to the probability of having a negative test given that the individual does not have the disease. Sensitivity and specificity can be expressed mathematically as follows:

Sensitivity:

Probability (Test + | Disease +) = True Positive/ (True Positive + False Negative)

Specificity:

Probability (Test - | Disease -) = True Negative/ (True Negative + False Positive)

A highly sensitive test will have few false negatives. When a highly sensitive test is negative, it is highly probable that the person does not have the disease. Therefore, the test is helpful at 'ruling out' the disease. A highly specific test will have few false positives. When a highly specific test is positive, it is highly probable that the person has the disease. Therefore, the test is helpful at 'ruling in' the disease.

In addition to sensitivity and specificity, the positive predictive value (PPV) is the probability that the patient has the disease given that he tested positive. Negative predictive value (NPV) is the probability that the patient does not have

the disease given that he tested negative. The PPV is influenced by the prevalence of the disease. As such, test for a rare disease i.e. disease with a low pre-test probability, will have a low PPV.

PPV:

Probability (Disease + | Test +) = True Positive/ (True Positive + False Positive)

NPV:

Probability (Disease - | Test -) = True Negative / (True Negative + False Negative)

Selecting an optimal cut-off for an index test

To assess the diagnostic accuracy of an index test, a cut-off score is selected above which the individual is said to be test positive. Ideally, an optimal cut-off would have a high sensitivity and a high specificity. However, increasing the sensitivity of a test may compromise its specificity due to increasing number of false positives. Similarly, increasing the specificity may compromise the sensitivity due to increasing number of false negatives. A number of factors have to be considered when deciding whether to compromise sensitivity or specificity for an imperfect test, and by weighing up the advantages and disadvantages or 'costs' of compromising one or the other. For example, an excess of false positives could lead to more people being diagnosed with a disease they do not have, and being offered treatment they do not need. This could have the untoward consequences of inducing anxiety or other distressing emotions in patients receiving the diagnosis, patients going through unnecessary treatment and developing possible harmful side effects. The economic costs of providing an excess of unnecessary treatments to false positive patients should also be

considered. On the other hand, maximising specificity while compromising sensitivity would leave some patients with the disease undetected and thus untreated. The untreated disease burden to the patients, their carers, and the health service should be considered.

Receiver operator characteristic curve and area under curve

The trade-off between sensitivity and specificity can be displayed graphically with the receiver operator characteristic (ROC) curve, in which sensitivity, the true positive rate, is plotted against (1 – specificity), the false positive rate. The area under curve (AUC) represents the discriminating ability of the instrument, ranging from 0.5 (no better than chance) to 1.0 (perfect discrimination)(114).

Reliability

Reliability refers to the consistency or stability of the measure across time, patients, or observers (114). In other words, reliability testing assesses the extent to which a score is free of random error(114). Reliability can be assessed by its reproducibility or 'agreement' between two observers (inter-observer reliability), or in repeated assessments by the same observer (intra-observer or test-retest reliability).

Another way of assessing reliability of a test is to assess whether all items within a scale measure the same construct—internal consistency(115). One approach is to see if sets of items within a test correlate with each other, for example by splitting the test into two halves (split-half reliability). A more common approach is to see if all possible item pairs contained within a test correlate with each other. The higher the inter-correlations among items, the more equivalent

the items are, so the more reliable the test. Cronbach's coefficient alpha is commonly used as a marker of internal consistency(116). The formula for the standardised Cronbach's alpha is shown below:

$$\alpha = \frac{Number\ of\ items\ \times\ average\ covariance\ between\ item\ pairs}{average\ variance + (Number\ of\ items - 1)\ \times\ average\ variance\ between\ item\ pairs}$$

(117)

A Cronbach's alpha of 0.70 or higher is generally considered 'acceptable'; 0.80 to 0.90 as 'good'; 0.9 or higher as 'excellent' in psychometric research(118).

My aim

To assess the diagnostic accuracy and reliability of two anxiety measures in a sample of stroke and TIA patients: the 7-item GAD questionnaire (GAD-7), and the modified FQ.

4.2 Methods

4.2.1 Sampling and recruitment

This study was carried out on the sample of participants recruited for my prospective cohort study from 9/9/2015 to 28/6/2016, reported in Chapter 3. I recruited additional participants by postal invitations from the NHS Lothian's stroke and TIA discharge database from 1/12/2014 to 6/8/2015. The inclusion criteria are the same as my study in Chapter 3. All participants completed a questionnaire containing the index tests—the GAD-7 (Table 17) and modified FQ (Table 6) by post or online based on their preference, at three to nine months

post-stroke/TIA. All participants then received the 'gold-standard' telephone psychiatric diagnostic interview from me one week later.

4.2.2 Index tests

i) GAD-7

The GAD-7 is a brief 7-item measure of GAD derived from the DSM-IV diagnostic criteria for GAD(119). It is commonly used and has been assessed in primary care for test-retest reliability and convergent validity with other anxiety measures(119). It has a diagnostic criterion validity for GAD at cut-point 9/10 (sensitivity of 89% and specificity 82%) in a primary care sample (119). Each item denotes an anxiety symptom and is scored on a Likert scale from 0 (not at all) to 3 (nearly every day) (Table 17). The GAD-7 has a total maximum score of 21. An online version of GAD-7 demonstrated similar reliability and validity(120).

ii) The FQ-agoraphobia subscale and social phobia subscales

I described the modified FQ (Table 6) in Chapter 3. In this study, I assessed the FQ-agoraphobia and FQ-social phobia of the original FQ, but not the FQ-specific phobia subscale. The FQ-agoraphobia subscale demonstrated good internal consistency in a previous phobic non-stroke sample (Cronbach alpha = 0.86)(121).

FQ-agoraphobia subscale items:

1. Going alone far from home
2. Walking alone in busy streets
3. Going into crowded shops
4. Travelling alone or by bus
5. Large open spaces

The FQ-social phobia subscale items:

1. Being watched or stared at
2. Talking to people in authority
3. Eating or drinking with other people
4. Being criticised
5. Speaking or acting to an audience

Each item denotes a situation, and is rated according to the level of avoidance from zero (would not avoid it) to eight (always avoid it). Each subscale has total maximum score of 40. FQ has not previously been validated in stroke or TIA samples.

4.2.3 'Gold-standard' psychiatric diagnostic interview

SCID is widely accepted as the 'gold-standard' psychiatric diagnostic interview in psychiatry research and has fair to excellent inter-rater agreement for diagnosing anxiety disorders and depression between experienced and newly trained clinicians(93), and between its telephone and face-to-face versions(94). I used the telephone version of SCID-DSM-IV-TR, including the modules on panic disorder, agoraphobia, social phobia, specific phobia, and GAD(34). All SCID diagnoses were made according to the SCID coding system and after confirmation with a neuropsychiatrist at weekly meetings. Participants who were unable to talk on the telephone had face-to-face interviews at home or at an outpatient clinic.

Table 17. GAD-7 questionnaire

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Feeling nervous, anxious or on edge?

☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly everyday

Not being able to stop or control worrying?

☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly everyday

Worrying too much about different things?

☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly everyday

Trouble relaxing?

☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly everyday

Being so restless that it is hard to sit still?

☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly everyday

Becoming easily annoyed or irritable?

☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly everyday

Feeling afraid as if something awful might happen?

☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly everyday

Blinding of interviewer to index test results

All returned postal questionnaires remained sealed and online questionnaires were stored in a protected database at the Edinburgh Clinical Trials Unit. I was unable to access the questionnaire data until after all study interviews were complete.

4.2.4 Statistical analyses

I analysed the sensitivity, specificity, PPV and NPV with 95% confidence intervals at a selected cut-point for each index test using STATA14(99). I plotted the ROC curve and analysed the AUC for each index test. I computed the inter-item correlations for all pairs of items for each index test and the Cronbach's alpha statistic for each index test using R statistical software.

Selection of cut-point

On deciding a clinically useful cut-point for each index test, I considered it more important that the test had a high sensitivity rather than a high specificity. This was so that the test could maximise detection of participants who were anxious and reduce the number of anxious participants being missed. By compromising the specificity, participants who were not anxious might be falsely identified as anxious by the test. I considered this a reasonable trade-off as I was planning to design the TASK intervention to be a low-intensity guided self-help psychological intervention, which was likely to be acceptable for all and unlikely to carry risk of significant harm even if given to patients who were not anxious. Furthermore, I intended to design the TASK intervention to be easily scalable at low financial costs. For this study, I considered a sensitivity of at least 80% and specificity of at least 70% to be clinically useful.

Missing data

All items on the online questionnaire must be scored to permit submission, preventing any unscored items. Any unscored item on a returned postal questionnaire was given the most conservative interpretation and imputed zero, assuming that the item was irrelevant or did not elicit any anxiety symptoms.

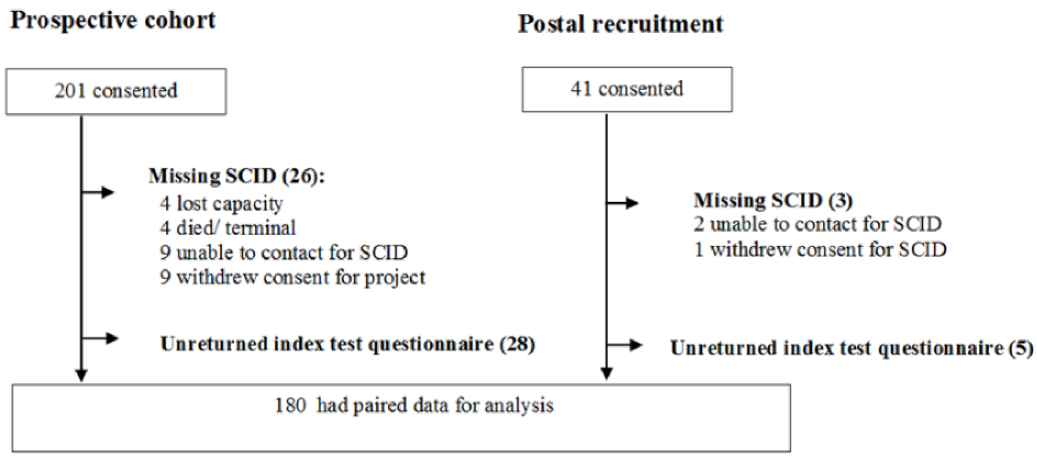
Sample size

The estimated sample size needed for the diagnostic accuracy test was 175, assuming the prevalence of anxiety would be 20%, and the test had a sensitivity of 0.70 and 95% confidence intervals of +/- 0.15.

4.3 Results

I performed 213 SCIDs in total (175 in the prospective cohort and 38 in the postal recruits, median time since stroke/TIA: 111 days) (Figure 17).

Figure 17. Sample recruited to the diagnostic accuracy study and loss of paired data



Paired data (Table 18) were available from 180 participants (mean age 70+/- 10.9; male: 61%; stroke 69%, TIA 31%). 33 did not return index test questionnaire. Non-responders were younger (non-responders: 65.6 years +/- 14.3, analysed: 70.0 years +/-10.9, p=0.046) but did not differ significantly in other characteristics (Table 18). Analysed participants completed index tests at a median of one day (IQR 0-5 days) before SCID. More than a quarter of participants completed index tests online (28%, 51/180). Almost all participants had telephone SCID (telephone: 173/180, 96%; face-to-face: 7/180, 4%). A fifth of the analysed sample had an anxiety disorder on SCID ('any anxiety disorder': 37/180, 21%; 'any phobic' 31/180, 17%; 'any GAD' 16/180, 9%).

Table 18. Characteristics of sample analysed in this diagnostic accuracy study and lost paired data

		Paired data analysed		**Loss of paired data**		**chi square** (or other specified)
		n=180	**%**	**n=33**	**%**	
Age	mean	70·0		65·6		t-test, **p=0·046**
	SD	10·9		14·3		
	median	71·3		64·2		
	IQR	63·1-78·2		56·7-77·6		
Sex						
Female		71	39%	14	42%	p=0·748
Male		109	61%	19	58%	
Recruitment method						
	Prospective	147	82%	28	84%	p=0.661
	Postal	33	18%	5	16%	
Diagnosis of any anxiety disorder on SCID	Yes	37	21%	11	33%	p=0·106
	No	143	79%	22	67%	
Diagnosis						
Ischaemic		121	67%	26	79%	
Primary intracerebral haemorrhage		4	2%	1	3%	p=0·520
TIA (probable or definite)		55	31%	6	18%	
Severity of stroke						
NIHSS	median	1		1		
	IQR	0-2		0-3		
Pre-stroke/TIA Status						
Lived alone before stroke	Yes	59	33%	15	45%	p=0·160
	No	121	67%	18	55%	
Independent before stroke	Yes	176	98%	31	94%	p=0·221
	No	4	2%	2	6%	
Past diagnosis of depression or anxiety disorder						
Depression only		31	17%	6	18%	
Anxiety only		11	6%	2	6%	p=0·882
Both depression and anxiety disorder		10	6%	3	9%	
No past diagnosis of anxiety or depression		128	71%	22	67%	

4.3.1 Diagnostic performance of index tests

Figure 18 displays the ROC curves plotted from all cut-points of all the index tests (Table 19). Table 20 summarises the diagnostic performance of GAD-7 and FQ-Agoraphobia at selected clinically useful cut-points.

GAD-7

For detecting any GAD, GAD-7 had an AUC of 0.94 (95%CI 0.89-0.98) and gave more than one clinically useful cut-points (At cut-point >=5: sensitivity 93.8%, specificity 76.8%; at cut-point >=6: sensitivity 87.5%, specificity 84.2%) (Table 20). For detecting any phobic disorder, GAD-7 had an AUC of 0.88 (95%CI 0.82-0.93). A lower cut-point of GAD-7 at >=4 gave a sensitivity of 83.9% and specificity of 73.2%.

FQ-agoraphobia

For detecting any phobic disorder, the FQ-agoraphobia had an AUC of 0.86 (95%CI 0.80-0.92). At a cut-point of >=7, sensitivity was 87.1% and specificity was 77.9%.

FQ-social phobia

FQ-social phobia did not have a clinically useful cut-off for detecting phobic disorder (Table 19).

Figure 18. ROC curves and AUC for each index test

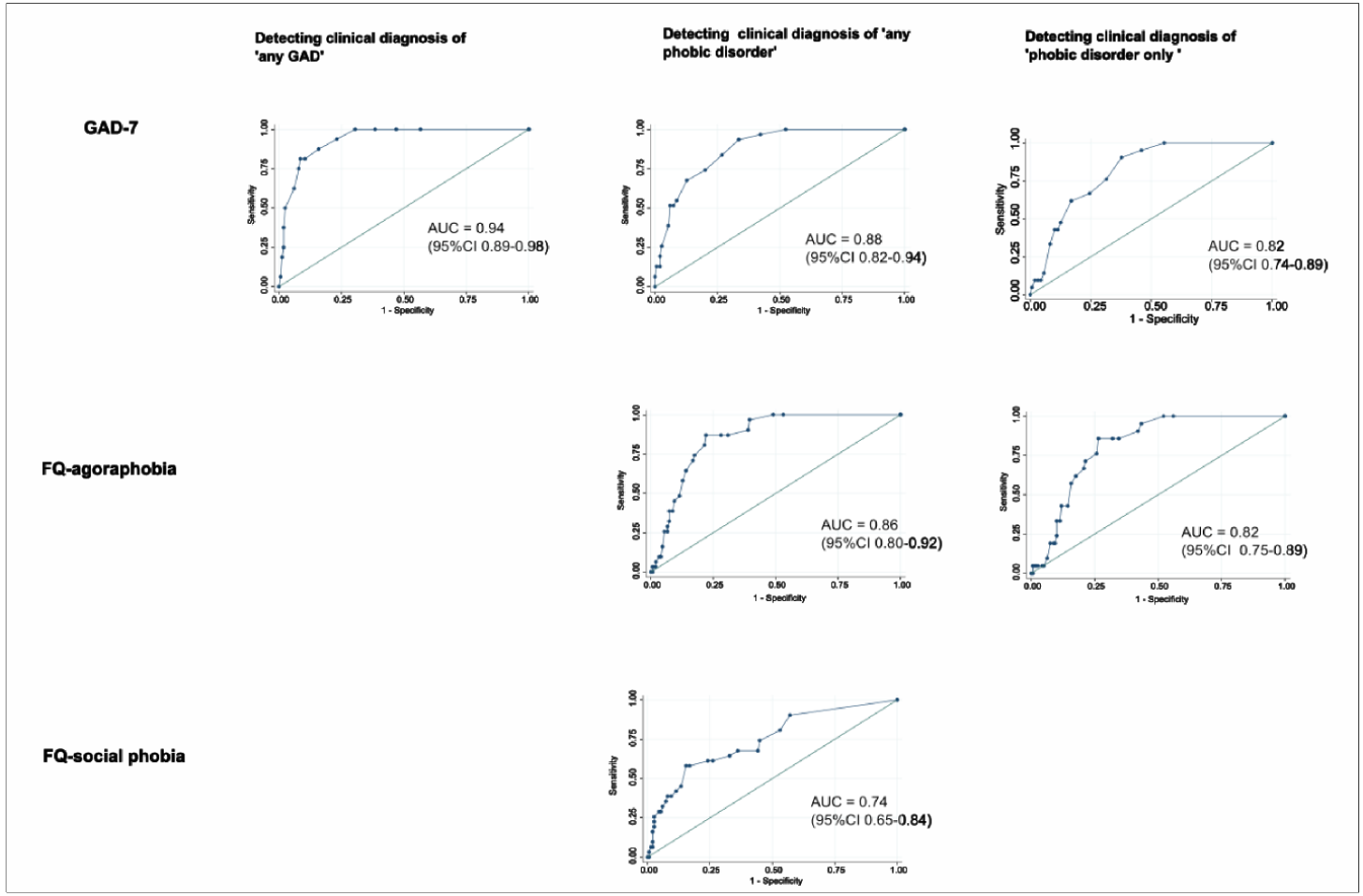


Table 19. Sensitivity and specificity at each cut-point for each index test; clinically useful cut-points are in bold

For detecting GAD			For detecting 'any phobic disorder'								
GAD-7			*GAD-7*			*FQ-Agoraphobia*			*FQ-Social phobia*		
Cut-point	Sensitivity	Specificity	Cut-point	Sensitivity	Specificity	Cut-point	Sensitivity	Specificity	Cut-point	Sensitivity	Specificity
>= 0	100.0	0.0	>= 0	100.0	0.0	>= 0	100.0	0.0	>= 0	100.00	0.00
>= 1	100.0	43.3	>= 1	100.0	47.7	>= 1	100.0	47.0	>= 1	90.32	42.95
>= 2	100.0	53.1	>= 2	96.8	57.7	>= 2	100.0	51.0	>= 2	80.65	46.98
>= 3	100.0	61.6	>= 3	93.6	66.4	>= 3	96.8	60.4	>= 3	74.19	55.03
>= 4	100.0	69.5	**>= 4**	**83.9**	**73.2**	>= 4	90.3	61.1	>= 4	67.74	55.70
>= 5	**93.8**	**76.8**	>= 5	74.2	79.9	>= 5	87.1	69.1	>= 5	67.74	63.76
>= 6	**87.5**	**84.2**	>= 6	67.7	87.3	**>= 6**	**87.1**	**71.8**	>= 6	64.52	67.11
>= 7	**81.3**	**89.6**	>= 7	54.8	91.3	**>= 7**	**87.1**	**77.9**	>= 7	61.29	73.83
>= 8	**81.3**	**91.5**	>= 8	51.6	92.6	**>= 8**	**80.7**	**78.5**	>= 8	61.29	75.84
>= 9	75.0	92.1	>= 9	51.6	94.0	>= 9	74.2	82.6	>= 9	58.06	83.22
>= 10	62.5	93.9	>= 10	38.7	94.6	>= 10	71.0	83.2	>= 10	58.06	84.56
>= 11	50.0	97.6	>= 11	25.8	97.3	>= 11	64.5	85.9	>= 11	45.16	86.58
>= 12	37.5	98.2	>= 12	19.4	98.0	>= 12	58.1	87.3	>= 12	41.94	88.59
>= 13	25.0	98.2	>= 13	12.9	98.0	>= 13	48.4	88.6	>= 14	38.71	90.60
>= 14	18.8	98.8	>= 14	12.9	99.3	>= 14	45.2	90.6	>= 15	38.71	91.95
>= 15	6.3	99.4	>= 15	6.5	100.0	>= 18	38.7	91.3	>= 16	35.48	92.62
> 15	0.0	100.0	> 15	0.0	100.0	>= 19	38.7	92.6	>= 18	32.26	93.96
						>= 20	32.3	92.6	>= 19	29.03	94.63
						>= 22	29.0	93.3	>= 20	29.03	95.30
						>= 23	25.8	93.3	>= 21	25.81	97.32
						>= 24	25.8	94.6	>= 22	22.58	97.32
						>= 26	16.1	95.3	>= 23	19.35	97.32
						>= 27	9.7	96.0	>= 24	16.13	97.99
						>= 28	9.7	96.6	>= 25	9.68	97.99
						>= 30	6.5	98.0	>= 26	6.45	97.99
						>= 31	3.2	98.0	>= 28	6.45	98.66
						>= 32	3.2	98.7	>= 36	3.23	99.33
						>= 34	3.2	99.3	>= 38	0.00	99.33
						>= 38	0.0	99.3	> 38	0.00	100.00
						> 38	0.0	100.0			

Table 20. Diagnostic performance of GAD-7, FQ-Agoraphobia at selected cut-offs in detecting anxiety subtypes diagnosed on psychiatric interview (n = 180)

	For detecting any GAD		**For detecting any phobic disorder**	
	GAD-7		***GAD-7***	***FQ-Agoraphobia***
Median score (IQR)	2 (0-5)		2 (0-5)	2 (0-10)
AUC (95%CI)	0.94 (0.89, 0.98)		0.88 (0.82, 0.93)	0.86 (0.80-0.92)
Selected cut-off	**>=5**	**>=6**	**>=4**	**>=7**
Sensitivity	93.8	87.5	83.9	87.1
(95%CI)	(69.8, 99.8)	(61.7, 98.4)	(66.3, 94.5)	(70.3, 96.4)
Specificity	76.8	84.2	73.2	77.9
(95%CI)	(69.6, 83.1)	(77.6 – 89.4)	(65.3, 80.1)	(70.4, 84.3)
PPV	28.3	35.0	39.4	45.0
(95%CI)	(16.8, 42.3)	(20.6, 51.7)	(27.6, 52.2)	(32.1, 58.4)
NPV	99.3	98.6	95.6	96.7
(95%CI)	(95.7, 100)	(94.9, 99.8)	(90.1, 98.6)	(91.7, 99.1)

4.3.2 Reliability of index tests

Internal consistency

All seven items on the GAD-7 are positively correlated with each other (Table 21). The item-rest correlation shows each item to be positively correlated with the total test score with that item omitted (>0.60) (Table 21). Cronbach's coefficient alpha of 0.92 indicates 'excellent' internal consistency of GAD-7. All five items of the FQ-Agoraphobia are positively correlated with each other (Table 22). The item on 'open space' has the weakest item-pair, item-test and item-rest correlation. Cronbach's coefficient alpha of 0.85 indicates 'good' internal consistency of the FQ-Agoraphobia.

Table 21. Item-test, item-rest and inter-item correlations and Cronbach's alpha of GAD-7

Item	Obs	Sign	item-test correlation	item-rest correlation
GA1Edge	180	+	0.86	0.80
GA2Control	180	+	0.88	0.83
GA3Worry	180	+	0.85	0.79
GA4Relax	180	+	0.89	0.84
GA5Restless	180	+	0.73	0.63
GA6Annoy	180	+	0.74	0.64
GA7Awful	180	+	0.81	0.73

Average inter-item correlation:	0.62
Number of items in the scale:	7
Scale reliability (Cronbach's alpha) coefficient:	0.92

Inter-item correlations (obs=180 in all pairs)

	GA1Edge	GA2Control	GA3Worry	GA4Relax	GA5Restless	GA6Annoy	GA7Awful
GA1Edge	1.00						
GA2Control	0.79	1.00					
GA3Worry	0.80	0.82	1.00				
GA4Relax	0.69	0.72	0.69	1.00			
GA5Restless	0.43	0.55	0.46	0.74	1.00		
GA6Annoy	0.55	0.56	0.52	0.60	0.51	1.00	
GA7Awful	0.67	0.63	0.64	0.68	0.53	0.52	1.00

Table 22. Item-test, item-rest and inter-item correlations and Cronbach's alpha of FQ-Agoraphobia

Item	Obs	Sign	item-test correlation	item-rest correlation
FQAg1Street	180	+	0.90	0.83
FQAg2Bus	180	+	0.81	0.68
FQAg3Crowd	180	+	0.84	0.73
FQAg4Far	180	+	0.85	0.75
FQAg5Open	180	+	0.53	0.31

Average inter-item correlation:	0.52
Number of items in the scale:	5
Scale reliability (Cronbach's alpha) coefficient:	0.85

Inter-item correlations (obs=180 in all pairs)

	FQAg1Street	FQAg2Bus	FQAg3Crowd	FQAg4Far	FQAg5Open
FQAg1Street	1.00				
FQAg2Bus	0.75	1.00			
FQAg3Crowd	0.75	0.57	1.00		
FQAg4Far	0.76	0.67	0.64	1.00	
FQAg5Open	0.29	0.17	0.34	0.27	1.00

4.4 Discussion

4.4.1 Key findings

This is a secondary analysis to assess the diagnostic validity of GAD-7 and FQ against 'gold-standard' clinical diagnosis made on diagnostic psychiatric interview in a stroke and TIA sample. Our findings support the diagnostic validity and internal consistency of GAD-7 and FQ-agoraphobia post-stroke/TIA. The GAD-7 has a similar AUC to FQ-agoraphobia in detecting phobic disorder.

4.4.2 Potential bias in my methodology

I received training from a neuropsychiatrist in performing the 'reference-standard' SCID in this study. The reference standard diagnosis was made in a uniform fashion with the neuropsychiatrist at weekly meetings. A systematic review of studies assessing the agreement between diagnostic telephone and face-to-face psychiatric interviews found good agreement (kappa 0.69-0.84) in psychiatric populations(100), supporting the use of telephone SCID for anxiety disorders and depression. However, there were no such comparability data in stroke. Telephone SCID limited the interviewer's ability to observe non-verbal signs, facial expressions, body language or any other idiosyncrasies that may help inform a psychiatric diagnosis. The use of telephone SCID as the reference standard thus limited the generalisability of this study's sensitivity and specificity values. While over a quarter of participants completed the FQ online as their preferred method I did not test the agreement between the two versions. My sample was at the milder end of the stroke spectrum. I lost paired data in this study through unreturned index tests. These non-responders were younger than the sample analysed. This could have led to a lower frequency of anxiety disorders in the sample.

4.4.3 Interpretation

My findings support the use of GAD-7 in detecting GAD and the FQ-agoraphobia subscale in detecting phobic disorders in stroke and TIA patients.

Discrepancy in GAD-7 cut-points between stroke and primary care samples

For detecting GAD in my sample, I found the threshold for a clinically useful cut-point to be at >=5 or >=6. These cut-points were lower than the threshold of >=10, a cut-point validated in a large primary care sample (n = 2740)(119). My sample size was small and so it was possible that the optimal cut-points for GAD-7 in this study were due to chance. My sample of stroke and TIA patients differed from a primary care sample in a number of ways that could explain this discrepancy. The primary care sample was multi-ethnic, much younger, had a higher proportion of women and a lower frequency of anxiety disorder than my sample. These factors could have influenced the likelihood and degree of scoring for each item on the GAD-7. It was also possible that anxious stroke and TIA patients who volunteered to take part in my research study, entitled 'Anxiety after Stroke', were primed, so were more likely to give higher scores on the GAD-7.

The ‘gold-standard’ interview used in the primary care study was different from the SCID interview used in my study. This could have led to variability in how the 'gold-standard' diagnosis of GAD was made. A structured interview format used in the primary care study was more rigid and did not allow for further clinical questioning by the interviewer. On the other hand, SCID followed a semi-structured format and allowed further clinical information to be gathered, which would provide a more accurate ‘gold standard’ diagnosis. Few in the primary care sample would have had a stroke or TIA. Raters in the primary care study, who were likely to have none or little experience in interviewing stroke and TIA

patients, would not have been aware that some stroke and TIA patients attributed their generalised anxiety as a normal response to their stroke event, and so might not report their symptoms unless they were probed further by the interviewer. As such, raters using a more rigid structured interview might only be able to give a diagnosis of GAD when the anxious symptoms were severe. On the other hand, my semi-structured SCID interview enabled patients to elaborate on their symptoms, providing more and richer clinical information. This might have led to the diagnosis of the milder forms of GAD.

Detecting phobic disorder after stroke/TIA

Currently, there are no anxiety measures validated for phobic disorder in stroke/TIA—the predominant anxiety subtype post-stroke/TIA that can occur in the absence of GAD(122). Other frequently used anxiety measures, for example, the Hospital Anxiety and Depression Scale, do not contain items on phobic disorder. My study findings offer preliminary data on the diagnostic validity of the FQ-Agoraphobia subscale for assessing phobic disorder in stroke and TIA patients. However, my data should be replicated before widespread use of this measure. A limitation in using the FQ-agoraphobia subscale to measure phobic anxiety after stroke is that it measures specifically the avoidance of agoraphobic situations. While agoraphobia accounted for most of the phobic cases after stroke/TIA in our recent prospective cohort(122), there were other specific phobic situations post-stroke that were reported: social situations, physical exertion, having sex, being home alone(122) that are not assessed by FQ-Agoraphobia. A desirable item/ scale for phobic disorder would measure the presence of phobic avoidance irrespective of the situation.

The GAD-7 had a slightly higher AUC for detecting phobic disorder than the FQ-Agoraphobia even though the GAD-7's sensitivity and specificity were marginally poorer than the FQ-Agoraphobia. These findings could be due to chance but other explanations include individuals presenting with mixed generalised and phobic anxiety and GAD-7's ability to detect some of the phobic anxiety symptomology. '*In the past two weeks, how often have you been bothered by i) nervousness, ii) restlessness, or iii) feeling afraid as if something awful might happen?*' on the GAD-7 could elicit positive responses in a phobic individual who regularly confronts his feared situation/ stimulus. These symptoms on the GAD-7 need not be present if the phobic individual avoids confronting or imagining the feared situation completely. It is possible that GAD-7 could detect some phobic individuals who regularly experience the symptoms on the questionnaire while missing others who do not.

Generalisability

My sample is probably representative of the mild stroke and TIA population but not of severe stroke, those who have significant communication difficulties, or those who do not wish to take part in the study.

4.5 Implications for trial design

GAD-7 and FQ-agoraphobic subscale demonstrated validity and reliability for detecting GAD and phobic disorder in stroke and TIA patients. My findings on the FQ are preliminary only. Further validation is required to assess reproducibility. Further analysis on the measures' sensitivity to change over time and in response to intervention could help me determine their suitability as outcome measures in a definitive RCT. The ability to detect the full spectrum of

phobic situations post-stroke/TIA remains limited so further research into scale development for phobic disorder post-stroke/TIA is needed.

4.6 Deriving 5 dichotomised anxiety screening items to be used for the RCT

I planned to design my intervention to be suitable for a broad spectrum of anxiety severity, ranging from very mild to very severe, and capturing both generalised and phobic subtypes. Using both the GAD-7 and FQ for screening eligibility in potential participants would be too burdensome. Furthermore, using any given cut-point on a questionnaire to screen for eligible anxious patients would miss those with milder symptoms.

I aimed to use my data on GAD-7 and FQ to derive five simple anxiety-screening items to be used for screening eligibility in my RCT. I would add a sixth item, a free-text box for potential participants to enter any anxious problem that they felt needed treating. I aimed to select those anxiety screening items which would maximise the inclusiveness of anxious stroke/TIA patients for trial recruitment.

Methods

I carried out this secondary analysis using the same dataset. First, I dichotomised all items on the GAD-7 and FQ so that all responses were binary (1= 'Yes', 0= 'No'). For both scales, scores above zero were converted to a positive response (1 = 'Yes') (Table 23).

I performed an exploratory principal factor analysis on this set of dichotomised items (GAD-7 + FQ = 23 items) in STATA14 to examine the factor structure. In principal factor analysis, the factor loadings are computed using the

squared multiple correlations as estimates of the communality (variance shared with other variables)(99).

Table 23 Dichotomising GAD-7 and FQ

GAD-7	**During the past 2 weeks, how often have you been bothered by any of the following problems?**	0=not at all 1=several days 2=more than half the days 3=nearly everyday	**Dichotomized** 'during the past 2 weeks, I have been bothered by' 0=Not at all 1-3=Yes I have
	Q1 "feeling nervous, anxious or on edge? Q2 "not being able to stop or control worrying?" Q3 "worrying too much about different things?" Q4 "trouble relaxing" Q5 "being so restless that it is hard to sit still?" Q6 "becoming easily annoyed or irritable?" Q7 "feeling afraid as if something awful might happen?"		
Fear Q	**How much would you avoid each of the situations below because of fear or other unpleasant feelings?** **0 1 2 3 4 5 6 7 8** **Would not avoid it** **Slightly avoid it** **Definitely avoid it** **Markedly avoid it** **Always avoid it**		**Dichotomized** 'I have avoided the following because of fear or other unpleasant feelings' 0 = no >1 = yes
Agoraphobia	Q8 "going alone far from home" Q9 "walking alone in busy streets" Q10 "going into crowded shops" Q11 "travelling alone or by bus" Q12 "large open spaces"		
Social	Q13 "being watched or stared at" Q14 "talking to people in authority" Q15 "eating or drinking with other people" Q16 "being criticised" Q17 "speaking or acting to an audience"		
specific	Q18 "physically exerting yourself" Q19 "having sex" Q20 "being alone at home" Q21 "any of your normal day-to-day activities for fear of having a headache" Q22 "any of your normal day-to-day activities for fear of having a stroke" Q23 "any of your normal day-to-day activities for fear of having a fall"		

Given that the two scales were designed to detect two anxiety subtypes, I would expect to find at least two factors to explain the most variance of the total score, reflecting the two dimensions of these items. An eigenvalue represents how much of the variance of the item a factor explains. Factors with eigenvalues

of >1 would be retained by convention(123). In addition, I would examine the internal consistency of each of these items, discarding those with the lowest values. The final selection of items would be based on the findings from these psychometric analyses and their clinical relevance.

Results

Principal factor analysis found a two-factor structure (only two factors with eigenvalues more than 1) with the first factor accounting for most of the variance (72%) (Table 24). The factor loadings showed that all 23 items loaded on Factor 1 (Table 25). All items had more weight on Factor 1 than any other factors. The GAD-7 items loaded on Factor 1 but negatively on Factor 2. The agoraphobic (Q8-12) and social phobic (Q13-17) items of the FQ loaded on both Factor 1 and Factor 2 but all items loaded with more weight on Factor 1. All items showed high internal consistency (Cronbach alpha's >0.90) (Table 26). Question 12 from the agoraphobic subscale ('large open space') and Question 17 from the social phobic subscale ('speaking or acting to an audience') had the lowest item-test and item-rest correlation.

Table 24. Principal factor analysis of my set of dichotomised items

Factor analysis/correlation Number of obs = 180
Method: principal factors Retained factors = 13
Rotation: (unrotated) Number of params = 221

Factor	Eigenvalue	Difference	Proportion	Cumulative
Factor1	8.93773	7.41416	0.7188	0.7188
Factor2	1.52357	0.62783	0.1225	0.8413
Factor3	0.89574	0.18401	0.0720	0.9134
Factor4	0.71174	0.18285	0.0572	0.9706
Factor5	0.52888	0.23174	0.0425	1.0131
Factor6	0.29715	0.03803	0.0239	1.0370
Factor7	0.25912	0.04253	0.0208	1.0579
Factor8	0.21659	0.05713	0.0174	1.0753
Factor9	0.15945	0.03450	0.0128	1.0881
Factor10	0.12496	0.07157	0.0100	1.0982
Factor11	0.05338	0.03388	0.0043	1.1025
Factor12	0.01950	0.00806	0.0016	1.1040
Factor13	0.01145	0.02123	0.0009	1.1049
Factor14	-0.00978	0.03838	-0.0008	1.1042
Factor15	-0.04817	0.00592	-0.0039	1.1003
Factor16	-0.05409	0.03504	-0.0043	1.0959
Factor17	-0.08912	0.03905	-0.0072	1.0888
Factor18	-0.12817	0.02535	-0.0103	1.0785
Factor19	-0.15352	0.01026	-0.0123	1.0661
Factor20	-0.16378	0.04098	-0.0132	1.0529
Factor21	-0.20476	0.01490	-0.0165	1.0365
Factor22	-0.21966	0.01414	-0.0177	1.0188
Factor23	-0.23380	.	-0.0188	1.0000

Table 25. Factor loadings (pattern matrix) and unique variances

Dichotomized items from GAD7 and FQ	Factor1	Factor2	Factor3 |	Uniqueness
Q1 “feeling nervous, anxious or on edge?	0.6430	-0.4319	-0.0152 |	0.3998
Q2 “not being able to stop or control worrying?”	0.7159	-0.4113	-0.1877 |	0.2831
Q3 “worrying too much about different things?”	0.7160	-0.4729	-0.1941 |	0.2261
Q4 “trouble relaxing”	0.7364	-0.3478	-0.0936 |	0.3280
Q5 “being so restless that it is hard to sit still?”	0.6462	-0.1527	-0.0652 |	0.5548
Q6 “becoming easily annoyed or irritable?”	0.5450	-0.2317	-0.2138 |	0.6035
Q7 “feeling afraid as if something awful might happen?”	0.6551	-0.2235	0.0926 |	0.5123
Q8 “going alone far from home”	0.7071	0.1087	0.0083 |	0.4881
Q9 “walking alone in busy streets”	0.7537	0.1708	0.0909 |	0.3944
Q10 “going into crowded shops”	0.7146	0.1525	-0.0378 |	0.4647
Q11 “travelling alone or by bus”	0.6736	0.1680	0.2422 |	0.4594
Q12 “large open spaces”	0.4678	0.2553	0.0595 |	0.7125
Q13 “being watched or stared at”	0.6068	0.3580	-0.3223 |	0.3998
Q14 “talking to people in authority”	0.6290	0.3159	-0.0515 |	0.5019
Q15 “eating or drinking with other people”	0.5772	0.2028	0.0808 |	0.6191
Q16 “being criticised”	0.6349	0.3278	-0.2766 |	0.4129
Q17 “speaking or acting to an audience”	0.4457	0.2873	-0.3610 |	0.5885
Q18 “physically exerting yourself”	0.5109	0.1182	0.1529 |	0.7017
Q19 “having sex”	0.4828	0.2493	0.0141 |	0.7045
Q20 “being alone at home”	0.5031	-0.0346	0.0892 |	0.7377
Q21 “any of your normal day-to-day activities for fear of having a headache”	0.6500	-0.0337	0.2786 |	0.4987
Q22 “any of your normal day-to-day activities for fear of having a stroke”	0.5947	-0.0336	0.3890 |	0.4938
Q23 “any of your normal day-to-day activities for fear of having a fall”	0.5827	0.0007	0.3211 |	0.5574

Table 26. Inter-item correlation of all 23 dichotomised items

Item	Obs	Sign	item-test correlation	item-rest correlation	average interitem covariance	alpha
q1bin	180	+	0.6474	0.6016	.081765	0.9292
q2bin	180	+	0.7134	0.6752	.0809357	0.9279
q3bin	180	+	0.7124	0.6734	.0808035	0.9279
q4bin	180	+	0.7354	0.6998	.0806774	0.9275
q5bin	180	+	0.6527	0.6108	.0822143	0.9290
q6bin	180	+	0.5731	0.5207	.0828775	0.9306
q7bin	180	+	0.6692	0.6293	.0820579	0.9288
q8bin	180	+	0.7217	0.6837	.0806693	0.9278
q9bin	180	+	0.7508	0.7181	.08071	0.9273
q10bin	180	+	0.7226	0.6852	.080768	0.9278
q11bin	180	+	0.6839	0.6448	.0817479	0.9285
q12bin	180	+	0.4956	0.4515	.0852971	0.9314
q13bin	180	+	0.6229	0.5782	.0825944	0.9296
q14bin	180	+	0.6501	0.6102	.0826024	0.9291
q15bin	180	+	0.5990	0.5573	.0835933	0.9299
q16bin	180	+	0.6526	0.6101	.0821204	0.9290
q17bin	180	+	0.4871	0.4282	.0841438	0.9322
q18bin	180	+	0.5499	0.4959	.083249	0.9310
q19bin	180	+	0.5155	0.4682	.0846332	0.9312
q20bin	180	+	0.5278	0.4809	.0844372	0.9310
q21bin	180	+	0.6582	0.6229	.0831667	0.9290
q22bin	180	+	0.6145	0.5675	.0825057	0.9298
q23bin	180	+	0.6069	0.5580	.0824493	0.9299
Test scale					.0824356	0.9322

'bin' indicates the questionnaire item has been dichotomised (binary)

Interpretation

All 23 dichotomised items address a common anxiety latent trait (Factor 1). Questions 8-19 address an additional second latent trait (Factor 2). These items are from the FQ, and are related to avoidant behaviour of a particular situation, suggesting that this second latent trait may be a 'phobic trait'. These findings are consistent with my knowledge that the set of items is made up of two questionnaires representing two anxiety subtypes. Not all variance could be explained by Factors 1 and 2 and it is unclear, based on the data available, what latent construct Factor 3 represents.

Question 12 'large open space' and Question 17 'speaking or acting to an audience' had the weakest internal consistency and will be excluded from my final item selection. This leaves 21 items to choose from.

Final selection of anxiety screening items for my RCT

Based on the data analysis, I considered the remaining 21 questions to be eligible to be included in the final selection. I selected Question 3 ‘worrying too much about different things?’ from the GAD-7; Question 9 ‘walking alone in busy streets’ and Question 10, ‘going into crowded shops’ from the FQ-agoraphobia subscale; Question 15 ‘eating or drinking with other people’ from the FQ-social phobia subscale; Question 21 ‘any of your normal day-to-day activities for fear of having a headache’ from the specific phobia subscale to be the final anxiety screening items. In addition to these five items, I would add a free-text item, ‘what anxiety problem(s) are you experiencing?’

Discussion

I performed this secondary analysis in order to derive five simple anxiety screening items suitable for use for eligibility screening for my RCT. My method combined a data-driven approach with clinical experience in assessing anxiety after stroke and TIA. The goal of this analysis was so that I could have a brief set of anxiety screening items that would be quick and easy to complete by potential participants. The selected items aimed to maximise inclusiveness of anxiety subtypes and of severity at trial recruitment. The additional free-text item hopes to capture any remaining anxious patients who respond negatively to the five selected items.

This secondary analysis was performed in a small sample. The psychometric data could be chance findings and were only exploratory. Most of the items appeared to agree with the a priori impression that anxiety had two dimensions (generalised and phobic). I applied my clinical judgement in the final selection of the items.

Chapter 5

TASK (Treating Anxiety after StroKe) Intervention Development

Publication status and acknowledgement of contributions

I submitted this chapter as a supplementary file to the TASK trial protocol, which has been published in the August 2018 issue of Pilot and Feasibility Studies.

My supervisors and I conceived the idea of designing a novel anxiety intervention that could be delivered remotely to stroke and TIA patients, one which would have the potential to overcome the barriers in accessing psychological therapy post-stroke. I followed this vision when designing the TASK intervention.

I wrote and designed all the content of the TASK intervention, including the graphics, interactive online tasks, and all online multimedia content with comments from my supervisors.

My colleagues Dr Gordon Blair and Dr Akila Visvanathan assisted at a patient advisor group meeting to co-produce the content of the TASK intervention.

My supervisors provided guidance in complex intervention development and patient involvement. I also attended a postgraduate course on ‘Developing and Evaluating Complex Public Health Interventions’ at the Usher Institute.

5.1 Introduction

It was clear to me, as I was conducting my research for Chapter 2 and 3, that the TASK intervention was going to be a psychological intervention adapted for stroke and TIA patients rather than a drug or single medical/ surgical procedure. A psychological intervention falls within the definition of a complex intervention (see below). I attended, as an auditing student, a postgraduate module of the Masters of Public Health on 'Developing and Evaluating Complex Public Health Interventions' at the Usher Institute. This course elaborated the well-known principles of the Medical Research council's (MRC) framework for complex intervention development and evaluation (Figure 19). It provided me with a systematic, logical and evidence-based methodology in developing a complex intervention, known as the Six essential Steps in Quality Intervention Development (6SQuID).

5.1.1 What is a complex intervention?

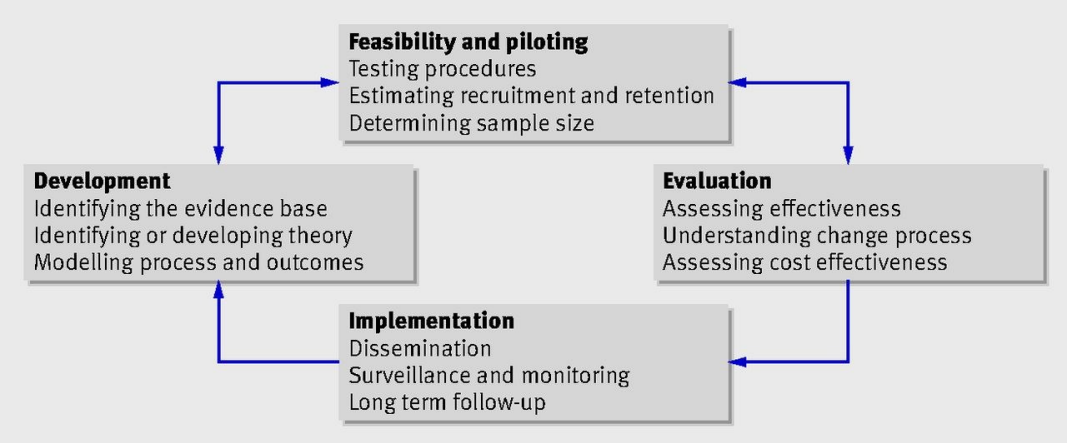
The MRC guidance describes a complex intervention as one containing several interacting components, characterised by the following(124):

- A number of interacting components within the experimental and control interventions
- A number of behaviours required by those delivering or receiving the intervention
- A number of groups or organisational levels targeted by the intervention
- A number of and variability of outcomes
- Degree of flexibility or tailoring of the intervention permitted

5.1.2 MRC framework for complex intervention development and evaluation

The MRC guidance states that the development of a complex intervention involves three key processes (Figure 19): 1) identifying existing evidence, 2) identifying and developing theory, and 3) modelling process and outcome(124).

Figure 19. Key elements of the development and evaluation process in the MRC framework



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5.1.3 Six Steps in Quality Intervention Development

6SQuID is a systematic, logical and evidence-based approach to developing complex intervention(125). It breaks down the intervention development process into six essential steps (Table 27), elaborating the MRC framework.

In Chapter 1, I covered the relevant existing literature on anxiety in both general adults and people after stroke. My research in Chapters 2, 3 and 4 generated new knowledge on the topic of anxiety after stroke and TIA. In this

chapter, I summarise briefly all of the work undertaken thus far, thereby laying the theoretical foundation for my TASK intervention.

Table 27. The six essential steps in complex intervention development
1. Define and understand the problem and its causes 2. Clarify which causal or contextual factors are modifiable and have the greatest scope for change 3. Identify how to bring about change: theory of change 4. Identify how to deliver the change: theory of action 5. Test and refine on a small scale 6. Collect sufficient evidence of effectiveness to justify rigorous evaluation/ implementation

5.2 TASK intervention development by 6SQuID

5.2.1 Step 1: Define and understand the problem and its causes

Epidemiology of anxiety after stroke

There are more than 150,000 strokes per year, and 1.2 million stroke survivors in the UK(126). Anxiety affects a quarter of stroke patients, equivalent to around 25, 000 patients per year. Anxiety is associated with dependence, poorer quality of life and restricted participation in work and social activities after even mild stroke and TIA. Stroke and TIA patients can present with two main anxiety subtypes—phobic and generalised. I found phobic disorder to be the predominant anxiety subtype after stroke and TIA. Younger people and those with a previous history of anxiety or depression are more likely to develop anxiety after stroke.

Longitudinal data in stroke suggest that anxiety post-stroke could last up to 10 years(58). When left untreated, anxiety disorder does not tend to resolve in non-stroke populations.

Assessment and treatment approaches for anxiety

In non-stroke populations, systematic repeated hierarchical exposure therapy, i.e. confronting the feared situation in small gradual steps, is an effective treatment for phobic disorders(44, 45), and yet it has never been evaluated in stroke patients with anxiety(46). Medications e.g. SSRIs, benzodiazepines (in short term only) and cognitive therapy are effective treatments for GAD(49, 50).

Currently, there is no definitive RCT evidence to guide treatment for anxiety after stroke. Anxiety assessment tools used in previous RCTs of stroke patients were measures of generalised anxiety, which may not detect individuals with phobic disorder. In Chapter 4, I demonstrated that GAD-7, a well-validated and reliable tool in primary care derived from the DSM-IV criteria for GAD, was also clinically useful for detecting GAD in a stroke and TIA sample. My study also provided some preliminary findings to support the clinical usefulness of the FQ-agoraphobia subscale in stroke and TIA patients.

Pathophysiology of anxiety

The study of anxiety and its pathological forms, in humans and animals, supports a multifactorial aetiology of clinical anxiety disorders—the complex interplay of biological (genetic, physiological), psychological, behavioural and social (environmental) factors. Studies of classical conditioning—a learning behaviour, and of maladaptive thinking (cognitive) patterns helped establish the

theoretical basis for CBT, which has been the mainstay and a first-line treatment for a range of anxiety disorders in general adults, supported by RCT evidence.

What provokes the maladaptive behaviour and maladaptive thinking patterns in stroke and TIA patients?

Based on the findings from my prospective cohort and patient narratives, most stroke and TIA patients perceived stroke to be a sudden and potentially life-threatening event that carried a high risk of recurrence. The finding that phobic disorder was predominant after stroke or TIA, and the high levels of avoidant behaviour in a range of defined situations amongst anxious patients suggested that fear conditioning could be a mechanism for anxiety after stroke and TIA. Narratives from my psychiatric interviews suggested that after a stroke or TIA event, some patients became conditioned to developing unpleasant anxious feelings and anxiety-provoking thinking in otherwise neutral situations, e.g. going out alone, taking the bus, going into a crowded shop, taking a shower, having a headache or 'twinge'. The anxiety-provoking thinking pattern was usually related to events that could threaten their safety or health: '*something bad, like a stroke, is going to happen to me*'. The three anonymised interview extracts below help illustrate this.

Extract 1, a 45 year-old woman after a posterior circulation 3 months ago with no residual neurological symptoms:

> *'I walked into a street that was very crowded. I felt I couldn't breathe. I was sweating and my chest felt funny. I had tingling down my arms.*
> *I stepped out of the crowd and told myself to calm down.*
> *I didn't want people to see me looking crazy!*
> *The same thing happened again in the supermarket.*

I suddenly felt like something bad was going to happen. I just wanted to get out of the shop as quickly as possible. I left quickly and didn't even finish paying for my shopping.
I felt better once I got back to my car. I definitely don't go out as much as I used to anymore.
I just felt something bad was going to happen, may be a stroke, or collapse, something like that.'

Extract 2, a 65 year-old man after a TIA 3 months ago:

'I had my TIA when I was having a shower. Since then I felt very anxious going into the shower. I would feel my heart pounding, breathless, nervous and panicky. It felt like I was having my TIA again, except there was no weakness down one side this time. I dread having a shower each day. My wife has to be in the bathroom while I shower very quickly. Even then I still feel very anxious. I just can't help feeling this way.'

Extract 3, a 69 year-old lady after a lacunar stroke 3 months ago with mild residual left arm weakness:

'I couldn't get on the bus after my stroke*. It was so bizarre!*
I used to take the bus everywhere without any problems.
The first time I tried since my stroke, I felt so frightened at the bus stop that I left the bus stop without getting on the bus! I worried about something happening, like a stroke, or I could fall on the bus.'

Other anxious patients expressed a fear of having to interact with people socially. They would find it distressing when other people enquired about their illness, or noticed their deficits. They feared these situations to the extent that they would avoid social gatherings or interactions with family, friends and colleagues (Extract 4).

Extract 4, a 42 year-old man, lacunar stroke 3 months ago with no residual neurological symptoms:

> *'I just wanted to be at home alone. I didn't want to see anybody, not even my friends.*
> *I felt like I was being judged when people looked at me and I hated it!*
> *When people were looking at me I would start to panic.*
> *When people saw me getting nervous it just made me panic even more!*
> *Once, I found myself looking to the ground, avoiding eye contact when I was talking to a potential client for some building works. I was worried that I was coming across as stupid, and the client would not give me the job.*
> *This was not like me at all. I used to be very confident before my stroke.'*

Many anxious patients did not understand why they had become anxious in everyday situations. They reported anxiety or panic feelings in these situations. The anxiety feelings were so unpleasant that they avoided these situations to the extent that their day-to-day life was affected.

The predominant thinking pattern amongst anxious individuals was fear of having another stroke, or other similarly dangerous or embarrassing mishaps e.g. falls, collapse, looking odd or stupid. I found many of the anxious individuals to perceive their risk of stroke to be far higher than the realistic risk of stroke recurrence in the long-term. They selectively paid more attention to the stimuli and situations e.g. odd sensations, headaches, physical exertion, going out alone, which they thought were associated with a risk of stroke or other dangerous mishaps. These stimuli further perpetuated their anxiety feelings (both affective and physiological) which reinforced their belief that these stimuli/ situations represented danger. Their avoidant behaviour was safety-seeking. These patients fitted well in the cognitive model described by Aaron Beck(47).

Maladaptive avoidant behaviours and unhelpful thinking patterns are the potential targets for my TASK intervention.

5.2.2 Step 2: Clarify which causal or contextual factors are modifiable and have the greatest scope for change

My 6SQUID Step 1 suggested that maladaptive avoidance and thinking patterns (e.g. exaggerated risk of stroke recurrence) were frequently reported in people with anxiety post-stroke or TIA and so could be targeted by CBT. Considering the existing RCT evidence on CBT's effectiveness in treating anxiety in non-stroke populations, adapting CBT approaches should offer the greatest scope for change in my TASK intervention. Medication (e.g. antidepressant) is also an evidence-based treatment for GAD. While my TASK trial will not include a pharmacological component, it would be possible to include a component in my TASK intervention that tells participants about medication being a possible helpful adjunct, and that should they wish to take this option, they should have a discussion with their general practitioner.

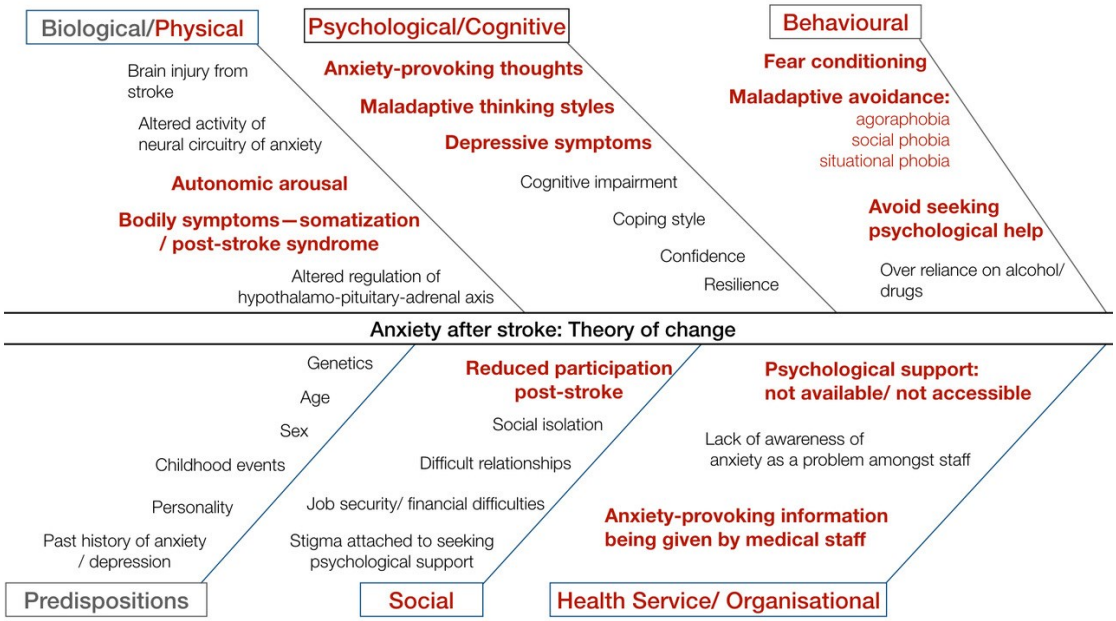
5.2.3 Step 3: Theory of change

Aside from maladaptive avoidance and thinking patterns, there are many other potential factors, theoretical or evidence-supported, which may contribute to anxiety after stroke. Younger age and a previous history of anxiety and depression are the most consistent predictors for anxiety after stroke/TIA. A systematic review did not find sufficient evidence to support any association with potentially modifiable psychological factors such as locus of control, coping style

or confidence, which have been implicated in anxiety in other disease populations e.g. multiple sclerosis(106, 127).

I summarized a list of potential contributory factors to anxiety after stroke in a 'theory of change' diagram, highlighting in red, factors that my TASK intervention hopes to address (Figure 20).

Figure 20. Theory of change in anxiety after stroke



5.2.4 Step 4: Theory of action

The theory of action in Step 4 of the 6SQUID emphasises that researchers must think about what resources or assets are available, what is feasible, and what is acceptable and ethical in the given context when designing a complex intervention. Failure to consider this step early in intervention development could lead to a waste of resources and costly evaluation of an intervention not fit for implementation in clinical practice(125).

Feasibility of delivering CBT post-stroke

In conventional CBT, a therapist delivers a course of face-to-face psychotherapy sessions of varying length between 6 weeks to 6 months. CBT is structured, time-limited, and goal orientated. Patient and therapist work collaboratively towards a defined goal by working through the key components of CBT: i) identify maladaptive thinking and behaviours, ii) self-monitoring, iii) psychoeducation, iv) cognitive restructuring, v) exposure techniques, vi) specific skills training (varies depending on patient's needs e.g. problem solving, time management), and vii) ongoing self-management(128). Delivering CBT in a conventional format requires highly trained psychotherapists and repeated clinic attendance.

A 'theory of action' is required to find a feasible way to deliver the 'active ingredients' of CBT to anxious stroke and TIA patients. I summarize the current context of psychological care post-stroke in the UK, and ways in which key stakeholders' input has helped me determine the final design of the TASK intervention.

Barriers in accessing psychological care post-stroke

Inadequate service provision in psychological care and the lack of routine screening in stroke units and primary care post-stroke across the United Kingdom are evident from the reports of the Sentinel Stroke National Audit Programme in England, Wales and Northern Ireland(129) and the latest Royal College of Physicians Stoke Guideline(130). The Scottish Stroke Improvement Programme highlighted access to psychological care as a priority area for improvement in 2017(131). The demand for better access to psychological care post-stroke has consistently been echoed by surveys and qualitative research of patients, carers

and health professionals, and through charitable organisations representing stroke patients(132-134). Delivering CBT in a conventional face-to-face format to all patients with anxiety post-stroke/TIA is not feasible in clinical practice given the high prevalence of anxiety and other common post-stroke neuropsychiatric complications in this population and limited resources. It is estimated that at least 50% of stroke patients will suffer from depression, anxiety, cognitive impairments that would require psychological support(129). Our stakeholder activity involving the clinical leads of stroke and clinical psychology services from across Scotland agreed that this demand was unlikely to be met by primary care providers alone, nor the traditional paradigm of referring patients for face-to-face psychotherapy delivered by highly-trained specialists.

5.2.4.1 Stakeholders input I: Clinical leads

The Scottish Government's Stroke Improvement Plan in 2017 set a priority to improve post-stroke access to clinical psychology services. The lead of this programme organised a workshop in September 2017, which was attended by the local leads of stroke clinical psychology services from across Scotland and the chair of Scottish Stroke Care Audit, Professor Martin Dennis, who was also my supervisor. I attended this meeting as an invited speaker. The workshop aimed to address ways of improving access to psychological support post-stroke. Everyone in attendance agreed that psychological care had to be provided to a large population of stroke patients who needed it—a quarter of stroke patients with anxiety was equal to an estimated 2000 to 3000 patients per year in Scotland (131). The shortage and geographical variation in the supply of highly trained psychotherapists in Scotland were evident from the local service evaluations

presented at the meeting. These were unlikely to be resolved in the foreseeable future within the NHS.

The stepped care model of psychological care, one that has been advocated by the NHS and the Royal College of Physicians Stroke Guideline, was considered the most feasible model to provide psychological care post-stroke (135, 136). In this model, an allied health professional with stroke experience e.g. stroke nurse would deliver a low-intensity psychological intervention within the lower levels (Level 1 and 2) of this stepped care model while receiving appropriate supervision by a specialist e.g. a consultant clinical psychologist or psychiatrist. This stepped care model was considered a feasible option. Severe or refractory cases would be escalated to the top level of this stepped care model (Level 3) to receive a high-intensity psychological intervention from a specialist.

Other potential barriers to accessing psychological therapy were discussed at this meeting. These included the inability to attend face-to-face appointments due to physical immobility and social stigma attached to seeking psychological treatment. Reluctance to travel in agoraphobia and the fear of being judged in social phobia are diagnosis-specific barriers to attending face-to-face sessions. People with social phobia symptoms were three times more likely to report a fear of what others might think or say about them if they sought psychological treatment compared to people with other anxiety disorders(137).

Conclusion from Stakeholder input I:

Based on the above, I considered modifying the conventional CBT format, repackaging its ‘active ingredients’ in a way that would enable the intervention to be delivered entirely remotely by an appropriate allied health professional—in other words, a remote guided self-help CBT-based intervention.

Next, I carried out patient involvement in the second part of the stakeholder input for TASK in order to assess the acceptability of a remote treatment model and to co-produce my TASK intervention content.

5.2.4.2 Stakeholder input II: Patient involvement

Aim:

To involve stroke patients who have experienced anxiety after stroke in order to co-produce the TASK intervention and design of the TASK RCT.

Methods:

I) A quantitative survey of patients on anxiety intervention design and mode of delivery

II) A patient advisory group (PAG) meeting to co-produce the content and treatment materials

I) A quantitative survey on intervention design and delivery

This was done as part of my prospective cohort study. At the end of the telephone SCID interviews I invited participants who reported anxiety problems to take part in this additional survey. 27 out of 49 invited participants were able to complete this survey. The remainder declined due to the feelings of tiredness and inability to continue with more questioning.

I administered nine-questions with set responses to choose from, on aspects of intervention design (Table 28).

Table 28. A survey of patients on anxiety intervention design and mode of delivery

If we were going to give you a treatment program to help with your anxiety……	
	Choice of responses
1) Would you prefer having it with or without guidance?	‘prefer with guidance’ ‘prefer self-help with no guidance’
2) How would you like to receive the guidance?	‘face-to-face’ ‘telephone’ ‘don’t mind—either or both is fine’ ‘none’
3) Would you find it acceptable to use online resources/ materials as part of your treatment?	‘yes’ ‘no’
4) Would you find it acceptable to use a handbook as part of your treatment?	‘yes’ ‘no’
5) Are you able to use the Internet?	‘yes’ ‘yes with help’ ‘no’
6) Would you accept having family involved in your treatment?	‘yes’ ‘no’ ‘maybe’
7) Where would you prefer to have your treatment?	‘at home’ ‘at clinic’ ‘no preference’
8) How often would you like to be contacted?	‘once per week’ ‘once every two weeks’ ‘once every three weeks’ ‘no contact at all’
9) When should the treatment program start?	‘within first month’ ‘within first two months’ ‘at three months or later’

II) A PAG meeting to co-design the content and treatment materials

The objective of this PAG meeting was for me to hear the perspectives of patients who experienced anxiety after stroke and to learn what they wished to include as part of the TASK intervention.

Selection of patients for the PAG

I contacted participants from my prospective cohort study who were anxious and also consented to be contacted again for future involvement in the design of my anxiety intervention. The local South East Scotland Research Ethics Office agreed that the proposed meeting was considered patient involvement activity so would not require further ethical review. I selected those who were anxious in order to maximize the relevance of their perspectives in the design of my TASK intervention. I sent a letter of invitation along with an event programme to ten people, followed by a telephone call the following week. Eight people confirmed intention to attend but only three turned up on the day of the meeting.

Structure and topic for the PAG

I referred to the 'INVOLVE Briefing notes for researchers: public involvement in NHS, public health and social care research' published by the National Institute for Health Research(138) and the guidance at a workshop—'A Practical Guide to Patient and Public Involvement in Research' at the Wellcome Trust Clinical Research Facility in Edinburgh in September 2015. I used a set of PowerPoint slides to guide the patient advisors through the PAG meeting. There were three open discussions. The topics and prompts are listed in Table 29.

Table 29. Topics and prompts for open discussions at the Patient Advisors Group meeting

First open discussion (40minutes) **Topic: Support for anxiety problems after stroke** **Prompts:** What were your anxiety, worries or fear after your stroke? What help or support, if any, did you receive? What would you have wanted from the stroke service?
Second open discussion (30minutes) **Topic: Treatment content and design of treatment materials** This discussion follows a review of existing resources e.g. leaflets, booklets, the stroke workbook **Prompts:** What are your initial thoughts about these materials? What recommendations do you have for designing the materials for anxiety after stroke? What messages do you think are most effective? Least effective?
Third open discussion (10minutes) **Topic: Why is testing treatment important?** **Prompts:** What makes people drop out of a clinical trial? What can we do to encourage people to: complete trial treatment? complete follow-up questionnaire several months after treatment has finished?

Personnel

I chaired the PAG meeting and acted as the facilitator for the open discussions. Two other researchers assisted at the event. One scribed and audio-recorded the open discussions on a digital recorder. Professor Gillian Mead was present at the meeting.

Consent to audio-recording, photography and publication of narrative

All patient advisors gave verbal consent to have their discussions audio-recorded and photographs taken. All consented to the publication of their narratives anonymously.

The PAG reviewed the following stroke resources:

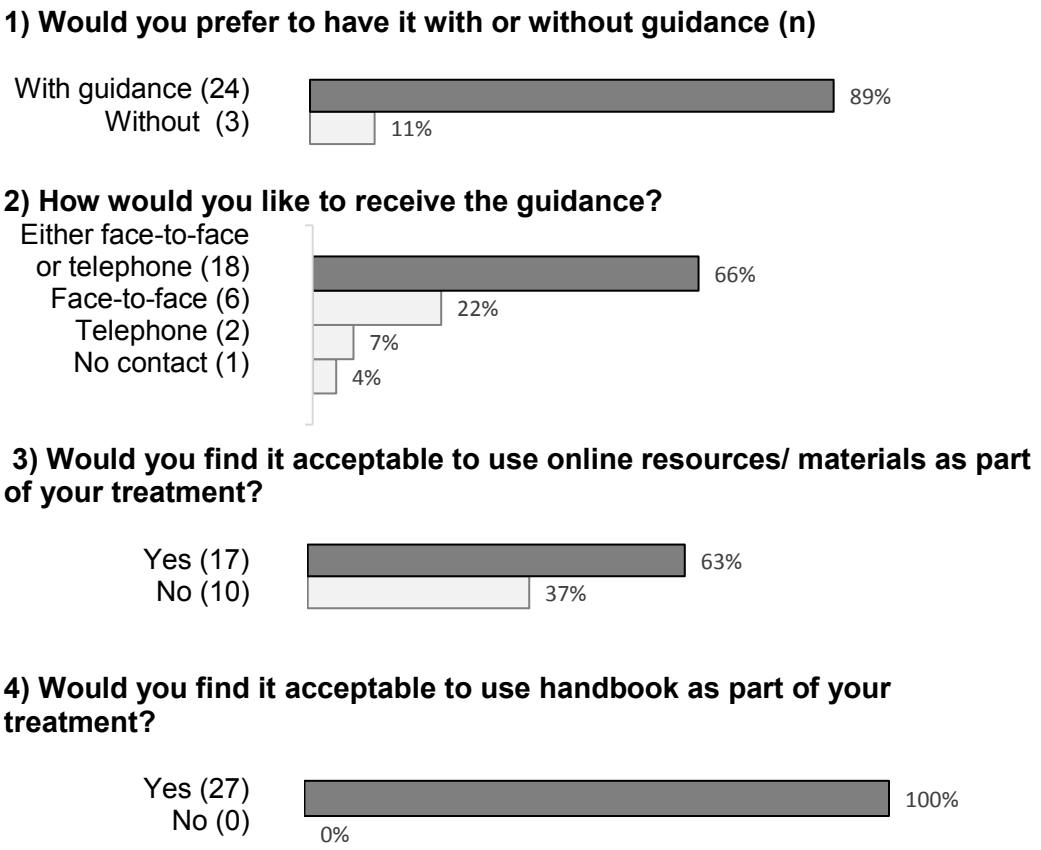
- 'Feeling overwhelmed—the emotional impact of stroke', a booklet published by the Stroke Association's 'Life After Stroke Campaign' in the Summer, 2013(134)
- 'Living with stress and anxiety' leaflet F23, September 2013, by Chest Heart & Stroke Scotland(139).
- A selection of leaflets and booklets by Chest Heart stroke Scotland (CHSS) on other issues e.g. air travel, sex after stroke illness, thinking and behaviour issues after stroke, stroke in younger people
- 'Stroke workbook', a supported self-management programme published by Lothian Health Board, 2011(140)
- Self-help for stroke website http://selfhelp4stroke.org/, developed by CHSS, in partnership with NHS Scotland, the University of Edinburgh and stroke survivors living in Scotland.

Results

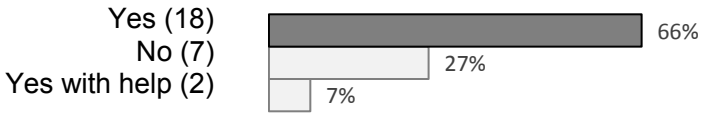
I) Quantitative survey of 27 patients with anxiety disorder

The survey results (Figure 21) showed an overwhelming preference (24/27, 89%) for a guided intervention rather than unguided self-help. Most preferred having treatment at home or had no preference (21/27, 78%); Two thirds did not mind whether the intervention was delivered face-to-face or by telephone (18/27, 66%). Over two thirds found it acceptable to use online materials as part of the intervention (17/27, 63%). Over two thirds were capable of using the Internet with or without help (20/27, 70%).

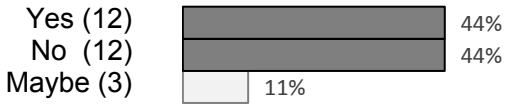
Figure 21. Quantitative survey of 27 patients with anxiety disorder



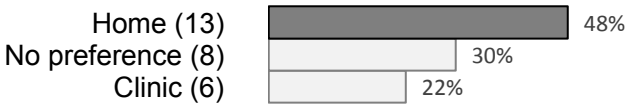
5) Are you able to use the Internet?



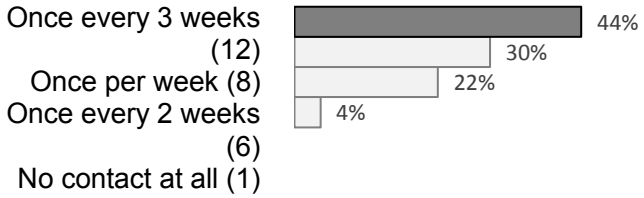
6) Would you accept having family involved in your treatment?



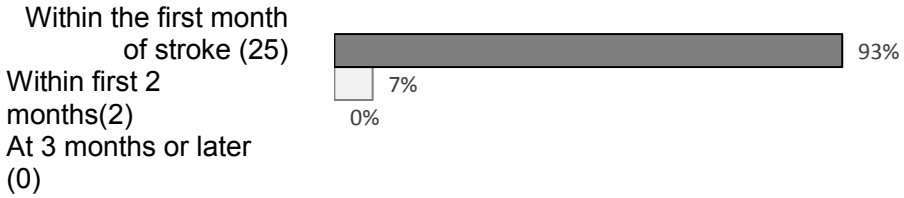
7) Where would you prefer having your treatment?



8) How often would you like to be contacted?



9) When should treatment program begin?



II) Patient involvement in developing TASK intervention

I extracted the relevant narratives from my patient advisors for each question (Table 30). To summarise, the fear of *'completely losing control in a public place in case of another stroke'* was the most frightening thought for all of my patient advisors. They feared for not only their own safety, but also how other people would react to them losing control of their body or speech. In addition, the experience of recurrent non-specific bodily symptoms e.g. headache, stabbing

pains, accompanied by the uncertainty of whether these symptoms represented stroke recurrence provoked a great deal of anxiety in our patient advisors.

Table 30. Narrative extracts from the PAG

Discussion 1) Support for anxiety problems after stroke	
Prompts: What were your anxiety, worries or fear after your stroke?	**Patient Advisor 1 (age 73)** *"It was a total shock for me. I just didn't understand why I got a stroke when I was the fit one. My first anxiety was that it was going to happen again"* *"I was afraid to go out for some time. I had this horrible vision that something awful would happen to me if I took the train"* *"It took me a long time even to get on the bus to visit my daughter. I was afraid of something happening."* *"My daughter was getting married not long after my stroke so I knew I had to turn up. So I did it and that was that!"* *"I thought to myself I could either sit here or get a grip. I told myself not to be silly"* **Patient Advisor 2 (age 72)** ***"**The anxiety was about leaving the house. The first six weeks was very difficult. When I took the bus or drove my car I just wanted to get back home."* *"A flash in the head would make me wonder—oops is there something wrong?"* *"It took a lot of effort. It took about 6 weeks before I could do a trip to London and to stay overnight. I had to work quite hard to persuade myself that I had to do it. I succeeded and so just got on with it."* *"I think we were all (**Patient advisors 1 and 3 agreed**) dreading the thought of being caught ill in a public place, and the total loss of control. That is the greatest fear of all."*

What help or support, if any, did you receive? What would you have wanted from the stroke service?	*"Living alone meant that one just had to get on with it! No choice in the matter. I still got work to do. No point sitting here twiddling my fingers. Forget yesterday and think about tomorrow."* **Patient Advisor 3 (age 62)** *"I was still very wobbly on my feet. I had other medical problems already and the stroke was another thing to add to my list."* **Patient Advisor 1:** *"I did not receive any help. Nobody asked me how I was."* **Patient Advisor 2:** *"I was visited by the Chest Heart Stroke Scotland community nurse at home. I didn't think it would be of any use initially, but he turned out to be excellent. I found him extremely helpful. He gave me a lot of information. We chatted for an hour. He offered contact details in case I needed anything"* *"I was pleased my GP surgery asked me to have my blood pressure checked quarterly"* **Patient Advisor 3:** *"I found the biggest support was by going to the community stroke service (Craighall)"* *"I found being amongst other people in the same situation really helped, to know that I was not odd."* *"It was easier to talk to strangers who had similar experience than talking about it at home."* *"They gave me confidence to try things"* **Patient Advisor 1:** *"I was just told everything was going to be fine but of course that was not the case."* *"I would have liked more information given to me after discharge"*

Further comments on what they would find helpful	**Patient advisor 2:** *"it's surprising that there is no follow-up after a stroke…while there was follow-up for my heart attack and after my hip operation"* **Patient advisor 3:** *"I would have liked some information on what services would be available after discharge?"* *"I only stumbled upon the stroke community centre by accident"* **Patient advisor 1** *"being told not to worry is not terribly helpful"* **Patient advisor 2** *"you have got to have something in place, have a list of emergency numbers in your wallet, and on your desk at home (if you live alone)"* *"I never leave my house without my mobile phone in my pocket"* *"for people who live alone, I would recommend a pendant alarm (pointing at his) and a note with emergency contact details"* *"A patient group will not work for me but it does for other people so I guess it depends on personal preference"*
Discussion 2: Treatment content and design of treatment materials This discussion follows a review of existing resources e.g. leaflets, booklets, the stroke workbook	
Prompts: What are your initial thoughts about these materials? What recommendations do you have for designing	Referring to the Stroke Association's 'Feeling overwhelmed' booklet **Patient advisor 2** *"this is excellent and it is most interesting reading about other people's experiences"* **Patient advisor 3** *"It is very valuable to learn from other people's experiences and how stroke affects other people. It*

the materials for anxiety after stroke? What messages do you think are most effective? Least effective?	*makes me less afraid to talk about things that I would otherwise tend to shy away from…"* **Referring to information leaflets and website** **Patient advisor 1** *"I would like information explaining this (stroke) is what happened to you, we don't know what caused it but these are the things that could help"* *"Acknowledging uncertainty is important"* *"I like the use of pictures—it's a way of learning things. Also the use of boxes—can really grab attention"* *"there is so much on the Internet, it's hard to know what is reliable"* **Patient advisor 2** *"I would highlight these particular sentences in a different colour—**learn how to recognise anxiety symptoms, you may often mistake your symptoms for illness….**this was absolutely key to what my symptoms were (I had odd sensations, headache)"* *"The busier you are the better. When I was busy I never noticed any of these symptoms"* *"it was important to keep myself both mentally and physically active"* **Patient advisor 3** *"any information is valuable"* *"I also found some exercises from a website to help with my balance"* **Referring to the Stroke Workbook** **Patient advisor 1** *"Wouldn't work at all for me. I already have the answers to what's in the book. It is not going to alleviate any stress I have. I need something to banish what's on my mind—the thoughts that things are going to happen to me again"*

	Patient advisor 3 *"I personally quite like reading this. I like the pictures. It is an easy way for me to learn things"* *"I think a diary is very boring"* **Additional comments:** *"Language needs to be simple and non-patronising"* *"A book with too much text makes people think they have to sit down properly to read it. With leaflets, you can just pick it up to have a read."* *"need positivity all the way through, try to get people with anxiety to think about what is stopping them from returning to their activities, then get them to think about how they used to enjoy these activities, and the positive things that came out of it"* *"for people who avoid social situations—it may help to tell other people that you have had a stroke" "if they don't know, they can't help you or understand you"*
Topic: Why is testing treatment important?	
Prompts: What makes people drop out of a clinical trial? What can we do to encourage people to: complete trial treatment? complete follow-up questionnaire several months after treatment has finished?	**Patient advisor 3:** *"people are always more enthusiastic at the beginning"* **Patient advisor 1:** *"there could be so many reasons, you'd probably have to ask the people who did not turn up to this meeting today and ask them why in a non-confrontational manner"* **Patient advisor 1:** *"establish people's expectations—often our expectations are very high for the trial treatment"* *"make us feel like we are all involved in the trial, and not just merely finishing a trial treatment"*

	"make people realise there is an end goal—we want to know the results of any research we take part in" *"tell us how our participation helps contribute to developing better treatment/care for other people, and how you will use this research"* *"emphasize on our participation and our involvement in the research instead of using the words like 'treatment' or 'intervention'--feels like something is being done to you"* **Patient advisor 2:** *"incentivise people by explaining that there will be something valuable yielded at the end. I was personally very fascinated to see the paper at the end of this cardiac MRI study I took part in"*
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What help or support, if any, did you receive? What would you have wanted from the stroke service?	*"A flash in the head would make me wonder—oops is there something wrong?"* *"It took a lot of effort. It took about 6 weeks before I could do a trip to London and to stay overnight. I had to work quite hard to persuade myself that I had to do it. I succeeded and so just got on with it."* *"I think we were all* (**Patient advisors 1 and 3 agreed**) *dreading the thought of being caught ill in a public place, and the total loss of control. That is the greatest fear of all."* *"Living alone meant that one just had to get on with it! No choice in the matter, still got work to do. No point sitting here twiddling my fingers. Forget yesterday and think about tomorrow."* **Patient Advisor 3 (age 62)** *"I was still very wobbly on my feet. I had other medical problems already and the stroke was another thing to add to my list."* **Patient Advisor 1:** *"I did not receive any help. Nobody asked me how I was."* **Patient Advisor 2:** *"I was visited by the Chest Heart Stroke Scotland community nurse at home. I didn't think it would be of any use initially, but he turned out to be excellent. I found him extremely helpful. He gave me a lot of information. We chatted for an hour. He offered contact details in case I needed anything"* *"I was pleased my GP surgery asked me to have my blood pressure checked quarterly"* **Patient Advisor 3:** *"I found the biggest support was by going to the community stroke service (Craighall)"* *"I found being amongst other people in the same situation really helped, to know that I was not odd."* *"It was easier to talk to strangers who had similar experience than talking about it at home."* *"They gave me confidence to try things"*

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Discussion 2: Treatment content and design of treatment materials This discussion follows a review of existing resources e.g. leaflets, booklets, the stroke workbook	

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Topic: Why is testing treatment important?	
Prompts: What makes people drop out of a clinical trial? What can we do to encourage people to:	**Patient advisor 3:** *"people are always more enthusiastic at the beginning"* **Patient advisor 1:** *"there could be so many reasons, you'd probably have to ask the people who did not turn up to this meeting today and ask them why in a non-confrontational manner"*

complete trial treatment? complete follow-up questionnaire several months after treatment has finished?	**Patient advisor 1:** *"establish people's expectations—often our expectations are very high for the trial treatment"* *"make us feel like we are all involved in the trial, and not just merely finishing a trial treatment"* *"make people realise there is an end goal—we want to know the results of any research we take part in"* *"tell us how our participation helps contribute to developing better treatment/care for other people, and how you will use this research"* *"emphasize on our participation and our involvement in the research instead of using the words like 'treatment' or 'intervention'--feels like something is being done to you"* **Patient advisor 2:** *"incentivise people by explaining that there will be something valuable yielded at the end. I was personally very fascinated to see the paper at the end of this cardiac MRI study I took part in"*

Qualitative evidence

In addition to patient involvement work, systematic reviews of qualitative research(141-143) conducted independently of my work complemented my research findings. Patients and carers expressed themes and gave narratives about the fear of stroke recurrence(141), insecurity about going out and going on the bus(142), fear of falling(144), and the feeling of body not under own control(141).

Patients' co-production of TASK intervention

To take into account of the patient perspectives and to co-produce the TASK intervention with my patient advisors, I plan to include patient stories in my

TASK intervention, and to place emphasis on the specific topics of agoraphobia, fear of losing control, bodily symptoms, and fear of stroke recurrence. I also plan to include a component that reminds patients to schedule an enjoyable activity to do regularly.

5.2.5 Modelling processes and outcomes of the TASK intervention

I conclude my TASK intervention development in a logic model diagram (Figure 22), which displays all the processes and outcomes of the TASK intervention—an essential step in the MRC framework of intervention development. This diagram encompasses the program theory (theory of change and theory of action), the final hypothesised model of the processes, the intended outcomes, and the mediators of the intended outcomes of my TASK intervention.

5.2.6 TASK intervention content

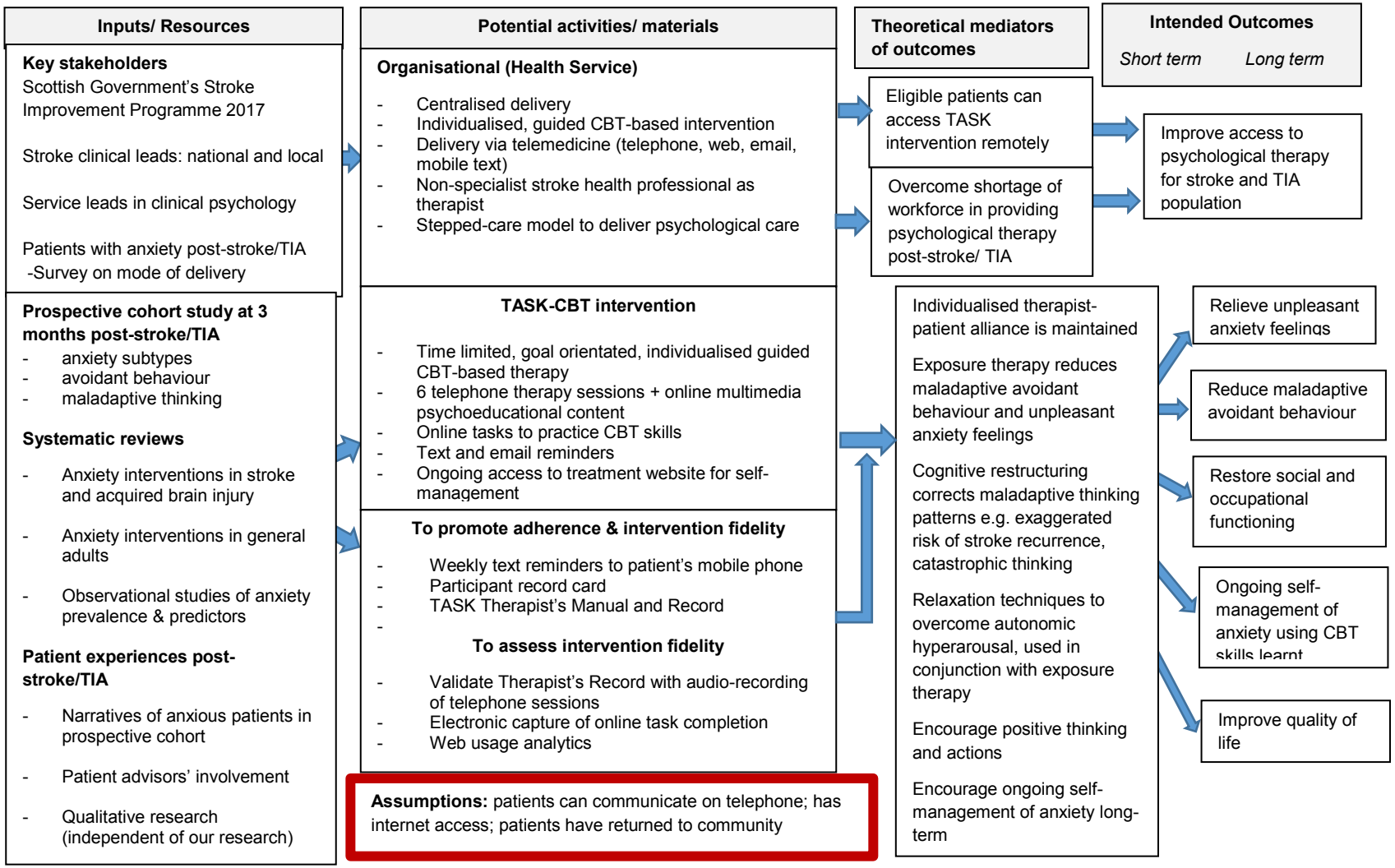
As my TASK intervention is a guided self-help CBT intervention, it will be referred to as the TASK-CBT intervention hereafter. I summarise the key features and the intended advantages of my TASK-CBT intervention.

Centralised delivery by telemedicine

In line with the views of the stakeholders, I designed my TASK-CBT intervention to be delivered by an appropriately trained health professional with experience working with stroke patients e.g. stroke nurse, stroke physician, stroke rehabilitation therapists under supervision of a specialist e.g. psychiatrist or clinical psychologist. The TASK-CBT intervention represents a low-level psychological intervention (steps 1 and 2) in the stepped care model(52).

Delivering CBT remotely via telemedicine would enable centralization of resources for staff, training, quality monitoring, and cross covering of different geographical areas, reducing travel time for therapists as well as patients. Digital content and treatment approaches in a telemedicine intervention could be updated and refined easily, thus making use of the latest best evidence. The provision, maintenance and updating of digital content could be commissioned or delivered via charitable organisations. Organisation delivering the intervention can continue to invest in research and development to utilise the latest technology to deliver the treatment content at lower costs. At present, it is not yet clear whether telemedicine-delivered CBT is cost-effective in stroke and TIA patients.

Figure 22. Modelling processes and outcomes of TASK-CBT



Maintaining an individualised patient-therapist alliance

Telemedicine could offer a way to overcome the barriers in accessing psychological therapy by treating patients remotely while maintaining an individualised therapist-patient alliance that is integral to CBT. Meta-analyses demonstrated guided internet-based CBT to be superior to waitlist control, and as efficacious as face-to-face CBT in treating anxiety disorders or depression in general adults, with face-to-face CBT spending 7 times more therapist time than guided internet-based CBT(54, 55). It is not yet certain whether these findings could be generalised to stroke and TIA patients, who tend to be older, have neurological deficits, and medical co-morbidities. The effect of such interventions on patient outcomes after stroke/TIA need to be evaluated in RCTs. To-date, RCTs of guided internet-delivered CBT for anxiety and depressive disorder in general adults have shown good patient adherence and satisfaction(54, 55).

Delivery of 'active ingredients' of TASK-CBT by telephone and web

I present the key 'active ingredients' of my TASK-CBT intervention in Figure 23. The TASK therapist delivers a course of six individualized telephone CBT sessions, 35-45 minutes each, at least one week apart, with the use of an electronic TASK Therapist's Manual and Record. Each session is supplemented by the prescription of an online task, and one or more of the psychoeducational videos on the TASK-CBT treatment website (Figure 24). To encourage adherence, a mobile text is sent to remind participant to complete the online task each week and to use the treatment website as much as possible via a computer, tablet or smartphone. This concludes the design of my TASK-CBT, a prototype

anxiety intervention for treating anxiety after stroke and TIA. Next chapter details the feasibility testing of the TASK-CBT intervention, step 5 of 6SQuID.

Figure 23. 'Active ingredients' of my TASK-CBT intervention

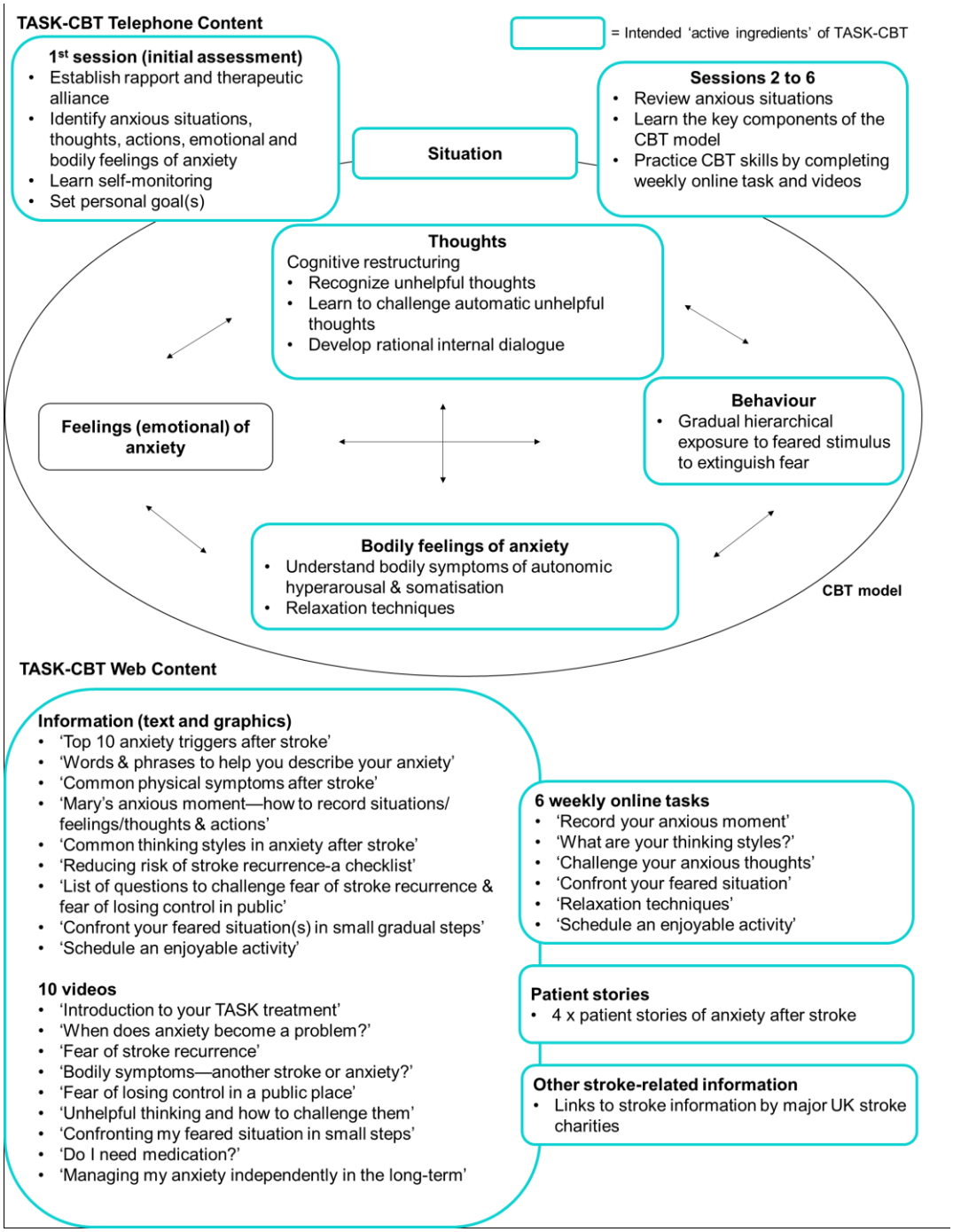
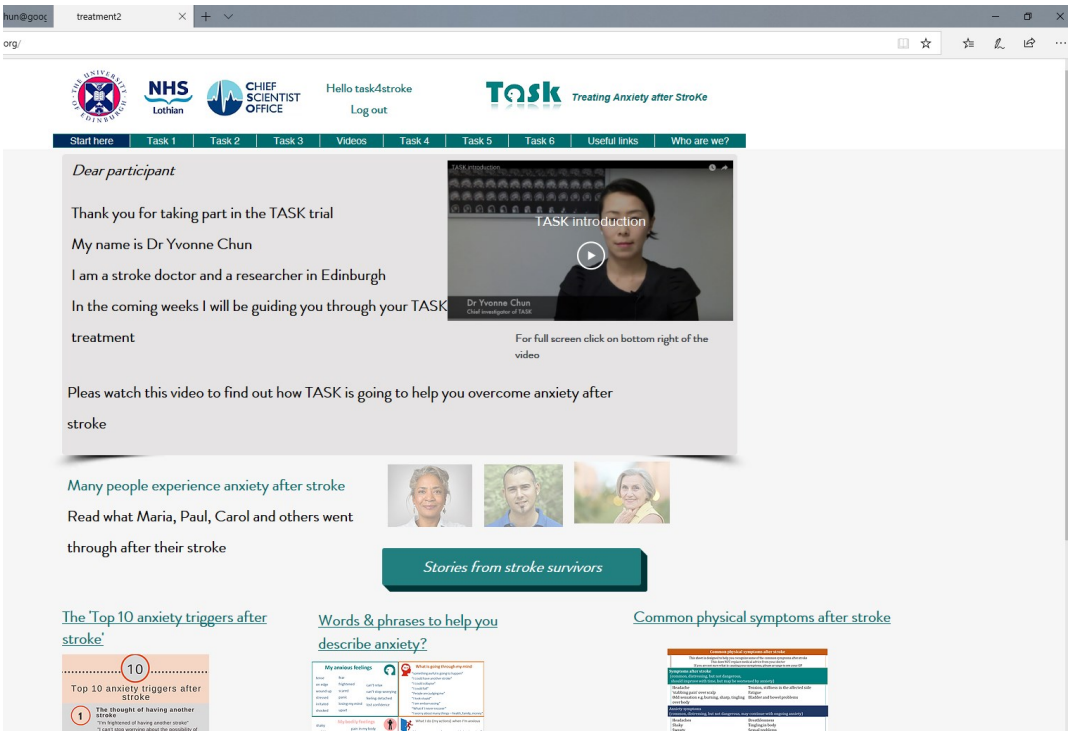


Figure 24. Screenshot of the TASK-CBT website



Chapter 6

Treating Anxiety after StroKe (TASK): Feasibility Phase of a Novel Streamlined Web-enabled RCT

Publication status and acknowledgement of contributions

This chapter contains the TASK trial protocol, which has been published in the August 2018 issue of Pilot and Feasibility Studies (Appendix C).

My supervisors provided the vision of designing an efficient streamlined trial, one that could be conducted centrally and remotely. We held numerous discussions on all aspects of the TASK trial design. I followed our shared vision and designed all of the innovative trial procedures.

I led the TASK trial as the chief investigator and produced all trial-related documents and materials with comments from my supervisors. I carried out all of the TASK trial procedures. Professor Alan Carson provided training and supervision of my TASK-CBT telephone sessions.

Our collaborator, Surgical Informatics at the Centre for Medical Informatics, Usher Institute granted me access to the Research Electronic Data Capture (REDCap) application.

I obtained extra funding from the Royal College of Physicians of Edinburgh for a smartwatch wearable sub study to be embedded within the TASK RCT. I designed this sub study and will be working in collaboration with Dr Thanasis Tsanas, a data scientist at the Centre for Medical Informatics on the analysis of this sub study.

6.1 Introduction

My TASK-CBT needs to be tested for feasibility on a small scale to enable further refinements prior to its definitive evaluation in a large-scale RCT. This represents the fifth step of the 6SQUID methodology. I will be able to identify first hand, the practical problems that may arise in delivering TASK-CBT down to the smallest detail.

The use of telemedicine to deliver TASK-CBT generated a unique opportunity for me to design my own RCT, a rarely afforded experience to a doctoral student researcher. Following numerous discussions with my supervisors, who had vast experience in conducting multicentre RCTs, we envisioned the current TASK trial to be:

- as close to the eventual design of the definitive RCT as possible
- efficient, with innovative solutions to overcome the challenges faced by clinical trialists in conducting large-scale RCTs
- of a high quality design with minimal bias

This trial represents my first attempt to find innovative solutions to overcome the administrative and practical barriers in running large-scale RCTs.

6.1.1 What is a randomised controlled trial?

An RCT is widely accepted as the most rigorous and reliable study design for determining treatment benefit. Randomisation helps distribute any known or unknown confounders between the treatment and control groups equally to minimise any systematic error or bias. However, randomisation alone does not ensure a trial will be free of bias. Bias might be introduced following randomisation if a trial has not been well designed or conducted according to the protocol.

By convention, there are five phases of clinical studies (Phase I – IV) to denote the development and testing of a new pharmacological intervention(145). Phase I refers to the non-randomised testing of the trial drug in a small group of healthy volunteers to establish the pharmacokinetics, metabolism, and toxicity of a new compound in humans. Phase II trials, which may or may not be randomised trials, involves testing the compound in a small group of patients with the target disorder in order to set and confirm dosage required for the desired pharmacodynamics effect, monitor toxicity, and to confirm the anticipated pharmacokinetic and metabolic effects. Phase III represents the full-scale efficacy RCT, which requires a sample size large enough with sufficient power to detect the minimally important difference. Determining the minimally important difference is not an exact science, but rather a decision based on a combination of the estimated effect and variability on the outcome measure, and what is important and meaningful to the patients clinically. A phase IV study refers to the post-marketing surveillance for rare and adverse outcomes of a new drug. While TASK-CBT is not a pharmacological intervention, the present TASK trial can be considered as equivalent to an early Phase II RCT, which aims to assess the feasibility—acceptability, practicality e.g. adherence, 'dosing' of the TASK CBT intervention.

6.1.2 What is a well-designed RCT?

A well-designed RCT should ask an important clinical question, answer it reliably, and keep trial participants safe. An important clinical question is one where there is uncertainty—'*a genuine uncertainty on the part of the expert clinical community about the comparative merits of two or more treatments for a defined group of patients or population*'(146). An RCT should have a clear plan, a

protocol with all elements of it well thought through in advance, and following the Patient, Intervention, Comparator, Outcome (PICO) format. The reliability of trial results may be influenced by the following methodological factors:

- Choice of study design e.g. parallel group, cross-over
- Sample size
- Duration of follow-up
- Trial procedures
- Randomisation
- Allocation concealment
- Adjudication of outcomes

All of these factors need to be considered carefully when designing an RCT to minimise systematic bias.

6.1.3 What challenges do I anticipate in conducting the definitive TASK RCT?

The experiences of the Edinburgh Stroke Research Group at conducting large-scale RCTs highlighted a number of key issues in running such trials.

Recruitment in a multicentre trial

A definitive RCT needs to recruit sample size large enough to have sufficient power to detect a clinically relevant treatment effect. Recruiting hundreds or thousands of patients usually involve recruiting from multiple centres nationally or internationally. One of the major costs of traditional multicentre trials is the setting up of multiple centres which includes establishing legal contract between the sponsor and local sites, identification and training of local staff, site initiation visits, monitoring, local closeout and archiving. Setting up local sites is

time-consuming and costly. Even after spending large sums of the trial budget, large-scale trials often fail to reach recruitment targets.

Recruiting community-based patients and consent

My experience at recruiting research participants for my prospective cohort was time-consuming and labour-intensive. Recruiting community-based stroke and TIA patients was particular challenging. The lack of a follow-up service for stroke and TIA patients in NHS Lothian and the strict ethical guidance that researchers must not be the first to approach potentially eligible patients meant that there was no easy way to provide study information to people once they had left the ward or clinic. Not only would this be a major barrier to recruiting sufficient patients to the definitive TASK RCT, it also raises the ethical question as to why patients are being disempowered by not being given access to the clinical trials that they are eligible to participate in. At present, I can only access community-based patients for research by sending them postal invitations. The current set up for trial recruitment is a hindrance to research progress in the field of 'life after stroke'—an area of stroke care that has been consistently voiced by stroke patients as a priority, but one which has been largely neglected in stroke research.

Quality assurance in intervention delivery

In trials of psychological interventions, many therapists are employed to deliver the trial intervention. This raises difficulty in quality assurance and monitoring. There is a risk of therapists systematically introducing non-protocolled 'active ingredients' while delivering the intervention, thus reducing the internal validity of the entire trial. Therapist training, the use of a manual, and methods to

monitor the therapists sessions e.g. audio-recording are some of the ways to help ensure intervention fidelity.

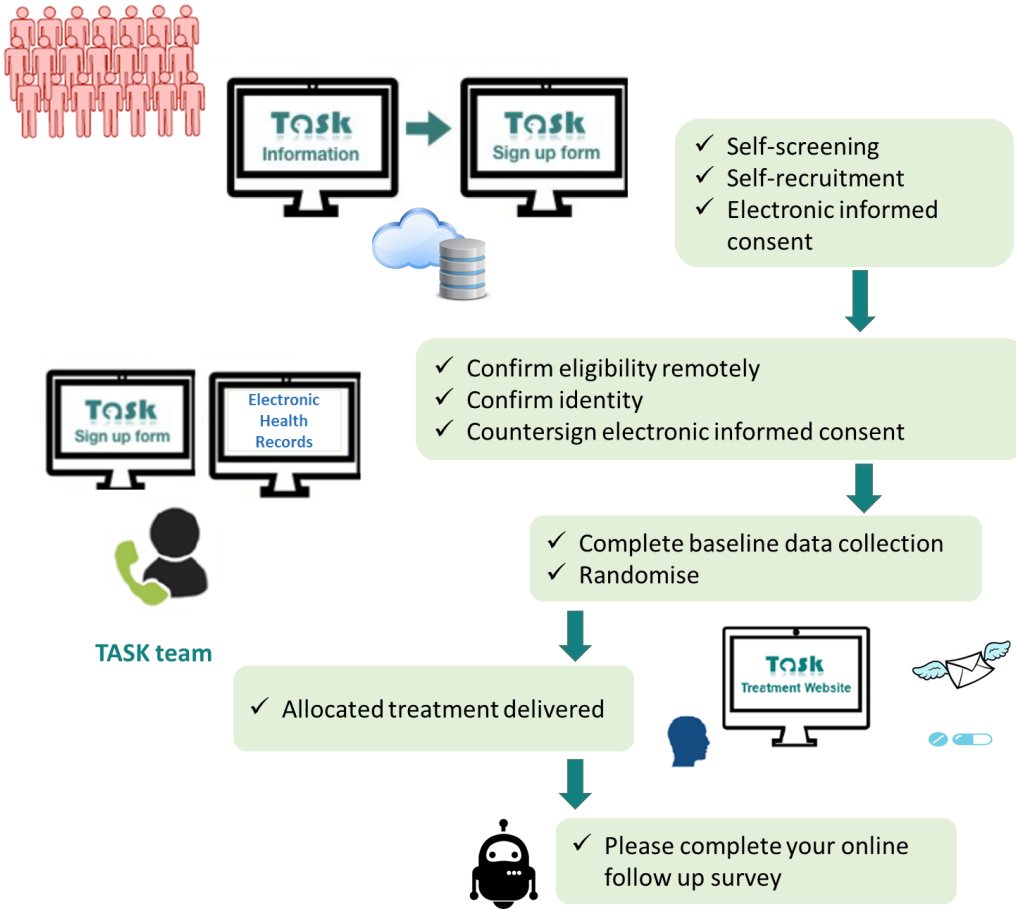
Attrition

Loss of follow-up or attrition leads to biased results and reduces the power of the study. Having made the colossal effort of recruiting sufficient number of patients to a large-scale trial just to fail on completing follow-ups would be a major waste of valuable research resources and time—a heart-breaking defeat. My experience as a researcher telephoning participants to complete their 6 and 12-month follow-ups in the multicentre FOCUS RCT (Fluoxetine or Control Under Supervision) taught me this simple fact—patients or their family simply had better things to do than to complete and return a lengthy postal follow-up research questionnaire. The less the effort participants have to put in, the easier it is to minimise attrition of follow-up data. In a trial of a psychological intervention such as TASK, self-reported measures would still play a central role as outcome measures. Simpler, more convenient ways of collecting patient reported outcomes, or alternative measures that require minimal or no effort from participants e.g. a wearable device, using routinely collected data could help overcome the challenge of attrition.

6.1.4 Applying technologies to make TASK RCT streamlined and efficient

The time and budget constraints of my fellowship meant that I had to find the quickest and best possible ways of designing, conducting and completing the TASK feasibility RCT which I envisaged (Figure 25).

Figure 25. My vision for a centralised RCT



In my vision, patients from all over the country or the world would be eager to sign up to a clinical trial. Patients would have access to information on ongoing recruiting trials. They would be empowered to recruit themselves to a trial that they are eligible to take part in. I envisaged patients screening themselves, recruiting themselves, and completing electronic informed consent forms remotely. A centrally-based research team would verify and confirm eligbilty using electronic health records and the telephone, collect baseline data, and randomise immediately. Allocated intervention would then be delivered or

despatched to the participants. Automated follow-ups would be sent to participants at scheduled timepoints.

Research Electronic Data Capture (REDCap)

Hiring a programmer or developer to design the TASK RCT was out of the question owing to my time and budget constraints. Through collaborative links with another research group at the University of Edinburgh, I gained access to REDcap, a secure web-based data management application created by Vanderbilt University in the United States, designed especially with the clinical researcher in mind(140). REDCap enables researchers to build a high quality database, data collection forms and surveys quickly and easily with no programming skills required.

The user interface is intuitive for both the researchers and research participants. Advanced features include data validation, branching logic, calculated fields, slider scales, randomisation module, and many more ways to customise each project. REDCap automatically generates the project's data dictionary and labels of all the variables created. Modifications are tracked and logged in an audit trail. Datasets can be exported easily in formats used by common statistical packages. Training resources on how to use REDCap are freely available. REDCap adheres to the HIPAA (Health Insurance Portability and Accountability Act of 1996, US) Security guidance to ensure the confidentiality, integrity and security of protected health information(147). REDCap at the University of Edinburgh is hosted within the University's Virtual Machine architecture, which is physically secured. Figure 26 shows screenshots of my REDCap project user interface for the researcher (26a), part of the study sign-up and consent form (26b), and electronic signature for informed consent (26c). I

embedded the electronic informed consent form on the TASK RCT recruitment website: www.task4stroke.org (Figure 27).

Figure 26. Screenshots of the REDCap project user interface

a. TASK project dashboard for the researcher on REDCap

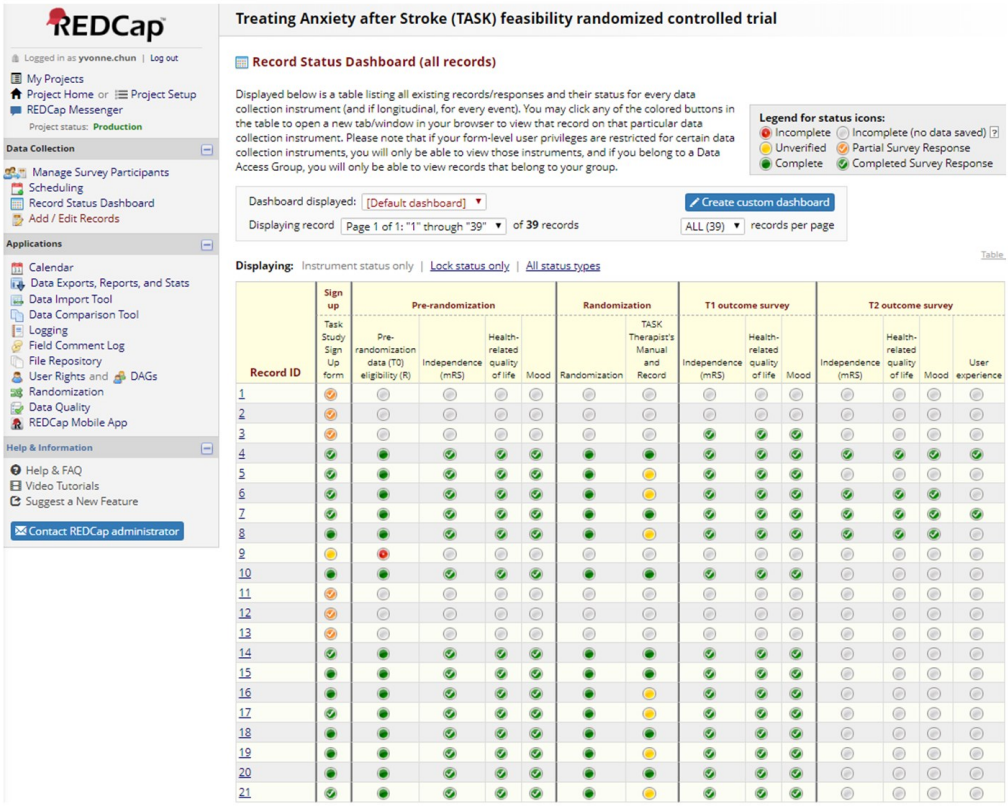
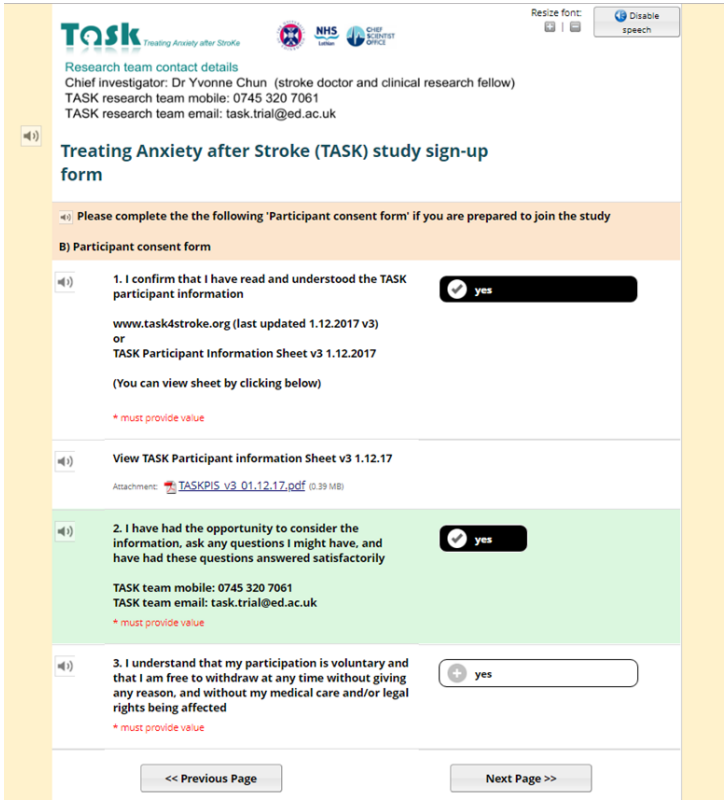


Figure 26b. TASK study sign-up and consent form



26c. Electronic signature on the TASK consent form

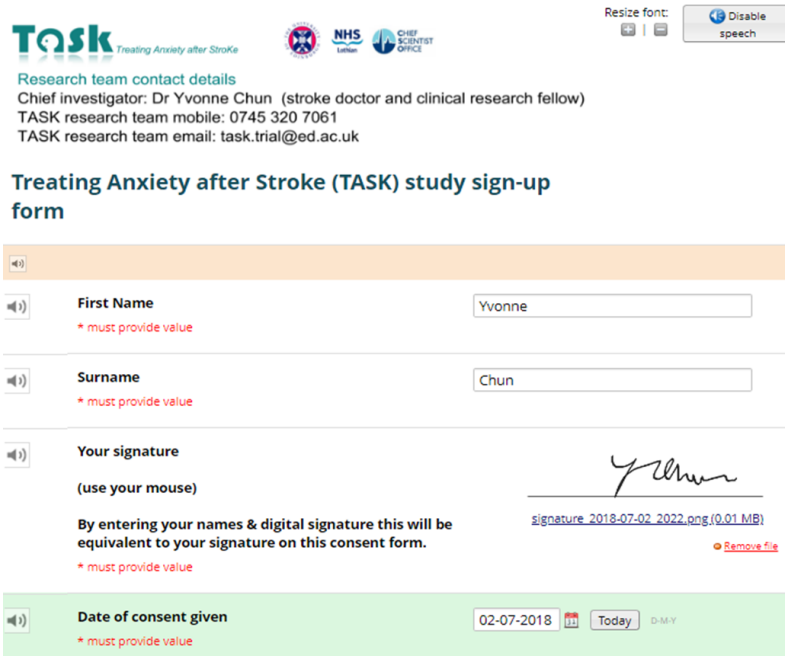
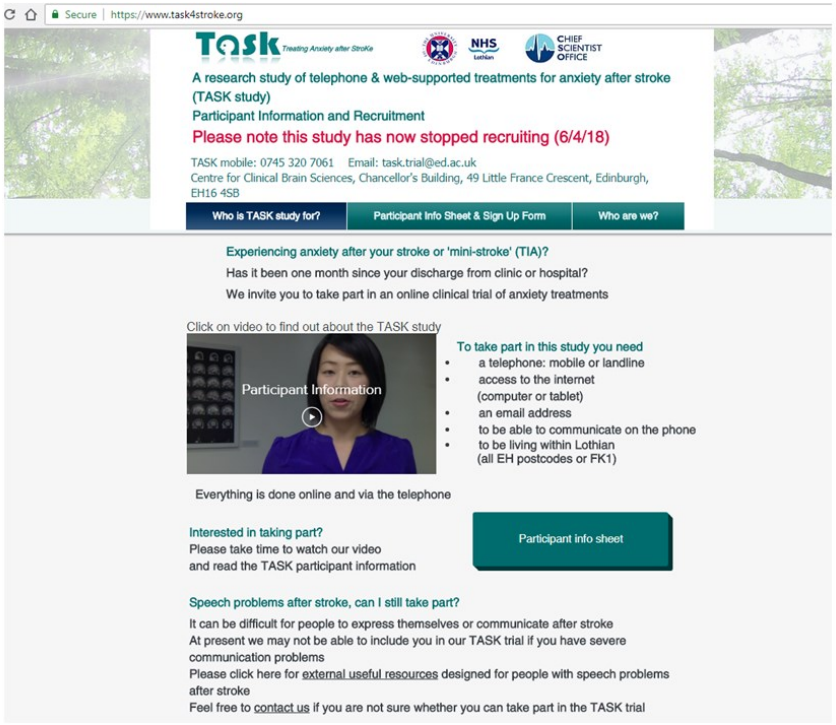
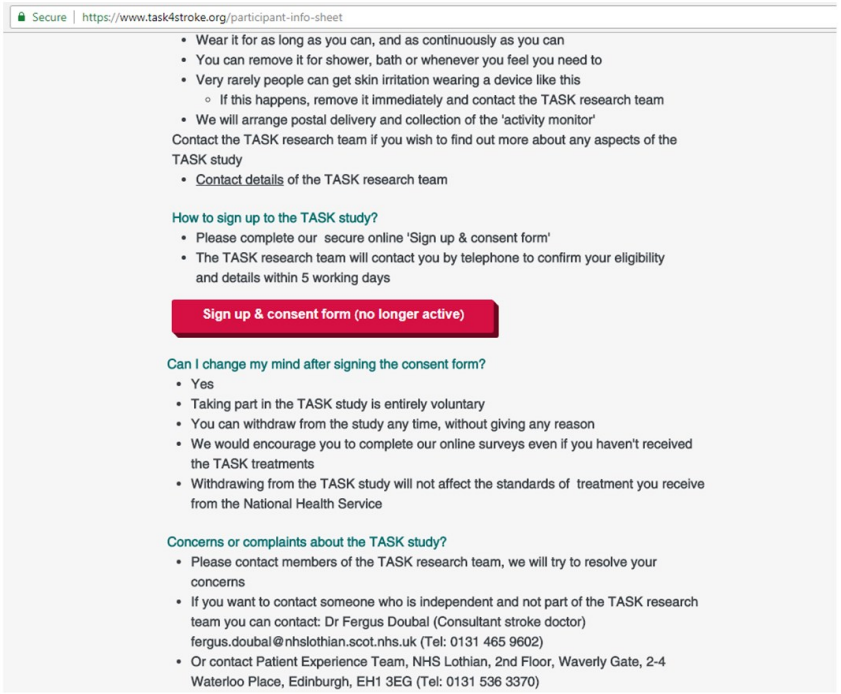


Figure 27. Screenshots of the TASK recruitment website: www.task4stroke.org





Website builder

I had to create three websites, one for online self-recruitment, one for the TASK-CBT intervention and one for the comparator, TASK-Relax. To create the websites quickly, I used an industry-led cloud-based web development platform for website building, designed for people with no knowledge in coding or script language. I directed Google analytics to all my websites to assess whether it would be possible to monitor aggregate usage.

Use of smartwatches to collect continuous data on activity/rest in an RCT

While designing the TASK RCT, I added a smartwatch sub study to measure actigraphy (non-invasive method of monitoring rest/activity cycles) as a study within a trial to investigate whether this method of collecting outcomes would be feasible in stroke and TIA patients. Anxious patients after stroke showed higher levels of avoidant behaviour across a range of situations e.g. going out alone, physical exertion, social situations compared with those who were not anxious. Disturbed sleep is a feature common to both anxiety and depression. RCTs of psychological interventions have conventionally relied on self-reported outcomes using questionnaires. This requires effort from participants. Non-responders (attrition) can bias results and reduce the power of the study, resulting in a waste of valuable research resources. A wrist-worn smartwatch that records actigraphy continuously could provide data on activity and sleep, offering the potential of measuring objective outcomes throughout the entire RCT with minimal patient effort. The feasibility of long-term continuous monitoring using this method has not previously been tested for feasibility in RCTs of psychological intervention, or RCTs of stroke/TIA patients. Data collected using this smartwatch could be analysed for correlations with clinical

outcomes e.g. mRS, anxiety levels. These smartwatches could be scalable methods of measuring objective outcomes in a large-scale RCT.

6.1.5 Objectives of the TASK feasibility RCT

This study aims to evaluate the feasibility of i) novel web-enabled trial procedures, ii) the TASK-CBT intervention, and iii) use of actigraph smartwatches to collect continuous data throughout the entire trial in stroke/TIA patients.

6.2 Methods

The report of this protocol follows the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) checklist[18]. Description of TASK-CBT adheres to items on TIDier (Template for intervention description and replication) [19]. The trial protocol is registered at ClinicalTrials.gov (NCT03439813).

6.2.1 Trial design

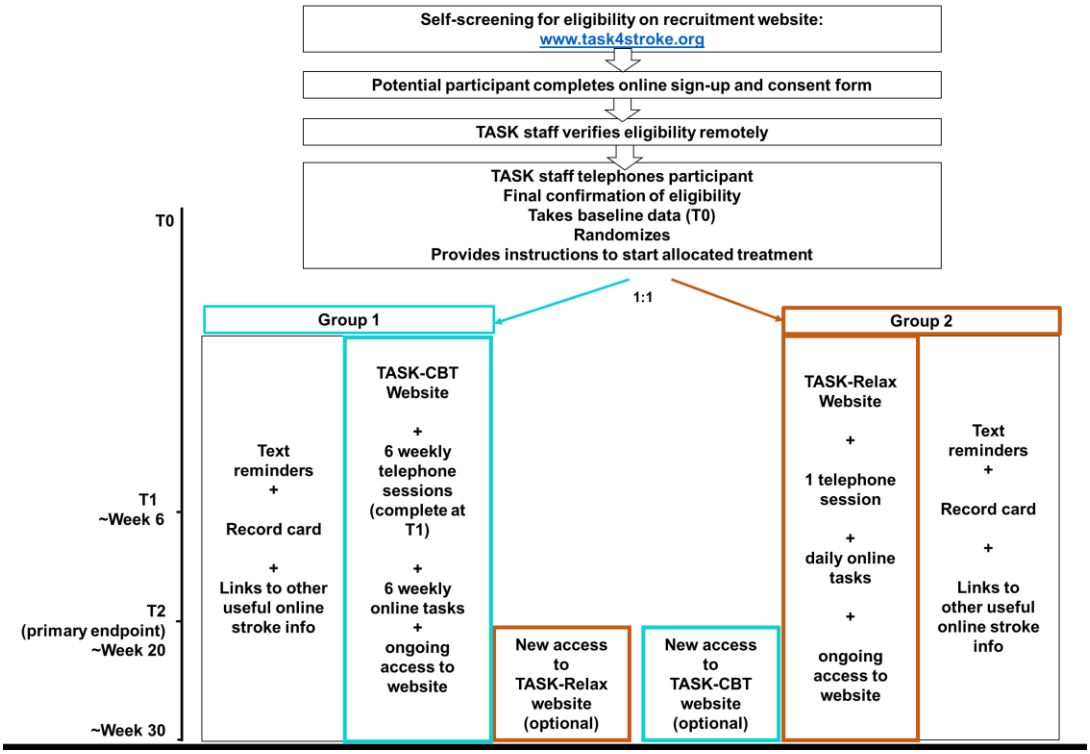
The TASK feasibility trial is a parallel two-armed RCT comparing TASK-CBT with TASK-Relax. Figure 28 illustrates the participant timeline in a schematic.

Information technology used in the design of the TASK feasibility RCT

Using REDCap, I embedded data collection forms in my recruitment website (www.task4stroke.org) for self-screening for eligibility and informed consent. On my TASK-CBT treatment website, I embedded data collection forms as individual weekly online tasks. Usage of all websites is monitored with Google Analytics. In my smartwatch sub study I am testing the feasibility of GENEActiv Original smartwatch *(Activinsights, www.activinsights.com/products/geneactiv/),* a

device designed primarily for research with validation data. Continuous data (triaxial accelerometry, temperature, light) are recorded and can be downloaded from each device for analysis of physical activity and sleep. No data are stored on a commercial 'cloud', and no patient identifiable data are stored on the device.

Figure 28. TASK RCT schematic



6.2.2 Participants and recruitment

Patient population: inclusion and exclusion criteria

I aimed to recruit 40 community-based residents within NHS Lothian (United Kingdom postcodes EH and FK1) who were aged 18 or above, with a diagnosis of stroke or TIA (probable or definite, cerebral or ocular), at least one month after being discharged to the community from clinic or hospital ward. Participants had to have capacity to give informed consent, be able to

communicate in English on the telephone, have internet access, and report at least one positive response on our 6-item anxiety screening questions (Figure 29). I derived these items from the GAD-7 and modified Fear Questionnaire using psychometric techniques including factor analysis and analysis of internal consistency to maximise the spectrum of anxiety levels included. I excluded people already taking part in a clinical trial of treatment intended to improve psychosocial outcomes post-stroke.

Recruitment methods

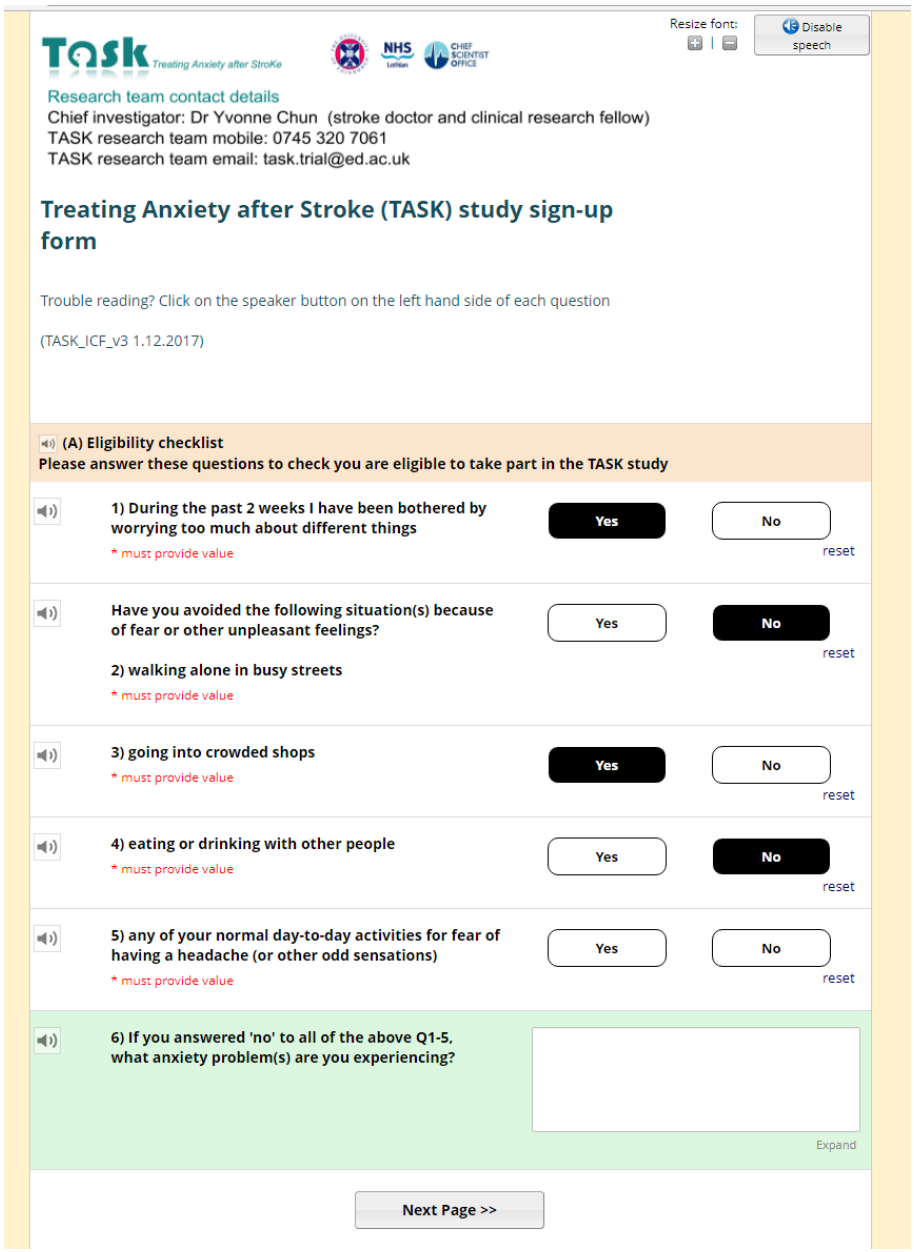
The TASK recruitment website: www.task4stroke.org was publically accessible, where participant information was available via a video or a readable format. Interested potential participants could complete the 'Sign Up and Consent Form' on the website. I disseminated the website address as widely as possible amongst patients, community stroke nurses, stroke physicians, stroke rehabilitation therapists, and stroke charities using printed 'business cards', flyers and social media. I offered trial information to stroke and TIA patients during their one-month telephone follow-up which I carried out as part of routine stroke care. In addition, I sent postal invitations to the eligible participants identified from the NHS Lothian Stroke Audit registry, which I screened retrospectively.

Screening of NHS Lothian Scottish Stroke Audit

I obtained the list of patients recorded as having had a stroke/TIA in a six-month period from the audit database manager. Using electronic health records I checked the potential eligibility for each patient on the list and excluded those who were obviously ineligible e.g. not a final diagnosis of stroke/TIA, severe dementia, aphasia.

On receiving the completed 'Sign Up and Consent Form', I verified the eligibility and identity of the potential participant using electronic health records and over the telephone with the participant within five working days. Baseline data were immediately collected at this point (T0), followed by randomisation.

Figure 29. 6-item anxiety screening questions in TASK RCT



6.2.3 Intervention and comparator

I designed the TASK-CBT intervention to be delivered via telemedicine—telephone, website, email and mobile text. The TASK-CBT intervention represented a low-intensity, guided self-help psychological intervention in a stepped care model. I delivered the TASK-CBT telephone sessions under the training and supervision of a neuropsychiatrist.

Delivery of 'active ingredients' of TASK-CBT by telephone and web

I summarized the key 'active ingredients' of the TASK-CBT intervention in Figure 23. In brief, the TASK therapist delivers a course of six individualized telephone CBT sessions, 35-45 minutes each, at least one week apart, with the use of an electronic TASK Therapist's Manual and Record I created on REDCap (Figure 30).

Each session was supplemented by the prescription of an online task, and one or more of the psychoeducational videos on the TASK-CBT treatment website.

To encourage adherence, I sent a mobile text to remind participants to complete their online task each week and to use the treatment website as much as possible via a computer, tablet or smartphone.

Active comparator: TASK-Relax

TASK-Relax is a web-based self-guided relaxation programme. Relaxation therapy is a commonly used comparator in RCTs of CBT in psychiatry research. The TASK-Relax website consisted of an introductory video, followed by five relaxation tasks: i) audio and visually-guided breathing exercise, ii) relaxing imagery and sounds, iii) music for relaxation, iv) audio-guided

progressive muscle relaxation, and v) a selection of sounds of nature (Figure 31). All relaxation videos or audios on the TASK-Relax website were also publically available on YouTube. Participants allocated to TASK-Relax received instructions to try out all of the relaxation exercises and to select their favourite one(s) to practice daily, for at least 5 minutes throughout their trial participation.

Figure 30. Section of the electronic TASK Therapist's manual and record

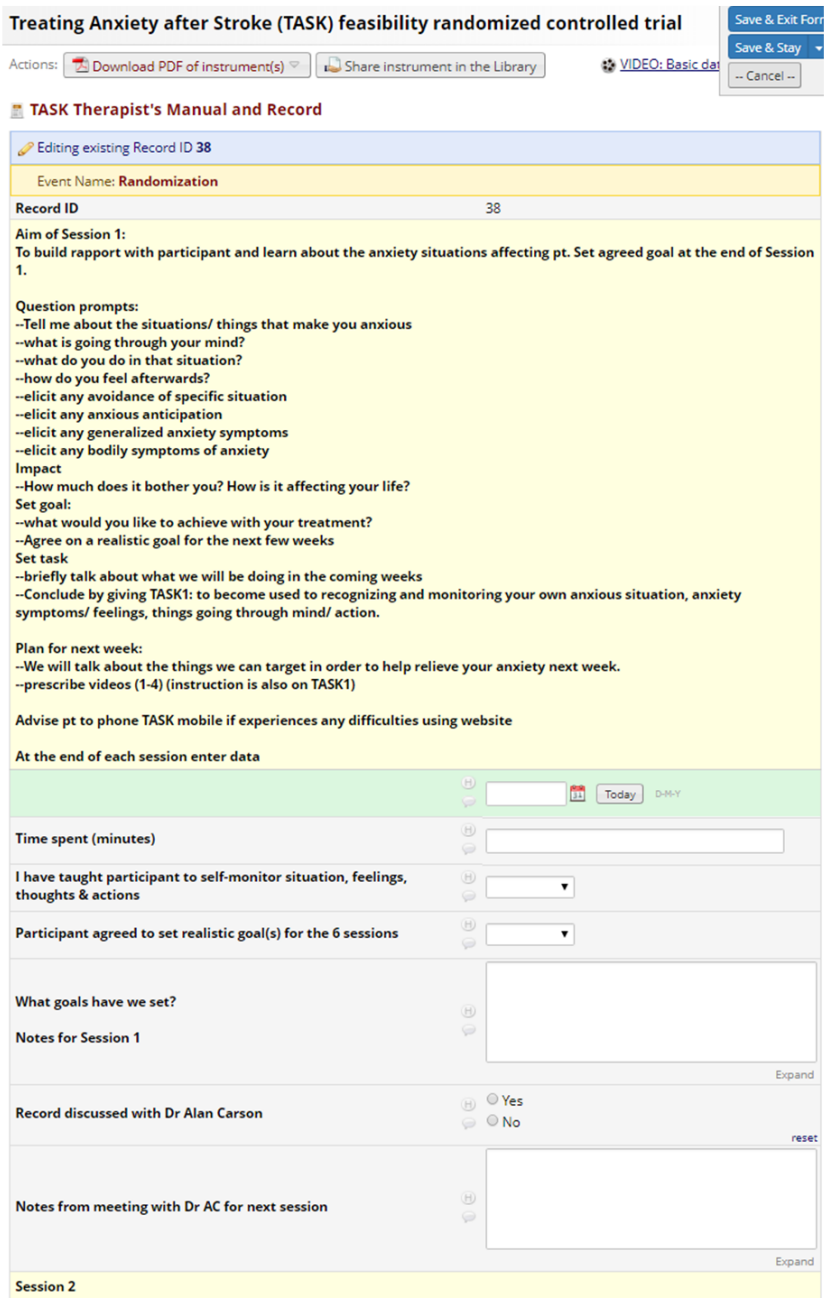
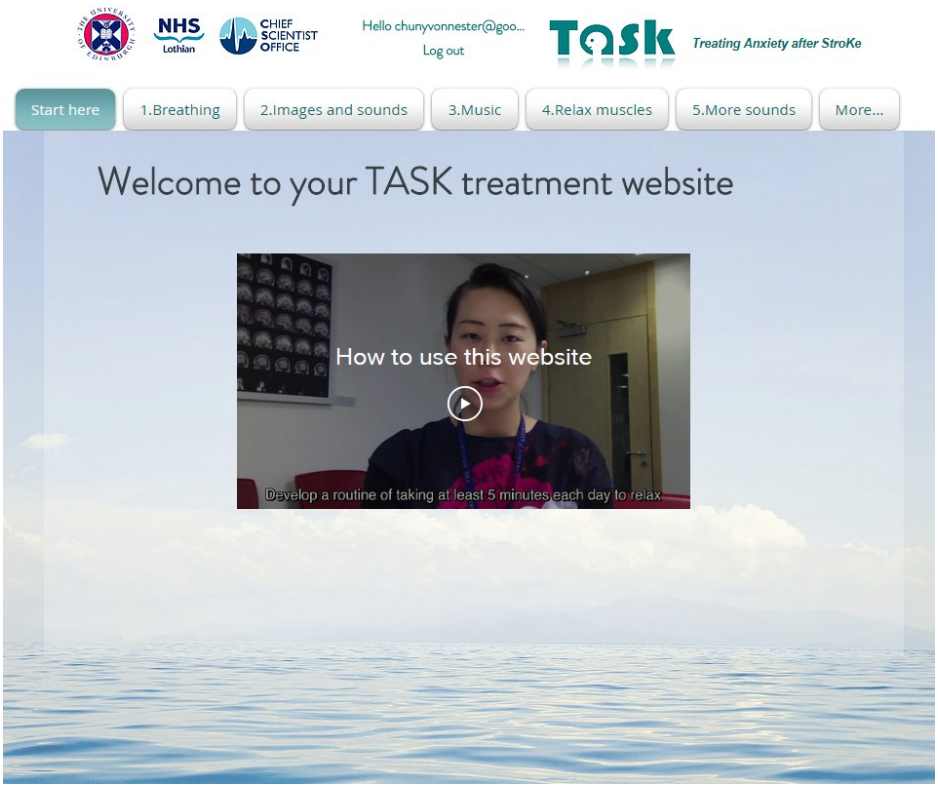


Figure 31. Screenshot of the homepage of TASK-Relax



Components common to both groups

Participants of both arms received weekly mobile text reminder and a participant record card to record progress and completion of follow-up surveys. Data collection occurs at T1 and T2 (primary endpoint) via emailed links to self-completed electronic surveys. Once the follow-up survey at T2 is complete, all participants are offered access to the website given to the other group for a further ten weeks.

Concomitant care and interventions

Concomitant standard clinical care and interventions (pharmacological or non-pharmacological) for anxiety or mood disorders, e.g. antidepressants, benzodiazepines were permitted and recorded in the follow-up surveys.

6.2.4 Randomisation and allocation concealment

A member of the research staff not involved in conducting the TASK trial generated a permuted block randomisation sequence with random block sizes using STATA14. The sequence was uploaded to the in-built randomisation module within REDCap, which was inaccessible to me. Once baseline data collection was complete, I randomised the participant and emailed him/her the allocated treatment website address and login details. Participants received my instructions on commencing the allocated treatment over the telephone. Participants allocated to TASK-CBT also received an appointment with me to have their first telephone session.

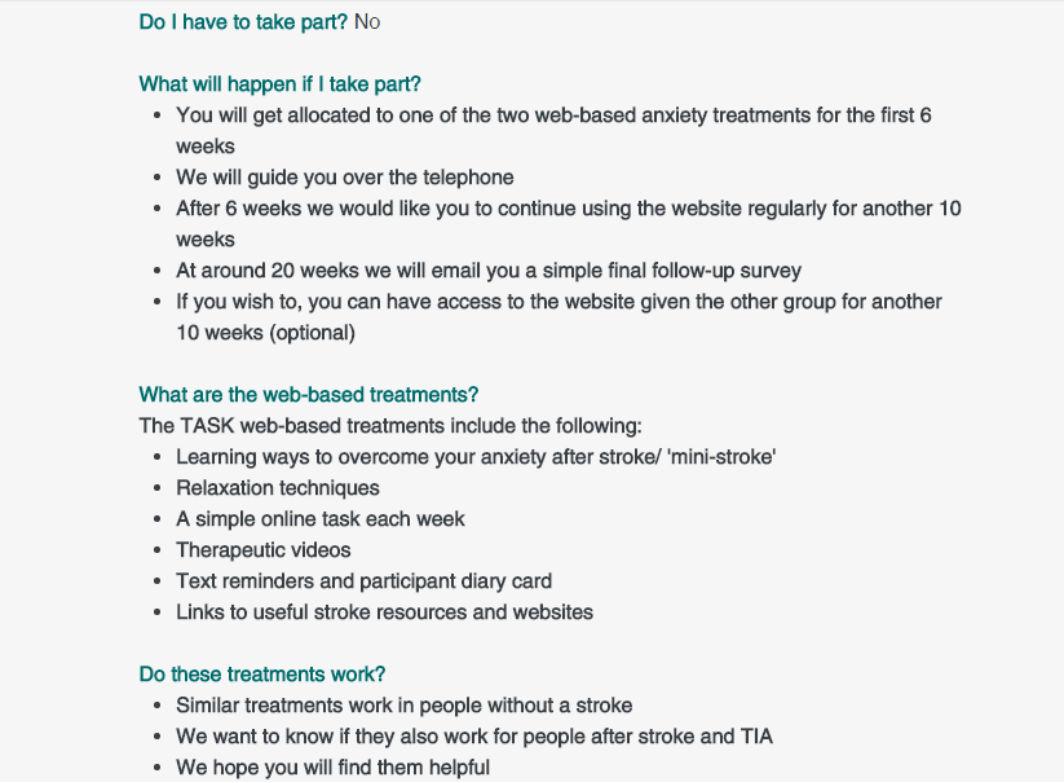
6.2.5 Masking

I was enrolling participants and delivering the allocated intervention in this feasibility trial. I was not blinded to the treatment group assignment. I attempted to mask participants to our hypothesis that one treatment was superior to the other by not revealing the exact contents and type of treatment in each group on the participant information (Figure 32), or at recruitment. At enrolment, I simply gave them this instruction over the telephone,

> *'You will get one of the two treatment websites we designed. After completing your final follow-up survey, you will get access to the website given to the other group'.*

The two treatment website addresses did not reveal content of the intervention e.g. treatment3.org, treatment2.org.

Figure 32. Screenshot of the electronic participant information sheet



Do I have to take part? No

What will happen if I take part?

- You will get allocated to one of the two web-based anxiety treatments for the first 6 weeks
- We will guide you over the telephone
- After 6 weeks we would like you to continue using the website regularly for another 10 weeks
- At around 20 weeks we will email you a simple final follow-up survey
- If you wish to, you can have access to the website given the other group for another 10 weeks (optional)

What are the web-based treatments?

The TASK web-based treatments include the following:

- Learning ways to overcome your anxiety after stroke/ 'mini-stroke'
- Relaxation techniques
- A simple online task each week
- Therapeutic videos
- Text reminders and participant diary card
- Links to useful stroke resources and websites

Do these treatments work?

- Similar treatments work in people without a stroke
- We want to know if they also work for people after stroke and TIA
- We hope you will find them helpful

6.2.6 Smartwatch sub study

In the smartwatch sub study, all TASK participants were invited to wear the actigraph smartwatch. Once consented, the smartwatch was posted to the participant with simple care instructions. At two months, the battery of the smartwatch would run out. With the participant's agreement and on the safe return of the first smartwatch, a second smartwatch was sent to the participant, so he/she could wear it for the rest of the trial. All smartwatches were returned using prepaid special delivery envelopes.

6.2.7 Feasibility Outcomes to be reported

Feasibility of the trial procedures: Recruitment (number per month); % completed consent, online or by post; time taken to complete remote eligibility confirmation via electronic health records (date of randomisation - date of 'Sign Up and Consent Form' received); self-completion of electronic follow-up surveys at T1, T2 (% completed surveys).

Feasibility of the TASK-CBT intervention: % drop out after fewer than three telephone TASK-CBT sessions; intervention fidelity—agreement with audio recording transcript and TASK therapist record, completion of online tasks, and web usage analytics.

No-go criteria

My supervisors and I defined a lack of feasibility of TASK-CBT and the current trial design as 1) recruitment number of <2 per month; 2) >50% of TASK-CBT patients dropping out after fewer than three telephone sessions; 3) >10% non-completion of follow-up surveys at T2, 4) participants reporting harm from the intervention.

Treatment relevant outcomes (Table 31) include the mRS for disability(20), EQ-5D5L(93), GAD-7(112), modified FQ(92), and a single question to elicit concurrent treatment for mood or anxiety. A user feedback survey automatically follows the T2 follow-up survey.

Table 31. Treatment relevant data collection in the TASK RCT

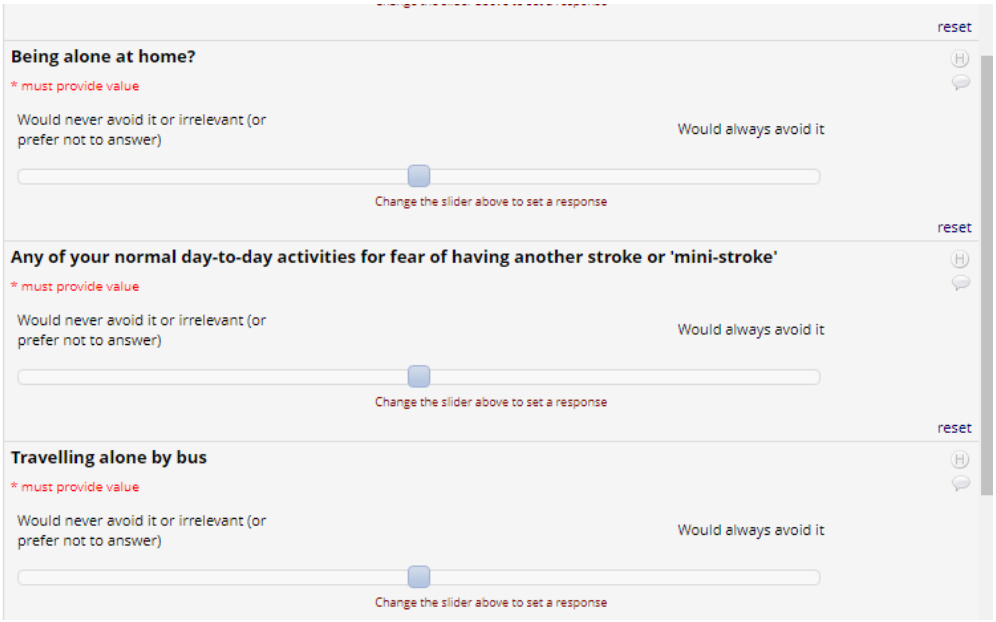
	T0 Baseline (pre-randomisation)	**T1 follow-up (~Week 6)**	**T2 follow-up primary endpoint (~Week 20)**
Demographics	*		
Diagnosis	*		
Past history of anxiety or depression	*		
Medications	*		
mRS	*	*	*
EQ5D5L-VAS	*	*	*
GAD-7	*	*	*
PHQ-2	*	*	*
Modified FQ	*	*	*
Single question on concurrent treatment for mood or anxiety (drug or non-drug)	*	*	*
User feedback survey	*	*	*
Sub study of wearing a smartwatch			
Smartwatch for measuring rest/activity	Continuous monitoring throughout the trial from T0 to T2		

mRS, modified Rankin Scale; EQ5D5L-VAS, EuroQol-5D5L-Visual analog score; GAD-7, 7-item Generalised Anxiety Disorder Questionnaire; PHQ-2, 2-item Patient Health Questionnaire; FQ, Fear Questionnaire

Visual sliders for the FQ

Each item on the modified FQ was scored using a visual slider (Figure 33) on the electronic survey throughout the trial, giving a score on a scale of 0-100. Scores were converted to a scale of 0 - 8 (by dividing by 12.5).

Figure 33. Visual sliders used in the modified FQ in the TASK RCT



Feasibility outcomes of the smartwatch sub study

I assessed the percentage of TASK participants who also consented to wearing the smartwatch; the 'wear time'—duration of the smartwatch being worn by each participant using the data recorded on the smartwatch; percentage of participants of this sub study who agreed to wear the smartwatch again after two months; % did not return smartwatch (attrition).

6.2.8 Assessing intervention fidelity and quality monitoring

For intervention fidelity, I aimed to assess i) % agreement between the Therapist's Record and transcripts of audio-recording of telephone sessions, assessed by a clinician independent of the study; ii) automated data capture of online task completion; iii) summary web usage data from Google Analytics.

6.2.9 Strategies to improve adherence in both arms

I sent a participant record card to every participant by postal mail and sent weekly text reminders to their mobile phone throughout their participation. All participants received text and email reminders to complete the follow-up surveys at T1 and T2. Non-responders would receive further text and email reminders, and a final phone call from a researcher blinded to the treatment allocation to complete unfilled online surveys over the telephone.

6.2.10 Discontinuation criteria

Participants were free to withdraw from the study at any point or a participant could be withdrawn by one of the TASK trial investigators if he/ she lost capacity during the study period.

6.2.11 Safety protocol

All participants had contact details of the TASK research team from the start of the trial. They were informed that if severe cases of anxiety or depression were identified during the trial, the TASK research team would liaise with their general practitioner to arrange appropriate care.

6.2.12 Data management

All study data were collected and managed using REDCap electronic data capture tools hosted at University of Edinburgh. Identifiable data were only accessible by the managing team of the REDCap database and myself. Statistical analysis was performed using STATA software. Anonymised data from all smartwatch devices were uploaded for analysis by a collaborating data scientist at the Centre for Medical Informatics, Usher Institute, University of Edinburgh for analysis.

Data monitoring body

There is no data monitoring committee planned for this study

6.2.13 Statistical analyses and power calculation

As this was a feasibility study I did not perform power calculation. Feasibility outcomes were summarized descriptively. All electronic items on the follow-up surveys had to be scored to permit submission, preventing any missing values. Only my supervisors and I had access to the final trial dataset.

6.3 Results

I enrolled 27 participants from 29/1/18 to 3/4/18 to the TASK feasiblity RCT from three main sources, the Scottish Stroke Care Audit Registry from a six-month period (1/6/17-30/12/17), my prospective 1-month telephone screening of all clinic patients from 1/1/18-3/2/18, and patients identified from two observational studies (Figure 34).

1481 patients were screened, of whom 31% (458/1481) were potentially eligible for the TASK RCT. I approached 30% (438/1481) by telephone and/ or by post and enrolled 2% (27/1481) of all patients screened (Figure 35).

Figure 34. Sources of TASK RCT participants

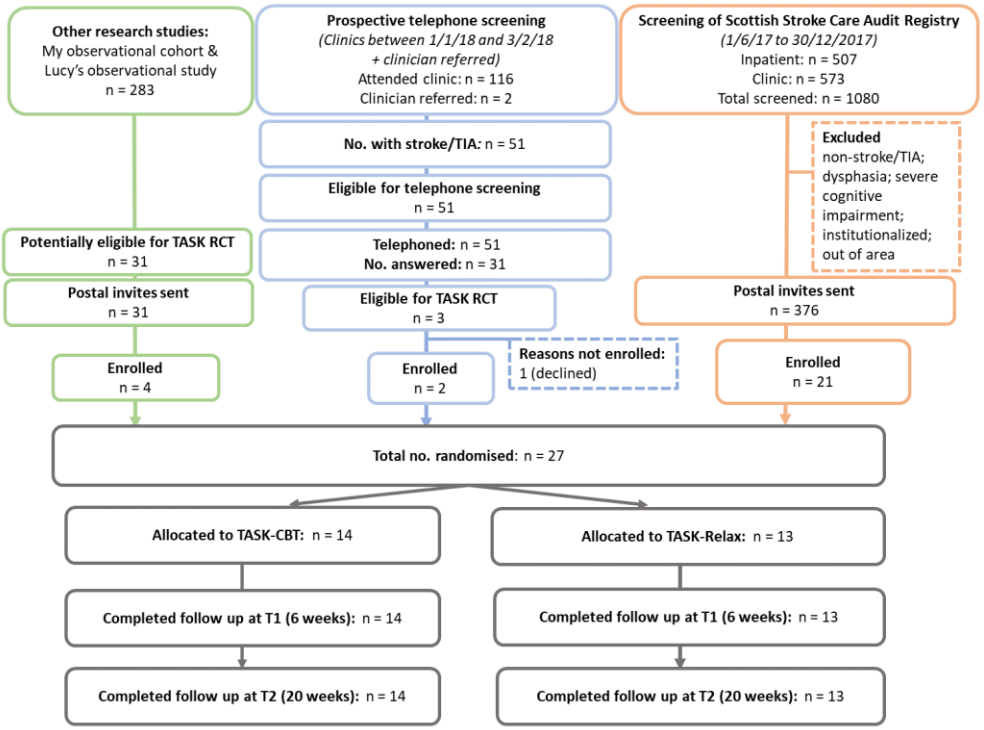
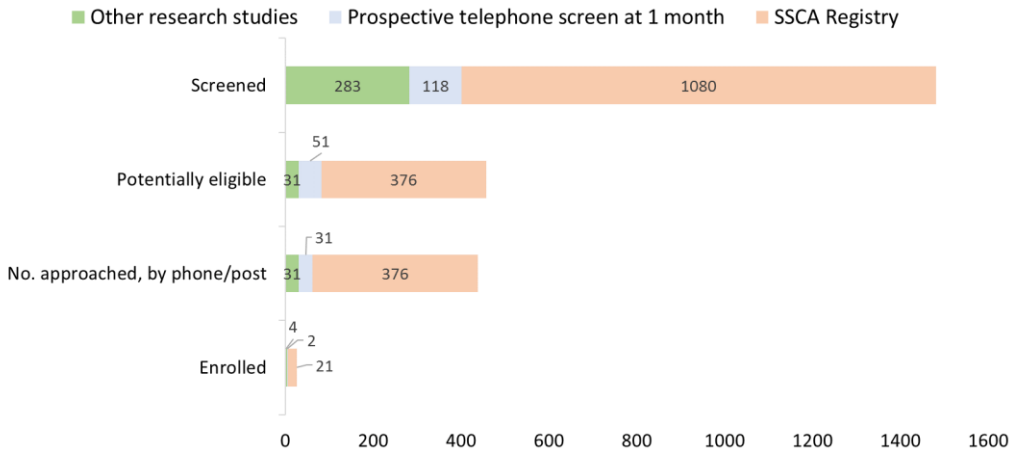
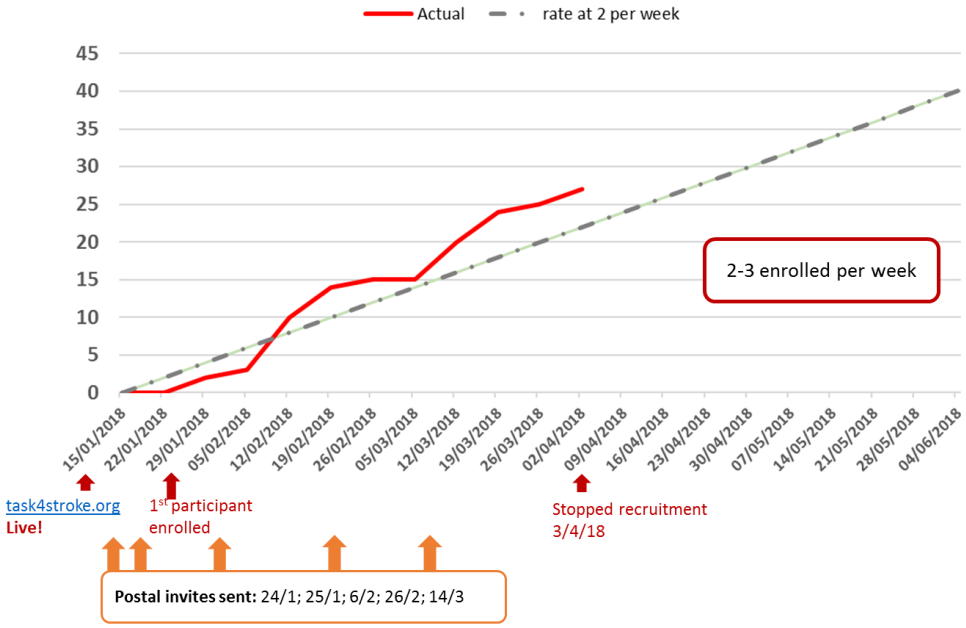


Figure 35. Number of people screened, approached, and enrolled in the TASK RCT



Recruitment rate was around two to three participants per week, exceeding our pre-defined feasibility outcome of recruiting at least two participants per month. I stopped recruitment on 3/4/18 due to my fellowship's time constraints. Figure 36 shows that if recruitment was to continue at a rate of 2 per week (dashed line), a sample size of 40 would have been reached by the beginning of June, 2018. Five members of the public contacted me by phone and email wishing to sign up but were not eligible as they resided outside Lothian or contacted me after the trial recruitment had closed.

Figure 36. TASK recruitment rate projection



Of the 27 participants enrolled (mean age [SD]: 65 [10]; men: 15/27, 56%), about two-thirds received a diagnosis of stroke (17/27, 63%) and one-third TIA (10/27, 37%) (Table 32). About half of the participants enrolled reported a past history of anxiety disorder or depression (15/27, 56%). At baseline (pre-randomisation), the majority reported a mRS of 0-2 (80%, 22/27). On the EQ5D-

5L, participants reported more problems on the domains of ‘usual care’, ‘pain and discomfort’, and ‘anxiety/depression’ than the domains on ‘mobility’ and ‘self-care’ (Figure 37). Participants had a range of anxiety symptoms and severity on GAD-7 and FQ subscales (Figure 38) at baseline. The median time from stroke/TIA event to randomisation was 19 weeks.

Table 32. Baseline characteristics (pre-randomisation) of sample in TASK RCT

	Total n = 27		**TASK-CBT n=14**		**TASK-Relax n=13**	
Age (mean, SD)	65 (10) range 39-81		64 (10)		65 (10)	
Men	15	56%	10	71%	5	38%
Diagnosis						
Stroke		63%		71%		54%
Ischaemic	16		9		7	
ICH	1		1		0	
TIA	10	37%	4	29%	6	46%
	median	IQR	median	IQR	median	IQR
Time (weeks) since stroke/TIA	19	12-33	21	13-33	18	7-31
Past history						
Stroke/TIA	5	19%	1	7%	4	31%
Myocardial infarction	2	7%	2	14%	0	0%
Anxiety disorder/ depression/ other mental health disorder	15	56%	8	57%	7	54%
Current psychotropics						
Medication *e.g. SSRI/SNRI/NaSSA/TCA/BZ* (not necessarily for anxiety/mood)	8	30%	5	36%	3	23%
On treatment to help with anxiety or mood	5	19%	1	7%	4	31%
	median	IQR	median	IQR	median	IQR
Verbal fluency number of words per minute	13	8-15	14	12-16	11	7-13
	median	IQR	median	IQR	median	IQR
Disability						
mRS score	1	0-2	1	1-2	1	0-2
mRS 0-1	17	63%	10	71%	7	54%
mRS >=2	10	37%	4	29%	6	46%
	mean	SD	mean	SD	mean	SD
EQ5D-5L-Visual analog	63	18	67	19	58	16
	median	IQR	median	IQR	median	IQR
Generalised anxiety						
GAD-7 (/21)	9	7-12	9	8-11	7	7-13
Number of probable GAD (>=6)	23	85%	11	79%	12	92%
Phobic anxiety						
FQ-Agoraphobia (/40)	19	3-24	11	2-22	22	10-31
Number of probable agoraphobic (>=7)	18	67%	7	50%	11	85%
FQ-Social phobia (/40)	19	6-25	10	5-23	20	14-28
FQ-Specific phobia (/40)	17	6-29	16	6-25	19	11-38
Depression						
PHQ-2 (/6)	2	0-2	2	0-3	2	1-2

SNRI, serotonin-norepinephrine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant

Figure 37. Baseline functional independence and health-related quality of life domains, by treatment allocation

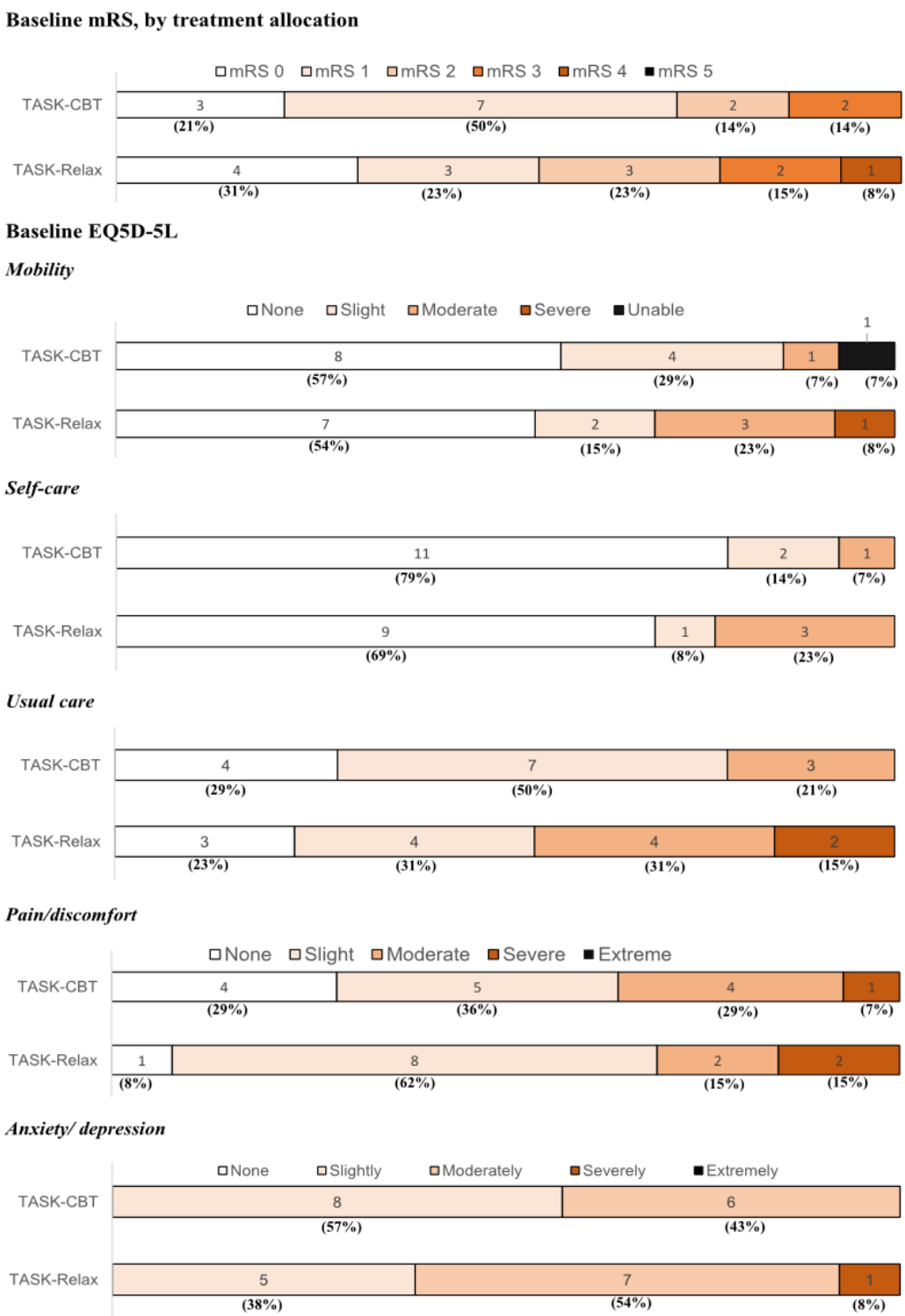
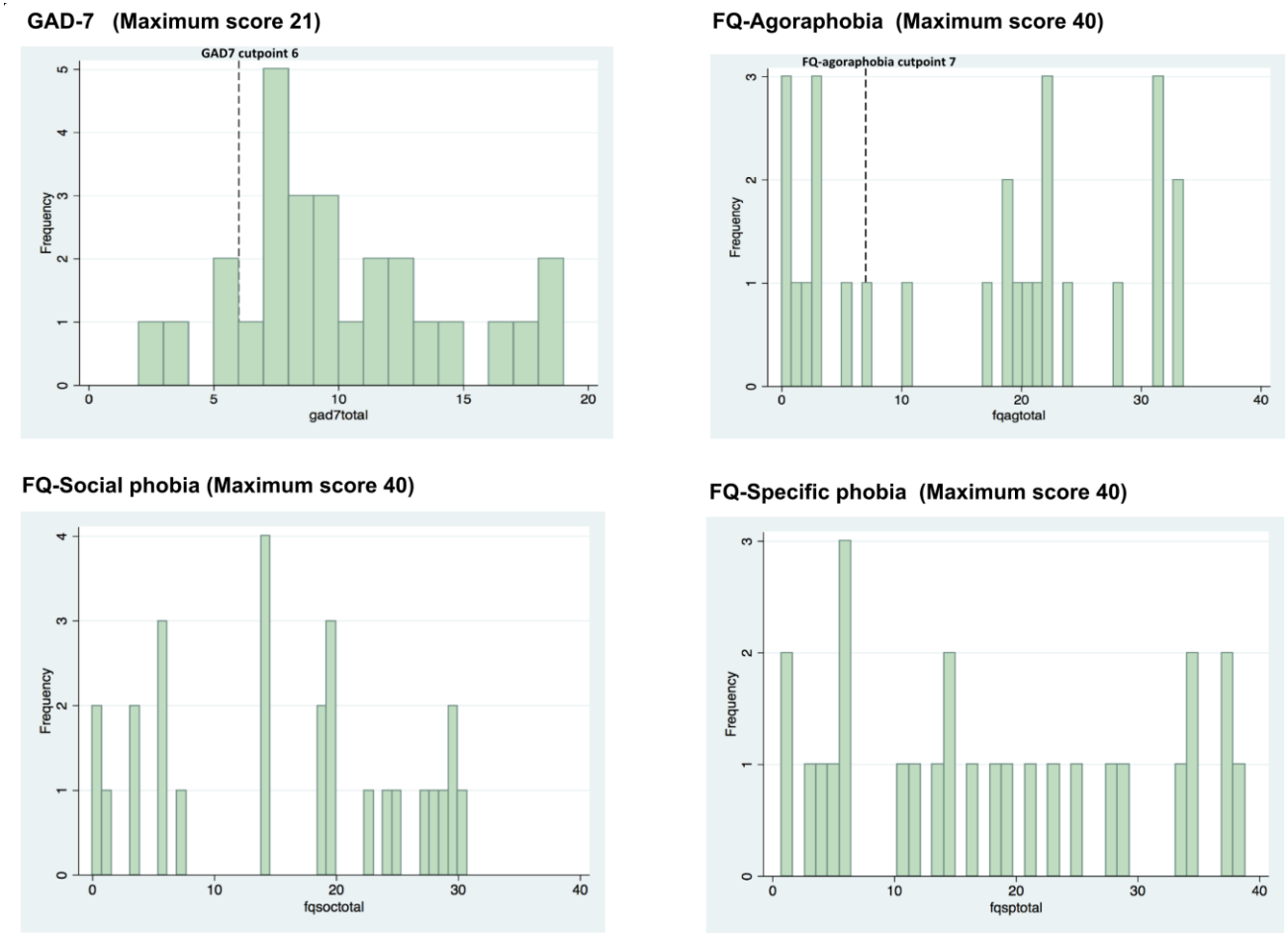


Figure 38. Histograms show distribution of baseline scores on all anxiety measures (n=27)



GAD-7 (gad7total), FQ-Agoraphobia (fqagtotal), FQ-Social phobia (fqsoctotal), FQ-Specific phobia (fqsptotal) subscales

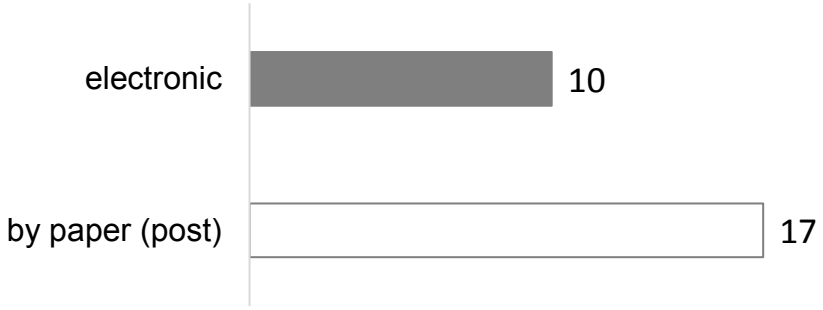
6.3.1 Feasibility of the TASK trial procedures

I conducted the TASK-RCT entirely remotely using the telephone and internet.

Electronic informed consent completion

All participants were recruited remotely. Just over a third of participants (10/27, 37%) completed the electronic informed consent forms on the recruitment website (Figure 39). The remainder returned the paper consent forms by post.

Figure 39. Proportion of TASK participants completed electronic consent



Eligibility confirmation by electronic health records

All participants had their eligibility confirmed using the electronic health records system in NHS Lothian. Median time taken between consent to randomisation was one day (IQR 0-3).

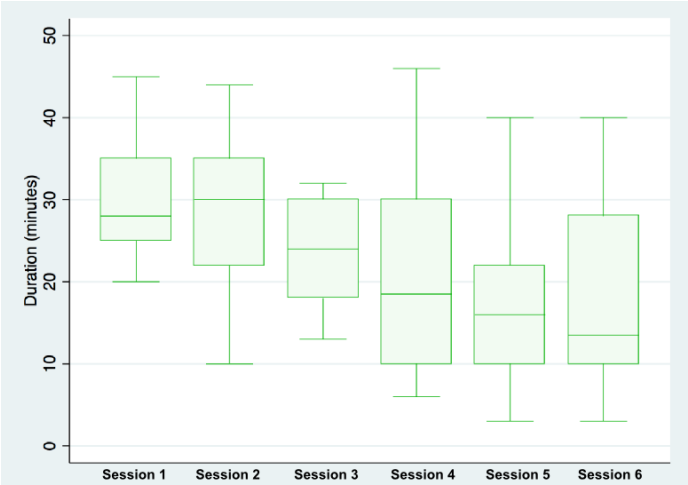
Completion of automated electronic follow-up survey

All participants (27/27) completed the automated electronic follow-up survey at T1 and T2. Most participants (21/27) completed the follow-up survey without any further reminders. I sent nine mobile text reminders to six participants before all T1 follow-up surveys were completed.

6.3.2 Feasibility of TASK-CBT intervention

All 14 participants randomised to TASK-CBT completed all six telephone sessions with no drop-out. Median duration of each session ranged from 14 to 28 minutes. After the first two telephone sessions, the median duration decreased with each successive session (Figure 40).

Figure 40. Duration of TASK-CBT telephone sessions



Thick line indicates median, box indicates IQR, whiskers indicate range

I carried out a total of 84 telephone sessions (6 sessions per TASK-CBT participant). One participant did not consent to audio-recording. I recorded 51/84 sessions in 13 participants using a digital recorder but transcribed only 13 sessions of three participants. The additional costs of transcription and administrative tasks of finding an independent clinician to review the transcripts led me to stop recording and paying for transcription. On average, transcript for each session had 4500 words (13-page long), and cost £36 per session to transcribe.

Online task completion in the TASK-CBT group was automatically captured. Most participants completed the first three tasks, with some participants completing the same task more than once (Table 33). Tasks 4 and 6 had lower completion compared to tasks 1 to 3.

Table 33. Completion of online tasks by TASK-CBT participants (n = 14)

Online tasks	Task topic	Number of participants completed each online task	%	Number of times online task was completed
1	Self-monitoring feelings/thoughts/actions	13	93	14
2	Identify unhelpful thinking styles	14	100	17
3	Fear of stroke recurrence/ losing control	12	86	14
4	Confronting your feared situation (exposure)	8	57	12
5	Relaxation for 5 minutes/ day	Not recorded		
6	Schedule an enjoyable activity	8	57	13

6.3.3 Feasibility of wearing a smartwatch in the TASK RCT

All TASK participants (27/27) consented to wearing the smartwatch. 21/27 agreed to wear a second smartwatch. The return of smartwatches is ongoing. So far, all participants have returned their first smartwatches by pre-paid post when requested (24/24). Three participants reported having to stop wearing the smartwatch and returned their smartwatches (1 ‘strap too tight’; 1 ‘had a broken

arm', 1 'too itchy'). 'Wear time' data will be analysed once all smartwatches have been returned.

6.3.4 Exploratory data on clinical outcomes at T1

Disability

All participants completed T1 follow-up at median 7 weeks (IQR 42-56 days) post-randomisation. mRS scores were similar between the two groups (median mRS in TASK-CBT: 1, IQR 0-1; TASK-Relax: 1, IQR 1-3). 12/14 (86%) was independent (scored mRS 0-2) in TASK-CBT compared to 9/13 (69%) in TASK-Relax (Figure 41).

Quality of life

While none of the participants scored 'I am not anxious or depressed' on EQ5D-5L at baseline, some patients did at T1 (TASK-CBT 7/14, 50%; TASK-Relax 2/13, 15%) (Figure 41). Participants scored their overall health using the EQ5D5L visual analogue scale (TASK-CBT median, IQR: 80, 72-86; TASK-Relax: 68, 41-80) (Figure 42).

Figure 41. Disability and quality of life at T1, by treatment allocation

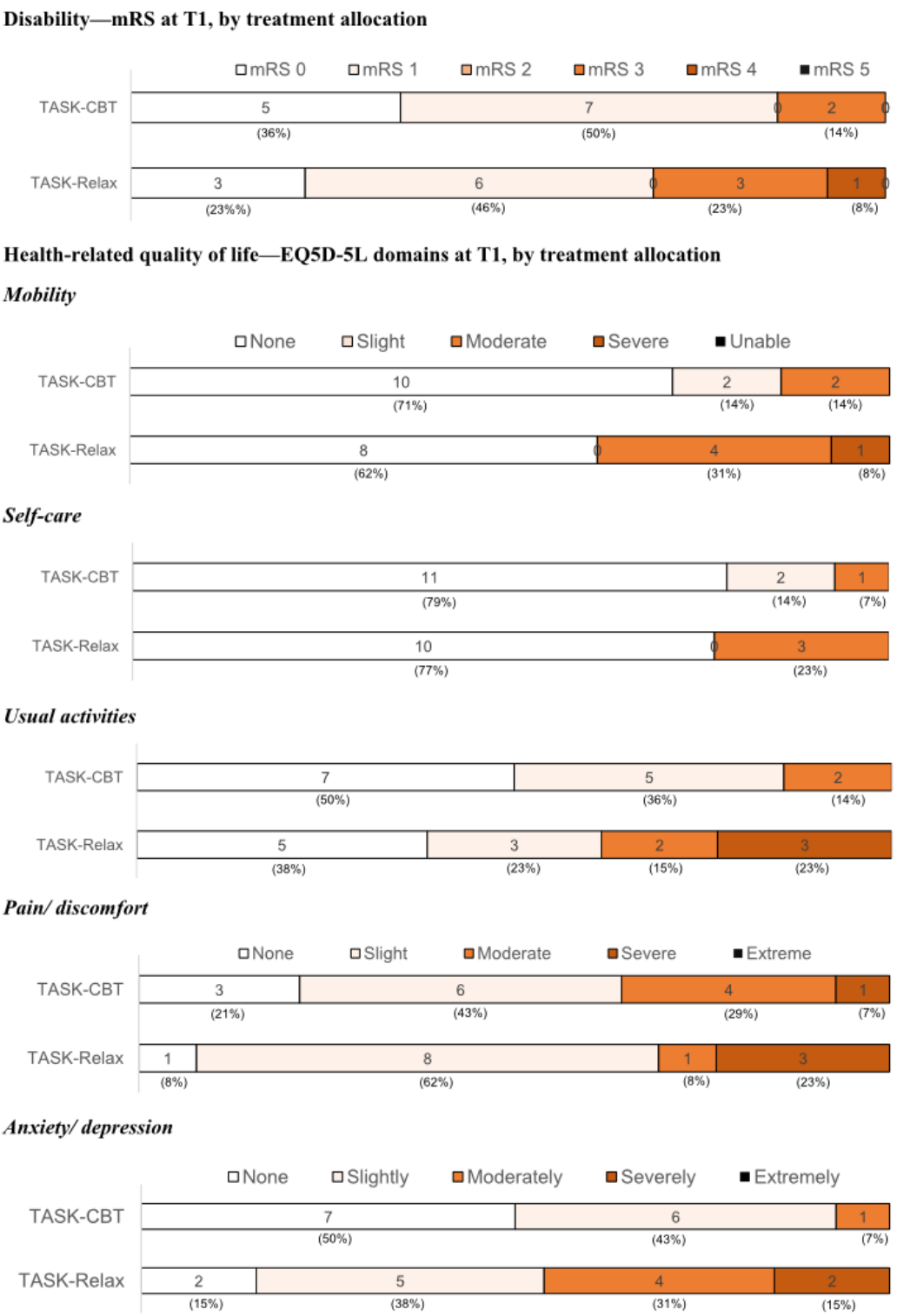
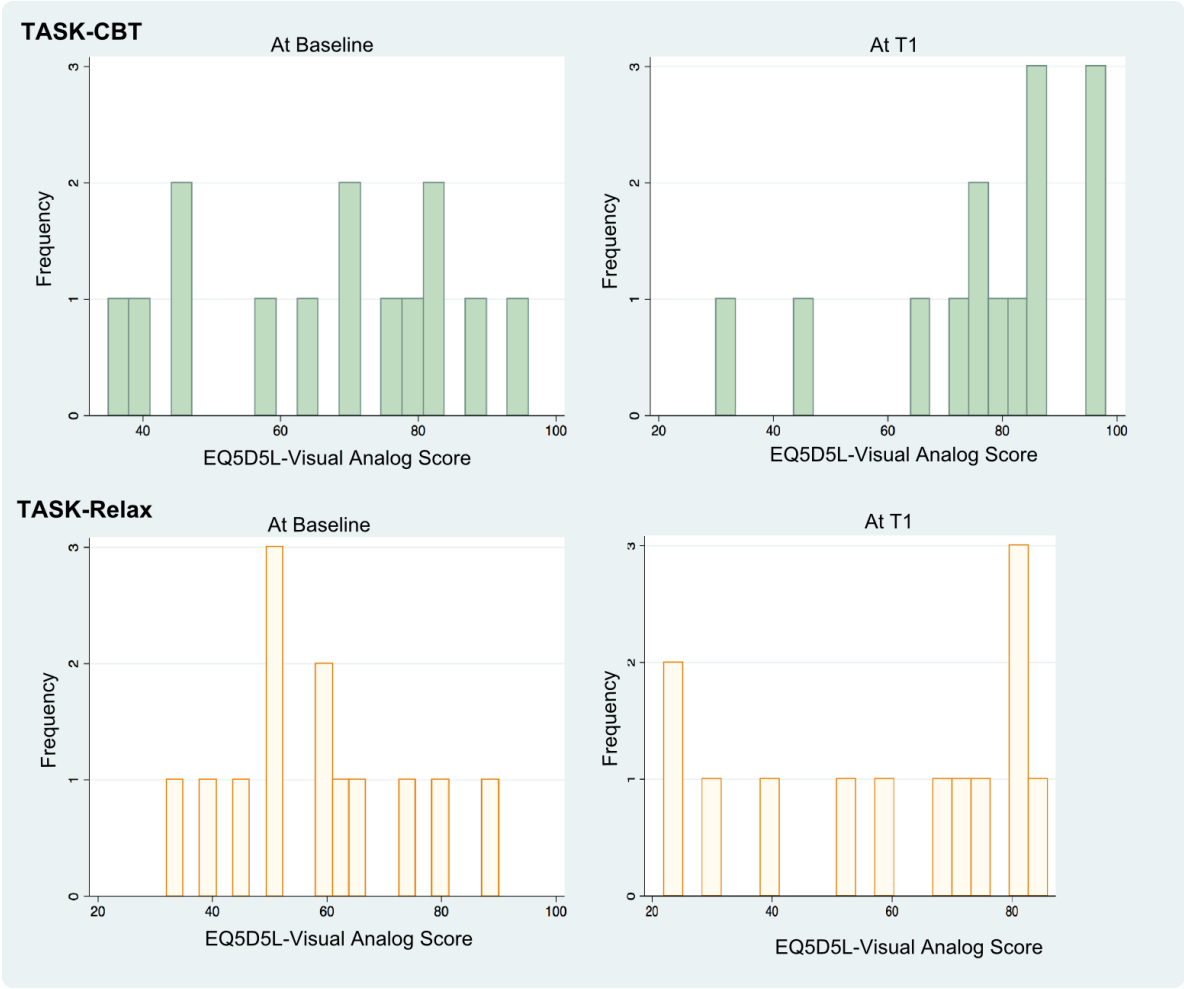


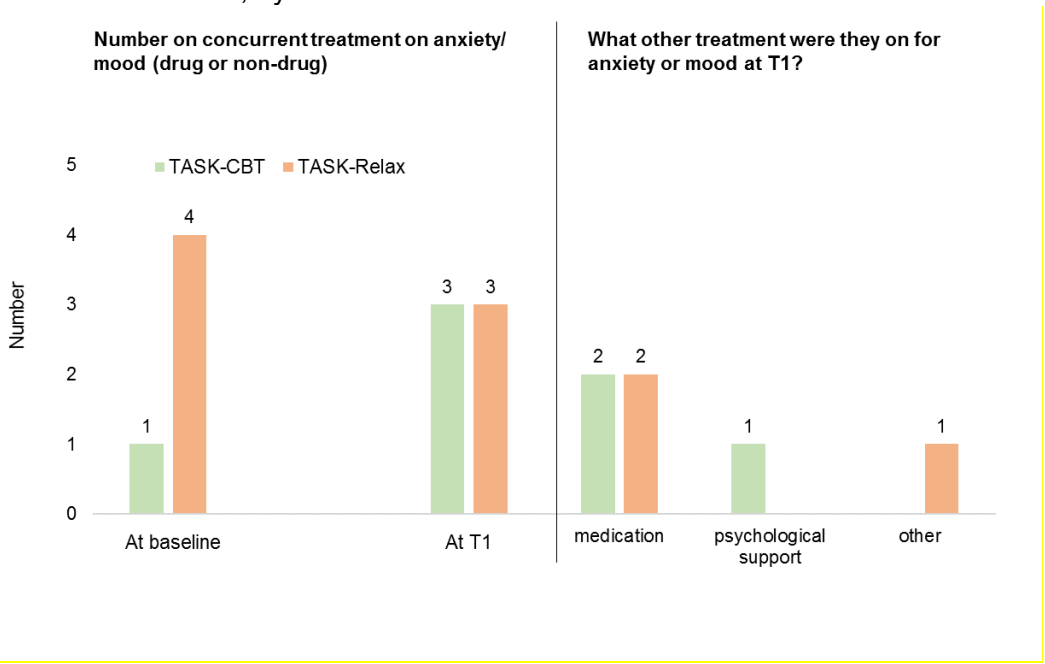
Figure 42. Histograms show distribution of self-reported overall health status on EQ5D5L-Visual analogue, by treatment allocation



Concurrent treatment for anxiety and mood problems

5 participants were receiving concurrent treatment (drug or non-drug) for anxiety or mood at baseline, and 6 participants at T1 (Figure 43)

Figure 43. Concurrent treatment (drug or non-drug) for anxiety or mood at baseline and at T1, by treatment allocation



Anxiety measures

Figure 44 shows the median, interquartile range, and range of scores on all anxiety measures at baseline and at T1, by treatment group.

Generalised anxiety

On GAD-7 (maximum score 21), participants in the TASK-CBT scored lower than participants in the TASK-Relax at T1 (TASK-CBT: median 3.5, IQR 0-5; TASK-Relax: median 8.0, IQR 6-15). At a cut-point of >=6 on GAD-7 , 3/14 (21%) TASK-CBT had a probable diagnosis of GAD compared to 11/13 (85%) in TASK-Relax. The TASK-CBT group was less likely to have a probable GAD compared to the TASK-Relax group (probable GAD: OR 0.05, 95%CI 0.01-0.36).

Phobic anxiety

At T1, FQ-agoraphobia subscale score (maximum score 40) was lower in the TASK-CBT group compared to TASK-Relax (TASK-CBT: median 1, IQR 0-7; TASK-Relax: median 20, IQR 10-24). At a cut point of >=7 on the FQ-agoraphobia subscale, 4/14 (29%) participants in the TASK-CBT group had probable agoraphobia compared to 10/13 (77%) participants in the TASK-Relax group.

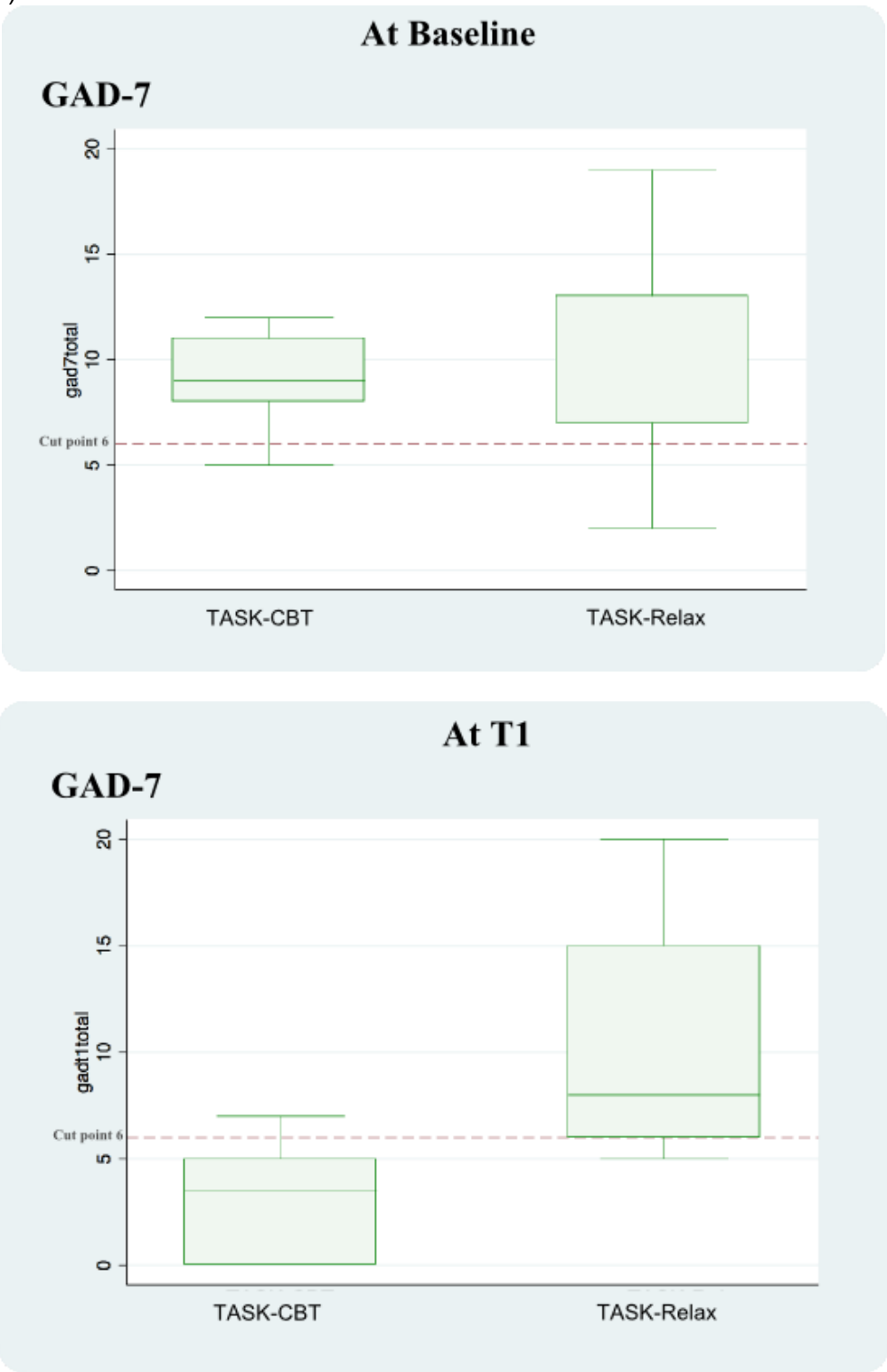
I found similar trends on the FQ-social phobia and FQ-specific subscales at T1 (median FQ-social phobia [IQR]: TASK-CBT 2 [1-4]; TASK-Relax 13 [11-24]; FQ-specific phobia: TASK-CBT 2 [1-5]; TASK-Relax 15 [9-27] (Figure 44).

Does TASK-CBT predict disability or diagnosis of GAD?—an exploratory analysis using logistic regression

At T1 (about 7 weeks post-randomisation), TASK-CBT greatly reduced the odds of having 'probable GAD' compared to TASK-Relax (‘probable GAD’ [GAD-7 >=6]: OR 0.05, 95%CI 0.01-0.36), though there was no detectable difference in disability (mRS 0-1 OR 2.7, 95%CI 0.40-17.9).

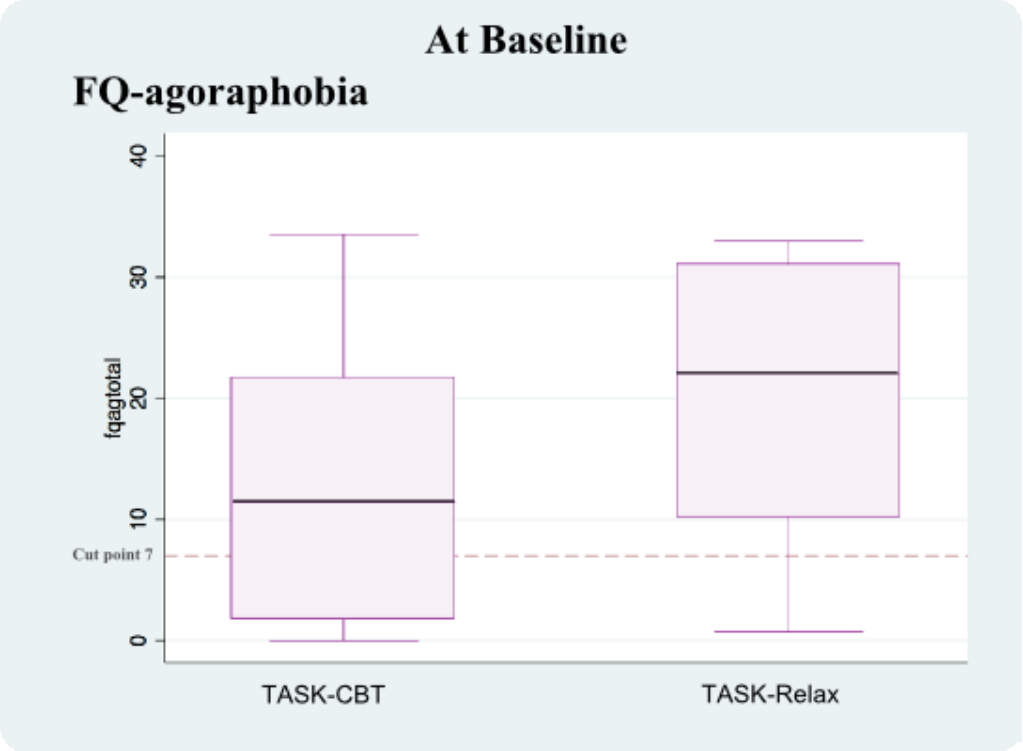
Figure 44. Scores on a) GAD-7, b) FQ-agoraphobia, c) FQ-social phobia, and d) specific phobia at baseline and at T1, by treatment group

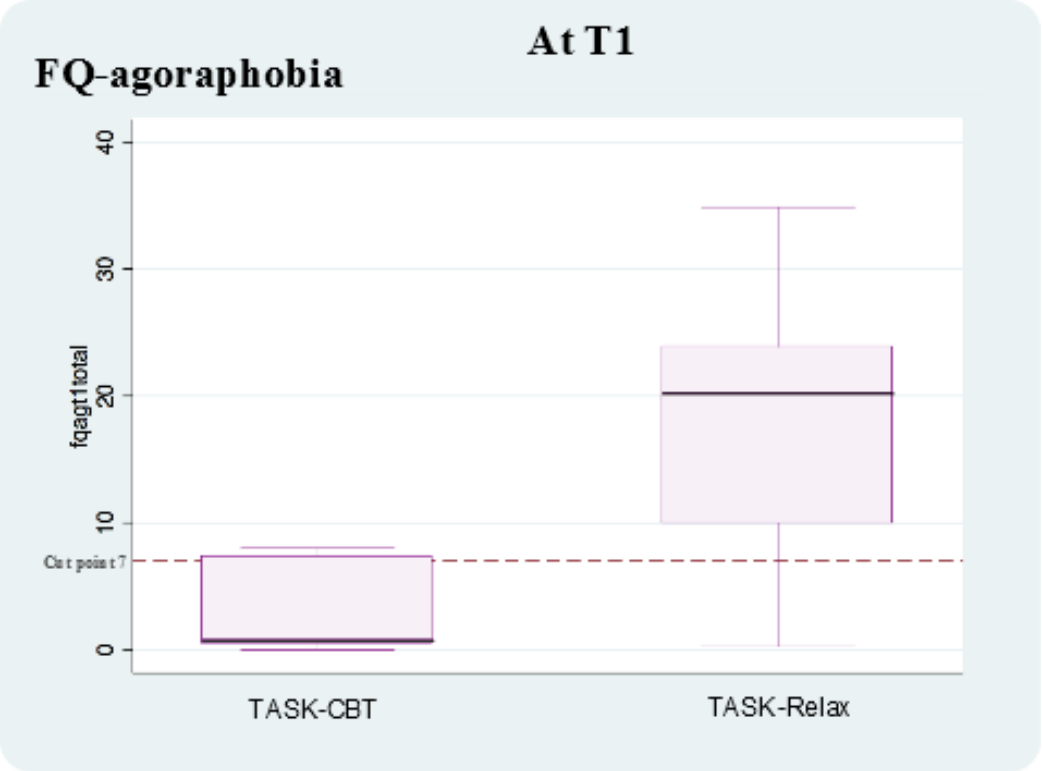
44a)



Thick line indicates median, box indicates IQR, whiskers indicate range

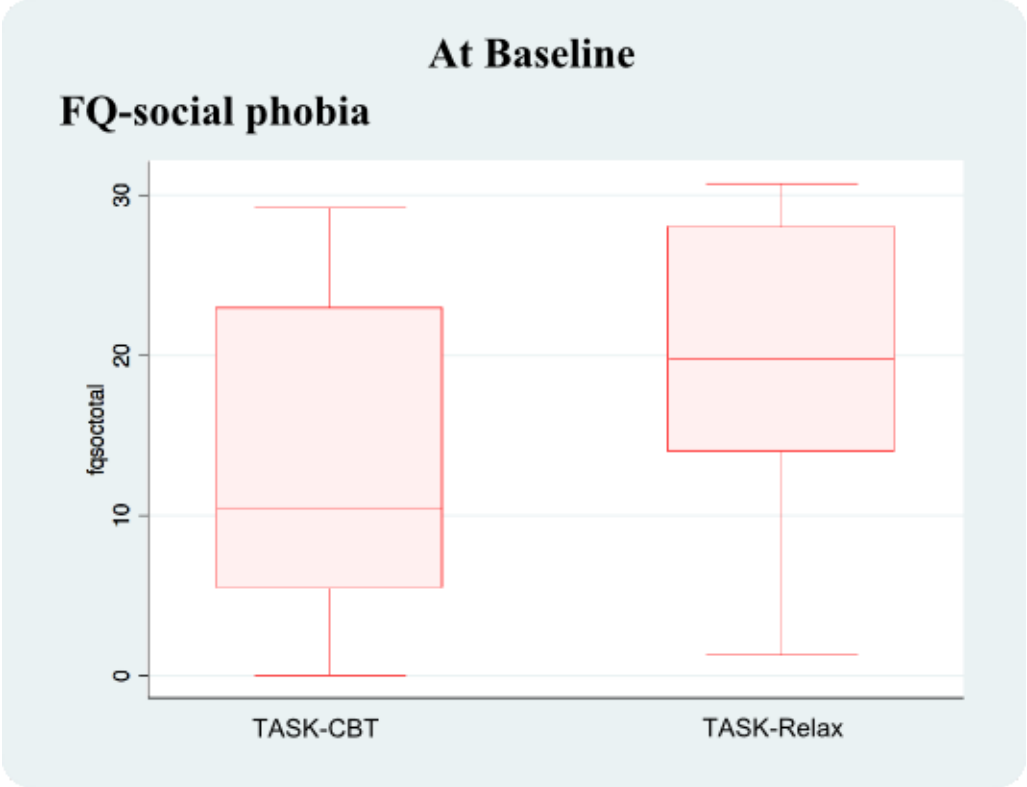
44b) FQ-agoraphobia subscale at baseline and at T1, by treatment group

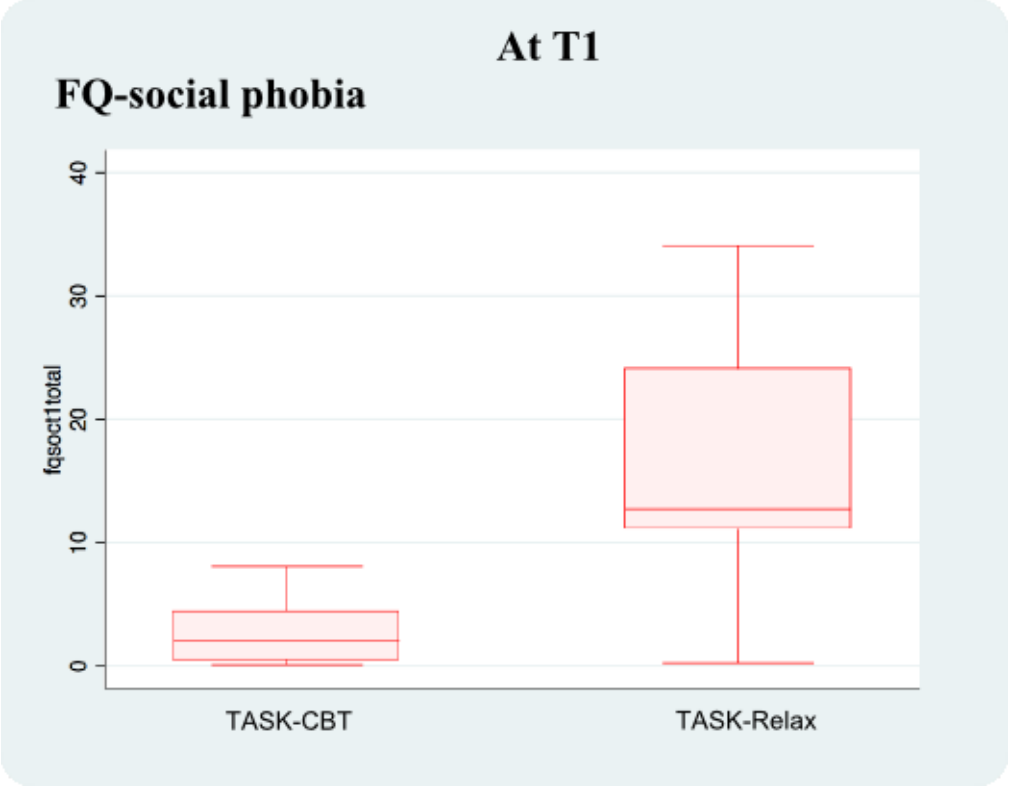




Thick line indicates median, box indicates IQR, whiskers indicate range

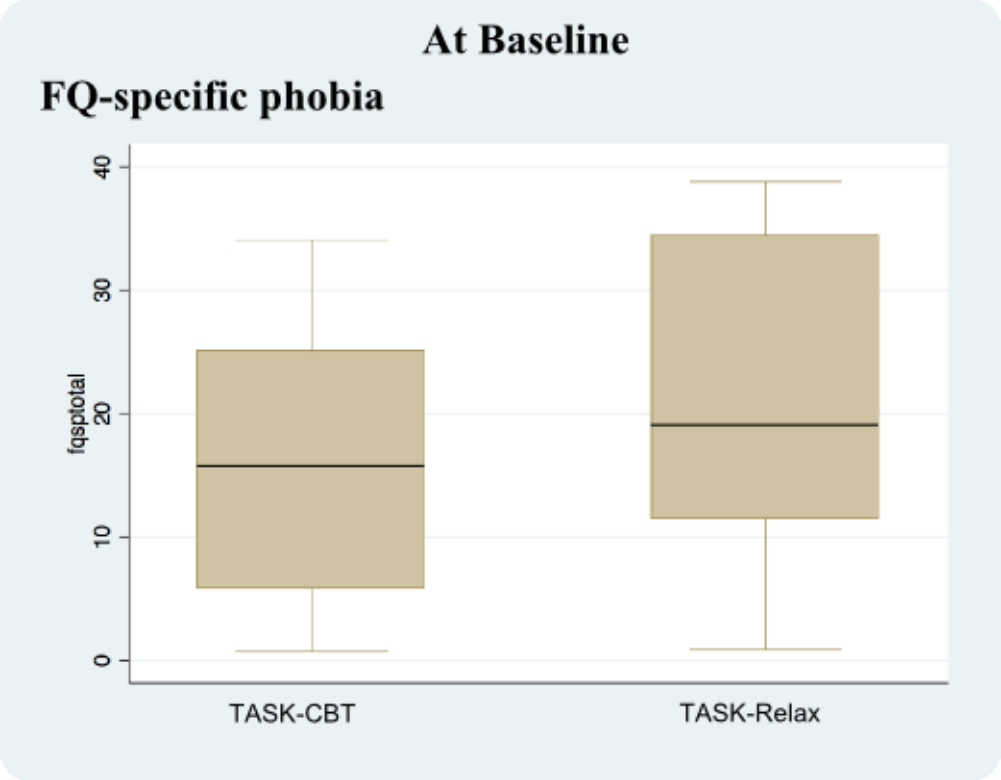
44c) FQ-social phobia subscale at baseline and at T1, by treatment group

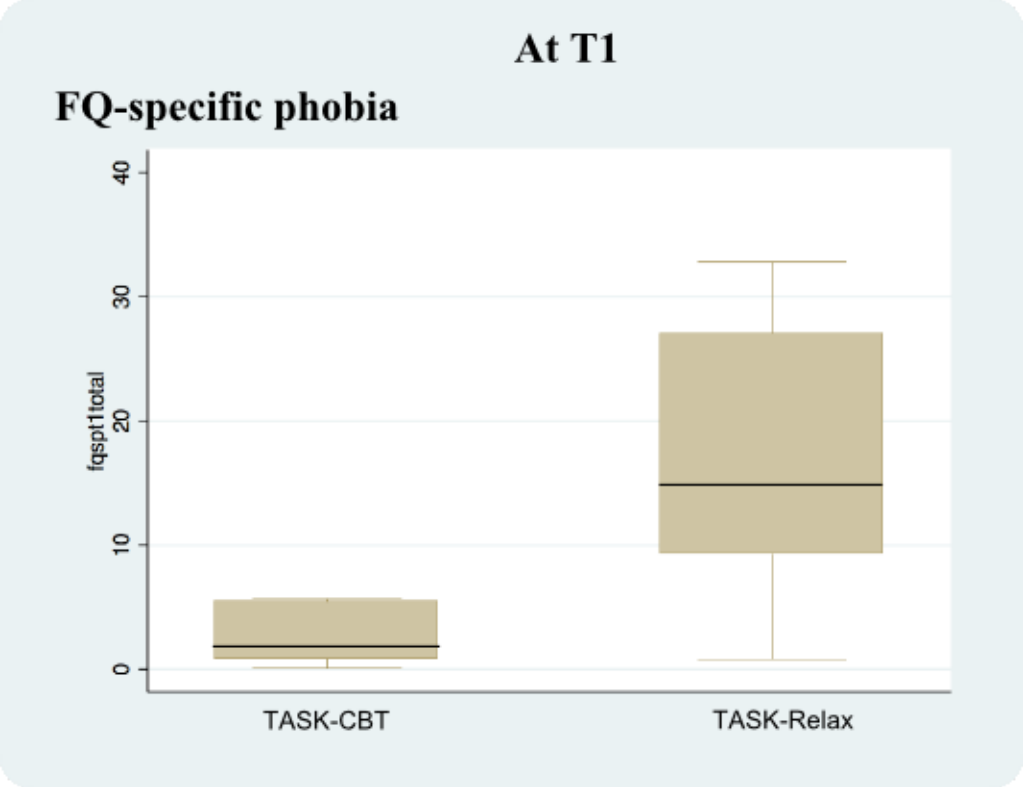




Thick line indicates median, box indicates IQR, whiskers indicate range

44d) FQ-specific phobia subscale at baseline and at T1, by treatment group





Thick line indicates median, box indicates IQR, whiskers indicate range

6.4 Discussion

6.4.1 Key findings

My novel technology-enabled trial procedures and the TASK-CBT intervention are feasible in a small scale. This is a streamlined RCT that evaluates a CBT-based intervention remotely for anxiety after stroke. The final data collection of this current study is ongoing so further feasibility outcomes will be reported after completion of my thesis. I have identified the limitations of the current trial and intervention design which I will need to address before the definitive TASK RCT.

Generalisability

The TASK trial participants were not representative of the general stroke population as they were younger and had a good outcome as defined by mRS 0-2 at baseline. The sample was probably representative of the anxious population after mild stroke/ TIA as their characteristics were similar to the anxious participants from my prospective cohort—younger and had a past history of anxiety or depression. Younger age and a past history of anxiety or depression are consistent predictors for developing anxiety after stroke or TIA(56, 59). The characteristics of my sample probably reflect the use of anxiety screening as an inclusion criterion for the TASK trial. I designed the anxiety screening criteria to be as inclusive as possible across the wide spectrum of anxiety levels.

The TASK trial design and the TASK-CBT intervention require individuals to communicate on the telephone and to use the Internet. This design therefore excludes stroke patients with aphasia, cognitive impairment, and severe motor dysfunction. In principle, CBT requires the ability to be aware of, examine, and understand own thoughts and feelings. CBT is therefore not a suitable treatment for anxiety in stroke patients with significant cognitive or communication

difficulties. It is likely that these patients would require highly specialised interventions, delivered by therapists skilled in using alternative means of communicating feelings and thoughts, or therapy that emphasises on behavioural techniques rather than cognitive abilities.

The web-enabled design excludes people who have no access to the Internet, or those who do not have a minimum level of skills in information technology. This is likely to be overcome by the trend towards wider adoption of home broadband and user-friendly devices amongst older people(148). Having carers or relatives to teach patients how to use the Internet and mobile devices, offering devices and formal training to trial participants are some of the potential solutions to overcome the barrier in using digital health interventions.

The TASK trial design has wide applicability, which extends beyond the stroke and TIA population. Its design was geared towards testing any interventions that could be delivered remotely e.g. guided or unguided self-management, remote symptom or physiological monitoring, remote drug dosing, clinic consultation via telemedicine.

6.4.2 TASK trial design

Recruitment strategy

While my recruitment rate of two to three participants per week exceeded the pre-defined feasibility outcome of recruiting two per month, it was clear that my recruitment strategy in the TASK trial was labour-intensive and time-consuming. I screened nearly one and a half thousand patients to enrol 27 participants in the TASK trial. The definitive TASK trial will need to recruit hundreds of patients or more. If the same recruitment strategy is to be used, it will need to be made efficient since thousands or tens of thousands of patients will

have to be screened. Screening huge numbers of patients from a registry or primary care routine data, and sending invitations en masse could be made efficient by automation technology.

Using technology to follow up patients after their discharge could improve patient care, patient access to clinical trials and trial recruitment. For example, the use of mobile text, mobile applications, tele-consultations could help address the lack of 'life after stroke' services after discharge—an experience likened to being abandoned according to patient reports from stroke charities(134). I envisage the potential of routinely sending all patients a 'follow up' mobile message at 1 month following their discharge from the ward or clinic. Those who respond with ongoing issues would receive a link to a website with information on ongoing clinical trials and useful life-after stroke services.

A change in attitude and practice in how patients should be approached for research could improve trial recruitment. Empowering patients with information about ongoing trials and the ability to recruit themselves to a trial of their own choosing would seem sensible and ethical. It would also remove the need for patients to be 'selected' by healthcare or research staff, potentially improving the generalisability of the research. Examples of trials that enable self-screening in other populations include the Migraine Intervention with STARFlex RCT (n=432) (149) and the Treatment in Morning versus Evening study RCT which evaluates morning and evening dosing of hypertensive medications (n = 21,116)(150). Similarly, the TASK trial's streamlined procedures for self-screening, self-recruitment, electronic informed consent, and remote eligibility confirmation would potentially enable a centralised model to recruit eligible patients anywhere in the country, or anywhere in the world without the need to have locally-based principal investigators or research staff. Larger sample sizes could be reached more easily

without significantly raising extra costs associated with setting up multiple local sites.

Verifying and confirming eligibility remotely using electronic health records was only achievable in the current study because the study was confined within one NHS health board. Making this centralised model of remote recruitment feasible nationwide or internationally would require more innovative solutions to confirm the identity and eligibility of potential participants. For example, potential participants could provide electronic proof of identity and eligibility to the research centre by sending a digital photograph of their driving license and a clinic letter detailing their stroke via a secure online form, email, or mobile messaging. A centrally-based research team could verify eligibility in a number of ways e.g. using electronic health records for local patients, sending a brief electronic confirmation form to the participant's GP, or local stroke services via secure email. Having named contacts across the country's stroke services such as stroke clinicians and using established clinical research network e.g. research nurses across the country could help facilitate this process without the need to establish multiple trial recruitment sites formally.

Technological innovations will make a centralised trial logistically possible. The regulatory complications, not technological ones will most likely be the barriers to running a large-scale centralised RCT.

Maximising the reach of trial recruitment advertisement

An efficient advertising strategy was necessary as patients could only self-recruit if they knew about the trial. Without an adequate 'life after stroke' service, I had no easy way of informing patients of the TASK trial's self-recruitment website www.task4stroke.org. My advertising campaign included posting on Twitter during

the recruitment period, handing out TASK 'business cards' to stroke clinicians, rehabilitation therapists and community stroke nurses, and emailing electronic flyers to clinicians of the local stroke services in NHS Lothian. I also contacted the Stroke Association Scotland, a major stroke charity, which tweeted the TASK trial advert separately. I found handing out business cards and sending out flyers to clinicians did not yield any TASK participants. Five patients contacted me on the TASK team mobile and via email wishing to sign up to the trial. They were from outside NHS Lothian, so were ineligible. One of them was referred by a stroke physician in London, who saw my tweet and felt that his patient would be a suitable participant. For two of the patients, their wife and son found out about the TASK trial while searching online for information on anxiety after stroke. These anecdotes showed that, if the TASK trial was open to patients regardless of where they lived, I would have enrolled additional participants within the recruitment period with minimal effort on my part. Working collaboratively with patient groups and charities, as well as local stroke rehabilitation services are potential ways to maximise the reach of trial recruitment advertisement.

Randomisation, allocation concealment

Owing to the small sample size intended for the current study, a permuted block randomisation sequence with random block sizes was used. For the definitive trial, stratified randomisation or minimisation may be required to distribute potential confounders equally between the two groups. Variables that could influence treatment outcome include age, sex, past history of anxiety and depression, concurrent use of psychotropic medications, disability, baseline anxiety. Allocation concealment was achieved in this current study using REDCap's in-built randomisation module. Using REDCap, a person independent

of trial enrolment was able to generate the randomisation sequence from a statistical software, upload the sequence while restricting access to it. In the current study, I had no access to the allocation sequence but I was not blind to the participants' treatment allocation. I found I was trying to predict which treatment group the next participant was likely to be allocated. For instance, after four participants had been randomised to TASK-Relax consecutively, I would predict the next participant to be allocated to TASK-CBT. As such, when I had multiple participants to randomise, it was possible for me to choose which participant to randomise first, based on my perception of their likelihood to benefit from TASK-CBT. As the current study was a very small trial, my predictions had a high chance of being correct even with varying block sizes. This should no longer be problematic in a large trial using stratified randomisation or minimisation, where the chance of anyone's predictions would be unlikely to be correct.

Intervention and comparator, masking

The use of a treatment website and the telephone to deliver TASK-CBT remotely made it technically straightforward to design a matching comparator. I simply created a comparator website, the TASK-Relax. Having a matching comparator is preferable to using 'usual care' or waitlist as controls, as these latter controls are known to exaggerate effect size in trials of psychological interventions(151). My systematic review (Chapter 2) showed that most trials of anxiety interventions in stroke used 'usual care' or waitlist as comparators. The description of what constituted 'usual care' was minimal across the included studies(46). My TASK-Relax website is transparent and reproducible. It also provides a degree of masking of trial participants. To enhance matching of the

TASK-Relax to TASK-CBT in the future, brief scripted or automated telephone prompts could be added to the TASK-Relax intervention.

It is possible that TASK-relax will have some effect on patient's anxiety, thus confounding the effect of TASK-CBT. Our hypothesis is that TASK-CBT is superior to TASK-Relax in the longer term at 20 weeks post-randomisation (T2). This remains to be tested in definitive TASK RCT(152).

My supervisors and I considered the appropriateness of a cross-over study design, in which we would extend the trial to measure outcomes after participants have completed the second intervention. A cross-over design is not appropriate given that CBT teaches participants to apply their newly learnt skills to self-manage their own anxiety for life. As such, there is not a washout period as would be expected from some pharmacological cross-over trial designs. One could consider collecting treatment outcomes again in TASK-Relax participants who then went on to use the TASK-CBT website. Doing so could provide pre- and post-treatment data in this group to support the effect of TASK-CBT without telephone guidance.

I could not assess the extent to which participants were masked to our hypothesis that TASK-CBT was superior to TASK-Relax. It was theoretically possible for participants to find out the detailed description of the TASK trial on publically accessible trial register. Our attempt at masking relies on the participants' perception that both treatment groups were designed to help with anxiety.

Automated electronic follow-up

There was no attrition at all follow-ups. The scheduling function for sending out electronic follow-up surveys automatically to participants' emails on

REDCap worked efficiently without any practical issues. Follow-up at T2 is currently ongoing and will be reported after completion of this thesis. Only minimal effort was required to achieve completion of all T1 follow-ups. I sent a standard text reminder describing the importance of completing the follow-up survey to participants who had not completed their scheduled survey:

Dear [participant's name]

Hope you are well.

I would be grateful if you could complete your final follow-up survey for the TASK study.

Your completion of the TASK survey is very important for our research. Please complete the survey even if you have not used the TASK treatment website.

Thank you for your participation in the TASK trial.

Yours sincerely,

Yvonne Chun

TASK team

6.4.3 TASK intervention design

Intervention adherence to the TASK-CBT was good with zero drop out of the telephone sessions. The TASK-CBT therapist manual and record (Figure 30) enabled me to discuss each case with a neuropsychiatrist at weekly supervision. I designed three ways of capturing fidelity to intervention: i) validating the TASK therapist record with transcripts of audio-recording, ii) automated electronic capture of online task completion, and iii) web usage data.

With a limited project budget, I found the costs of transcribing all telephone sessions prohibitive (£36 per session). The transcripts from the current study are still to be validated by a clinician independent of the trial. Reading each transcript is likely to be time consuming and may not be feasible in a large-scale TASK trial. An alternative way of validating treatment sessions without the need of transcribing would be for the independent clinician to listen to randomly selected audio-recorded sessions stored in a database.

Having a better audio-recording set up, automated voice-recognition and transcription technology, and the use of natural language processing for automated transcript validation could make this method of assessing intervention fidelity more efficient.

Telephone session duration decreased with each successive session. I designed the first session to gather information from the participants on their anxiety problem before setting a specific goal and introducing them to the task of self-monitoring. The second session began to introduce CBT techniques so participants could start practising them during the week. Subsequent sessions involved recapping the participant's progress that week and their use of CBT techniques, which could vary in length depending on the individual. There is not an optimal session duration applicable to all patients. I found having a flexible session duration between 20-40 minutes to be reasonable. The flexibility would enable the TASK therapist to tailor the session according to the individual's needs.

Online task completion was excellent for the first few tasks but less so for the later tasks. This was in spite of all participants receiving a standard weekly text reminder to complete their online tasks. It was likely that I had influenced task completion by placing more emphasis on completing the first three tasks than the

later tasks during my telephone sessions. The first three tasks were on the core topics of CBT, relevant to all TASK-CBT participants. On the other hand, not all participants had phobic anxiety, so would find task 4 irrelevant. I designed these online tasks to make the TASK-CBT intervention interactive outside the telephone sessions. These tasks served to consolidate the CBT skills that I introduced to participants during their telephone sessions. Having a specific task on exposure therapy (task 4) enabled me to tailor the TASK-CBT intervention to those who suffered from predominantly phobic symptoms.

I have not analysed the data collected using Google Analytics in the current study. It became apparent that there were many issues associated with using Google Analytics in clinical trials, including its validity, inability to collect all the interaction data needed, and the inability to collect individual participant data. The absence of informatics support at the time of designing the TASK trial prevented me from setting up the TASK trial's own customised web usage monitoring. With appropriate informatics support, it would be possible to embed an in-house web usage analytic program within the TASK treatment websites to collect precisely the data required.

TASK therapist training

The TASK therapist training materials are still to be developed and therapist's manual needs to be refined based on my experience in the current trial, the anonymised audio transcripts, and my supervisors' experience in providing therapist training.

6.4.4 Exploratory findings on clinical outcomes

Based on the exploratory analysis, TASK-CBT greatly lowered the odds of probable GAD compared to TASK-Relax without any detectable difference in disability on the mRS. Our current trial suggest that TASK-CBT may be effective.

The mRS is a widely accepted primary outcome in stroke trials. The conventional definition for a non-disabling stroke is an mRS of 0-2. At baseline, the majority of my sample were in the mRS 0-2 category. This probably reflects the characteristics of a sample of minor stroke and TIA. mRS may not be appropriate as a primary outcome in a trial that targets the milder spectrum of stroke patients, or one that evaluates an intervention that does not target motor-related functions. mRS may not be sensitive to a change in the clinical status of participants in the TASK RCT. To determine an appropriate primary outcome measure to be used in the definitive TASK trial, a range of candidate outcome measures of anxiety, disability, quality of life, and participation should be considered. Selection of the primary outcome will be based on the measure's sensitivity to change or difference between groups, its practicality for use in large-scale RCT, and its clinical meaningfulness.

Patients after stroke/TIA can present, to varying degree, predominantly phobic, predominantly generalised, or mixed anxiety types. This poses an additional challenge as different anxiety measures are required to assess the two anxiety subtypes. It may be necessary to have different primary outcomes defined for different anxiety subtypes. Other considerations include how to define the responder's anxiety status; whether to use the minimal relevant change from baseline, or dichotomised outcome, or an absolute anxiety level post-intervention to assess the between-group difference.

GAD-7, paper or electronic version, is a validated measure of GAD in primary care and stroke. My research showed that GAD-7 could be a candidate anxiety measure in the definitive RCT. The use of FQ is limited to specialist clinics and its validation data is scarce. The FQ is rarely used in general adults or stroke, probably reflecting the low prevalence of phobic disorders amongst adults. In the TASK trial, my supervisors and I changed the format of our modified FQ by using a horizontal visual slider to indicate the level of avoidant behaviour for each FQ item. We felt that visual sliders would maximise the ease of use, generate a continuous variable, which would be more powerful, and potentially improve the clinical meaningfulness of the measure. However, I did not perform any formal validation of this latest version.

6.4.5 Further results to be reported

The final follow-up of the current study is ongoing. I intend to report all feasibility outcomes in a future publication once the trial has completed. Further outcomes to be reported from this study include the completion of T2 follow-up, return of the first and second smartwatches, smartwatch 'wear time', intervention fidelity, feedback survey on TASK-CBT and TASK-Relax, and any harmful effects reported by the participants.

Chapter 7

General Discussion

Acknowledgements of contributions

I wrote this chapter with comments from my supervisors.

7.1 A summary of my research

The aims of my thesis were to develop an intervention for anxiety after stroke and TIA, provide some information on its acceptability and ease of delivery, and test the feasibility of the TASK RCT procedures.

Anxiety after stroke

To develop an intervention tailored to the anxiety problems for stroke patients I had to gain a thorough understanding of the anxiety problems that these patients experienced. SCID, a semi-structured psychiatric interview, was regarded as the 'gold-standard' diagnostic tool in psychiatry research. The use of SCID enabled me to investigate the frequency of different anxiety subtypes and provided me an opportunity to obtain more qualitative information on patients' experiences of anxiety after stroke/TIA. I could not have achieved this by administering simple anxiety measures. My findings that phobic anxiety was the predominant anxiety subtype post-stroke/TIA, together with the descriptive data on specific anxiety-provoking situations had immediate implications in how I would design the TASK intervention. It became clear from my prospective cohort study and my patient involvement work that my TASK intervention had to include components on exposure therapy, agoraphobia, risk of stroke recurrence, and bodily symptoms that might be mistaken as stroke or illnesses. Integrating these

specific components with the general principles of CBT would make the intervention relevant to anxious stroke or TIA patients.

My experience at conducting the SCID interviews and delivering the TASK-CBT intervention as the therapist provided further insights into people's anxiety after stroke/TIA. Anxiety was ubiquitous in people's daily life and could be adaptive. Given that stroke was a potentially life-threatening and severe debilitating condition, it was unsurprising to find that participants felt some anxiety about their future after a stroke/TIA. What became very clear to me was that not all anxiety was adaptive. People could become severely limited in their activities because of their anxiety and the maladaptive behaviours that ensued. Participants gave vivid description of their disproportionate fear in normal daily situations since the onset of their stroke/TIA e.g. going into the shower alone, getting on a crowded train, walking alone. They often described these experiences as peculiar, out-of-character, and completely novel to them. In my experience, exposure techniques seemed to have helped the participants in overcoming their phobic fears. Some participants, without realising it themselves, were already applying exposure techniques to overcome their feared situations even before therapy. They simply understood the need to face their fears and were able to confront the situations with little formal support. Other participants found it difficult to apply exposure techniques without any formal guidance. These participants gave a description of consistently escaping or avoiding their feared situations in order to seek relief and comfort. These participants tended to have more severe anxiety symptoms or even panic attacks. Their anticipatory anxiety could be so severe that it prevented them from even imagining themselves confronting their feared situations.

I designed the exposure therapy component of the TASK-CBT intervention to teach participants to recognise their maladaptive behaviours—escape and avoidance, and the techniques for confronting their fears in a gradual hierarchical fashion. The aim of this component was to equip participants with the skills so that they could continue applying exposure techniques themselves after completion of the six telephone-guided sessions.

Anecdotally, I found participants with generalised anxiety were those who had always had the tendency to worry about many things, or even a past diagnosis of GAD before their stroke. The principles of cognitive restructuring are the same for anxious individuals regardless of whether they have a stroke or not. My role was to repackage these CBT principles into contents that were easily comprehensible and relevant to stroke and TIA patients so that they could learn, practice, and continue applying these techniques independently after the six telephone-guided sessions.

In my prospective cohort and TASK RCT, I found anxious participants to have a distorted perception of their risk of stroke recurrence. They selectively paid more attention to the stimuli and situations e.g. odd sensations, headaches, physical exertion, going out alone, which they thought were associated with a risk of stroke or other dangerous mishaps. These stimuli further perpetuated their anxiety feelings (both affective and physiological) which reinforced their belief that these stimuli/ situations represented danger. Their avoidant behaviour was safety-seeking. These patients fitted well in the cognitive model described by Aaron Beck(47). Accordingly, I designed the TASK-CBT intervention to provide anxious patients an alternative view of their risk of stroke recurrence in order to guide them to correct their own distorted thinking. Simply asking participants how high they thought their stroke risk was, followed by the reassuring statement that

their stroke risk was no more than 2-5% per year in the long term was often all it took to relieve their anxiety feelings. Of course, this statement had to be supplemented by a general education on stroke risk reduction including maximising secondary prevention and promotion of a healthy lifestyle etc. Through explaining the cognitive behavioural model with the TASK-CBT participants, I guided them to recognise their own maladaptive thinking patterns and unhelpful avoidant behaviours.

Anxiety assessment in clinical trials

Identifying that there were two main anxiety subtypes post-stroke/TIA generated another problem, the assessment and screening of anxiety in this population. Prior to my research, none of the RCTs of anxiety intervention in stroke used measures that were designed or validated for detecting phobic anxiety. These trials assumed all anxiety was generalised. The use of SCID or similar diagnostic interviews would be too time-consuming to be practical for use in a large-scale clinical trial or in day-to-day clinical practice. GAD-7 was an obvious choice for detecting GAD, given its derivation from the DSM-IV criteria and validation data in primary care. Initially, my supervisors and I selected and modified the FQ so that I could obtain data on phobic avoidance and specific anxiety-provoking situations in my prospective cohort study. I saw the opportunity to incorporate a diagnostic accuracy study within the prospective cohort. This generated the first validation data for our modified FQ, demonstrating preliminary findings supporting the use of FQ-agoraphobic subscale in patients after stroke/TIA. Agoraphobia accounted for most of the phobic disorder cases, which probably explained why the FQ-agoraphobic subscale performed well at detecting ‘any phobic disorder’. Issues remain as to how best to measure phobic anxiety

when present in other specific phobic situations post-stroke: social situations, physical exertion, having sex, being home alone. A desirable item or scale for phobic disorder would measure the presence of phobic avoidance irrespective of the situation. GAD-7 may be able to detect some phobic patients who regularly experience anxiety feelings but may not detect those who completely avoid confronting or imagining their feared situations. Further scale development work is likely required.

Selecting outcome meaures for TASK RCT

Given that TASK-CBT is an intervention on anxiety, an anxiety measure should be included in assessing the effect of this intervention in a clinical trial. However, changes in the scoring of an anxiety scale may not translate to clinically relevant improvement. A functional measure or a measure of social participation, such as the WSAS might be more clinically relevant given that the goal of treating someone's anxiety is to help that individual return to normal functioning and activities. Unfortunately, I did not test the feasibility of WSAS in my feasibility RCT and chose the mRS, a crude but more widely used functional measure in stroke. WSAS is short and simple so should not pose a feasibility issue in a large-scale RCT. For the next phase of TASK RCT, I plan to pilot a selection of potential primary outcome measures including the WSAS to assess their sensitivity to change and responsiveness.

Complex intervention development

The 6SQuID's systematic, logical, and evidence-based approach in developing a complex intervention gave me a clear framework to follow when

designing my TASK-CBT. It ensured my TASK-CBT development was transparent and reproducible for the wider research community.

Another strength of this approach was that it made me consider the wider context of our health service, the barriers to accessing psychological therapies, and the views of our stakeholders. These factors were all crucial in ensuring that the eventual intervention was going to be feasible for large-scale evaluation and fit for implementation in the future.

Designing an innovative efficient clinical trial

My supervisors are clinical researchers with experience in conducting RCTs. Their insights in the practical issues and inner workings of large scale RCTs inspired me to take on the challenge of designing novel technology-enabled trial procedures to improve efficiency of RCTs. The design of TASK RCT was geared towards evaluating any remotely delivered interventions such as TASK-CBT. Our vision to design an efficient, streamlined centralised trial that could be conducted remotely from start to finish seemed ambitious, but not unfeasible. In order to achieve our envisioned trial, I had to identify and apply technological solutions in the design of all trial procedures. These technological solutions enabled me to design, execute, and complete the TASK feasibility trial all within the time and budget constraints of my fellowship. The absence of any technical support led me to the incredibly useful REDCap application, a versatile tool which I used to design all the trial procedures and data collection instruments. Having full creative control of the trial database, data collection instruments, and the trial websites gave me the freedom to design novel features of the TASK trial and the TASK-CBT intervention with relative ease.

Limitations

The biggest limitation of my entire programme of research in this thesis was generalisability. My findings were not generalisable to the stroke population. Findings from my prospective cohort were probably generalisable to the mild stroke and TIA population. Studying the anxiety issues in severe stroke patients with cognitive and communication difficulties would require specialised methods and expertise, and likely involve family and caregivers. My findings that phobic anxiety was present after stroke/TIA could at least provide a starting point for those embarking on anxiety research in this particular group of patients. One could make observations of the behavioural manifestations of phobic fears e.g. escaping, avoiding, and the autonomic symptoms of anxiety e.g. shaking, cold sweats, being startled easily. Exposure therapy could be adapted to enable caregivers to help phobic patients confront their feared daily situations.

The exclusion of people without internet access and those who do not have the technical ability to use the Internet also limited the generalisability of the TASK-CBT intervention and the TASK RCT. Potential solutions to overcome this technological barrier include involving caregivers and family members, supplying user-friendly mobile devices, offering training etc. Technological barriers will no longer exist in the near future when all strata of the society have access to the Internet and the availability of user-friendly devices or specially-adapted devices for people with disabilities.

7.2 Future and wider implications of my work

Designing and testing the TASK-CBT intervention and the TASK RCT go hand-in-hand towards achieving the vision of the latest Scottish Government's

Digital Health and Care Strategy, which recognises the potential of digital technology in transforming the way in which the public interact with the health service(153). The effective use of data, improving broadband coverage, increasing digital participation are some of the key goals set out in this strategy(153). The design and testing of TASK-CBT in particular, is firmly in line with the Scottish Government's Mental Health Strategy for 2017-2027, which includes the action points: to test and evaluate the most effective and sustainable models of supporting mental health in primary care; to develop more accessible psychological self-help resources and support national rollout of computerised CBT within the NHS(154) .

My TASK-CBT intervention would enable centralisation of resources for staff, training, quality monitoring, and cross covering of different geographical areas, reducing travel time for therapists as well as patients. Digital content and treatment approaches in a telemedicine intervention could be updated and refined easily, thus making use of the latest best evidence. The provision, maintenance, and updating of digital content could be commissioned or delivered via charitable organisations. Organisations delivering the intervention could continue to invest in research and development to utilise the latest technology to deliver the treatment content at lower costs. At present, it is not yet clear whether TASK-CBT is cost-effective in stroke and TIA patients. I plan to include a health economic analysis of the TASK-CBT intervention using EQ5D-5L data in the definitive TASK RCT.

The TASK trial design is geared towards testing any intervention that could be delivered remotely e.g. digital self-management interventions, remote symptom or physiological monitoring, drug management and dosing. The designs of my TASK RCT and TASK-CBT intervention are potentially applicable in many other patient groups.

Applying informatics in efficient clinical trial design

I am likely to encounter many logistical challenges at scaling up the TASK trial in the future. Many of these challenges can be overcome by evolving innovative technologies. The most laborious repetitive tasks should be automated e.g. screening patient registry, sending out postal invites, data entry, or at least be made more efficient by centralising resources. Having an online platform where the public can access information on ongoing clinical trials, screen and recruit themselves could improve trial recruitment. Reducing the effort required by participants when collecting outcomes in trials could help minimise attrition e.g. use of wearable technology.

The creation of pseudo-anonymised copy of the entire electronic health records system for research, use of natural language processing technologies including mining semantic data from clinical notes; customised queries that allow clinical researchers to use Google-like search engines to find patients with particular phenotypes; automated generation of patient summaries etc. are just some of the innovative technologies that could make trial recruitment and measuring outcomes more efficient.

Secure ways of sending personal identifiable information between patients and researchers that also satisfy data protection regulations would make conducting a large-scale centralised trial feasible across the whole country or internationally. REDCap already made it feasible for me to recruit TASK participants remotely in our local health board. Verifying eligibility remotely for participants outside our health board without the costly set up of a local recruitment centre remains a big challenge. Innovative ways of confirming eligibility with the patient, the patient's primary or secondary care provider would be necessary to achieve our vision.

7.3 A final note

My thesis addresses the topic of anxiety, a common and debilitating complication affecting around a quarter of people after a stroke or TIA. Definitive evidence for its treatment is still unavailable. Efficient trials will enable clinical trialists to speed up the generation of high quality evidence for a range of treatments, which ultimately will improve patient care. This thesis represents merely my first step in designing scalable procedures to enable centralised large-scale RCTs to be conducted efficiently in the future. Building on what I have learnt from the feasibility testing, I will now refine the TASK-CBT intervention and the scalable TASK-RCT trial procedures in preparation for TASK-II, a large-scale RCT. The role of informatics specialists will be crucial as they continue to develop innovative technologies, with which I will apply in future trial design in order to achieve our vision of conducting efficient clinical trials.

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Appendices

Appendix A

Contents lists available at ScienceDirect

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A systematic review of anxiety interventions in stroke and acquired brain injury: Efficacy and trial design

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ABSTRACT

Objective: There is little randomized controlled trial (RCT) evidence to guide treatment for anxiety after stroke. We systematically reviewed RCTs of anxiety interventions in acquired brain injury (ABI) conditions including stroke and traumatic brain injury (TBI) in order to summarize efficacy and key aspects of trial design to help guide future RCTs.

Methods: We searched the Cochrane trial register, Medline, Embase, PsychInfo and CINAHL systematically up to August 2017. Two independent reviewers systematically selected studies and extracted data. We summarized the effect size, key study characteristics and sources of potential bias in trial design.

Results: 14 studies (12 stroke; one stroke & TBI; one TBI) with 928 participants were included. Meta-analysis of five psychotherapy comparisons favoured intervention over control (standardized mean difference (SMD): −0.41 [−0.79, −0.03], I^2 = 28%); Overall effect size of pharmacotherapy comparisons favoured intervention over control (SMD: −2.12 [−3.05, −1.18], I^2 = 89%). One comparison of mixed pharmacotherapy and psychotherapy favoured intervention over usual care (SMD: −4.79 [−5.87, −3.71]). One comparison favoured forest therapy versus urban control (SMD: −2.00 [−2.59, −1.41]). All positive studies carried high or unclear risk of bias. Sample sizes were small in all included studies.

Conclusions: There is low quality evidence to suggest that psychotherapy and pharmacotherapy may be effective interventions in the treatment of anxiety after stroke based on underpowered studies that carried high risk of bias. Large-scale well-designed definitive trials are needed to establish whether pharmacological or psychotherapy works. Our review highlighted key considerations for investigators wishing to design high quality trials to evaluate treatments for anxiety after stroke.

1. Introduction

Anxiety is a common neuropsychiatric complication of stroke with an estimated frequency between 20 and 25% [1]. There are two main subtypes of anxiety—phobic and generalized in non-stroke populations, requiring different treatment approaches. Phobic disorder is characterized by fear disproportionate to the threat posed by a well-defined situation, and marked avoidance of the situation [2]. Generalized anxiety disorder (GAD) presents with diffuse anxiety about events of daily life that is persistent and unremitting that the individual finds difficult to control [2]. In the general population, phobic disorder is treated with exposure techniques [3] whereas GAD responds to selective serotonin reuptake inhibitors (SSRI), short-term benzodiazepines and/or other cognitive behavioural therapy (CBT) techniques e.g. cognitive restructuring, problem solving [4,5]. Randomized controlled trials (RCTs) of anxiety intervention in stroke have not yielded any definitive evidence in a recent Cochrane review—only three trials (2 pharmacological, 1 relaxation CD) with 196 participants were included [6]. These had high risk of bias and were of small sample size. Aware of the lack of RCT evidence in anxiety after stroke we aimed to review systematically the wider evidence base encompassing both stroke and traumatic brain injury (TBI). To date, there is no evidence to suggest that pathophysiological mechanism underlying anxiety disorders differs from one acquired brain injury (ABI) condition to another. The last systematic review of anxiety interventions in TBI in 2007 included three studies, providing some evidence for CBT in acute stress disorder, and in improving generalized anxiety symptomology but these studies had small sample sizes and were done in mild TBI only [7]. The current review

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would enable us to extrapolate from one ABI to the other as these conditions have abrupt onset, result in varying degrees of brain damage, and transient or long-term neurological and neuropsychiatric impairments. Furthermore, summarizing the key considerations in trial design (anxiety subtype targeted, setting and timing of intervention and outcome measure), and the sources of potential bias would help guide trialists to design high quality trials to evaluate anxiety treatments in the future.

1.1. Aims

To evaluate the efficacy of anxiety treatments and to summarize key aspects of trial design, we systematically reviewed RCTs of interventions—psychotherapy, pharmacotherapy or other types, for anxiety disorders in ABI conditions including stroke—ischaemic, haemorrhagic or subarachnoid haemorrhage (SAH), and TBI.

2. Methods

We followed a pre-defined protocol in conducting this systematic review and reported our review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [8].

2.1. Searches and information sources

We searched electronically for RCTs on Medline (1946-18/8/17), Embase (1980-17/8/17), PsychInfo (1940-17/8/17), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (inception-16/10/17), the Cochrane Stroke Register (16/10/17), and the Cochrane Central Register of Controlled Trials (CENTRAL) (inception-16/10/17) using search strategies supplied by the trials search co-ordinator of the Cochrane Stroke Group (Supplement B). We reviewed the reference list of key systematic reviews to date to identify additional titles [6,7]. We contacted authors of eligible titles that were trial protocols, conference abstracts or trial register entries for published or unpublished primary data.

2.2. Inclusion criteria

We included RCTs that evaluated interventions designed to target anxiety symptoms/anxiety disorder as a primary outcome, with any comparator group (placebo, usual care, waitlist control, active comparator). We included RCTs that recruited participants aged 18 or over with ABI conditions: ischemic or haemorrhagic stroke; SAH, confirmed by brain imaging with or without a lumbar puncture; moderate-to-severe TBI as defined according to the Scottish Intercollegiate Guidelines Network [9]. We excluded mild TBI, a clinical group that is difficult to diagnose reliably [10]. Where studies were carried out in a mixed sample, we included only those that recruited over 70% of stroke/SAH/moderate-to-severe TBI. We excluded trials that recruited exclusively military veterans. No language restrictions were applied.

2.3. Data collection

Two reviewers (HYYC and RN) screened titles and abstracts independently and excluded ineligible titles. They assessed full text for eligibility and resolved discrepancies through discussion. A third reviewer (AJC) was consulted if a consensus could not be reached. They extracted data independently using an electronic data extraction form. HYYC collated final data. One reviewer (HYYC) assessed studies that were only available in Chinese.

2.4. Data extracted

We recorded key characteristics of the study population: ABI diagnosis, age, sex, exclusion of specific deficit, baseline anxiety level, and intervention type (e.g. psychotherapy, pharmacotherapy, other).

2.4.1. Quality assessment

We reported the level of bias across six domains of study design for the included studies: (A) random sequence generation, (B) allocation concealment, (C) blinding of participants and personnel, (D) blinding of outcome assessment (E) incomplete outcome data, and (F) selective reporting. We categorised the level of bias into 'low', 'high' or 'unclear' and recorded justification for our judgement for each domain in accordance with the Cochrane Risk of Bias Tool (http://methods.cochrane.org/bias/assessing-risk-bias-included-studies).

2.4.2. Efficacy of intervention

We estimated effect size for each comparison by calculating the standardized mean difference (SMD) with 95% confidence intervals (CI) using the mean and standard deviation (SD) of the post-intervention anxiety severity. Meta-analysis was carried out for studies of the same intervention type using inverse variance and random-effects models. All analysis was performed using the Cochrane Review Manager (RevMan) Version 5.3 [11]. Where data were not reported in study publication we contacted the corresponding authors for further information.

2.4.3. Key study characteristics and potential bias in trial design

We summarized the key study characteristics: anxiety type targeted, the setting and timing of intervention, outcome measures, the type of comparator, and ways that could have introduced or minimized potential bias in study design.

3. Results

The electronic searches yielded 8218 titles after removal of duplicates (Fig. 1). Of the 59 full text articles reviewed, we included 14 eligible studies with 928 participants. Sample size ranged from 17 to 206. Four studies were in Chinese [12–15]. No clear evidence of publication bias on funnel plot (Supplement C).

3.1. Characteristics of study population

Table 1 summarizes the characteristics of the 14 included studies. 12 studies recruited stroke patients only (ischaemic and primary haemorrhage) [12–23], one study recruited stroke and moderate-to-severe TBI [24], and one study recruited moderate-to-severe TBI only [25]. No study recruited patients with SAH. The mean age ranged from 48 to 72 years in studies of stroke patients only, and from 35 to 58 years in the two studies that included TBI patients. More men than women were recruited in all included studies. 12 studies excluded patients with communication difficulties due to aphasia or cognitive impairment [12–14,16–22,24,25]; one yoga exercise intervention excluded participants who were unable to ambulate independently [17]. Seven studies required participants to have a baseline diagnosis of anxiety disorder or 'emotional distress' either made on standardized diagnostic criteria e.g. Diagnostic Statistical Manual (DSM-IV TR), or by meeting a defined cut-off on a rating scale [12,13,19,22–25]. Six studies did not specify a baseline anxiety level for inclusion [14–18,20]. One study of a preventative intervention excluded the diagnosis of GAD on DSM-IV TR at baseline [21]. Studies used different anxiety rating scales at baseline and outcome assessment (Table 1): Hamilton Anxiety Rating Scale (HAMA) in five studies [12,13,15,21,23], Hospital Anxiety and Depression Scale-anxiety subscale (HADS-A) in three studies [19,20,25]; State-Trait Anxiety Inventory (STAI) in three studies [16–18]; Depression Anxiety Stress Scales (DASS) in one study [24]; Zung Self-rating Anxiety Scale (SAS) in one study [14]; Beck Anxiety Inventory (BAI) in one study [22].

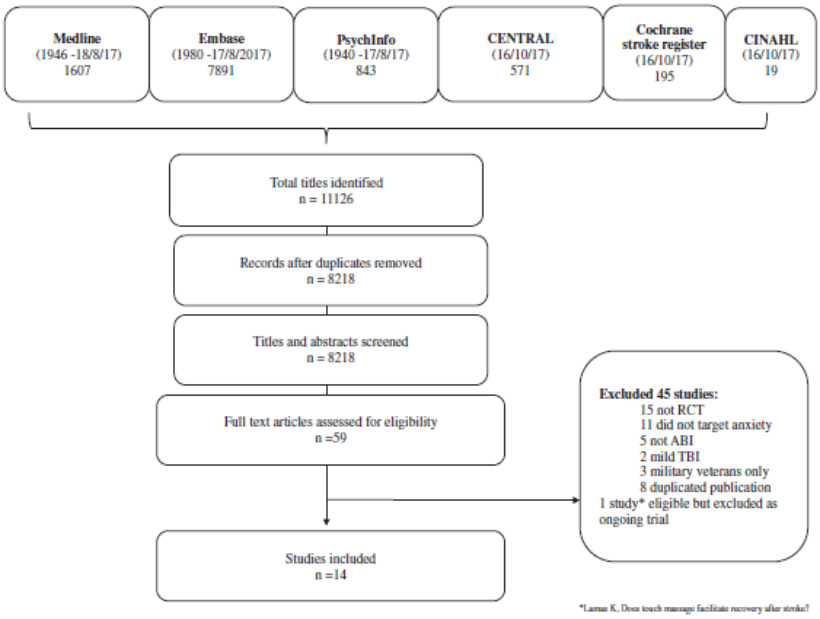

Fig. 1. PRISMA diagram of included studies.

3.2. Quality assessment

None of the 14 studies scored 'low' risk of bias across all six domains (A-F) of study design (Fig. 2). Three studies scored 'low' risk across five domains [20,21,25]. Two studies scored 'low' risk across four domains [22,24]. One studies scored 'low' risk across three domains [17]. Eight studies scored 'low' risk on fewer than three of the six domains [12–16,18,19,23], including six studies that scored 'high' risk or 'unclear' risk across all six domains [12–16,23].

3.3. Efficacy of intervention

The 14 included studies provided 19 comparisons: eight psychotherapy [14,20–22,24,25], five pharmacotherapy [12,13,15,21], one combined pharmacotherapy and psychotherapy [12], two exercise [16,17], and three other interventions [18,19,23]. We carried out meta-analyses for psychotherapy and pharmacotherapy studies.

3.3.1. Psychotherapy

Six studies provided eight comparisons of psychotherapy interventions, the content of each is summarized in Table 1. Data were not available for three comparisons after contacting study authors. Meta-analysis of the five comparisons showed an overall positive effect favouring psychotherapy intervention over control (SMD: −0.41 [95%CI -0.79, −0.03]). I^2 statistic of 28% suggests a low-to-moderate level of heterogeneity across studies (Fig. 2). The only study that demonstrated an effect favouring *'psychotherapy'* over usual care [14] received 'unclear' risk of bias across all six domains of study design. The remaining four neutral comparisons (one '*brief positive psychotherapy*' versus usual care(24), one '*motivational interviewing & CBT*' versus usual care [25]; one '*non-directional counselling & CBT*' versus usual care [25], one '*computerised CBT*' versus computerised cognitive remediation therapy [22]) received 'low' risk of bias across at least three domains of study design; all had small sample sizes. One comparison not included in our analysis reported that group receiving placebo was four times more likely to develop GAD compared to 'problem-solving' therapy (adjusted hazard ratio: 4.00 [95%CI 1.84, 8.70]) [21]. The other two comparisons not included in our analysis reported a non-statistically significant reduction in adjusted mean HADS-anxiety score with psychotherapy: 'coping skills' vs usual care (− 0.5, [95%CI −2.0, 1]); 'self-management' vs usual care (− 0.6, [95%CI −2.0, 0.8]) [20].

3.3.2. Pharmacotherapy

Four studies provided five comparisons of pharmacotherapy versus control, data were not available in one comparison after contacting study author [21]. Meta-analysis of these four comparisons showed an overall effect favouring pharmacotherapy intervention over control (SMD: −2.12 [95%CI −3.05, −1.18]). I^2 statistic of 89% suggests a high level of heterogeneity across studies. Two of these comparisons were between paroxetine, an SSRI and usual care [12,13]. One comparison was between imipramine, a tricyclic antidepressant and usual care [13]. One study compared buspirone, an azapirone anxiolytic with usual care [15]. All four comparisons are from three studies which scored 'high' risk or 'unclear' risk of bias across all domains of study design. The study without available data for analysis reported an increased reported that group receiving placebo was four times more likely to develop GAD compared to escitalopram (adjusted hazard ratio: 4.95 [95%CI 1.54–15.93]) [21].

3.3.3. Combined pharmacotherapy and psychotherapy

One comparison of combined paroxetine and psychotherapy with usual care demonstrated a large effect favouring combined therapy (SMD: −4.79 [95%CI −5.87, −3.71]) [12]. This study scored 'unclear' and 'high' risk of bias across all six domains of study design.

3.3.4. Exercise intervention

Two studies evaluated exercise interventions, One study compared yoga and exercise with exercise only and showed a neutral effect [17].

Table 1
Characteristics of included studies.

Study (by year of publication)	ABI diagnosis	Anxiety disorder/type targeted	Eligible time since injury	Setting	Exclusion of specific deficit (e.g. speech)	Sample size	Type of intervention (I) and control (C), number randomized (n) ('*description*')	
							I	C
Zhang et al. [14]	Stroke	Unspecified	Not specified	Setting not given, China	NA	206	Psychotherapy (n = 103) '*Weekly sessions, each lasting 20-30 min, for 5-6 weeks, delivered by trained researcher using in-house manual*'	Usual care (n = 103) '*Usual care*'
Ye et al. [13]	Stroke	'Mixed anxiety and depression'	Not specified	Neurology inpatient, China	Impairment of comprehension	90	1) Paroxetine (*n* = 31) '*20 mg daily for 12 weeks*' 2) Imipramine (n = 32) '*incremental regime of 50-150 mg daily for 12 weeks*'	Routine care (n = 30) 'Routine care: for 12 weeks'
Wang et al. [12]	Stroke	'Mixed anxiety and depression'	'Acute' stroke	Neurology inpatient, China	Aphasia; severe cognitive impairment	81	1) paroxetine (n = 27) '*20 mg daily for 6 weeks*' 2) paroxetine + psychotherapy (n = 27) '*Paroxetine 20 mg daily + weekly psychotherapy session lasting 30-60 min, delivered by psychiatrist for 6 weeks*'	Routine care (n = 27) '*routine stroke care*'
Zhang et al. [15]	Stroke	Unspecified	Not specified	Neurology inpatient, China	NA	94	Buspirone butylbromide (n = 47) '*A 2-week course of buspirone butylbromide (first week 20-30 mg/day, second week 40-60 mg per day)*'	Routine care (n = 47) '*Routine care*'
Wu and Liu [23]	Stroke	'Post-stroke neurosis'	Not specified	Outpatient, China	Aphasia; cognitive impairment	67	Acupuncture (n = 34) '*acupuncture once a day for 2 courses with 15 times as one course*'	Alprazolam (n = 33) '*0.4–0.8 mg 3 times a day for 4 weeks*'
Aidar et al. [16]	Ischaemic stroke	Unspecified	≥ 1 year	Community, Portugal	Aphasia	29	Resistance exercise training (n = 14) '*4 familiarization sessions + 3 pre-treatment sessions + 12 treatment sessions delivered 3 times a week, focused on walking & strength training. Duration: each session lasted 45–60 min with minimum 48-hour rest between sessions.*'	Usual care (n = 15) '*continue normal daily activities*'
Chan et al. [17]	Stroke	Unspecified	≥ 6 months	Community, Australia	Unable to follow 2-stage commands; unable to ambulate for 10 m or more	17	*Yoga and exercise (YEX)* (n = 9) '*90-minute group yoga class once per week for 6 weeks plus 24 individual 40-min home practice sessions + Exercise (EX)*'	Exercise only (EX) (*n* = 8) '*50-minute exercise class, once per week for 6 weeks*'
Hsieh et al. [25]	Moderate-to-severe TBI	Unspecified	Not specified	Community, Australia	Language impairment	27	1) Motivational interviewing (MI) + Cognitive Behavioural Therapy (CBT) (n = 9) '*3 weekly MI sessions + 9 weekly CBT sessions*' 2) Non-directional counselling (NDC) + CBT (n = 10)	Usual care and waitlist (n = 8) '*offered CBT after waitlist period*'

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Table 1 *(continued)*

Study (by year of publication)	ABI diagnosis	Anxiety disorder/type targeted	Eligible time since injury	Setting	Exclusion of specific deficit (e.g. speech)	Sample size	Type of intervention (I) and control (C), number randomized (n) (*'description'*)	
							I	C
							'3 weekly NDC sessions + 9 weekly CBT sessions' *Both delivered by clinical psychologist or clinical neuropsychologist*	
Mikami et al. [21]	Stroke	Generalized anxiety disorder (GAD)	Within 3 months	Community, USA	Severe comprehension deficits	149	1) Escitalopram (n = 47) *'5 or 10 mg per day for 12 months'* 2) Problem solving therapy (PST) (n = 53) *'manual-based, 6 treatment sessions (weeks 1, 2, 3, 4, 6 and 10), plus 6 reinforcement sessions (months 4, 5, 6, 8, 10 and 12)'*	Placebo (n = 49) *'Placebo pills'*
Hoffmann et al. [20]	Stroke	Unspecified	Not specified	Stroke unit inpatient & community, Australia	Communication difficulties/cognitive impairment	33	1) Coping skills (n = 11) *'cognitive and behavioural exercises, delivered by clinical psychologist'* 2) Self-management (n = 12) *'information provision and activities to learn problem solving skills, delivered by occupational therapist'*	Usual care (n = 10) *'multidisciplinary care on stroke unit'* *Both interventions 1) and 2) consist of 8 one-hour face-to-face sessions, with first 2 sessions delivered pre-discharge, and remaining sessions at patient's home*
Cullen et al. [24]	Stroke; moderate-severe TBI	'Emotional distress—anxiety and/or depression'	3–36 months	Outpatient clinic, UK	Significant communication impairments	27	Brief positive psychotherapy (n = 14) *'One-to-one weekly sessions with psychologist for 8 weeks—Psychoeducation about ABI and positive psychology (Week 1), therapeutic exercises and homework (Weeks 2–7), midpoint review at (Week4), final review and plan for maintenance (Week 8)'*	Usual care (n = 13) *'Within clinical service'*
Golding et al. [19]	Stroke	Unspecified	Not specified	Community, UK	Unable to complete telephone questionnaire	21	I: relaxation CD *'self-help autogenic relaxation CD, five times per week for a month with diarly sheets; each session 20-min in length, instructions on body awareness'*	Waitlist
Chun et al. [18]	Stroke	Unspecified	At least 1 year after stroke onset	Community, Korea	Severe cognitive or communication impairment	59	I: Forest therapy *'4-day and 3-night program at recreational forest area, consisting of 1) promoting positive emotion through meditation, 2) experiencing the forest through all five sense and 3) walking in the forest'*	Urban group *'stay in a hotel, with similar mediation and walking activities in the urban area'*

Table 1 *(continued)*

Study (by year of publication)	ABI diagnosis	Anxiety disorder/type targeted	Eligible time since injury	Setting	Exclusion of specific deficit (e.g. speech)	Sample size	Type of intervention (I) and control (C), number randomized (n) ('*description*')	
							I	C
Simblett et al. [22]	Stroke	'Emotional distress—anxiety and/or depression'	Within 5 years	Community, UK	Impairment of comprehension; visual or auditory problem that would interfere participation and could not be corrected	28	Computerised cognitive behavioural therapy (cCBT) (n = 19) '*An 8-module online course- 'Beating the Blues', one module per week for 8 consecutive weeks*' *Both the intervention and active control are delivered* via *computer, facilitated by a researcher* via *telephone/email/ face-to-face*	Computerised Cognitive remediation therapy (cCRT) (n = 9) '*An 8-module online course- 'ForamenRehab', one module per week for 8 consecutive weeks*'

Study (by year of publication)	Age (mean (SD))		Female (%)		Baseline anxiety level (measure: mean (SD))	Time of intervention since injury (mean (SD))	
	I	C	I	C		I	C
Zhang et al. [14]	NA	NA	NA	NA	SAS I) 34(8) C) 31 (8)	NA	NA
Ye et al. [13]	1) 58.04 (8.28) 2) 56.9 (11.36)	59.21 (9.52)	1) 26 2) 37	43	HAMA 1) 18.2 (4.6) 2) 18.9 (4.4) C) 17.9 (2.24) Required diagnosis of mixed anxiety and depression on CCMD	NA	NA
Wang et al. [12]	1) 62.4 (6.1) 2) 64.0 (5.3)	63.2 (5.7)	1) 48 2) 48	48	HAMA 1) 14.0 (2.8) 2) 13.9 (2.9) C) 13.8 (2.8) Required diagnosis of mixed anxiety and depression on CCMD	1) 21.7 days (4.9) 2) 22.0 days (4.7)	21.4 days (5.0)
Zhang et al. [15]	57.8 (6.4)	59.2 (5.8)	36	38	HAMA I) 22.7 (5.2) C) 22.5 (4.3)	NA	NA
Wu and Liu [23]	48–72	49–70	44	48	HAMA I) 22.31 (3.1) C) 22.3 (3.2) Required diagnosis of post-stroke neurosis on ICD-10	Range: 15–53 days	Range: 15–61 days
Aktar et al. [16]	51.7 (8.0)	52.5 (7.7)	45	31	STAI (data not available)	NA	NA
Chan et al. [17]	67.1 (15.4)	71.7 (12.7)	13	17	STAI-state I) 36.8 (11.6) 2) 37 (5.8)	6.4 years (3.0)	11.2 years (5.8)
Hsieh et al. [25]		35.6 (9.8)		13			23.0 months (18.5)

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Table 1 *(continued)*

Study (by year of publication)	Age (mean (SD))		Female (%)		Baseline anxiety level (measure: mean (SD))	Time of intervention since injury (mean (SD))	
	I	C	I	C		I	C
	1) 41.8 (15.2) 2) 36.4 (14.1)		1) 22 2) 30		HADS-A 1) 11.9 (3.3) 2) 13.0 (5.0) C) 11.8 (4.3) DSM-IV TR anxiety disorder or adjustment issues required	1) 37.2 months (45.4) 2) 50.4 months (89.7)	
Mikami et al. [21]	1) 61.5 (13.7) 2) 68.3 (10.4)	64.8 (13.5)	1) 36 2) 45	33	HAMA 1) 7.1 (5.6) 2) 8.3 (5.4) C) 6.8 (4.4) Excluded DSM-IV TR GAD diagnosis	NA	NA
Hoffmann et al. [20]	1) 63.6 (13.0) 2) 60.8 (11.7)	57.0 (14.2)	1)36 2) 25	40	HADS-A 1) 5.3 (2.9) 2) 5.7 (0.5) C) 8.4 (3.1)	NA	NA
Cullen et al. [24]	Median 54.0 (IQR 46.0–59.0)	median 58.0 (IQR 56.0–68.0)	36	39	DASS-21 anxiety I) 17.6 (9.7) C) 21.1 (9.4) Had to score moderate-to-above on at least depression or anxiety subscale on DASS-21	Median: 5.8 months (IQR 3.5–8.2)	Median: 5.6 months (IQR 3.1–8.4)
Golding et al. [19]	67.8 (7.5)	62.4 (8.4)	40	50	HADS-A I) 10.9 (3.4) C) 10.5 (3.5) Had to score at least 6 on HADS-A	118 months (101)	70 months (70)
Chun et al. [18]	62.1 (8.3)	59.5 (9.7)	37	28	STAI I) 38.1 (11.0) C) 34.3 (12.1)	140 months (90)	153 months (84)
Simblett et al. [22]	62.1 (11.4)	64.6 (8.1)	47	11	BAI I) 11.2 (7.6) C) 8.3 (6.2) Required 'emotional distress': BDI > 13 or BAI > 7	Median: 1.19 years (IQR 0.5–1.1)	Median: 0.89 years (IQR 0.6–4.1)

I indicates intervention; C, control; n, number; SD, standard deviation; IQR, interquartile range; NA, data not available; DASS, Depression Anxiety Stress Scales; DSM-IV, Diagnostic Statistical Manual of Mental Disorders, fourth edition; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; CCMD, Chinese Classification of Mental Disorders, third version; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Rating Scale for Depression; SAS, Zung Self-Rating Anxiety Scale. STAI, State Trait Anxiety Inventory.

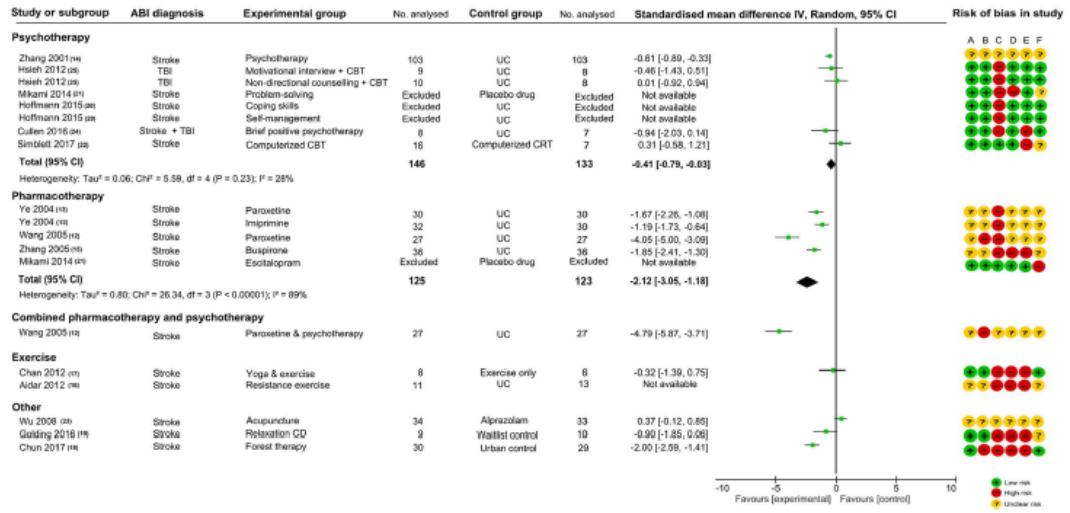

Fig. 2. Effect sizes, meta-analysis, and bias assessment for included studies.
ABI, acquired brain injury; IV, inverse variance; CI, confidence intervals; UC, usual care; TBI, traumatic brain injury; CBT, cognitive behavioural therapy; CRT, cognitive remediation therapy;
Risk of bias.
(A) Random sequence generation (selection bias).
(B) Allocation concealment (selection bias).
(C) Blinding of participants and personnel (performance bias).
(D) Blinding of outcome assessment (detection bias).
(E) Incomplete outcome data (attrition bias).
(F) Selective reporting (reporting bias).

One study on resistance exercise reported lower state anxiety favouring resistance exercise over usual care but data were unavailable for calculating SMD after contacting the study author [16]. Both studies had small sample sizes. The yoga study scored 'low' risk of bias across three domains of study design and the study on resistance exercise scored 'high' and 'unclear' risk of bias across all six domains.

3.3.5. Other therapies

One study compared acupuncture with alprazolam [23], one study compared relaxation CD with waitlist control [19]. Both of these studies were neutral. The study of acupuncture scored 'unclear' risk of bias across all six domains, and the study of relaxation CD scored 'high' risk of bias across more than three domains of study design. One study compared forest therapy with urban control and demonstrated an effect favouring forest therapy (SMD: − 2.00 [− 2.59, − 1.41]). This study scored 'high' risk of bias on four domains of study design. All three studies had small sample sizes.

3.4. Key study characteristics

3.4.1. Anxiety subtype targeted

One study specified GAD as the target of its interventions (escitalopram; problem solving therapy) [21]. No study targeted phobic disorder. Two studies of pharmacotherapy (SSRI, TCA), and combined pharmacotherapy (SSRI) and psychotherapy specified a diagnosis of 'mixed anxiety and depression' as an inclusion criterion and had positive results [12,13]. Two studies of psychotherapy (brief positive psychotherapy; computerised CBT) targeted 'emotional distress'—anxiety and/or depression and were neutral [22,24]. One study of acupuncture and alprazolam targeted 'post-stroke neurosis' which is now a defunct diagnosis [23]. The remaining eight studies targeted 'anxiety' without subtyping [14–20,25], three of them were positive [14,15,18].

3.4.2. Setting of intervention

Seven studies were carried out in the community [16–19,21,22,25], three studies in an inpatient setting [12,13,15], two in outpatient clinic [23,24], and one commenced in an inpatient setting then continued in the community [20]. One study did not report setting of the intervention [14]. Only one community-based study was positive [18]. All three inpatient studies and the study with unknown setting were positive.

3.4.3. Timing of intervention since injury

Seven studies specified time since injury as an inclusion criterion: 'acute stroke' [12], within 3 months [21]; between 3 and 36 months [24]; anytime within 5 years [22]; at least 6 months [17]; at least one year [16,18]. The actual time of intervention since injury in the studied sample ranged from 15 days to 13 years. Of the five positive studies, three did not report timing of intervention since injury in studied samples, one study reported intervention at 21 days from injury [12], and one reported intervention at 140–150 months [18].

3.4.4. Timing of outcome measures

Eight studies measured anxiety outcome at the end of the intervention [12,13,15–18,23,25]. Other studies measured primary outcome at various time points post-intervention: 2 weeks; 8 weeks; 12 weeks; 12 months. Four of the five positive studies measured primary outcome at the end of intervention [12,13,15,18] and one measured at two weeks post-intervention [14].

3.4.5. Comparator

'Usual care' was the most commonly used control condition. Four studies used an active comparator [17,18,22,23] and one study used a placebo control [21]. Four of the five positive studies used 'usual care' as control conditions (12–15) and one used an active control [18].

3.5. A summary of sources of potential bias in study design

3.5.1. Random sequence generation

Studies scoring 'unclear' risk of bias in this domain only reported that patients were randomly allocated but did not give detail on how, and by whom the randomisation sequence was generated. Studies scoring 'low' risk reported the type of randomisation carried out e.g. computerised randomisation, stratified randomisation with blocking, random number generator, and by whom the randomisation was performed e.g. person external to the study/independent of the study.

3.5.2. Allocation concealment

Studies scoring 'high' risk of bias reported that it was the study personnel who performed randomisation and provided the treatment allocation. Studies scoring 'low' risk reported methods that would prevent the study team from knowing the allocation in advance e.g. allocation informed via mailed letters by external person who carried out randomization, study personnel were blinded to randomization block length with randomisation performed externally, use of opaque/sealed envelopes pre-filled by person independent of the study.

3.5.3. Blinding of participants and personnel

Most studies scored 'high' risk in this domain as blinding of participants was rarely attempted. The most common comparator group was 'usual care'. We considered participant blinding sufficient in the study that used computerised CRT as a comparator of computerised CBT, and the study that used placebo as a comparator of escitalopram.

3.5.4. Blinding of outcome assessment

Studies scoring 'high' risk reported outcome assessment being performed by the same study personnel that delivered the interventions. Studies that scored 'low' risk reported methods to blind outcome assessment e.g. a second research assistant performed outcome assessment using a standard script to prevent unblinding, use of self-rated questionnaires and data entry by blinded assessor.

3.5.5. Incomplete outcome data

All studies scoring 'high' risk lost follow-up data (attrition ranged from 2 to 22%) and did not perform intention-to-treat analysis. Reasons for attrition were: personal reasons, additional health concerns/injury unrelated to intervention, improved mood, other commitments, lack of time, found it distressing to talk about difficulties, wish to discontinue involvement.

3.5.6. Selective reporting

We examined the published trial protocol, if available, for each included study to detect whether selective reporting was present. One study scoring 'high' risk reported results on anxiety from the same study in an earlier publication that evaluated intervention for depression prevention.

4. Discussion

Our findings suggest efficacy of psychotherapy and pharmacotherapy interventions in the treatment of anxiety after ABI. The positive effect sizes were driven entirely by studies of low quality. These findings alone are not definitive evidence to guide treatment of anxiety after stroke. Compared to previous systematic reviews in stroke and TBI [6,7] we opted to include studies from a broader ABI population encompassing stroke (ischaemic, primary haemorrhage, SAH) and moderate-to-severe TBI, and included a wider continuum of baseline anxiety levels (i.e. not limited to patients with a baseline anxiety diagnosis). This approach led to more studies to be included in our review, and enabled us to meta-analyse results for the same type of anxiety interventions for the first time. Furthermore, we found studies that were better reported and of better quality which were excluded in the previous reviews. This enabled us to summarize key aspects of trial design and measures to minimize bias in order to help guide trialists in designing high quality RCTs in the future.

4.1. Intervention design

4.1.1. Anxiety subtype targeted

Studies have targeted 'mixed anxiety and depression', 'emotional distress (anxiety and/or depressive symptoms)', or 'anxiety'. Only one study specified the prevention of GAD as the target of intervention. No studies targeted phobic disorder.

Phobic disorders e.g. agoraphobia may be more common than GAD after stroke [1]. Intervention design should reflect the treatment approaches known to be effective at treating these anxiety subtypes in non-stroke populations. Anxiety with a phobic element invariably requires some form of behavioural therapy with exposure work, while generalized anxiety is treated with other CBT techniques e.g. cognitive restructuring, problem solving, and/or medications e.g. SSRI.

Although the content of psychotherapy interventions varied across our included studies, the majority of interventions consisted of some form of, or a combination of psychoeducation, skills learning e.g. problem solving, positive psychology, therapeutic exercises, and CBT. Interventions for anxiety after stroke should encompass components that aim to address the symptomology of both phobic and generalized anxiety subtypes.

A variety of anxiety rating scales were used to assess primary outcome in our included studies. These are validated for generalized anxiety and none for the phobic subtype. The choice of outcome measures should reflect both types of anxiety symptomology given that phobic disorder is also common after stroke.

4.1.2. Setting and timing of intervention, and timing of outcome measures

Most of the positive studies were carried out in an inpatient setting and measured primary outcome immediately post-intervention. This approach does not address the consistent finding from other studies that anxiety continues to be frequent at six-months or more post-stroke [1] and cannot generalize to patients who have returned to living in the community. An anxiety intervention should aim to relieve anxiety and its debilitating impact on stroke patients in the long-term. Determining the best time of outcome measure should be based on this goal, and be balanced against the feasibility of study procedures to ensure completion of long-term follow-up. We suggest that outcome measures should be taken at the end of the intervention and then after a period with no treatment to see whether any benefits are sustained.

4.2. Measures to minimize bias

Most of the positive studies in our review were poorly reported across all aspects of study design on the Cochrane bias assessment tool. All trialists should adhere to standardized reporting guidelines e.g. CONSORT checklist on RCTs, and the TiDier (Template for Intervention Description and Replication) checklist when evaluating complex interventions, both of which can be found on the EQUATOR (Enhancing the QUAlity and Transparency of health Research network) website: http://www.equator-network.org/reporting-guidelines/consort/.

4.2.1. Participant blinding and control conditions

Most of our included studies did not attempt participant blinding. 'Usual care' was the commonest comparator in our review and in four out of the five positive studies. The description of what constituted 'usual care' was minimal across our included studies. 'Usual care' and waitlist controls have been shown to exaggerate effect size in meta-analyses of trials evaluating psychotherapy [26]. A recently published transparent decision framework help guide trialists select the appropriate type of control based on several factors: participants' interests (expected benefit, or harm or worsening of symptoms induced by the

control condition), the researchers' interests (available resources, maximizing validity of findings), and trial purpose (e.g. phase 2, phase 4) [27]. Placebo is the gold-standard comparator for pharmacotherapy intervention. In a trial of psychotherapy or other non-pharmacological intervention, an active comparator or another established treatment that is known to be effective and widely available in the 'real world' would be more appropriate as a control in phase 3 or phase 4 (pragmatic/real world) trials [27].

4.2.2. Other measures to minimize bias

Some included studies provided examples of good practice in minimizing bias in other domains: external personnel to randomize patient; allocation concealment to ensure study personnel cannot foresee allocation while recruiting; use of outcome assessors blinded to allocation; use of standard script at telephone follow up to prevent unblinding; use of self-completed outcome measures; data input by blinded external assessor; reporting missing data and methods for handling missing data; intention-to-treat analysis; publishing protocol on trial registries. Studies should also provide detailed description of the experimental intervention and control condition to ensure standardized procedures are given to all participants of each arm e.g. use of manuals. Adherence to the allocated treatment and any deviation from standardized procedures should be recorded and reported.

4.3. Study limitations

Data for calculating SMDs were missing in four comparisons despite contacting corresponding authors. We included one mixed ABI (strokes in > 85% of intervention and control groups), and one TBI-only samples. Almost all studies excluded patients who had communication impairments e.g. dysphasia, cognitive impairment, and varied in settings, timing since injury, timing of outcome measures, limiting the generalizability of our findings.

4.4. Considerations for future studies

Compared to pharmacological interventions, psychological or behavioural interventions pose unique challenges in trial methodology, both in its execution and in bias minimization. While the current review cannot provide definitive evidence on efficacy of anxiety treatments in stroke due to poor study quality and small sample sizes of the included studies, we provided a summary of key considerations in trial design (anxiety type targeted, setting, timing of intervention and outcome measure, methods to minimize bias) to guide trialists and clinicians on what would constitute a high quality RCT. High quality definitive RCTs of sufficient sample size are now warranted to evaluate psychotherapy and pharmacotherapy interventions in the treatment of anxiety after stroke.

5. Conclusion

There is low quality evidence to suggest psychotherapy and pharmacotherapy may be effective interventions in the treatment of anxiety after stroke. However, the evidence is from underpowered studies that carried high risk of bias. Large-scale well-designed definitive trials are needed to establish whether pharmacotherapy or psychotherapy works. Our review highlighted key considerations for investigators wishing to design high quality trials to evaluate treatments for anxiety after stroke.

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Appendix B

Stroke
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Anxiety After Stroke: The Importance of Subtyping

Ho-Yan Yvonne Chun, William N. Whiteley, Martin S. Dennis, Gillian E. Mead and Alan J. Carson

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Anxiety After Stroke
The Importance of Subtyping

Ho-Yan Yvonne Chun, MBBS; William N. Whiteley, PhD; Martin S. Dennis, MD; Gillian E. Mead, MD; Alan J. Carson, MD

Background and Purpose—Anxiety after stroke is common and disabling. Stroke trialists have treated anxiety as a homogenous condition, and intervention studies have followed suit, neglecting the different treatment approaches for phobic and generalized anxiety. Using diagnostic psychiatric interviews, we aimed to report the frequency of phobic and generalized anxiety, phobic avoidance, predictors of anxiety, and patient outcomes at 3 months poststroke/transient ischemic attack.

Methods—We followed prospectively a cohort of new diagnosis of stroke/transient ischemic attack at 3 months with a telephone semistructured psychiatric interview, Fear Questionnaire, modified Rankin Scale, EuroQol-5D5L, and Work and Social Adjustment Scale.

Results—Anxiety disorder was common (any anxiety disorder, 38 of 175 [22%]). Phobic disorder was the predominant anxiety subtype: phobic disorder only, 18 of 175 (10%); phobic and generalized anxiety disorder, 13 of 175 (7%); and generalized anxiety disorder only, 7 of 175 (4%). Participants with anxiety disorder reported higher level of phobic avoidance across all situations on the Fear Questionnaire. Younger age (per decade increase in odds ratio, 0.64; 95% confidence interval, 0.45–0.91) and having previous anxiety/depression (odds ratio, 4.38; 95% confidence interval, 1.94–9.89) were predictors for anxiety poststroke/transient ischemic attack. Participants with anxiety disorder were more dependent (modified Rankin Scale score 3–5, [anxiety] 55% versus [no anxiety] 29%; $P<0.0005$), had poorer quality of life on EQ-5D5L, and restricted participation (Work and Social Adjustment Scale: median, interquartile range, [anxiety] 19.5, 10–27 versus [no anxiety] 0, 0–5; $P<0.001$).

Conclusions—Anxiety after stroke/transient ischemic attack is predominantly phobic and is associated with poorer patient outcomes. Trials of anxiety intervention in stroke should consider the different treatment approaches needed for phobic and generalized anxiety. (***Stroke*. 2018;49:556-564. DOI: 10.1161/STROKEAHA.117.020078.**)

Key Words: anxiety ■ ischemic attack, transient ■ neuropsychiatry ■ phobic disorders ■ stroke

Anxiety is common, affecting around a quarter of stroke[1] and nearly a third of transient ischemic attack (TIA).[2] It can hamper stroke rehabilitation effort and prevent patients from returning to their usual activities. Despite earlier observations that phobic anxiety might be present after stroke,[3–5] intervention studies have treated anxiety poststroke as one unitary phenomenon and evaluated general approaches, such as relaxation and antidepressants,[6] which are unlikely to be effective in phobic anxiety. Clinical trials have not yielded any definitive evidence to guide treatment for anxiety after stroke.[6] It is well recognized in nonstroke populations that phobic disorder and generalized anxiety disorder (GAD) need different treatment approaches.

Phobic and Generalized Anxiety

Phobic anxiety is characterized by a disproportionate fear of well-defined situations or stimuli.[7] Exposure to the feared situation triggers unpleasant anxiety symptoms, accompanied by marked avoidant behavior of that feared situation: the hallmark of phobic anxiety.[7] Although avoidant behavior may relieve anxiety in the short term, it can become disabling if the behavior becomes consolidated through conditioning; for example, becoming housebound in agoraphobia as a result of learning to associate danger with leaving house. Treatment of phobic disorders requires systematic, repeated, hierarchical exposure to the specific anxiety-provoking stimulus.[8] By contrast, GAD is diffuse and unremitting, characterized by persistent and multiple worries; for example, finances, health, and an inability to stop worrying.[7] Selective serotonin-reuptake inhibitors, benzodiazepines (in short term only), and other cognitive behavioral therapy (CBT) techniques, for example, cognitive restructuring and problem solving, are effective at treating GAD.[9,10]

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Our Aims

To determine the target for anxiety treatment after stroke, we need to know the proportions of anxiety subtypes; if phobic, the specific stimuli; the predictors for anxiety; the impact of anxiety on functional outcomes and quality of life. We aimed to report (1) the frequency of phobic disorder and GAD at 3 months after stroke and TIA, (2) avoidant behavior of specific anxiety-provoking situations, (3) the predictors of anxiety, and (4) the associations with dependence, quality of life, and social participation.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request as per the journal's Transparency and Openness Promotion Guidelines.

Sampling and Recruitment

Prospective Recruitment

We screened consecutive eligible patients admitted to the acute stroke unit and TIA clinics in National Health Service Lothian—the sole provider of stroke and TIA services for the city of Edinburgh, Midlothian, and East Lothian regions in Scotland, between September 9, 2015, and June 28, 2016. We included participants who (1) were aged ≥18, (2) had a new clinical diagnosis of stroke or definite or probable TIA, (3) had mental capacity to give informed consent, and (4) were able to communicate in English on the telephone. We excluded patients with subarachnoid hemorrhage, subdural and extradural hematoma, ocular TIA, patients at terminal stage of life, or who were difficult to follow-up–no fixed abode, current illicit, or alcohol dependence

Definitions of Stroke and TIA

We used clinical diagnosis of stroke or TIA made by consultant stroke clinicians according to the following: stroke—the sudden loss of focal cerebral function, lasting ≥24 hours, thought to be caused by an inadequate blood supply to part of the brain (ischemic stroke), or spontaneous hemorrhage into the brain substance (primary intracerebral hemorrhagic), where brain imaging was normal or showed evidence of recent ischemia or hemorrhage[11]; TIA—a clinical time-based definition of symptoms lasting <24 hours; TIA was definite when a diagnosis of TIA was the only one considered for the symptoms and probable when a TIA was the most likely of several differential diagnoses.

Baseline Characteristics

We used hospital electronic health records to gather data on age, sex, diagnosis on discharge, vascular territory of stroke/TIA, and the National Institutes of Health Stroke Scale score—a measure of neurological impairment on admission.[12] We assigned a National Institutes of Health Stroke Scale of zero to all TIAs. We recorded whether the participants lived alone prestroke or TIA, had a history of stroke or ischemic heart disease, and past diagnosis of anxiety or depression by checking the electronic heath records first, then confirmed at the time of interview.

Assessment of Anxiety and Other Neuropsychiatric Disorders

At 3 months, a trained member of medical staff (H.-Y.Y.C.) performed a semistructured psychiatric interview (SCID) using the telephone version of the Structured Clinical Interview for Diagnostic Statistical Manual-IV-Text Revision of mental disorders.[13] The SCID has fair-to-excellent interrater agreement for diagnosing both anxiety disorders and depression between experienced and newly trained clinicians[14] and between its telephone and face-to-face versions.[15] The following conditions were screened using the relevant SCID modules: panic disorder, agoraphobia, social phobia, specific phobia, GAD, obsessive-compulsive disorder, post-traumatic stress disorder (PTSD), and minor and major depressive episodes. All SCID diagnoses were made according to the SCID coding system and after confirmation with a consultant neuropsychiatrist (A.J.C.) at weekly meetings. Participants who were unable to talk on the telephone had face-to-face interviews at home or at an outpatient clinic. We measured cognition with the telephone Montreal Cognitive Assessment.[16]

Assessment of Avoidant Behavior in Specific Anxiety-Provoking Situations

One week before the SCID interview, we sent the participant a Fear Questionnaire (FQ) for completion by post or online. The FQ consists of an agoraphobic subscale (5 items), a social phobia subscale (5 items), and a blood/injury phobia subscale (5 items).[17] Each item denotes a situation and is rated according to the level of avoidance from zero (would not avoid it) to 8 (always avoid it). We replaced the blood/injury items with 6 other specific situations that we encountered in our clinical practice—(1) physical exertion, (2) having sex, (3) being alone at home, and any of your normal day-to-day activities for fear of having (4) a headache (5) another stroke, or (6) a fall. During the interview, we also recorded positive responses to a list of 11 predefined anxiety-provoking stimuli, similar to the ones on the FQ (Table I in the online-only Data Supplement). We derived these additional anxiety-provoking stimuli from the shared clinical experience of our multidisciplinary stroke team in neuropsychiatry and postacute stroke settings.

Potential Predictors for Anxiety Disorder at 3 Months After Stroke/TIA

We prespecified age, sex, living alone prestroke/TIA, and a past diagnosis of anxiety or depression as potential predictors for having anxiety disorder at 3 months after stroke/TIA.

Measures of Dependence, Quality of Life, and Social Participation

Measures of dependence, quality of life, and social participation were completed at the time of SCID with the modified Rankin Scale,[18] the EuroQoL-5D5L,[19] and the Work and Social Adjustment Scale.[20]

Statistical Analyses

We used descriptive statistics to summarize data, exact confidence intervals for proportions, and univariable and multivariable logistic regression to calculate unadjusted and adjusted odds ratios for associations. Group differences were assessed using univariable logistic regression, *t* tests, and Mann–Whitney *U* tests as appropriate to data type. Only returned FQs were analyzed for avoidant behavior. All items on the online questionnaire must be scored to permit submission, preventing any unscored items. Any unscored item on a returned postal questionnaire was given the most conservative interpretation and imputed zero, assuming that the item was irrelevant or did not elicit any anxiety symptoms. We performed all statistical analyses using STATA14.[21] We aimed for a target sample size of ≈200 to achieve a desired precision of ±0.05 around our estimated frequency of poststroke anxiety of 0.20.

Reporting Standards and Ethics Approval

We reported the study in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines. We obtained approval from the South East Scotland Research Ethics Committee (15/SS/0087) on September 1, 2015. All participants gave written informed consent.

Results

We recruited 201 participants between September 9, 2015, and June 28, 2016. Twenty-six of 201 participants did not have

Table 1. Baseline Characteristics of Sample, by Anxiety Disorder at 3 Months

	Prospective Cohort		SCID Diagnosis				Univariable Logistic Regression		
	All		Any Anxiety Disorder		No Anxiety Disorder				
No. of Patients	175		38	22%	137	78%	OR	95% CI	Likelihood Ratio Test
Demographics									
Age, y; mean (SD)	69.6	(11.6)	64.2	(12.3)	71.0	(10.9)			
Age group, y									
<65	62	35%	23	61%	39	28%	1		*P*=0.001*
65–75	55	31%	6	16%	49	36%	0.21	0.08–0.56	
>75	58	33%	9	24%	49	36%	0.31	0.13–0.75	
Sex									
Women	70	40%	18	47%	52	38%	1.47	0.71–3.04	*P*=0.298
Men	105	60%	20	53%	85	62%	1		
Recruitment setting									
Clinic	95	54%	21	55%	74	54%	1		*P*=0.891
Acute stroke unit	80	46%	17	45%	63	46%	1.05	0.51–2.17	
Diagnosis									
Ischemic stroke	109	62%	24	63%	85	62%	1		*P*=0.140
Primary intracerebral hemorrhage	5	3%	3	8%	2	1%	5.31	0.84–33.6	
TIA (probable or definite)	61	35%	11	29%	50	36%	0.78	0.35–1.72	
Hemisphere of stroke/TIA symptoms									
Left anterior circulation	82	47%	17	45%	65	47%	1		*P*=0.662
Right anterior circulation	53	30%	13	34%	40	29%	1.24	0.55–2.83	
Posterior circulation	35	20%	6	16%	29	21%	0.79	0.28–2.21	
Uncertain	5	3%	2	5%	3	2%	2.55	0.03–16.49	
Neurological impairment (NIHSS)									
Median (IQR)	0	(0–2)	0	(0–2)	0	(0–2)			
TIA	61	35%	11	29%	50	36%	1		*P*=0.575
Stroke, NIHSS									
0	30	17%	9	24%	21	15%	1.95	0.70–5.39	
1–4	71	41%	16	42%	55	40%	1.32	0.56–3.11	
>4	13	7%	2	5%	11	8%	0.83	0.16–4.27	
Prestroke status									
Lived alone before stroke/TIA									
Yes	60	34%	15	39%	45	33%	1.33	0.64–2.80	*P*=0.450
No	115	66%	23	61%	92	67%	1		
Independent before stroke/TIA									
Yes	169	97%	37	97%	132	96%	1.4	0.16–12.37	*P*=0.753
No	6	3%	1	3%	5	4%	1		
Past diagnosis of depression or anxiety disorder									
None	123	70%	15	39%	108	79%	1		*P*<0.001*
Depression only	30	17%	10	26%	20	15%	3.6	1.42–9.14	
Anxiety only	11	6%	6	16%	5	4%	8.64	2.35–31.83	
Both depression and anxiety	11	6%	7	18%	4	3%	12.6	3.29–48.21	

(*Continued*)

Table 1. Continued

	Prospective Cohort		SCID Diagnosis				Univariable Logistic Regression		
	All		Any Anxiety Disorder		No Anxiety Disorder				
No. of Patients	175		38	22%	137	78%	OR	95% CI	Likelihood Ratio Test
History of stroke									
Yes	22	13%	7	18%	15	11%	1.84	0.69–4.89	*P*=0.237
No	153	87%	31	82%	122	89%	1		
History of ischemic heart disease									
Yes	30	17%	8	21%	22	16%	1.39	0.56–3.44	*P*=0.479
No	145	82%	30	79%	115	84%	1		

CI indicates confidence interval; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCID, Structured Clinical Interview for Diagnostic Statistical Manual-IV-Text Revision; and TIA, transient ischemic attack.
*$P<0.05$.

D at 3 months—3 had died, 1 was on palliation for termi- cancer, 4 had lost mental capacity, 9 withdrew consent for D, and 9 were not contactable (Figure I in the online-only a Supplement). Participants lost to follow-up were more ly to live alone (losses: 15 of 26, 58%; analyzed: 60 of 175, ; P=0.024); otherwise, they were similar to those who e analyzed (Table II in the online-only Data Supplement). he analyzed sample (Table 1), 175 participants (mean age], 70 [12]; women, 70 of 175; 40%) had SCID at 3 months stroke/TIA. The majority had ischemic stroke, a third had , and few had primary intracerebral hemorrhage (ischemic ke: 109 of 175, 62%; TIA: 61 of 175, 35%; primary intrace- al hemorrhage: 5 of 175, 3%). We recruited similar numbers n the acute stroke unit and TIA clinic (acute stroke unit: 80 75, 46%; TIA clinics: 95 of 175, 54%). Our sample, there- , consisted of patients with mild stroke and TIA (National itutes of Health Stroke Scale: median [interquartile range], –2]). Nearly all participants were interviewed by telephone phone: 168 of 175, 96%; face to face: 7 of 175, 4%).

quency of Anxiety Disorders and Psychiatric norbidity at 3 Months After Stroke/TIA

ifth of our sample had at least 1 anxiety disorder at 3 nths after stroke/TIA (38 of 175, 22% [95% confidence rval, 16–29]). Phobic disorder was the most frequent anxi- subtype (phobic disorder only: 18 of 175, 10%; both pho- disorder and GAD: 13 of 175, 7%; GAD only: 7 of 175, Figure 1A; Table 2). PTSD appeared as a comorbidity in phobic disorder-only cases (6 of 18), GAD-only cases (1 of 7), and both phobic disorder and GAD cases (4 of 13; Table 2). Half of all people with anxiety disorder also had a minor or major depressive episode (20 of 38, 53%; Figure 1B). We found no difference in cognitive function between patients with anxiety disorder and those without (telephone Montreal Cognitive Assessment median, interquartile range: [anxiety disorder] 18, 16–21; [no anxiety disorder] 19, 17–20; P=0.692). Of the TIA patients, 18% (11 of 61) had an anxiety disorder, 10% (6 of 61) had phobic disorder only, 3% (2 of 61) had both phobic disorder and GAD, and 5% (3 of 61) had GAD only.

Avoidant Behavior and Anxiety-Provoking Situations/Stimuli

Eighty-four percent (147 of 175) returned completed FQ for analysis. Nonresponders were younger than the FQ sample analyzed (mean age: nonresponders, 64.8±14.9; FQ analyzed, 70.5±10.6; P=0.017) but did not differ statistically in other characteristics (Table III in the online-only Data Supplement). Participants with an anxiety disorder at 3 months reported significantly higher level of avoidant behavior across all situations on the FQ compared with participants without (Figure 2). Similarly, during SCID, positive responses to all of the 11 predefined situations were more common in participants with anxiety disorder compared with those without (Figure II in the online-only Data Supplement). The fear of stroke recurrence had the most positive responses in those with anxiety disorder (31 of 38; 82%) and in those without (40 of 137; 29%). We

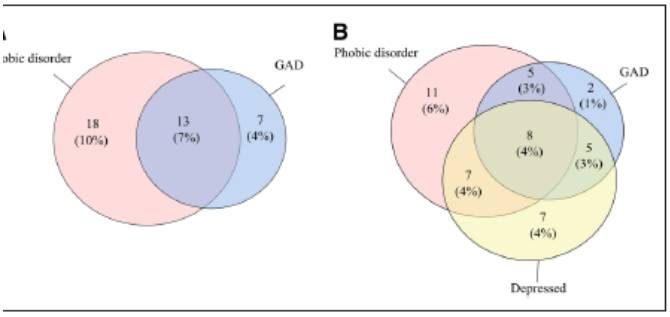

Figure 1. A, Number of cases (sample frequency) of phobic disorder and GAD, (**B**) comorbid depression in sample at 3 months (n=175). GAD indicates generalized anxiety disorder.

Table 2. Sample Frequencies of SCID-Diagnosed Phobic Disorder, GAD, and Psychiatric Comorbidity (n=175)

SCID Diagnosis	Total (n=175)	Sample Frequency, %	95% Confidence Intervals
Any anxiety disorder	38	22	16–29
Phobic disorder only	18	10	6–16
Comorbidity			
Panic disorder	5	3	1–7
PTSD	6	3	1–7
OCD	0	0	0–2
Depressive episode (minor+major)	7	4	2–8
GAD only	7	4	2–8
Comorbidity			
Panic disorder	2	1	0–4
PTSD	1	0.5	0–3
OCD	0	0	0–2
Depressive episode (minor+major)	5	3	1–7
Both phobic disorder and GAD	13	7	4–12
Comorbidity			
Panic disorder	7	4	2–8
PTSD	4	2	1–6
OCD	2	1	0–4
Depressive episode (minor+major)	8	5	2–9
All depressed (minor or major depressive)	27	15	11–22
Depressed with an anxiety disorder	20	11	7–17
Depressed without anxiety disorder	7	4	2–8
Not depressed	148	85	79–90

GAD indicates generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, Post-traumatic stress disorder; and SCID, Structured Clinical Interview for Diagnostic Statistical Manual-IV-Text Revision.

listed any additional anxiety-provoking situations reported during SCID (Table IV in the online-only Data Supplement).

Associations With Dependence, Health-Related Quality of Life, and Social Participation at 3 Months

Despite similar baseline neurological impairment (National Institutes of Health Stroke Scale 0–4, [anxiety disorder] 95% versus [no anxiety disorder] 92%; P=0.575), participants with anxiety disorder were more dependent (modified Rankin Scale score 3–5, [anxiety disorder] 55% versus [no anxiety disorder] 29%; P<0.0005), reported more problems across all health-related quality of life domains on the EQ-5D5L (Figure 3), and more restriction in social participation (Work and Social Adjustment Scale: median, interquartile range: [anxiety disorder] 19.5, 10–27; [no anxiety disorder] 0, 0–5; P<0.001).

Predictors of Anxiety Disorder at 3 Months After Stroke/TIA

The odds of having an anxiety disorder at 3 months after stroke or TIA decreased by a third per decade increase in age (adjusted odds ratio, 0.64; 95% confidence interval, 0.45–0.91) and increased 4-fold when there was a past diagnosis of anxiety or depression (adjusted odds ratio, 4.38; 95% confidence interval, 1.94–9.89; Table 3). Sex or living alone prestroke/TIA were not statistically associated with anxiety disorder at 3 months.

Discussion

Key Findings

In our sample of stroke and TIA patients, a fifth had an anxiety disorder diagnosed at psychiatric interview at 3 months. We found phobic disorder to be the predominant anxiety subtype after stroke or TIA. Anxious patients reported more avoidance in agoraphobia-related, social, and other specific situations or stimuli—physical exertion, having sex, being alone at home, activities related to fear of having a headache, another stroke, or a fall. PTSD was more common than we had anticipated. Younger age and having a history of anxiety or depression increased the likelihood of developing anxiety poststroke/TIA. Despite having a similar level of neurological impairment at baseline, participants with anxiety disorder were more dependent, had poorer health-related quality of life, and were more restricted in social participation at 3 months after stroke or TIA compared with those without anxiety disorder.

Potential Bias in Our Methodology

Our trained interviewer was a stroke clinician who received training in performing the SCID. We minimized any variability in diagnosis by having all final diagnoses discussed and confirmed with a consultant neuropsychiatrist at weekly meetings. A systematic review of studies assessing the agreement between diagnostic telephone and face-to-face psychiatric interviews found good agreement (κ=0.69–0.84) between the 2 versions in psychiatric populations,[22] supporting the use of telephone SCID for anxiety disorders and depression. However, there are no such comparability data in stroke. The use of telephone SCID in our study could have influenced the accuracy of the true estimates of our SCID diagnoses. SCID diagnosis was made based on formal diagnostic criteria and coding system, taking into account detailed narrative of the patient's experience. Temporary distress experienced by the participant at the time of SCID, if any, was unlikely to influence the final diagnosis. Our final sample size of 175 fell short of the 200 we intended to recruit. This impacted slightly on the precision of our frequency estimate for any anxiety disorder, from ±0.05 to ±0.06.

We note a high proportion of previous anxiety or depression in our sample. Case ascertainment relied on participants' recollection of any past diagnosis made throughout their lifetime, potentially leading to overestimates. We had losses to follow-up in the prospective cohort. More people lived alone in the

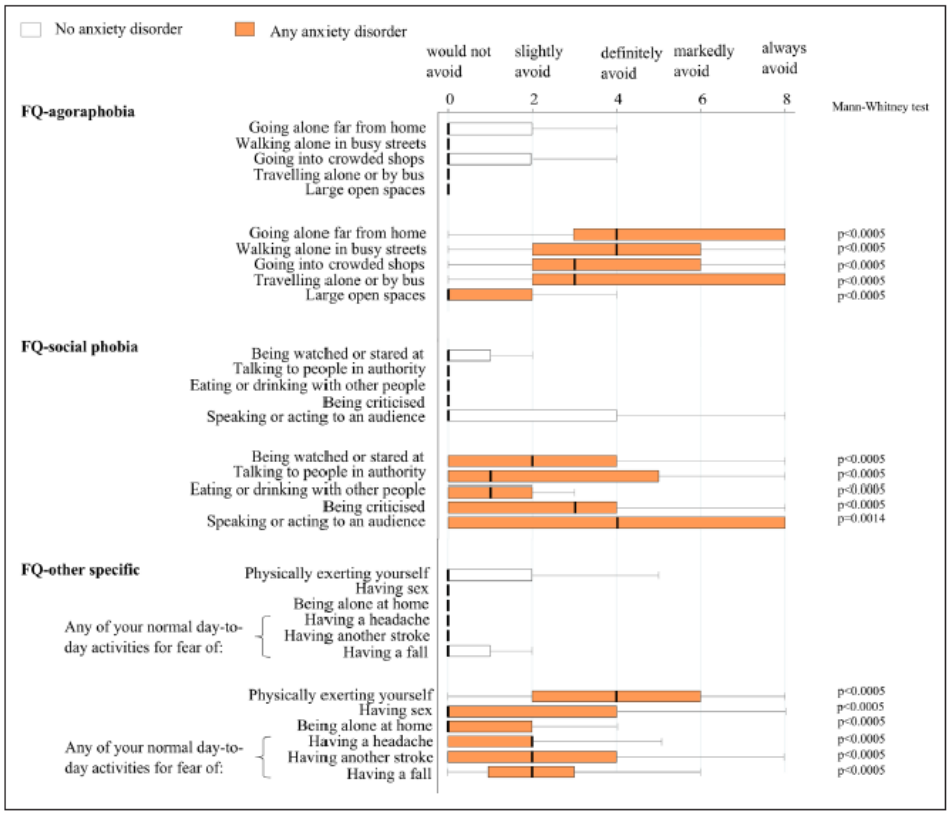

Figure 2. The thick lines represent median; boxes represent interquartile range; and whiskers represent range. Avoidant behavior in agoraphobic, social, and other specific situations (n=147). FQ indicates Fear Questionnaire.

losses compared with those who underwent SCID. This could have led to underestimates of anxiety disorder and depression because living alone is associated with a higher psychiatric morbidity in the general population.[23] We lost FQ data through nonresponders, and they were younger compared with the FQ sample analyzed. Although over a quarter of participants completed the FQ online as their preferred method, we did not test the agreement between the 2 versions. Our population was at the milder end of the stroke spectrum.

Interpretation

Our frequency estimate falls within the range of frequencies reported in a recent meta-analysis of anxiety poststroke: 18% to 25%.[1] We found phobic disorder to be the predominant anxiety subtype poststroke/TIA and quantified for the first time, the avoidant behavior of specific anxiety-provoking situations in people with anxiety poststroke/TIA. Our study is the first to have assessed the frequency of anxiety subtypes using diagnostic interview in TIA patients.[24] Similar to our main analysis, phobic disorder was the most frequent anxiety subtype post-TIA. Our frequency estimate of anxiety disorder post-TIA is similar to that reported using a rating scale cutoff for definite anxiety in a regional stroke registry.[2]

Earlier studies suggested phobic anxiety might be present after stroke,[3–5] yet clinical trials of anxiety intervention did not translate this finding, treating anxiety poststroke as a unitary phenomenon. Thus far, only general approaches, such as relaxation and antidepressants, have been evaluated in stroke,[6] which are unlikely to be effective in patients with predominantly phobic anxiety. Our findings suggest the need to evaluate exposure techniques—an approach known to be effective in phobic disorder in nonstroke populations[8] but one that has never been evaluated in stroke. We identified the specific situations/stimuli avoided in our anxious participants, which could be potential targets for psychotherapy; for example, CBT.

Fear of Stroke Recurrence

The fear of stroke recurrence was the most commonly reported anxiety-provoking stimulus in our participants, with or without anxiety disorder. In our interviews, we found this anxious anticipation—the experience of anxiety by thinking about an event in the future, to have led to differential behaviors in our participants. In some, this anticipatory anxiety brought about a desire for better health and increased positive health behaviors; for example, complying to medications and doctor's advice on lifestyle and giving up smoking. In others, this anticipatory anxiety became

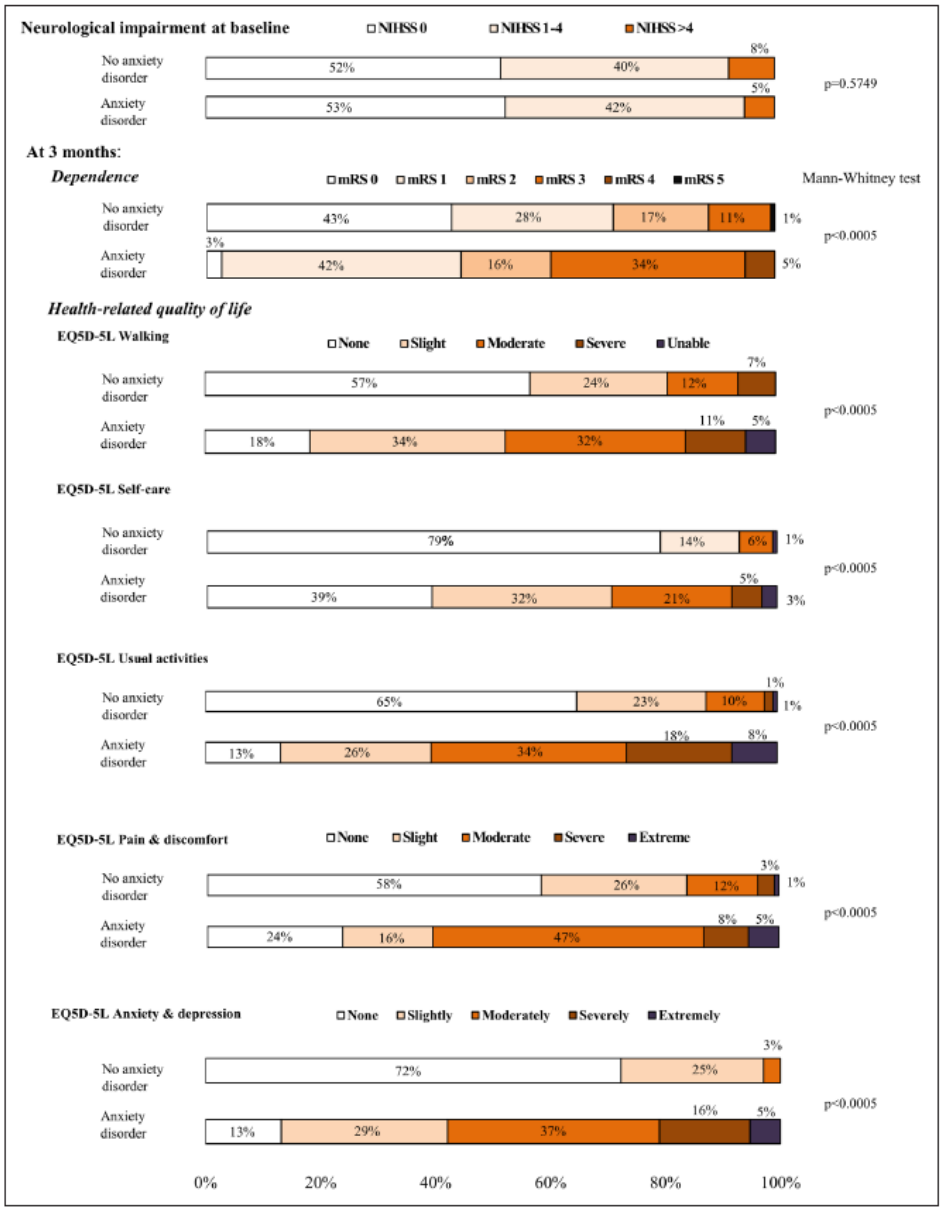

Figure 3. Baseline NIHSS, mRS and EuroQoL 5D-5L domains, by anxiety disorder at 3 months poststroke/TIA (n=175). mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and EQ5D-5L, EuroQoL-5D5L.

disproportionate and perpetuated maladaptive avoidant behaviors of specific situations; for example, travelling alone, crowds, physical exertion, and social gatherings. The fear of stroke recurrence, accompanied by a sense of complete loss of control in a public place, seemed to underlie the agoraphobia in our participants. These maladaptive thinking patterns and avoidant behaviors are potential targets for cognitive restructuring and exposure therapy in a CBT intervention. In exposure therapy, phobic patients confront their specific feared situation in a graduated hierarchical fashion, until the unpleasant anxiety feelings diminish. The individual's realization that catastrophe has not occurred, despite confronting his/her feared situation, for example, taking the bus, can be used to help challenge a maladaptive belief; for example, "I am going to have a stroke if I travel on the bus."

Table 3. Unadjusted and Adjusted ORs of Our Predictors for the Outcome of Any Anxiety Disorder at 3 Months Poststroke/TIA (n=175)

	Unadjusted OR (95% CI)	Multivariable Logistic Regression			
		Adjusted OR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
Age, y (per decade increase)	0.60 (0.44–0.83)	0.67 (0.47–0.94)	0.65 (0.46–0.92)	0.65 (0.46–0.92)	0.64 (0.45–0.91)
Past diagnosis of anxiety or depression	5.71 (2.65–12.32)	4.85 (2.21–10.66)	4.51 (2.01–10.12)	4.66 (2.10–10.31)	4.38 (1.94–9.89)
Being a woman	1.47 (0.71–3.04)		1.37 (0.61–6.14)		1.33 (0.58–3.07)
Living alone prestroke/TIA	1.33 (0.64–2.80)			1.31 (0.89–3.08)	1.29 (0.56–2.99)
Likelihood ratio test comparing models with model 1			P=0.4526	P=0.4873	P=0.6294

CI indicates confidence interval; OR, odds ratio; and TIA, transient ischemic attack.

Psychiatric Comorbidity

Psychiatric comorbidity in our sample was common, and its symptoms should be considered in the treatment of anxiety poststroke/TIA. Few studies have estimated the frequency of clinical diagnosis of PTSD poststroke/TIA.[25] Like phobic and generalized anxiety, PTSD has specific treatment strategies in nonstroke populations—trauma-focused CBT and eye movement reprocessing.[26,27] These now need to be tested in stroke. Our finding on PTSD adds weight to our general thesis that treating anxiety as a unitary condition after stroke will lessen the likelihood of finding effective treatments. In PTSD, individuals persistently reexperience the traumatic event in the form of distressing flashbacks, intrusive thoughts, and nightmares.[7] In our cases of PTSD, emotional distress was provoked by bodily sensations or situations that reminded the individuals of their index event; for example, headaches, odd sensation in affected limb, and meeting people who were likely to enquire about the index event. Panic disorder was nested within our phobic and GAD cases. It refers to a tendency to have panic attacks—the most extreme and unpleasant form of anxiety state with marked autonomic symptoms and the feeling of impending catastrophe. Panic disorder is usually managed with CBT or medications.

Consistent with the literature,[1,28] concurrent depression was common among anxiety cases, reaffirming the need to manage depression in those with anxiety poststroke. Our frequency estimate of poststroke depression was half of what is usually reported.[29] This is probably because our sample consisted of mainly mild stroke and TIA patients and that stroke severity and physical disability are the most consistent predictors for poststroke depression.[30]

Predictors of Anxiety Poststroke/TIA

The likelihood of developing anxiety after stroke or TIA increased in younger people and in those with a history of anxiety or depression, consistent with anxiety in the general population. In contrast to the general population, men were as likely as women to develop anxiety poststroke/TIA. We found no association between lesion location and anxiety poststroke/TIA.

Associations With Dependence, Quality of Life, and Social Participation

Our study findings on dependence, quality of life, and social participation challenge the pervasive view among stroke clinicians that these patients are not disabled by their seemingly minor cerebrovascular event. Anxiety disorders, PTSD, and depression can be profoundly disabling and need to be considered as important outcomes in stroke and TIA.

Implications for Future Research

The lack of evidence-based anxiety interventions is a barrier to improving outcomes in patients with anxiety poststroke/TIA. Trialists must recognize the need for different treatment approaches for phobic and generalized anxiety. Given the predominance of phobic disorder poststroke/TIA, exposure therapy needs to be evaluated in a clinical trial in this population. Individually tailored CBT (augmented CBT) is feasible in clinical trial setting of poststroke depression[31,32] and may be similarly applied in anxiety poststroke/TIA.

Generalizability

Our sample is different from the population of patients with stroke, in that all our participants could communicate by telephone, hence in general had mild deficits. Based on the Scottish Stroke Care Audit registry data, we would expect around a fifth of the National Health Service Lothian stroke population to have communication difficulties. Furthermore, competing research studies were recruiting patients with more severe deficits at the same time as this study's recruitment. We recruited half of our sample from clinic where patients tended to have mild or resolution of neurological symptoms. We, therefore, consider our sample as representative of the mild stroke and TIA population with limited generalizability to severe stroke or those who have significant communication difficulties. The telephone Montreal Cognitive Assessment scores in our sample are consistent with findings in a similar sample of stroke and TIA patients[16] and suggest the presence of mild cognitive impairment—a known manifestation of mild stroke and TIA.[33]

Conclusions

Phobic disorder is the predominant anxiety subtype and can occur in the absence of GAD after a mild stroke or TIA. Future trials of anxiety intervention in stroke must consider the presence of phobic disorder and should consider the use of exposure therapy techniques and augmented CBT.

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Disclosures

Dr Carson is a paid associate editor of *Journal of Neurology, Neurosurgery, and Psychiatry* and is involved in 2 not-for-profit websites: www.neurosymptoms.org and www.headinjurysymptoms.org. He holds a small grant £10 000 from the Health Technology Assessment in the United Kingdom to develop an app to deliver cognitive behavioral therapy after mild traumatic brain injury. This grant is shared with commercial partners. The other authors report no conflicts.

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Appendix C

Chun *et al. Pilot and Feasibility Studies* (2018) 4:139
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Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

Treating anxiety after stroke (TASK): the feasibility phase of a novel web-enabled randomised controlled trial

Ho-Yan Yvonne Chun*, Alan J. Carson, Martin S. Dennis, Gillian E. Mead and William N. Whiteley

Abstract

Background: Anxiety affects a quarter of strokes. It can be disabling even after mild stroke and transient ischaemic attack (TIA). It is not feasible to deliver conventional psychological therapies to the large population of anxious stroke and TIA patients. We are testing the feasibility of a web-enabled randomised controlled trial (RCT) to compare an individualised telemedicine cognitive behavioural therapy (CBT)-based intervention with a self-guided web-based relaxation programme. This study aims to evaluate the feasibility of novel trial procedures and the delivery of the TASK interventions in stroke and TIA patients.

Methods: We aim to recruit 40 community-based stroke and TIA patients experiencing anxiety at least 1 month post-discharge in Lothian, Scotland. We will assess the (1) recruitment number per month; (2) percentage completion of electronic consent; (3) time taken for remote eligibility confirmation; (4) percentage completion of follow-up surveys: modified Rankin scale, EuroQol-5D5L, 7-item generalised anxiety disorder, Patient Health Questionnaire-2 and modified fear questionnaire; (5) data capture of intervention fidelity and (6) use of actigraph smartwatches to obtain continuous data of rest/activity.

Discussion: The current study will provide feasibility data on streamlined web-enabled trial procedures and the use of smartwatches to obtain objective measures in stroke and TIA patients, offering potential for large efficient RCTs to be conducted centrally and remotely with far fewer resources in the future. This study will inform further refinements of the TASK interventions before evaluation in a definitive RCT.

Trial registration: Clinicaltrials.gov NCT03439813. Retrospectively registered on 20/2/2018.

Keywords: Telemedicine, Web-enabled, Cognitive behavioural therapy, Stroke, Anxiety, Wearable

Background

There are more than 100,000 strokes per year and 1.2 million stroke survivors in the UK [1]. Anxiety affects a quarter of stroke patients [2], equivalent to around 25,000 patients per year. Anxiety is associated with dependence, poorer quality of life and restricted participation in work and social activities after even mild stroke and TIA [3].

Phobic and generalised anxiety

Anxiety is a universal emotion that helps people adapt to changing situations. However, it can become maladaptive when anxiety becomes pervasive or out-of-proportion to the danger posed by a situation. When maladaptive anxiety starts to interfere with a person's occupational or social functioning, it is considered an anxiety disorder. Anxiety can be broadly divided into two clinical subtypes—phobic and generalised. Phobic anxiety is characterised by a disproportionate fear of well-defined situations or stimuli and marked avoidance of those situations [4]. By contrast, generalised anxiety disorder is diffuse and unremitting, characterised by persistent and multiple worries, e.g. finances, health and an inability to stop worrying [4]. In our recent prospective cohort, we found phobic disorder to be the predominant anxiety subtype after stroke and TIA [3].

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What are stroke patients anxious about?

Patients with anxiety disorder reported more avoidance in agoraphobia-related situations, e.g. going out alone, going to crowded places and travelling on public transport; social situations and specific situations, e.g. physical exertion, having sex, being alone at home and activities related to fear of having a headache, another stroke or a fall [3]. In our recent study, we found that the fear of stroke recurrence is the most commonly reported anxiety-provoking thought post stroke/TIA. This fear appeared to have led to differential behaviours in our patients. In some, this anticipatory anxiety brought about a desire for better health and increased positive health behaviours, e.g. complying with medications and doctor's advice on lifestyle, while others developed a grossly distorted view of their risk of stroke recurrence despite adhering to secondary prevention [3]. These patients feared having a debilitating stroke on a regular basis, perpetuating maladaptive avoidance of daily situations. Both avoidant behaviours and distorted thinking are targets for a CBT-based intervention.

Predictors for anxiety after stroke/TIA

Younger people and those with a previous history of anxiety or depression are more likely to develop anxiety after stroke [3, 5]. Longitudinal data suggested anxiety post stroke could last up to 10 years [6].

Barriers to accessing CBT in stroke and TIA

Inadequate service provision in psychological care post stroke across the UK is evident from the reports of the Sentinel Stroke National Audit Programme in England, Wales and Northern Ireland [7] and the latest Royal College of Physicians Stroke Guideline [8]. The demand for better access to psychological care post stroke has consistently been echoed by surveys and qualitative research of patients, carers and health professionals, and through charitable organisations representing stroke patients [9–11]. Delivering CBT in a conventional face-to-face format to all patients with anxiety post stroke/TIA is not feasible in clinical practice given the high prevalence of anxiety in this population and limited resources. In Scotland alone, a quarter of stroke patients equate to 2000–3000 patients per year. Our stakeholder activity involving the clinical leads of stroke and clinical psychology services from across Scotland (Additional file 1) agreed that this demand was unlikely to be met by primary care providers alone, nor the traditional paradigm of referring patients for face-to-face psychotherapy delivered by highly-trained specialists. The shortage of highly trained staff and geographical variation was unlikely to be resolved in the near future.

Other potential barriers to accessing psychological therapy include the inability to attend face-to-face appointments due to physical immobility and social stigma attached to seeking psychological treatment. Reluctance to travel in agoraphobia and the fear of being judged in social phobia are diagnosis-specific barriers to attending face-to-face sessions. People with social phobia symptoms were three times more likely to report a fear of what others might think or say about them if they sought psychological treatment compared to people with other anxiety disorders [12]. To date, randomised controlled trials (RCT) of guided internet-delivered CBT for anxiety and depressive disorder in general adults have shown good patient adherence and satisfaction [13].

Potential of a telemedicine CBT-based intervention

Telemedicine could offer a way to overcome the barriers in accessing psychological therapy by treating patients remotely while maintaining an individualised therapist-patient alliance that is integral to CBT. Meta-analyses demonstrated guided internet-based CBT to be superior to waitlist control and as efficacious as face-to-face CBT in treating anxiety disorders or depression in general adults, with face-to-face CBT spending seven times more therapist time than guided internet-based CBT [13, 14]. It is not yet certain whether these findings could be generalised to stroke and TIA patients, who tend to be older, have neurological deficits and medical co-morbidities. The effect of such interventions on patient outcomes after stroke/TIA needs to be evaluated in RCTs.

Delivering CBT remotely via telemedicine would enable centralisation of resources for staff, training, quality monitoring and cross-covering of different geographical areas, reducing travel time for therapists as well as patients. Digital content and treatment approaches in a telemedicine intervention could be updated and refined easily, thus, making use of the latest best evidence. The provision, maintenance and updating of digital content could be commissioned or delivered via charitable organisations. Organisation delivering the intervention can continue to invest in research and development to utilise the latest technology to deliver the treatment content at lower costs. At present, it is not yet clear whether telemedicine-delivered CBT is cost effective in stroke and TIA patients.

TASK intervention development

We developed the treating anxiety after stroke (TASK) CBT intervention following the UK Medical Research Council's framework for complex intervention development [15], elaborated by the Six essential Steps in Quality Intervention Development (6SQUiD) [16]—a formal methodology using a systematic, logical

and evidence-based approach for complex intervention development. Using this approach, we employed existing research findings, our original research and stakeholders' activities in developing TASK-CBT, reported in detail in Additional files 1 and 2. We modelled the processes and outcomes of the TASK-CBT intervention in a logic diagram in Fig. 1. Our current study represents the process evaluation and feasibility testing in a small scale before TASK-CBT can be evaluated in a definitive RCT.

Conducting an RCT entirely remotely by applying information technology

A definitive RCT needs to recruit and retain large number of patients to provide sufficient power to detect a clinically relevant treatment effect. Web-enabled and automated trial procedures can centralise processes and resources, offering the potential for scaling up an RCT with far fewer resources and costs than conventional procedures. For instance, one of the major costs of traditional multicentre trials is the setting up of multiple centres which includes establishing legal contract between the sponsor and local sites, identification and training of local staff, site initiation visits, monitoring, local closeout and archiving. Adopting a novel centralised system could avoid the need for these and streamline a large trial. Feasibility of remotely performed trial procedures need to be tested in stroke and TIA patients: online self-screening and recruitment, remote eligibility confirmation, electronic informed consent, remote intervention delivery, automated self-reported outcome measures and data capture of intervention fidelity.

Use of smartwatches to collect continuous data on activity/rest in an RCT

Anxious patients after stroke showed higher levels of avoidant behaviour across a range of situations, e.g. going out alone, physical exertion and social situations

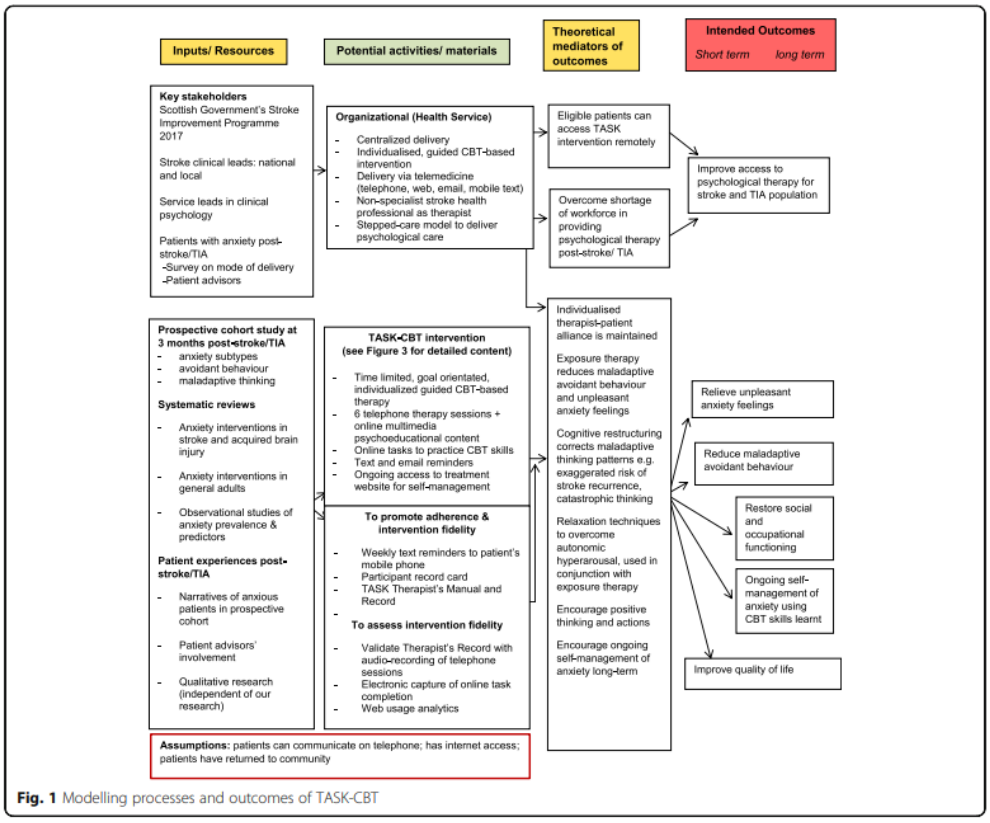

Fig. 1 Modelling processes and outcomes of TASK-CBT

compared with those who were not anxious [3]. Disturbed sleep is a feature common to both anxiety and depression. RCTs of psychological interventions have conventionally relied on self-reported outcomes using questionnaires. This requires effort from participants. Non-responders (attrition) can bias results and reduce the power of the study, resulting in a waste of valuable research resources. A wrist-worn smartwatch that records actigraphy (non-invasive method of monitoring rest/activity cycles) continuously could provide data on activity and sleep, offering the potential of measuring objective outcomes throughout the entire RCT with minimal patient effort. The feasibility of long-term continuous monitoring using this method has not previously been tested in RCTs of psychological intervention or RCTs of stroke/TIA patients [17]. The requirement for participants to return smartwatches during an RCT could pose an attrition issue which we will explore in the current study.

Objectives

This study aims to evaluate the feasibility of (i) novel web-enabled trial procedures, (ii) the TASK-CBT intervention and (iii) actigraph smartwatches to collect continuous data throughout the entire trial in stroke/TIA patients.

Methods

We report the protocol of the TASK feasibility RCT in accordance with the SPIRIT checklist [18] Additional file 3). Description of TASK-CBT adheres to items on the TiDier (template for intervention description and replication) checklist [19] (Additional file 4). The trial protocol is registered at ClinicalTrials.gov (NCT03439813).

Trial design

The TASK feasibility trial is a parallel two-armed RCT comparing TASK-CBT with TASK-Relax. Figure 2 illustrates the participant timeline in a schematic.

Information technology used in the design of the TASK feasibility RCT

We designed the TASK trial procedures using Research Electronic Data Capture (REDCap), a secure web-based database management application [20]. We created three

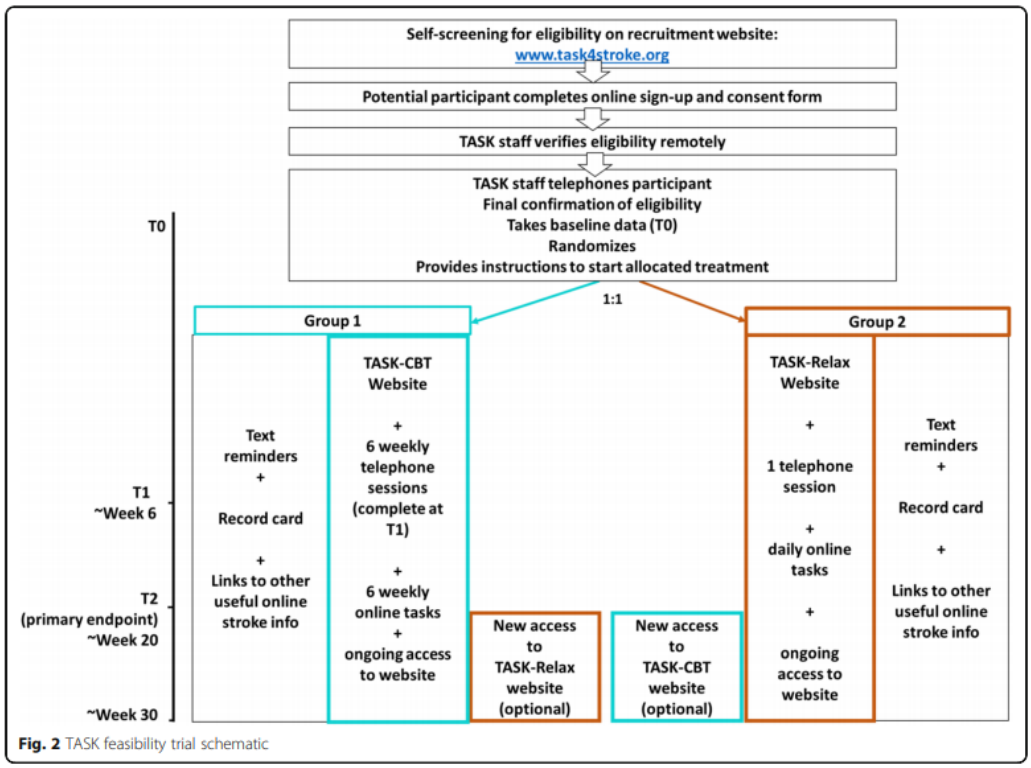

Fig. 2 TASK feasibility trial schematic

websites, one for recruitment (www.task4stroke.org) [21], one for the TASK-CBT intervention and one for the comparator TASK-Relax using an industry-led website builder. Using REDCap, we embedded data collection forms in our websites for self-screening for eligibility, informed consent and online tasks for TASK-CBT. Usage of all websites is monitored with Google Analytics. In our smartwatch sub study, we are testing the feasibility of GENEActiv Original smartwatch [22], a device designed primarily for research with validation data [22]. Continuous data (triaxial accelerometry, temperature, light) are recorded and can be downloaded from each device for analysis of physical activity and sleep. No data are stored on a commercial 'cloud,' and no patient identifiable data are stored on the device.

Patient population—inclusion and exclusion criteria

We aim to recruit 40 community-based residents within NHS Lothian (United Kingdom postcodes EH and FK1) who are aged 18 or above, with a diagnosis of stroke or TIA (probable, definite or ocular), at least 1 month after being discharged to the community from clinic or hospital ward. Participants need to have capacity to give informed consent, be able to communicate in English on the telephone, have internet access and report at least one positive response on our 6-item anxiety screening questions (Additional file 5). These items were derived from the GAD-7 [23] and modified fear questionnaire [3, 5] using psychometric techniques including factor analysis, analysis of internal consistency and Mokken scaling [Chun, H.-Y.Y., et al. Deriving the 6-item anxiety screening questions for a randomised controlled trial in stroke. Unpublished 2018].

We exclude people already taking part in a clinical trial of treatment intended to improve psychosocial outcomes post stroke.

Recruitment methods

The TASK recruitment website: www.task4stroke.org [21] is publically accessible, where participant information is available via a video or a readable format. Interested potential participants can complete the 'Sign Up and Consent Form' on the website. We disseminate the website address as widely as possible amongst patients, community stroke nurses, stroke physicians, stroke rehabilitation therapists and stroke charities using printed 'business cards,' flyers and social media. We offer trial information to stroke and TIA patients during their one-month telephone follow-up by a stroke clinician as part of routine stroke care. In addition, we sent postal invitations to eligible participants identified from the NHS Lothian stroke audit registry retrospectively.

On receiving the completed 'Sign Up and Consent Form,' the TASK research team verifies the eligibility and identity of the potential participant using electronic health records and over the telephone with the participant within five working days. Baseline data are immediately collected at this point (T0), followed by randomisation.

Intervention and comparator

We designed the TASK-CBT intervention to be delivered via telemedicine—telephone, website, email and mobile text. This enables remote delivery of the intervention while preserving the individualised therapeutic alliance between the therapist and the patient that is integral to CBT. The TASK-CBT intervention represents a low-intensity, guided self-help psychological intervention in a stepped care model [24]. A health professional with experience working with stroke patients, e.g. stroke nurse, stroke physician delivers TASK-CBT under the supervision of a specialist, e.g. psychiatrist or clinical psychologist.

Delivery of 'active ingredients' of TASK-CBT by telephone and web

We summarise the key 'active ingredients' of the TASK-CBT intervention in Fig. 3. In brief, the TASK therapist delivers a course of six individualised telephone CBT sessions, 35–45 min each, at least 1 week apart, with the use of an electronic TASK therapist's manual and record. Each session is supplemented by the prescription of an online task and one or more of the psychoeducational videos on the TASK-CBT treatment website. To encourage adherence, we send a mobile text to remind participant to complete the online task each week and to use the treatment website as much as possible via a computer, tablet or smartphone.

Active comparator: TASK-Relax

TASK-Relax is a web-based self-guided relaxation programme. Relaxation therapy is a commonly used comparator in RCTs of CBT in psychiatry research [25]. The TASK-Relax website consists of an introductory video, followed by five relaxation tasks: (i) audio- and visually-guided breathing exercise, (ii) relaxing imagery and sounds, (iii) music for relaxation, (iv) audio-guided progressive muscle relaxation and (v) a selection of sounds of nature. All relaxation videos/audios on the TASK-Relax website are also publically available on YouTube. Participants allocated to TASK-Relax receive instructions to try out all of the relaxation exercises, then select their favourite one(s) to practice daily, for at least 5 min throughout their trial participation.

Components common to both groups

Participants of both arms receive weekly mobile text reminder and a participant record card to record progress

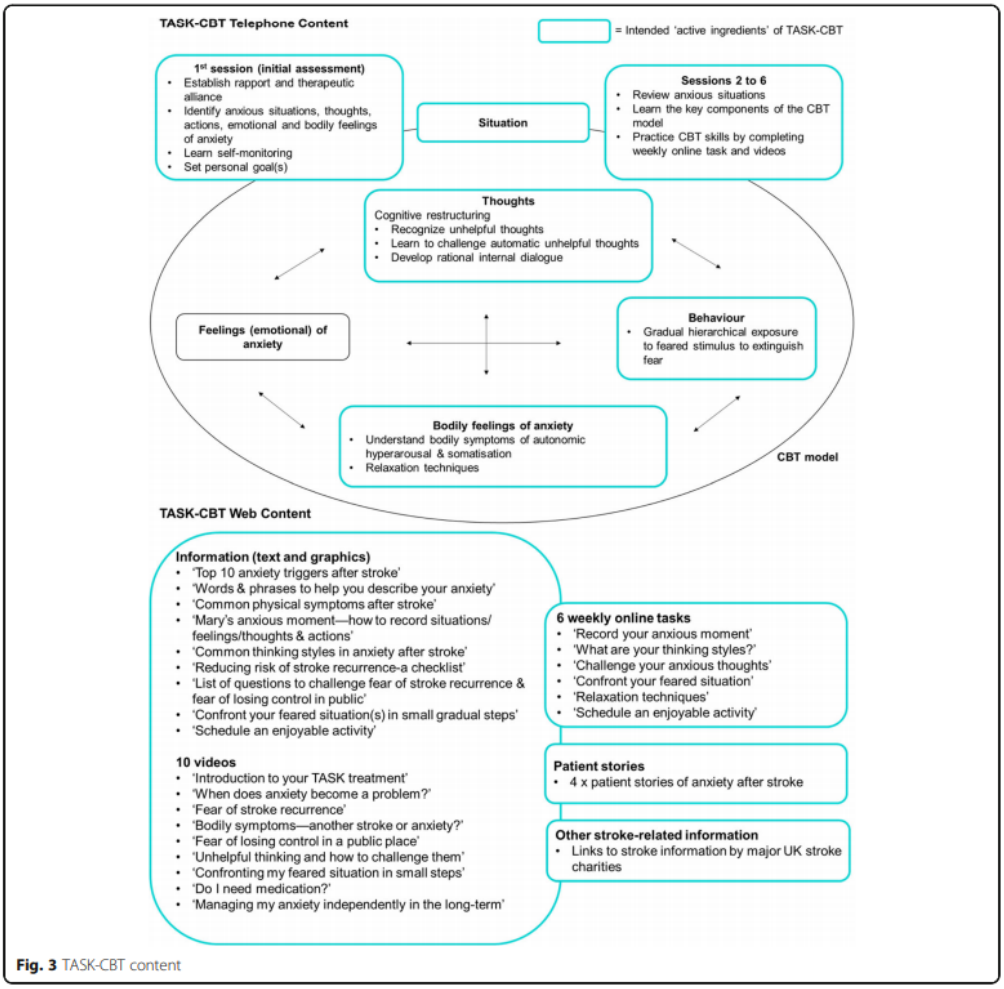

Fig. 3 TASK-CBT content

and completion of follow-up surveys. Data collection occurs at T1(week 6) and T2 (week 20, primary endpoint) via emailed links to self-completed electronic surveys. Once the follow-up survey at T2 is complete, we offer all participants access to the website given to the other group for a further 10 weeks.

Concomitant care and interventions

Concomitant standard clinical care and interventions (pharmacological or non-pharmacological) for anxiety or mood disorders, e.g. antidepressants, benzodiazepines are permitted and recorded in our follow-up surveys.

Randomisation and allocation concealment

A member of the research staff not involved in conducting the TASK trial generates a permuted block randomisation sequence with random block sizes using STATA14 [26]. The sequence is uploaded to the in-built randomisation module within REDCap, which is inaccessible to the TASK researcher enrolling participants. Once baseline data collection is complete, the TASK researcher randomises the participant and emails him/her the allocated treatment website address and login details. Participants receive telephone instructions on commencing the allocated treatment. Participants allocated to TASK-CBT also

receive an appointment for their first telephone session.

Masking

The TASK researcher (HYC) enrolling participants and delivering the allocated intervention is not blinded to the treatment group assignment. The TASK researcher informs participants that they will be randomly allocated to one of two anxiety interventions by the computer and receive the login details to their allocated website via email. Participants are masked to the contents and type of anxiety intervention allocated to the other group. This method attempts to mask participants to our hypothesis that one treatment is superior to the other.

Sub study of using a smartwatch to measure actigraphy continuously

In a sub study embedded within the TASK trial, all TASK participants are invited to wear the actigraph smartwatch. Once consented, the smartwatch is posted to the participant with simple care instructions. At 2 months, the battery of the smartwatch will run out. With the participant's agreement and on the safe return of the first smartwatch, a second smartwatch will be sent to the participant, so he/she can wear it for the rest of the trial. All smartwatches are returned using prepaid special delivery envelopes.

Feasibility outcomes

The current trial assesses the feasibility of the TASK-CBT intervention and the technology-enabled trial procedures. Feasibility data collected: recruitment (number per month), percentage of completed consent (online or by post), time taken to complete remote eligibility confirmation via electronic health records (date of randomisation–date of 'Sign Up and Consent Form' received), percentage drop out after fewer than three telephone TASK-CBT sessions and self-completion of electronic follow-up surveys at T1 and T2 (percentage of completed surveys).

We define a lack of feasibility of TASK-CBT and the current trial design as (1) recruitment number of < 2 per month, (2) > 50% of TASK-CBT patients dropping out after fewer than three telephone sessions, (3) > 10% non-completion of follow up surveys at T2 and (4) participants reporting harm from the intervention.

Treatment relevant outcomes (Table 1) include the modified Rankin Scale for dependence [27], EuroQol-5D5L [28], 7-item generalised anxiety disorder [23], modified fear questionnaire (FQ) [3, 29], Patient Health Questionnaire-2 (PHQ-2) [30] and a single question to elicit concurrent treatment for mood or anxiety. A user feedback survey automatically follows the T2 follow-up survey.

Feasibility outcomes of the smartwatch sub study

We will assess the percentage of TASK participants who also consent to wearing the smartwatch, the duration of the smartwatch being worn by each participant using the data recorded on the smartwatch, percentage of participants of this sub study who agree to wear the smartwatch again after 2 months, percentage of participants who did not return smartwatch (attrition).

Assessing intervention fidelity and quality monitoring of therapist

The therapist for this feasibility trial is a stroke physician (HYC) who has received training on delivering CBT from

Table 1 Treatment relevant outcomes

	T0 Baseline (pre-randomisation)	T1 follow-up (~ week 6)	T2 follow-up primary endpoint (~ week 20)
Demographics	*		
Diagnosis (stroke or TIA)	*		
Past history of anxiety or depression	*		
Medications for anxiety or mood	*		
mRS	*	*	*
EQ5D5L-VAS	*	*	*
GAD-7	*	*	*
PHQ-2	*	*	*
Modified FQ	*	*	*
Single question on concurrent treatment for mood or anxiety (drug or non-drug)	*	*	*
User feedback survey			*
Sub study of wearing a smartwatch			
Smartwatch for measuring rest/activity	Continuous monitoring throughout the trial from T0 to T2		

mRS modified Rankin Scale, *EQ5D5L-VAS* EuroQol-5D5L-Visual analogue score, *GAD-7* 7-item generalised anxiety disorder questionnaire, *PHQ-2* 2-item Patient Health Questionnaire, *FQ* fear questionnaire

and has ongoing supervision by a consultant neuropsychiatrist (AJC) at weekly meetings during the TASK trial. For intervention fidelity, we will assess (i) percentage agreement between the therapist's record and transcripts of audio-recording of telephone sessions, assessed by a clinician independent of the study; (ii) automated data capture of online task completion; (iii) summary web usage data from Google Analytics.

Strategies to improve adherence in both arms

We post a participant record card to every participant and send weekly text reminders to their mobile phone throughout their participation. All participants will receive text and email reminders to complete the follow-up surveys at T1 and T2. Non-responders will receive further text and email reminders and a final phone call from a researcher blinded to the treatment allocation to complete unfilled online surveys over the telephone.

Discontinuation criteria

Participants are free to withdraw from the study at any point, or a participant can be withdrawn by one of the TASK trial investigators if he/she loses capacity during the study period.

Safety protocol

A trained medical doctor delivers the TASK-CBT intervention in the current feasibility trial. All participants have contact details of the TASK research team from the start of the trial. They are informed that if severe cases of anxiety or depression are identified during the trial, the TASK research team will liaise with their general practitioner to arrange appropriate care. Trial investigators will assess these cases and report as adverse events to the sponsor according to good clinical practice.

Data management

All study data are collected and managed using REDCap electronic data capture tools hosted at University of Edinburgh. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies [20]. Identifiable data are only accessible by the TASK trial investigators and managing team of the REDCap database. Anonymised data from all smartwatch devices will be downloaded as binary files and sent to our collaborating data scientist at the Centre for Medical Informatics, Usher Institute, University of Edinburgh for analysis.

Data monitoring body

There is no data monitoring committee planned for this study.

Statistical analyses and power calculation

As this is a feasibility study, we did not perform power calculation. Feasibility outcomes will be summarised descriptively. All electronic items on the follow-up surveys must be scored to permit submission, preventing any missing values. Only the trial investigators have access to the final trial dataset. Actigraphy data from the smartwatch device will be sent anonymously for time-series analysis at the Centre for Medical Informatics, Usher Institute, University of Edinburgh.

Discussion

Using innovative information technology, we designed a streamlined web-enabled trial to be tested for the first time in stroke and TIA patients: online self-screening and recruitment, remote eligibility confirmation, electronic informed consent, remote intervention delivery, automated self-reported outcome measures and data capture of intervention fidelity. Our trial design offers a number of potential advantages. For instance, a centralised model could enable recruitment of eligible patients anywhere in the country, or anywhere in the world without the need to have locally-based principal investigators or research staff. Larger sample sizes could be reached more easily without significantly raising extra costs. Potential participants with proof of identity and eligibility could sign up themselves regardless of their locations. This model of recruitment could empower patients to choose to participate in a clinical trial without being screened or 'selected' by local healthcare or research staff. Generalisability could be increased as a result. While this method of recruitment remains aspirational for clinical trialists at present, owing to the regulatory and administrative challenges in conducting multicentre RCTs, it is of vital importance that we continue to evaluate the feasibility of novel procedures that would increase the ease of recruiting participants to large-scale RCTs, regardless of where they live. A centralised system of intervention delivery could be easily scaled up but also quality assured—a particular challenge in clinical trials where many therapists are employed to deliver the intervention in different centres.

There has been limited use of wearable devices to assess therapeutic outcomes in RCTs in stroke patients and RCTs of psychological interventions [17]. We recently observed high levels of avoidant behaviour across a range of situations, e.g. going out alone, physical exertion and social situations in people experiencing anxiety after mild stroke and TIA [3]. An actigraph smartwatch that records continuous data on activity/rest throughout the entire RCT offers an easily scalable way of collecting objective measures in large clinical trials with minimal patient effort. This study will inform whether using smartwatches could reduce attrition in RCTs, thus

reducing bias in trial results and avoiding waste of valuable research resources.

Improving access to psychological therapy via a centralised model of delivery

Anxiety is one of the commonest neuropsychiatric complications post stroke or TIA. Psychological care post stroke/TIA is inadequate, and the traditional paradigm of delivering face-to-face CBT at clinic is not feasible for the large population of stroke and TIA patients owing to limited resources and other barriers related to anxiety after stroke, e.g. agoraphobia and social phobia. Innovative ways of delivering psychological intervention remotely to the patient's home, e.g. individualised CBT via telemedicine could be a feasible model to treat the large population of stroke and TIA patients experiencing anxiety. If feasible, the TASK-CBT intervention could provide an exemplar model for delivering psychological intervention for a range of post-stroke psychological complications. Web-enabled features embedded in our TASK-CBT and TASK-Relax websites, e.g. data capture of completion of weekly online tasks and web usage analytics, provide novel ways of measuring intervention fidelity objectively—an important aspect of internal validity that can be challenging to assess and is infrequently reported in trials of complex intervention [31].

The TASK trial design has the potential to be applied in RCTs of any self-management or guided self-management interventions for a range of patient groups. Our design has the obvious limitation of excluding people who have no access to the internet, or those who do not have a minimum level of skills in information technology. This is likely to be overcome by the trend towards wider adoption of home broadband and user-friendly devices amongst seniors [32], and the encouragement and assistance provided by family members.

Considerations for the next phase, TASK II RCT

The current trial represents feasibility testing of the TASK-CBT intervention and the technology-enabled trial procedures. This will lead to further refinements of intervention design and trial procedures. Our current trial does not inform the efficacy of TASK-CBT. A number of important aspects of the TASK trial design will need to be considered in the next phase, the TASK II trial, before proceeding to the definitive trial, TASK III.

Choice of primary outcome

In TASK II, we will determine an appropriate primary outcome measure to be used in the definitive trial. We will consider a range of candidate outcome measures of anxiety, functional independence, quality of life and participation. We will select the primary outcome based on the measure's sensitivity to change/difference between groups, its practicality for use in large-scale RCT (to minimise attrition) and its clinical meaningfulness. Our observational data suggested that stroke/TIA patients with anxiety disorder reported a statistically significantly higher level of functional dependence on the modified Rankin Scale, a poorer quality of life on EurolQol-5D-5L and worse participation on a the Work and Social Adjustment Scale, compared to those without anxiety [3].

Patients after stroke/TIA can present, to varying degree, predominantly phobic, predominantly generalised, or mixed anxiety types. This poses an additional challenge as different anxiety measures are required to assess the two anxiety subtypes. It may be necessary to have different primary outcomes defined for different anxiety subtypes.

Other considerations include defining the responder's status: for example, whether to use the minimal relevant change from baseline on an anxiety measure, a dichotomised outcome, or an absolute anxiety level post-intervention to assess between-group difference.

Choice of comparator

Our choice of using TASK-Relax, a web-guided relaxation programme as an active control was to avoid exaggerating the effect size—a known effect of using 'waitlist' or 'treatment as usual' as control condition in RCTs of psychological interventions [33]. We accept that TASK-Relax could have an effect on anxiety in the short-term, but our hypothesis is that TASK-CBT will have a long-term effect while TASK-Relax would not (at week 20). TASK II will provide information on the outcome measure and variability in the two groups, informing the minimally important difference for our power calculations.

TASK intervention design

We will refine the TASK-CBT intervention based on participants' feedback from this current trial. The TASK therapist training materials will be developed based on our experience and the use of anonymised audio-recording transcripts. We will consider using audio recording for within-trial training, maintenance and enhancement of intervention fidelity in the next phase of TASK, where therapists will be employed to deliver the TASK-CBT intervention.

Cost effectiveness

As it is not yet clear whether TASK-CBT is cost-effective in stroke and TIA patients, health economics analysis of the TASK-CBT intervention using EuroQoL-5D-5L data will be conducted in the definitive RCT.

Efficient large-scale RCT using web-enabled procedures

Testing the feasibility of self-recruitment and remote eligibility confirmation in our local centre represents only the first step in finding novel efficient ways of recruiting

patients to large-scale nationwide RCTs. We believe all patients should be empowered to self-recruit to an RCT that they are eligible to regardless of where they live. Verifying eligibility remotely using electronic health records across different health boards in RCTs could be a viable option in the future but at present remains aspirational due to administrative barriers.

Trial status

Protocol version: AC17087 version 3, 1/12/2017.

Recruitment commenced on 17/1/2018. Estimated completion date 1/5/2018.

Additional files

Additional file 1: TASK-CBT Intervention development using the 6SQuID approach. (PDF 725 kb)

Additional file 2: Report of patient involvement in TASK. (DOCX 463 kb)

Additional file 3: SPIRIT checklist items. (DOC 120 kb)

Additional file 4: TiDier template items. (DOCX 28 kb)

Additional file 5: Screening questions in 'Sign up and consent form'. (PDF 173 kb)

Additional file 6: Research ethics approval letter. (PDF 134 kb)

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Availability of data and materials

The datasets generated during the current study will be available from the corresponding author on reasonable request. Results from this trial will be disseminated via peer-review publication.

Trial sponsor

University of Edinburgh and Lothian Health Board.
Contact: ACCORD, The Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ. Reference: AC17087

Authors' contributions

All authors conceived the idea and contributed to the design of the TASK intervention and the TASK feasibility RCT. HYC designed all study websites using wix.com and the web-enabled trial procedures using REDCap. HYC wrote the content of TASK-CBT intervention, the first draft and final version of the protocol with input from AJC, MSD, GEM and WNW. HYC leads this study as chief investigator. AJC provides HYC weekly supervision for the TASK-CBT telephone sessions. The study sponsor and funders had no role in the design or the reporting of the TASK trial protocol. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The TASK feasibility trial received a favourable opinion from the local research ethics committee (Additional file 6). All participants provided written informed consent.

Consent for publication

Not Applicable.

Competing interests

AJC is a paid associate editor of the Journal of Neurology, Neurosurgery and Psychiatry and is involved in two not-for-profit websites: www.neurosymptoms.org and www.headinjurysymptoms.org. He holds a small grant £10,000 from the Health Technology Assessment in the United Kingdom to develop an app to deliver cognitive behavioural therapy after mild traumatic brain injury. This grant is shared with commercial partners. He has given independent testimony in court on a range of neuropsychiatric topics including anxiety after stroke. Other authors have declared that they have no competing interests.

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