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InterventionsforMoodDisordersafterStroke

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Thesis Portfolio Abstract

Background: In recent years, there have been many advancements in clinical research and rehabilitation of stroke. However, current gaps in the literature remains as it is yet to draw conclusions on the best available tools for measuring health-related quality of life (HR-QOL), and the best evidenced interventions for post-stroke mood disorders.

Aim: This research portfolio aimed to provide a comprehensive review of the current evidence for stroke-specific HR-QOL measurements, as well as the intervention treatments used for post-stroke mood disorders, namely post-stroke depression (PSD), post-stroke anxiety (PSA) and post-stroke emotionalism (PSE).

Design: A systematic review identifies existing HR-QOL measures that are used within the stroke population and assessed them for clinical utility, psychometric properties and coverage of HR-QOL domains. The empirical paper systematically identifies randomised controlled trials (RCTs) on treatment intervention for PSD, PSA and PSE domains. Network meta-analyses (NMA) is conducted on the evidence for each domain to synthesise the findings based on direct and indirect comparisons.

Results & conclusions: The systematic review identified seventeen HR-QOL measures commonly in stroke, and a flow-chart recommending five measures which best met the clinical utility and psychometric criteria. No measure comprehensively covered all HR-QOL domains. The NMA presented the wide range of interventions available for PSD, PSA and PSE, and highlights the disproportionate focus of research within these domains. There is paucity of replicated evidence in the area. Thus, the NMA was not able to provide confident predictions of treatment rankings for either of the domains. Overall, both the systematic review and empirical paper reiterated the need for more quality research in the field.

Keywords: stroke, health-related quality of life, post-stroke mood disorders, post-stroke depression, post-stroke anxiety, post-stroke emotionalism

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CHAPTER ONE: Introduction to Thesis

Chapter Overview

This chapter provides a general overview of the thesis portfolio and introduces the rationale behind it.

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Introduction to the Thesis Portfolio

1.1 Stroke

Every year, approximately 110, 000 people are affected by stroke in England (Burton & Tyson, 2015). The consequence of stroke results in a wide range of disability (Adamnson, Beswick & Ebrahim, 2004, as cited in Pindus et al., 2016). Pinter and Brainin (2012) reported that over 5 million stroke survivors are left permanently disabled (WHO, 2009), with complications including impaired cognition (43.9%), impaired consciousness (44.7%) (Lawrence et al., 2001), language difficulties (30-50%), (Kirmness & Maher, 2010), visual neglect (50%)(Buxbaum et al., 2004), and psychological problems (62-70%)(Kauhanen et al., 2000) (Paul, Srikanth & Thrift, 2007). Despite the worldwide decrease in stroke mortality in recent years, the overall burden caused by stroke (years of life lost and years lived with disability) remains great and is increasing (Feigin et al., 2010).

1.2 Emotional / mood disorders after stroke

Psychological adjustment to stroke can be a distressing process (Broomfield, Kneebone & Laidlaw, 2014; Taylor et al., 2011). Difficulty in adjusting may result in significant impact on mood, with about one third of stroke survivors developing major depression (Medeiros et al., 2020), and 18-24% affected by anxiety disorders (Knapp et al., 2020). There is also evidence of prevalent mood impairment even following a Transient Ischemic Attack (Broomfield et al., 2014). Furthermore, around 21% of people living with stroke report symptoms of emotionalism (Gillespie et al., 2016). A large-scale survey reported only just under one third of stroke survivors who report emotional problems receive the support they need (McKevitt et al., 2011).

Post-stroke depression (PSD) can have a significant impact on a person's response to rehabilitation (Ghose et al., 2005; Jia et al., 2006), quality of life after stroke (Bays, 2001; Neau et al., 1998) and functional outcome (Pohjasvaara et al., 2002; Chemerinski, Robinson & Kosier, 2001). Post-stroke depression may see a decrease in patient motivation and engagement with rehabilitation, hence negatively impacting recovery and exacerbating their experienced level of disability (Astuti, Kusnanto & Novitasari, 2020). Research has also found that stroke survivors' post-stroke depression is associated with a higher mortality rate than those without (Morris et al., 1993; House et al., 2001; Townend et al., 2007; Towfighi et al., 2017). Similar to depression outside the context of stroke, prevention and treatment for PSD typically consists of administration of antidepressant medications and psychotherapy (Hildebrand, 2015; NICE, 2013). However, to date, the evidence for psychological interventions for this population remains inconclusive (Wang et al., 2018).

Generalised anxiety, as well as phobic anxiety are the most common forms of post-stroke anxiety (PSA) (Burton et al., 2013). This is often co-morbid with PSD, with papers reporting as many as 85% of people with PSA having co-morbid depression post-stroke (Castillo et al., 1993, 1995). Despite its prevalence, very few studies have evaluated the effectiveness of potential treatments of PSA (Chun et al., 2018). Systematic reviews have included few trials (Burton et al., 2011; Knapp et al., 2017) and found limited evidence for the use of pharmaceutical drugs, and reported no significant additional benefits in combining pharmaceutical treatment with psychotherapy.

Psychologically, post-stroke emotionalism (PSE) describes a reduced ability to control emotional expression. Sufferers typically experience episodes of increased tearfulness and may cry uncontrollably at events that are only moderately sad. PSE

can cause severe distress, embarrassment, social avoidance, and impaired quality of social interactions for the persons experiencing it (Carota & Calabrese, 2013; McAleese, 2019). To date, there are several papers which have reviewed pharmacological interventions for PSE (House et al., 2004; Hackett et al., 2010), with a growing body of recent research to add to this literature (Zorowitz et al., 2016; Patatanian & Casselman, 2014;Imarhiagbe &Abidakun, 2018; Allida et al., 2019). In comparison to pharmacological interventions, psychological interventions for PSE are poorly understood and under researched. Despite noting two case reports of psychological therapy (Brookshire 1970; Sacco, 2008), Hackett et al. (2010) did not find any RCTs evaluating psychological interventions to include in their review, indicating a marked gap in current research and literature.

1.3 Health-related quality of life

Of growing interest within stroke rehabilitation is the impact of stroke on a person's health-related quality of life (HR-QOL) (Golomb, Vickrey & Hays, 2001). HR-QOL specifically refers to an individual's health and how it affects their ability to function, as well as their perceived well-being in physical, mental and social domains of life (Coons et al., 2000). Measurements of HR-QOL can provide clinicians and patients with a comprehensive assessment of a person's health status, as well as serve as a baseline for clinical treatment and for assessment of intervention effectiveness (Solari, 2005). As such, HR-QOL measures are important and routinely used in primary care settings when working with patients who experience a range health conditions, such as atrial fibrillation (Badia et al., 2007), multiple sclerosis (Solari, 2007) and chronic conditions (Hand, 2016), including stroke (Hackett et al., 2000).

To assess the HR-QOL of patients with stroke, a variety of measures can be used. These measures can vary in design, where some are used generically across health conditions, and others are designed for a particular clinical population (Golomb, Vickrey & Hays, 2001). Therefore, it is important to understand and compare the content and psychometric properties of HR- QOL scales to aid the clinical decision-making in selecting the appropriate tools (Hand, 2016). Identifying specific HR-QOL measures for patients with stroke can allow for better assessment of the impact of the disease and in turn significantly improve patient outcomes (Badia et al., 2007).

In a review conducted by Golomb, Vickrey and Hays (2001), 32 measures of HR-QOL were identified for use in patients with stroke. This paper presented the strengths, limitations and information needed for each identified measure to aid in a clinician's decision-making about which tools will best suit their purpose. Whilst many measures assess the domains of HR-QOL of interest in stroke settings, there were no measures identified to cover all domains relevant to stroke patients (Golomb, Vickrey & Hays, 2001). Since then, more work has been done to address the gap in developing a HR-QOL scale that can address all the domains of interest in patients with stroke. Updated versions of existing measures have been introduced with improved sensitivity, such as the EuroQoL-5-Dimensions-3-Level (EQ-5D-5L) questionnaire (Herdman et al., 2011), as opposed to the EQ-5D version included in the Golomb, Vickrey and Hays (2001) review. Newer measures such as the Stroke Impact Scale (Duncan et al., 2003) and the SEIQoL-DW (LeVasseur, Green & Talman, 2005) have since been introduced.

1.4 Rationale for empirical paper and systematic review

It is clearly established in the literature that stroke has profound and wide-ranging consequences on the physical, emotional, cognitive, and social domains of a person's life, which in turn impacts their quality of life (Golomb, Vickrey & Hays, 2001). Therefore, more work needs to be done in the research of post-stroke mood interventions to evaluate the impact of these interventions on a person's quality of life. The current portfolio presents a review of research to explore both these themes, with the aim to provide recommendations for clinicians and to identify gaps for further research.

Firstly, the systematic review summarizes a comparison of existing HR-QOL measures to identify the most suitable tool for stroke clinical practice. The review explores the characteristics and psychometric properties of the tools used to assess the impact of stroke and intervention on a person's functioning and perceived well-being. A discussion of the clinical implications and recommendations for further research was also presented.

Secondly, the empirical paper presents a network meta-analysis of current evidence for post-stroke depression (PSD), post-stroke anxiety (PSA) and post-stroke emotionalism (PSE) treatments. Despite the growing body of research on post-stroke mood interventions, there remains no clear consensus on the most efficacious treatment. As such, the empirical paper explores the evidence in head-to-head comparisons using a network meta-analysis. Network meta-analysis is also known as multiple-treatments meta-analysis or mixed- treatment comparison (Salanti et al., 2008), and allows for a method of ranking different interventions against one another (Sun et al., 2017). This assimilates evidence for both pharmacological and non-pharmacological treatment interventions, therefore providing a comprehensive and overarching view of current evidence.

CHAPTER TWO: Systematic Review

Assessment of Health-Related Quality of Life after Stroke: A Review of Psychometric Properties and Clinical Utility

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(Author guidelines in Appendix B)

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Assessment of Health-Related Quality of Life after Stroke: A Review of Psychometric Properties and Clinical Utility

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Abstract (243 words)

Purpose: Most people who experience a stroke will survive the initial condition, but often with detriment to their emotional, cognitive and functional abilities. The long-term consequences for patients after a stroke can have a direct impact on their health-related quality of life (HR-QOL), which may in turn affect their rehabilitative outcomes. Although there is growing interest in assessing HR-QOL ass part of a person's progress and clinical outcome, there is no consensus on which tools are best to measure this. This paper aims to systematically review the existing HR-QOL measures that are used with the stroke population and compare them to provide a conclusion with recommendations on the most suitable HR-QOL measures for stroke. **Method:** Electronic databases (MedLine, PsycINFO, and Embase) were searched to identify studies assessing HR-QOL measures for the stroke population. Identified measures were then assessed for clinical utility, psychometric properties and coverage of HR-QOL domains following methodology set out by previous reviews (Burton & Tyson, 205; Golomb, Vickrey & Hays, 2001). **Findings:** Twenty-four papers examining 17 HR-QOL measures were identified. This included 11 stroke-specific and 6 generic HR-QOL measures. **Discussion and Conclusion:** Through assessment of clinical utility and availability of psychometric data, a flow chart resulted in a recommendation of 1 generic measure (SF-12), which takes approximately ≤5 minutes to administer, and 4 stroke-specific measures (SIS 2.0; SIS 3.0; SAQOL-39; SS-QOL), all of which take ≥11 minutes to administer. No HR-QOL measure comprehensively covered all HR-QOL domains.

Keywords: Stroke, Health-Related Quality of Life, Assessment Tools

Assessment of Health-Related Quality of Life after Stroke: A Review of Psychometric Properties and Clinical Utility

Introduction

Stroke is one of the leading causes of death and disability impacting people worldwide (Harshfield et al., 2020; GBD, 2015 DALYs and HALE Collaborators, 2015; GBD 2015, Mortality and Causes of Death Collaborators, 2015). Although mortality rates have declined in recent years (Feigin et al., 2014), stroke continues to significantly impact the lives of stroke survivors and their families (Feigin, et al., 2014). It is well established that stroke affects an individual's physical, mental and social domains of life such as their ability to practise self-care, their mobility, speech, language, memory, problem-solving abilities and socialisation skills (Golomb, Vickrey & Hays, 2001). Moreover, stroke may result in emotional disturbances, as reported by approximately 50% of stroke survivors (Hildebrand, 2015). Hence, clinicians should consider the multi-faceted impacts of stroke when assessing post-stroke outcomes among stroke survivors.

Stroke rehabilitation measures have traditionally been based on objective indicators of physical function, such as the Barthel Index (BI) and modified Rankin scale (mRS; Lam, McMillan, Li & McGarth, 2014). Although commonly used, these scales are limited in assessing psychosocial outcomes such as pain, mood and cognitive qualities. This suggests that they may misrepresent, or may not consider the full impact of stroke on a person's life (Carod-Artal & Edigo, 2009; Lam, McMillan, Li & McGarth, 2014). For example, disabilities such as cognitive impairment, mood

disturbance or communication impairments that result from a stroke may be overlooked when denoting outcomes, or when it interferes with the assessment process and impacts functional recovery (Golomb, Vickrey & Hays, 2001). Thus, it is vital for quality of life measures to be incorporated when assessing health outcomes, particularly in populations with chronic disease (Burckhardt & Anderson, 2003), including stroke (Russell, Dempster & Donnelley, 2011).

Conceptualising and defining 'quality of life' (QOL) can be difficult as no universal definition for this term exists (Burckhardt & Anderson, 2003). QOL is often used interchangeably with concepts of health status and functional status, however it may also include 'non-health-related' aspects such as a person's socioeconomic status and environmental factors (Guyatt, Feeny & Patrick, 1993). Although these aspects can influence a person's health, focusing on health-related quality of life (HR-QOL) may be more appropriate in measuring the impact of stroke and the rehabilitative outcomes of its treatments (Carod-Artal & Egido, 2009).

HR-QOL refers to the impact of health on an individual's ability to function and their perceived well-being, encompassing critical physical, mental and social outcome domains (Coons et al., 2000). HR-QOL differs from general QOL, which considers the perceptions of a person's status, culture and value in relation to their goals, expectations, standards and concerns (Carod-Artal & Egido, 2009). Conversely, assessment of HR-QOL includes functional capacity (e.g. daily activities) and emotional well-being (e.g. feelings or perceptions about one's life) (Golomb, Vickrey & Hays, 2001), both areas in which patients are most interested and familiar (Guyatt, Feeny & Patrick, 1993). Measuring HR-QOL also takes a person- centred approach whereby it is acknowledged that post-stroke functional and emotional impacts vary across patients with similar clinical criteria (Guyatt, Feeny &

Patrick, 1993). As HR-QOL measures significantly influence therapeutic decisions for people with chronic diseases (van Uem et al., 2016), and are often a primary outcome variable in clinical trials (van Uem et al., 2016; Martinez-Martin et al., 2011; Gurcay, Bal & Cakci, 2009), there should be more caution in using the terms 'QOL' and 'HR- QOL' interchangeably (Carod-Artal & Edigo, 2009).

Existing HR-QOL measures vary in design and utility, and can be categorised as two approaches: 1) generic instruments – used within the normal population to provide a summary of HR-QOL, and 2) specific instruments – target problems associated with specific disease states, patient groups, or areas of function, such as stroke (Guyatt, Feeny & Patrick, 1993). The clinical utility of measures depends on its validity, reliability, appropriateness, interpretability and practicality (Chen, Li & Kochen, 2005). Specifically, among stroke survivors, HR-QOL measures may also need to take into account specific post-stroke limitations such as cognitive impairment and fatigue (Golomb, Vickrey & Hays, 2001). Thus, it is important for the clinical utility of HR-QOL measures to be demonstrated specifically for the stroke population, rather than only being extrapolated from other groups (Golomb, Vickrey & Hays, 2001).

In considering HR-QOL measures for stroke patients, it is important for researchers and clinicians to make decisions on the most appropriate instrument and mode of administration that is suited to the individual's abilities. Although self-reported assessments are ideal (Lam, 1997), this may be difficult for stroke survivors with cognitive and communication difficulties (Golomb, Vickrey & Hays, 2001). In such instances, a surrogate respondent (Guyatt, Feeny & Patrick, 1993) such as a caregiver or proxy can respond on behalf of the patient based on what they believe the patient would say had they been capable of answering. Hence, where available, the validity of proxy ratings for an instrument is vital in instrument selection.

HR-QOL is gaining increased attention from healthcare professionals (Chen, Li & Kochen, 2005) as an important health outcome indicator (Lam, 1997). To evaluate the impacts of stroke and stroke interventions, Golomb, Vickrey and Hays (2001) identified important criteria which HR-QOL measures should meet, namely; 1) domain coverage of HR-QOL post-stroke, 2) modes of administration suitable for stroke patients, and 3) instruments have undergone reliability and validity assessment completed specifically for stroke patients. Although Golomb, Vickrey and Hays (2001) conducted a comprehensive summary of HR-QOL measures in stroke, this was over nineteen years ago. The present review therefore aims to replicate and update this prior review, again using a systematic review methodology that will consider the present scope of HR-QOL instruments in stroke. Other stroke-specific reviews have either focused on the participation of stroke caregivers (Opara & Jaracz, 2010) or used specific frames of reference, such as the International Classification of Functioning, Disability and Health (ICF), which may come with its limitations (Geyh et al., 2007). Moreover, where Golomb, Vickrey and Hays (2001) and Geyh et al. (2007) examined the domain coverage of HR-QOL measures and reported on psychometric information, this review will additionally assess each measure for its clinical utility, which is its feasibility of use in clinical practice (Burton & Tyson, 2015a; 2015b).

In summary, this paper will systematically review and identify effective HR-QOL measures from existing stroke literature. This paper aims to provide an updated review and recommendation of measures to inform both clinical practice and research (Duncan et al., 1999) in the measurement of HR-QOL in stroke rehabilitation and stroke trial settings. Comparisons will first be made on the clinical utility of the measures and the methods set out by research within the stroke literature (Burton & Tyson, 2015a; 2015b) to determine the most suitable HR-QOL tools for clinical practice. Psychometric properties (e.g. validity, reliability) will be identified and

synthesised for each measure. The HR-QOL domain coverage for measures will then identified as done by Golomb, Vickrey and Hays (2001).

Method

Protocol and Registration

The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher, Liberati, Tetzlaff & Altman, 2009) and is registered with PROSPERO: International prospective register of systematic reviews (ID: CRD42019158565).

Search strategy

Electronic databases MedLine, PsycINFO, and Embase were searched from their inception to 2nd February 2020, using the following keywords: stroke OR cerebrovascular accident OR CVA and screen* OR tool OR measure* OR questionnaire OR scale AND quality of life OR wellbeing OR well-being OR life satisfaction OR health OR health-related quality of life. All searches were limited to human studies that are published in the English language.

The specific search terms used are adapted across different databases to match different search interfaces and options, whilst following as close as possible to the keywords identified (see Appendix A). Using a Boolean strategy, all searches included the clinical population of interest ('stroke') and instrument of interest ('health-related quality of life', 'measurement', 'tool').

Eligibility Criteria

Following the initial search, all titles and abstracts were screened by one author (JP) for its relevance to the research question. They were later further screened by two authors (JP & KH) against the eligibility criteria set for this systematic review.

The inclusion criteria included:

1) Studies published in the English language within a peer-reviewed journal;

2) Studies with adult stroke (ischemic and/or haemorrhagic) survivors over 18 years of age;

3) Studies with original data on stroke patients using measurements that assessed some aspect of HR-QOL;

4) Studies outlining the properties of the HR-QOL tool (e.g. HRQOL domains being measured, measure characteristics and psychometric properties such as validity and reliability)

The exclusion criteria were as follows:

1) Studies validating a language translation of a tool;

2) Conference papers or abstracts where data could not be extracted;

3) Studies with less than 50% stroke participants or data from stroke patients could not be extracted;

4) Studies including participants with Transient Ischemic Attacks (TIA) and Subarachnoid Haemorrhage (SAH). This exclusion is because TIAs are defined by focal neurological symptoms that last for <24 hours (Easton et al., 2009). In contrast, stroke patients typically experience severe debilitating symptoms which require further rehabilitation treatment (Lam, Bloom & Kha, 2019). Although SAHs can be associated with stroke, it includes trauma resulting from head injuries, and may therefore be diagnosed and treated differently from a stroke (Chong, 2020). Exclusion of TIA and SAH participants from post-stroke studies and reviews have been noted within the literature (Hackett, Anderson, House & Xia, 2008; Sagen et al., 2009; Knapp et al., 2017).

5) Studies with restrictive assessments, e.g. of neurological function, social function or mental status, which although may influence HR-QOL, were not HR-QOL measures and/or were not constructed for this purpose (Golomb, Vickrey & Hays, 2001).

Data extraction & management

The primary author (JP) extracted data independently from the selected articles which met the eligibility criteria. Data were extracted based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidance, as set out by Von Elm et al. (2007). Following this guidance, demographic information (e.g. patient samples, settings), selection criteria, name of tools evaluated, domains assessed, and data for reliability and validity of the measures were extracted where available. Moreover, the following data were extracted from each HR-QOL measure: (i) clinical utility (following Burton & Tyson, 2015), (ii) psychometric properties, and (iii) HR-QOL domain coverage (following Golomb, Vickrey & Hays, 2001).

Clinical Utility

To assess a measure's clinical utility, the criteria and scores are as follows:

1) Administration and scoring times: ≤5 min (score 2); 6–10 min (score 1); ≥11 min (score 0).

2) Initial costs to purchase measures (e.g. starter kit including manual): 2=freely available; 1=cost<£100; 0=cost >£100 or unavailable.

3) Additional cost per record form: 1=no additional costs; 0=additional cost or unavailable.

4) Need for specialist training for administration and scoring: 1=no specialist training required; 0=specialist training required.

The sum of these scores comes to a maximum of six points, with higher scores indicating greater clinical utility.

Psychometric Properties

Information on the psychometric properties, namely reliability and validity of each measure was extracted.

Where available, this included inter-rater reliability ('IR'), test-retest reliability ('TR'), and internal consistency reliability ('IC'). Where additional information was available on construct validity, criterion validity and content validity, this data was also recorded. This included information on proxy administration.

HR-QOL Domains

In their review, Golomb, Vickrey and Hays (2001) identified a set of HR-QOL domains which may be affected by the onset of stroke. These domains cross the traditional boundaries of classifying clinical outcomes, which places emphasis on impairments and disabilities (Ford, 1984). The HR-QOL domains include physical functioning, role functioning, emotional well-being, cognitive functioning, communication, social functioning, recreation, energy, general health perceptions, overall QOL and symptoms. Selected measures were evaluated for their domain coverage, and given the following ratings: 'no coverage', which is represented by the symbol ('-') , 'limited coverage' (1 item), represented by the symbol ('+') and 'noteworthy coverage' (≥2 items), represented by the symbol ('++').

Assessment of Quality

The methodological quality of all included articles was considered to screen for risk of bias in studies to ensure quality and trustworthiness of content (Mokkink et al.,2018; Prinsen et al., 2018; Terwee et al., 2018). The Consensus-based Standards for the selection of health Measurement Instruments (COSMIN)'s risk of bias checklist, which was developed to standardize systematic reviews of Patient Reported Outcome Measures and identify areas of refinement, was used (Mokkink et al., 2018). This checklist comprised of eight domains, all of which match the guidelines set out by the Medical Outcomes Trust (MOT; Terwee et al., 2007). The domains included content validity, internal consistency, criterion validity, construct validity, reproducibility, responsiveness, floor or ceiling effects and interpretability. All items were rated on a four-point rating system: 'inadequate'. 'doubtful', 'adequate', or 'very good' (Mokkink et al., 2018). For each domain, the quality judgement was made by its lowest rated item (Terwee et al., 2012).

The methodological qualities of each domain are then labelled 'poor', 'fair', 'good' or 'excellent'. The final overall quality rating for each study was arrived as a mean across all domains. The domain-level and overall quality ratings for each study can be found

as Appendix C.

Quality of study was assessed by the primary author (JP). To ensure process rigour, a second-rater (KH) randomly selected and co-rated 30% of the articles. Any inconsistencies in assessments between the two independent reviewers were discussed until a shared conclusion was agreed. There were minimal differences in ratings between the reviewers, which did not change the overall quality rating of the study. Appendix C indicates the studies that were co-rated for quality.

Results

The search strategy yielded 1056 papers, and 1 additional paper was identified through scanning reference lists from relevant articles. After removing 109 duplicates, 948 abstracts were available for screening. These abstracts were screened for relevance to the research question, resulting in 894 papers to be excluded and 54 papers remaining to be examined for full text eligibility. Of the 54 relevant articles, 12 used a non-English translation of the HR-QOL tool and 1 involved non-adult stroke participants. Additionally, 14 articles did not have sufficient information or data for the review and 1 article was not published in a peer reviewed journal. There were 2 studies were excluded as it was assessed to not fit with the aims of the review, such that it explored novel modifications of an existing HR-QOL scale for its use over the telephone, and tools specific for the brain-injury population. This process resulted in 24 studies meeting the inclusion criteria for the review. Figure 1 shows a flow chart for the article identification and selection process.

Figure 1. *Study selection flow diagram, N= Number of articles*

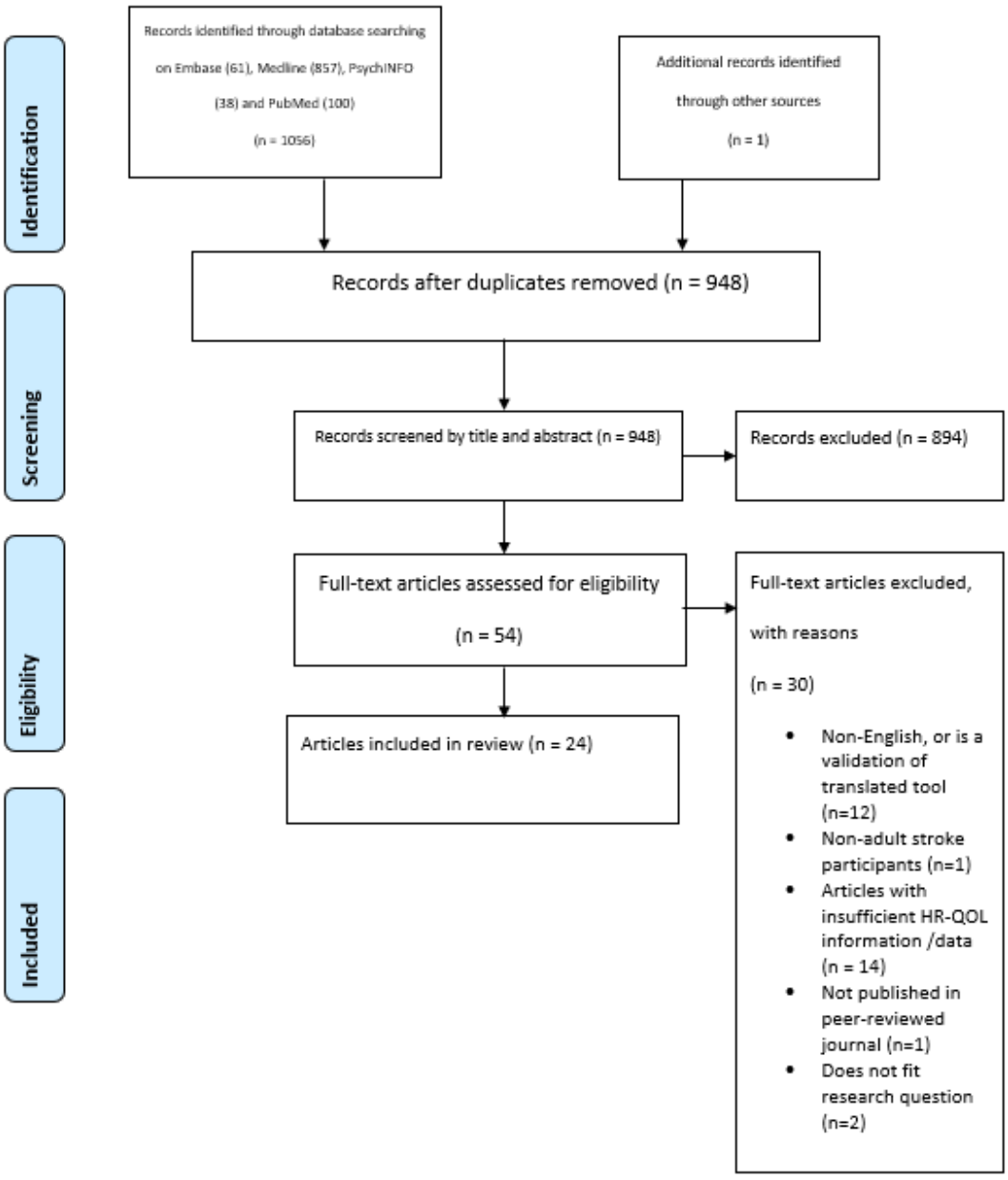

Figure 1 Diagram adapted from PRISMA; detailing flow of articles retrieved from searches through to inclusion. N= Number of studies

Included studies / articles

Table 1 shows the 24 articles considered for this systematic review, as well as the key information about each study. The included studies comprise a total of 4469 stroke participants at different stages of recovery. Fifteen articles studied the measurement properties of an already existing HR-QOL measure, whereas nine described the development and validation of a new HR-QOL measure.

From the 24 studies, seventeen HR-QOL measures applied in stroke participants were identified. Several papers identified the same HR-QOL scale, as detailed in Table 2. The measures identified included six 'generic' measures and eleven 'stroke-specific' measures, some of which are shortened or updated versions of each other (see Table 2).

Ten of the 24 studies were conducted in North America; seven in the United States and three in Canada. There were also articles from the United Kingdom (n=3) and European countries (n=2). Non-western studies included those conducted in Asia (n=4), South America (n=1), Australia (n=1) and Africa (n=1). Two studies were conducted on a multi-national level, using cross-cultural data.

Clinical utility

Table 2 presents the clinical utility ratings of included measures. In terms of administration time, seven tools took approximately 5 minutes, whereas other took up to 20 minutes. This criterion is important in selecting measures as it considers response burden in patients which is particularly salient for stroke survivors who may experience reduced attention and/or fatigue. Conversely, longer measures may assess a wider number of domains and provide more useful clinical information about a person's HR-QOL. Most measures were freely available and easily accessible for non-commercial use, although the availability for

clinical use of some newer tools (beyond the published paper) was unclear (HSQuale, Stroke-PROM, NEWSQOL and HRQOLISP-40). All but one measure did not require a licensing fee (HUI) and specialised training to administer the tool. For some of the measures, the training required to administer the tool was described as 'minimal' (n= 8), involving studying a manual or having basic skills and experience in test administration.

Psychometric properties

Psychometric properties for each measure are presented in Tables 3 and 4. The results in Tables 3 and 4 illustrate that information on reliability and validity of these measures in patients with stroke is limited and have not been thoroughly assessed.

Table 3 synthesises information on reported reliability tests for each measure (IC, TR and IR). As seen in Table 3, only ten of the seventeen HR-QOL measures had information on reliability. Of the ten measures reporting reliability data, seven were stroke-specific HR-QOL tools and three were generic HR-QOL tools. No reliability data was identified for seven measures (three of which are stroke-specific tools and four generic tools.

Table 4 presents the available data for validity tests. Where information was available, various constructs of validity were recorded. Evaluations of validity were reported for thirteen of the seventeen HR-QOL measures. Information on validity was reported on a range of concepts (e.g. content-related and criterion-related validity).The thirteen measures included all eleven stroke-specific measures and three of the generic HR-QOL tools. No validity data was identified for three generic HR-QOL measures.

Recommended measures

The information gathered from this review is summarised in Table 5. Table 5 presents the recommended HR-QOL measures for clinical and research practice. Starting from the top, this table differentiates between generic and stroke-specific HR-QOL measures. It then outlines the process for excluding recommended HR-QOL measures by stages. At each stage, information on deciding factors such as clinical utility, psychometric properties (reliability

and validity data) and availability of the measure were used to ‘eliminate’ tools that do not provide sufficient information, may incur additional costs or is not widely available for use. This results in five recommended HR-QOL measures. The recommended measures include one generic measure (SF-12; ≤5 minutes administration time) and four stroke-specific measures (SIS 2.0; SIS 3.0; SAQOL-39; SS-QOL; ≥11 minutes administration time). Clinicians and researchers following information from this table are then encouraged to make decisions on the best tool to use based on its domain coverage, and whether it fits the patient or participant’s presentation.

To aid the use of this information, a print-friendly design of this table was created as a flow chart (Appendix K). This flow-chart identifies clearly the key questions for clinicians and researchers, such as ‘Is the person presenting with stroke-specific symptoms?’, ‘Does the person have aphasia?’, and lastly, ‘How much time do you have to administer the tool?’. It is also supplemented with information on HR-QOL domains covered by each of the recommended measures.

Domain coverage

Table 6 shows the domain coverage HR-QOL measures identified in previous research as pertinent to the stroke population (Golomb, Vickrey & Hays, 2001). As some measures also assessed additional unlisted domains, this was noted in the presenting table.

It is apparent from Table 6 that some generic measures had appropriate HR-QOL domains coverage and were comparable to stroke-specific measures. Some shorter measures (e.g. EQ-5D-5L, SF-6D) were unable to evaluate a wider range of domains in comparison to longer measures. No measure was found to cover all domains.

Quality of studies

In accordance with the COSMIN rating, nineteen of the 24 studies were rated to be of 'Fair' quality, five of 'Good' quality and one of 'Poor' quality.

Proxy administration

Most measures identified were self-reported tools but with the option for interviewer-administration. For nine measures, the use of proxy administration was specified. Notably, either no or minimal instructions were available to guide this process. Only the EQ-5D-5L provided a specific proxy version, whereas the HUI had a separate measure for interview-administration. Overall, information on proxy administration of HR-QOL measures is scarce.

Table 1. *Description of selected papers*

Study author and year	Setting and country	Stroke participants,N (Mean Age)	Inclusion criteria	Exclusion criteria	Proxy respondent	HR-QOL Measure used	Time post-stroke assessmentwas made (SD)	Quality Rating
Bohannon, Maljanian, Lee & Ahlquist (2004)	Neurology Service, Hospital, United States	N= 90 (70.4)	Ischemic stroke patients	NA	NA	SF-12	3 months & 12 months	Fair*
Buck et al. (2003)	3 stroke services, 1 rehabilitation unit, United Kingdom	Phase 1:N=28; N=30; N= 100 Phase 2: N= 106 (70)	NA	NA	NA	NEWSQOL	NA	Fair*
Chen et al. (2012)	7 study sites, Taiwan	N= 126 (55.26)	(i) first-ever stroke, (ii) demonstratio n of brunnstrom stage II or higher for the proximal and distal parts of the affected upper limb (13), (iii) no severe cognitive deficits	(*i*) excessive spasticity at any joint of the arm (Modified Ashworth Scale score < 2), and (*ii*) severe physician-determined medical problems (e.g. severe aphasia, a	NA	SS-QoL-12	16.87 (16.1)	Fair

			(Mini-Mental State examination score > 21) (14), and (iv) ability to understand the study and respond to questions.	vision problem, or poor physical condition)				
Chen et al. (2016)	5 medical centres, Taiwan	N= 70 (52.8)	(i) No serious cognitive function deficits (based on Mini-Mental State Examination) ; (ii) No excessive spasticity in the upper extremity (Modified Ashworth Scale <3); (iii) Able to follow instructions to complete questionnaire and perform	NA	NA	EQ-5D-5L; EQ-VAS; SIS 3.0	17 months (median, range 0.4-94)	Fair

			therapeutic activity; (iv) Aged 20-80					
Duncan et al. (1999)	Subset participants of a wider stroke study, United States	Minor stroke, N =33 (69.2); Moderate stroke, N= 58 (71.9)	Diagnosis of minor or moderate stroke	NA	NA	SIS 2.0	1, 3 & 6 months	Fair
Guo, Togher, Power & Koh (2016)	Subset participants of a wider stroke study, Singapore	N=97 (63.7) N= 36 English subset (60.4)	First-time stroke survivors as evidenced by brain imaging	Participants with a known history of dementia and/or major psychiatric illness or other severe / potentially terminal co-morbidities	Proxy respondent for participants with severe aphasia results not reported	SAQOL-39	3 months, repeated again within 1 week	Fair
Hamedani et al. (2001)	Subset participants of a wider stroke study, 44 hospitals across 6 states, United States	Phase 1: N=71 (63.4)	Patients hospitalized for a primary, nontraumatic intracranial haemorrhage	(i) Patients who are unable to communicate within 30 days of their stroke; (ii) History of prior stroke or other brain lesion predisposing	NA	HSQuale	1 year	Poor*

				to haemorrhage.				
Hilari, Byng, Lamping & Smith (2003)	2 speech and language service providers, 1 inner city, 1 semirural, 1 not-for-profit organisation for people with aphasia, United Kingdom	N=83 (61.67)	Participants with long-term aphasia resulting from stroke (of at least 1-year duration) (ii) Participants living at home before the stroke	(i) Known pre-stroke history of severe cognitive decline or mental health problems; (ii) Unable to self-report on questionnaires	Frenchay Aphasia Screening Test (FAST) receptive core of 7 (of 15) was used as a cut-off, below which significant others provided proxy reports	SAQOL-39	3.5 years (3.09)	Good
Hilari et al. (2009)	Hospitals, United Kingdom	2-weeks: N=87;3-months: N= 87; 6-months: N=76	(i)Over 18 years; (ii) admitted with first ever stroke; (iii) hospital stay due to stroke of at least 3 days	(i)Did not live at home prior to stroke; (ii) known history of mental health problems or cognitive decline prior to stroke; (iii) other severe or potentially terminal comorbidity; (iv) unable or too unwell to	Frenchay Aphasia Screening Test (FAST) receptive core of 7 (of 15) was used as a cut-off, blow which significant others provided proxy reports	SAQOL-39	2 weeks, 3 months & 6 months	Fair

				give informed consent; (v) does not speak English pre-morbidly				
Hobart et al. (2009)	3 hospital sites, United States	N=177 (62)	(i) Patients with ischemic stroke; (ii) National Institutes of Health Stroke Scale Language Score <2; (iii) Completed the SF-36	History of dementia	NA	SF-36	1-11 months	Fair*
Hunger et al. (2012)	Participants part of a wider stroke study, Germany	N=212 (12.8)	(i)Diagnosis of stroke based on ICD-10; (ii) Age 18-80; (iii) Cognitively able to participate in group intervention; (iv) Good	(i)Impairments that will hinder participation in a group intervention; (ii) Memory deficits; (iii) History of psychiatric disorders	No proxies used	EQ-5D; SIS 2.0	NA	Fair

			command of the German Language; (v) Barthel index score >35; (vi) Signed consent	prior to stroke				
Kerber et al. 2013)	Participants part of a wider stroke study, United States	N=45 (66.0)	(i)Patients with validated ischemic stroke and self-reported assessments	(i)Assessments performed in Spanish; (ii) Incomplete assessment measures (>5 missing items); (iii) Proxy interviews	No proxies used	SSQOL	90 days	Fair
Kwon et al. (2006)	13 hospital sites, United States	Telephone responders: N=136 (68.04); Non-telephone responders: N=62 (68.05)	(i)Diagnosis of stroke, confirmed by medical reports	NA	NA	SIS	12 weeks; 16 weeks	Fair*
Luo et al. (2015)	9 hospital sites, China	Phase 1: N=133; Phase 2: N=475	(i)Diagnosis of stroke, based on ICD-9	Individuals with tetraplegia, psychosis or serious	Investigators helped patients with severe visual impairments fill in the	Stroke-PROM	NA	Good

				comorbidities (e.g. cancer)	questionnaires according to patient's verbal responses			
MasIsaac et al. (2016)	Data from the Virtual International Stroke Trial Archive	N=5549 (68.5)	NA	NA	NA	SF-SIS	NA	Fair
OjoOwolabi et al. (2010)	Hospital sites; Nigeria, Germany	N=100 (59.4); N=103 (66.9)	(i)Clinical or radiological diagnosis of stroke; (ii)Stroke occurrence 1 or more months prior to the interview	(i)Ambiguous diagnosis of stroke; (ii) Has other medical conditions that were neither risk factors for nor complications of stroke but could interfere with HRQOL	Proxies were judged to be reliable if they lived with the participant, had close relations to them and were sure of the answers to questionnaire items	HRQOLISP-40	NA	Fair
Pickard et al. (2005)	2 hospital sites; Canada	N= 98 (67.0)	(i)Ischemic stroke, confirmed via computerized tomography or imaging	(i)Diagnosis of haemorrhagic stroke, lower brain stem stroke, coma, global	No proxies	EQ-5D; SF-6D; HUI2; HUI3	NA	Fair

			scans; (ii) Aged 18 years or older; (iii) Able to comprehend an English questionnaire ; (iv) Lives within 150km of Edmonton, Alberta	aphasia, Wernicke's aphasia, dementia, cognitive impairment; (ii)Life expectancy <6 months for any medical reason (judgement of clinical assessor)				
Possiant et al. (2003)	Community; Canada	Phase 1: N=493 (70.0); Phase 2: N=91(69.0); Phase 3: N=68 (72.0); Phase 4: N=32 (68.0); Phase 5: N=91 (69.0)	NA	NA	NA	PBSI	NA	Good
Post et al. (2011)	Data from 3 previous studies of inpatient and outpatient	N=105(60.8)	(i)Aged <85 years; (ii)No comorbidity that might affect outcome and	(i)Pre-existing drug abuse/depression/activities of daily life dependence/c	NA	SS-QoL-12	6 – 11 months	Fair

	sites; Netherlands		testable within 21 days after stroke; (iii)Stroke diagnosis based on imaging scans	ognitive impairment; (ii) disturbed consciousnes s or inability to comprehend task instructions; (iii) recurrent stroke; (iv) comorbidity that might affect outcome				
Richardson et al. (2016)	Community stroke service; Canada	Baseline=164 (66.7); 6-months: N=108 (66.2); 12-months: N=37 (69.35)	NA	NA	NA	SIS 3.0	NA	Fair*
Silva et al. (2016)	Outpatient clinic; Brazil	N=81	(i)Diagnosis of primary or recurring stroke more than 6 months earlier; (ii)Weakness and/or spasticity in	(i)Clinical conditions other than hemiparesis stemming from a stroke, those with motor aphasia and	NA	SS-QoL	NA	Good*

			the affected half of body	impaired cognition				
Strum et al. (2002)	Participants part of a wider stroke study, Australia	N=93 (72.0)	(i)First ever or recurrent stroke, with neuroimaging scans	NA	16% were assessed by means of a proxy response from the best available informant	AQoL	NA	Fair
VincentOnabajo et al. (2013)	Hospital, Nigeria	N=55 (58.0)	(i)First-incidence stroke; (ii) Able to communicate	(i)Patients with impaired cognition and severe comorbidities	Proxy administration was carried out by family members who are primary caregivers for participants who had difficulty communicating or exhibited frailties that impeded self-report	HRQOLISP-40	NA	Fair*
Williams et al. (1999)	3 hospital sites; United States	N=32(61.0)	(i)Diagnosis of acute ischemic stroke; (ii) Aged >18	(i)Prior stroke with persistent deficit; (ii) intracerebral	No proxy respondents	SS-QOL	NA	Fair*

		years; (iii)Able to return for follow-up 1 month after stroke	or subarachnoid haemorrhage; (iii)dysphasia at 1 month after stroke affecting communication; (iv) significant comorbidities likely to concurrently affect HR-QOL	

*AQoL. Assessment of Quality of Life; EQ-5D, EQ-5D-5L, EuroQoL 5-Dimensions Questionnaire; EQ-VAS, EuroQoL Visual analogue scale; (HUI2, Health Utility Index Mark 2; HUI3, Health Utility Index Mark 3;HSQuale, Haemorrhagic Stroke Quality of Life ; HRQOLISP-40, Health-Related Quality of Life in Stroke Patients 40-items; NEWSQOL, Newcastle Stroke-Specific Quality of Life Measure; PBSI, Preference-Based Stroke Index; SF-12, SF-6D, SF-36, Medical Outcomes Study Short-Form Health Survey (12 item, 6-dimensions, 36-item); Quality ratings marked * indicate papers that were co-rated.*

Table 2. *Brief description of each identified measure and the derivation of its clinical utility score for each criteria.*

Measure	Brief Description	Type of tool	Administration	Time to administer	Training required	Initial costs	Recurring costs	Clinical utility score /6
AQoL-4D	Patients choose one of four statements (graded according to severity) for 12 items, spanning 4 dimensions. Items are scored between 1 to 4 points. This has a total minimum score of 12 and maximum score of 48.	Generic	Self-report; interview; proxy	5 minutes	No	Freely available	NA	6
EQ-5D-5L	Patients choose one of 5 responses (graded according to severity) for 5 items. Each item refers to different dimensions to reflect a person's current health state.	Generic	Self-report; interview; (proxy version available); Includes visual analogue scale (VAS)	< 5 minutes	No	Freely available for non-commercial use	NA	6
HUI (2 & 3)	HUI encompasses 8 standard questionnaires specific to mode of administration (self/interview) and recall periods ('usual	Generic	Self-report (15-item); Interview (40-item)	5 – 10 minutes (15Q); 3 minutes (40Q)	Yes	Minimum licensing fee of $USA 3,000	Depending on license type	1

	health'; 'during past 4-weeks'; '…-2-weeks';'…-1 week'). Responses to the questions are then mapped to two classification systems, HUI2 and HUI3.							
HSQuale	Patient is interviewed on this 54-item scale, where 38 items are scored and 16 unscored. The items cover 7 domains. For each item, patients choose one of four statements (graded according to severity). Domain scores are determined by averaging item scores included in a domain.	Specific; Stroke	Interview	15 minutes	No	Unavailable	Unavailable	1
HRQOLISP-40	Patient responds to 40 statement on a 5-point Likert scale. Items correspond to 7 domains. Domain scores are the sum of all item scores, with a maximum transformed score of 100.	Specific; Stroke	Self-report; proxy	19 minutes	No	Unavailable	Unavailable	1
NEWSQOL	Patient responds to 56 statement items on a 4-	Specific; Stroke	Interview	20 minutes	Minimal	Unavailable	Unavailable	1

	point Likert scale. These items correspond to 11 domains,							
PBSI	Stroke-specific health index consisting of 10 items, developed primarily for use as an outcome in cost-effectiveness studies. For each item, patient chooses one of 3 statements (graded according to severity) based on their ability to perform different activities.	Specific; Stroke	Self-report; Proxy	10 - 15 minutes	No	Unavailable	NA	5
SF-6D	The SF-6D is a variation of the SF-36 scale, which derivates a single quality-of-life index. It focuses on 6 domains of the SF-36	Generic	Self-report; interview	<5 minutes	No / Minimal	Freely available	NA	6
SF-12	The SF-12 is a shortened version of the SF-36, created to reduce response burden. It uses the same 8 domains of the SF-36. On the SF-	Generic	Self-report; interview	<5 minutes	No / minimal	Freely available	NA	6

	12, the patient responds to statements and questions on a 2 (YES/NO), 3 and 5-point Likert scale.							
SF-36	Patient scores 36 items, which is categorised into 8 subscales. Each of the subscales is scored separately using item weighting and additive scaling. Summed data are transformed onto a 0-to-100-point scale. The 8 subscales can be combined into 2 summary health status measures, physical function and mental health.	Generic	Self-report; interview	10 minutes	No / Minimal	Freely available	NA	5
SIS 2.0	This scale consists of 64 items, grouped into 8 domains. Each item is rated on a 5-point Likert scale about the patient's difficulties in the past week. Scores for each domain range from 0 to 100, where a higher score indicates better HRQOL. There is no	Specific; Stroke	Self-report; Proxy; Includes VAS.	15 – 20 minutes	Minimal	Freely available	NA	4

	overall score, but a combination of 4 subscales can provide a physical domain score. There is also a VAS of 0 to 100, for patients to rate their percentage of recovery.							
SIS 3.0	Patient responds to 59-items on the scale, which is grouped into 8 domains. Scores for each domain range from 0 to 100, where a higher score indicates better HRQOL. There is no overall score, but a combination of 4 subscales can provide a physical domain score. There is also a VAS of 0 to 100, for patients to rate their percentage of recovery.	Specific; Stroke	Self-report; Proxy; Includes VAS.	15 – 20 minutes	Minimal	Freely available	NA	4
SF-SIS	The SF-SIS is a shorter version of the SIS 2.0 and 3.0. The patient responds to 8 statement items on a 5-point Likert scale, graded according to severity of difficulties experienced.	Specific; Stroke	Self-report; Proxy	< 1 minute	Minimal	Freely available	NA	6

Stroke-PROM	This scale consists of 46 items describing 4 domains, further categorised into 10 subdomains. Patient responds to each item on a 5-point Likert scale ranging from 0 - 4 (graded by severity), on how often they experience a difficulty. Each item produces a score of 1 – 5 for each item. Higher scores reflect a more positive outcome.	Specific; Stroke	Self-report	9 minutes	No	Unavailable	Unavailable	2
SAQOL-39	The SAQOL-39 is an adapted version of the SS-QOL, for use with stroke patients with aphasia. For those with receptive aphasia, people who score ≥ 7/15 on the receptive domains of the FAST (Enderby et al., 1987) able to self-report reliably on the SAQOL-39 (Hilari et al., 2001; 2003). The patient responds to 39 items on a 5-point Likert scale,	Specific; Stroke	Interview	10 – 15 minutes	Minimal	Freely available	NA	4

	which corresponds to 3 domains.							
SS-QOL	Patient responds to 49 items that are assessed on 5-point Guttman-type scales. Each item is answered using 1 of 3 different response sets. This covers 12 domains, providing domain and summary scores (unweighted averages) that range from 49-245. Higher scores indicate better functioning.	Specific; Stroke	Self-report; Proxy	15 – 20 minutes	No	Freely available	NA	4
SS-QOL-12	One item was selected from each of the 12 domains of the SS-QoL. These are then grouped into two dimensions, physical and psychosocial.	Specific; Stroke	Self-report; Proxy	10 min	No	Unavailable	NA	4

AQoL. Assessment of Quality of Life; EQ-5D, EQ-5D-5L, EuroQoL 5-Dimensions Questionnaire; EQ-VAS, EuroQoL Visual analogue scale; (HUI2, Health Utility Index Mark 2; HUI3, Health Utility Index Mark 3;HSQuale, Haemorrhagic Stroke Quality of Life ; HRQOLISP-40, Health-Related Quality of Life in Stroke Patients 40-items; NEWSQOL, Newcastle Stroke-Specific Quality of Life Measure; PBSI, Preference-Based Stroke Index; SF-12, SF-6D, SF-36, Medical Outcomes Study Short-Form Health Survey (12 item, 6-dimensions, 36-item); SIS 2.0, 3.0,

Stroke Impact Scale (Version 2.0, 3.0); SF-SIS, Short-Form Stroke Impact Scale; Stroke-PROM; Stroke-Patient Reported Outcome Measure, SAQOL-39, Stroke and Aphasia Quality of Life Scale-39; SS-QOL, 12-item Stroke-Specific Quality of Life Scale, NA; Not Available

Table 3. *Reliability of measures for health-related quality of life in stroke*

Measure	Study	Sample and settings	Reliability			
			Internal consistency reliability (IC)	Test-retest reliability (TR)	Inter-rater reliability (IR)	Proxy agreement
AQoL-4D	Strum et al. 2002	N/A	NDI	NDI	NDI	NDI
EQ-5D-5L	Chen et al. 2016	N/A	NDI	NDI	NDI	NDI
	Hunger et al. 2012	N/A	NDI	NDI	NDI	NDI
	Pickard et al. 2005	N/A	NDI	NDI	NDI	NDI
HUI	Pickard et al. 2005	N/A	NDI	NDI	NDI	NDI
HSQuale	Hamedani et al. 2001	98 stroke participants	Cronbach's α For HSQuale domains: General outlook (0.78), physical functioning (0.89), cognitive functioning (0.88), social & leisure activities (0.85), emotional well-being (0.83), work & financial status (0.89) and relationship (0.56).	The OSQ had excellent test-retest reliability (κ= 0.833) on Cicchetti weighted κ ratings.	NDI	NDI
HRQOLISP-40	OjoOwolabi et al. 2010	100 stroke participants in Ibadan, 103 stroke participants in Berlin	Cronbach's α was ≥.7 in every domain in both cities	In both cities, the single-rater test-retest weighted κ	NDI	NDI

				statistics were excellent (>0.75) for most items (37 in Ibadan and 39 in Berlin) and good for the remainder items		
	Vincent-Onabajo et al. 2013	N/A	NDI	NDI	NDI	NDI
NEWSQOL	Buck et al. 2003	106 stroke patients at Phase 2 of measure development.	High for all domains (Cronbach's α 0.71 – 0.90)	Intraclass correlation coefficients (ICC) based on 50 informants, 2 weeks apart was high (0.78 – 0.92)	NDI	NDI
PBSI	Poissant et al. 2003	N/A	NDI	NDI	NDI	NDI
SF-6D	Pickard et al. 2005	N/A	NDI	NDI	NDI	NDI
SF-12	Bohannon et al. 2004	90 ischemic stroke patients admitted to a neurology service	Cronbach's α Before stroke (0.833) 3 months after stroke (0.878) 12 months after stroke (0.894)	NDI	NDI	NDI

SF-36	Hobart et al. 2002	177 stroke participants	Cronbach α coefficients ranged from 0.68 – 0.90	Intraclass correlation coefficients for test-retest reliability of SIS domains ranged from 0.16 – 0.55	NDI	NDI
SIS 2.0	Duncan et al. 1999	91 participants with minor and moderate stroke	Cronbach α coefficients ranged from 0.83 to 0.90 and meet criteria for measuring change over time	Intraclass correlation coefficients for test-retest reliability of SIS domains ranged from 0.70 to 0.92, except for the emotion domain (0.57)	NDI	NDI
SIS 3.0	Richardson et al. 2016		Cronbach α coefficients ranged from 0.81 to 0.97	NDI	NDI	NDI
SF-SIS	MasIsaac et al. 2016	N/A	NDI	NDI	NDI	NDI
Stroke-PROM	Luo et al. 2015	475 stroke participants, 104	Cronbach α coefficients for overall = 0.905, Domains = 0.861-0.908	NDI	NDI	NDI

		control participants				
SAQOL-39	Guo et al. 2016	24 stroke participants	Cronbach α coefficients for overall = 0.96, for domain scores = 0.94-0.98. Item-total correlations range from 0.37 – 0.79 (overall) and 0.42 to 0.98 (domains).	Intraclass correlation coefficients Overall = 0.99 Physical domain = 0.99 Psychosocial = 0.98 Communication = 0.99	NDI	NDI
	Hilari et al. 2003	83 stroke participants	Cronbach α coefficients for overall = 0.93, Subdomains = 0.74-0.94	Intraclass correlation coefficients Overall = 0.98 Subdomains = 0.89-0.98	NDI	NDI
	Hilari et al. 2009	87 stroke participants	Cronbach α coefficients for overall = 0.95, Subdomains = 0.92-0.95	Intraclass correlation coefficients Overall = 0.96 Subdomains = 0.92-0.98	NDI	NDI
SS-QOL	Chen et al. 2012	N/A	NDI	NDI	NDI	NDI
	Kerber et al. 2013	N/A	NDI	NDI	NDI	NDI

	Silva et al. 2016	75 stroke participants	NDI	Intraclass correlation coefficients= 0.95 (inter-rater), 0.96 (intra-rater)	NDI	NDI
	Williams et al. 1999		Cronbach's α values for each domain>0.73, ranging from 0.73-0.89			
SS-QOL-12	Post et al. 2011	N/A	NDI	NDI	NDI	NDI

AQoL. Assessment of Quality of Life; EQ-5D, EQ-5D-5L, EuroQoL 5-Dimensions Questionnaire; EQ-VAS, EuroQoL Visual analogue scale; (HUI2, Health Utility Index Mark 2; HUI3, Health Utility Index Mark 3;HSQuale, Haemorrhagic Stroke Quality of Life ; HRQOLISP-40, Health-Related Quality of Life in Stroke Patients 40-items; NEWSQOL, Newcastle Stroke-Specific Quality of Life Measure; PBSI, Preference-Based Stroke Index; SF-12, SF-6D, SF-36, Medical Outcomes Study Short-Form Health Survey (12 item, 6-dimensions, 36-item); SIS 2.0, 3.0, Stroke Impact Scale (Version 2.0, 3.0); SF-SIS, Short-Form Stroke Impact Scale; Stroke-PROM; Stroke-Patient Reported Outcome Measure, SAQOL-39, Stroke and Aphasia Quality of Life Scale-39; SS-QOL, Stroke-Specific Quality of Life Scale ; SS-QOL-12, 12-item Stroke-Specific Quality of Life Scale, N/A; Not Applicable, NDI; No data identified

Table 4. *Validity of measures for health-related quality of life in stroke*

Measure	Study	Validity	Findings	Sample
AQoL-4D	Strum et al. 2002	Spearman's rank correlation with Barthel Index	Independent living dimension; Rho = 0.85 Physical senses dimension; Rho= 0.45 AQoL total score; Rho = 0.77	92 patients with a first-ever or recurrent stroke
		Spearman's rank correlation with SF-36	Independent living dimension with SF-36 physical functioning subscale; R = 0.77 Social relationships dimension with SF-36 social functioning; R = 0.48 and SF-36 mental health subscale; R = 0.50. Psychological well-being dimension with SF-36 bodily pain; R = 0.61 and mental health subscale (R = 0.41).	
		Other findings	When adjusted for age, sex and 3-month impairment score, AQOL score at 3 months is a significant predictor of death or institutionalization (p = 0.006).	
EQ-5D-5L	Chen et al. 2016	Concurrent validity, predictive validity and acceptable responsiveness for detecting HR-QOL in stroke patients.	EQ-Index has reasonable concurrent validity and performed better than its visual analogue scale component (EQ-VAS). EQ-Index has better power for predicting the rehabilitation outcome in activities of daily living than other motor-related outcome measures.	65 stroke patients

			EQ-Index is moderately responsive to change (SRM=0.63), whereas EQ_VAS is only mildy responsive to change.	
	Hunger et al. 2012	NDI	NDI	N/A
	Pickard et al. 2005	NDI	NDI	N/A
HUI	Pickard et al. 2005	NDI	NDI	N/A
HSQuale	Hamedani et al. 2001	Construct validity. Discriminant validity.	Construct validity was strong when comparing HSQuale and SF-36 domains. Of 5 possible correlations, 4 were found to be strong (Pearson correlation coefficients > 0.50). Strong evidence for discriminant validity (mean Overall Summary Question scores significantly different for patients dichotomized into clinically distinct groups (pP<0.05).	98 stroke participants

HRQOLISP-40	OjoOwolabi et al. 2010	Discriminant validity. Construct validity.	Good content and face validity. There is good discriminant validity between stroke and control participants, particularly for domains in the physical sphere (physical, psychological, cognitive and eco-social domains). Interdomain correlations among National Institutes of Health Stroke Scale (NIHSS), Stroke Levity Scale (SLS), modified Rankin Scale (mRS) and the domains pf HRQOLISP-40 demonstrate convergent validity among domains within the same sphere and discriminant validity between domains in different spheres. This demonstrates construct validity.	100 stroke participants in Ibadan, 103 stroke participants in Berlin
	Vincent-Onabajo et al. 2013	NDI	NDI	N/A
NEWSQOL	Buck et al. 2003	Construct validity. Discriminant validity.	Construct validity was supported by all but 1 of the predicted correlations (cognition) with the NIHSS. Evidence of discriminant validity is provided by significant differences between participants of different age, NIHSS score and comorbidity in relevant NEWSQOL scores.	106 patients at Phase 2 of development.
PBSI	Poissant et al. 2003	Convergent validity	Pearson correlations between the PBSI and most of the SF-36 subscales were moderately high and significant ($p<0.005$), ranging from $r = 0.33$ (role emotional) to $r=0.48$ (bodily pain).	67 stroke participants

			Pearson correlations between the PBSI and EQ-5D was moderately high (r=0.76).	
SF-6D	Pickard et al. 2005	NDI	NDI	N/A
SF-12	Bohannon et al. 2004	Content validity.	A principal components analysis without varimax rotation calculated component scores of the SF-12. Pre-stroke, 3- and 12-month post-stroke HRQOL scores were compared to one another and to age-grouped reference values. These scores were consistent over time.	
SF-36	Hobart et al. 2002	NDI	NDI	N/A
SIS 2.0	Duncan et al. 1999	Discriminant validity, assessed by comparison with Rankin scale levels.	Discriminant validity was addressed by comparing mean scores for each domain to the groups defined by the Rankin scale. 6 of 8 domains were significantly different ($p>0.02$ to $p<0.0001$) across the Rankin levels. The	91 participants with minor and moderate stroke

			memory and thinking domain and emotion scores are not significantly different across the Rankin levels.	
		Criterion validity, assessed by Spearman Rank correlation coefficients with the following measures; Barthel Index, Functional Independence Measure, Fugl-Meyer, the Mini-Mental State Examination, the NIH Stroke Scale, the SF-36, the Duke Mobility Scale and the Geriatric Depression Scale.	Measures of disability were highly correlated with the established measures (correlation coefficients ranging 0.82 to 0.84). Correlations for domains that measure memory and communication were modest (0.44 to 0.58). Participation domain showed moderate correlation with SF-36 social function domain (0.70), but low correlations with SF-36 emotional (0.28) and physical role functions (0.45). Correlations between SIS 2.0 domains and patient's global rating of recovery was good (0.53 to 0.63), but weaker for correlations with memory, communication and emotion (0.21 to 0.39).	
SIS 3.0	Richardson et al. 2016	Concurrent validity assessed by correlating with EQ-5D-5L domains and EQ-VAS scores.	Pearson's correlation between SIS and EQ-5D-5L domains was moderate at baseline (r=0.50) and increased to r=0.74 at 6 and 12 months.	164 stroke participants at baseline, 108 stroke participants at 6 months, 37 stroke participants at 12 months

			The independent domain correlations between SIS and EQ-5D-5L Index score vary from weak – high across time. Correlation was moderate ate baseline (r= 0.50) but increased to high correlation at six and twelve months (r = 0.74). Weak to moderate correlation (r=0.23-0.593) was found for SIS cognition, memory and thinking, and communication domain. High correlation (r=0.71-0.76) was found for SIS physical domain at baseline.	
SF-SIS	MasIsaac et al. 2016	Content, convergent and discriminant validity. Correlation assessed using Spearman's ρ for each domain item relative to the domain total score. .	Acute: Agreement of SF-SIS with SIS-16 was excellent, Cornbach's α=0.92. SF- SIS showed strong correlations with all our chosen outcome measures: mRS (-0.83), BI (0.82), NIHSS (-0.77), EQ-5D (0.82), and EQ-VAS (0.72); correlations were equivalent to those seen for full SIS (-0.87, 0.89, -0.77, 0.88, and 0.73, respectively) Rehabilitation: Agreement of SF-SIS with SIS was excellent, Cornbach's α=0.96. SF-SIS showed significant (P<0.0001) correlation with BI (ρ=0.65), EQ-5D (ρ0.69), EQ-VAS (ρ=0.45), and SIS-VAS (ρ=0.57). Correlations were roughly equivalent to those seen for full SIS (0.72, 0.69, 0.46, and 0.58, respectively)	5549 acute study patients, 332 rehabilitation patients' part of a wider stroke trial

Stroke-PROM	Luo et al. 2015	Content, construct and discriminantvalidity	Content validity was achieved and confirmed using the content validity index (CVI). Authors referred to relevant literature and consulted experts as well as patients to ensure that all items were appropriate and relevant. Construct validity was met by using confirmatory factor analysis with the index of model fit. Discriminant validity was assessed by comparing the mean scores for every subdomain of the Stroke-PROM among healthy participants with those among groups of stroke patients as defined by the Rankin Scale, except for the subdomain of treatment. Overall, the Stroke-PROM was able to differentiate varying degrees of disability and dependence as defined by the modified Rankin scale.	
SAQOL-39	Guo et al. 2016	Convergent validity, assessed by correlating with Barthel Index (BI), modified Rankin Scale (mRS), EQ-5D-Index, EQ-5D-Visual Analogue Scale, center for epidemiologic studies depression scale (CES-D)	Correlation, r BI, r =0.64 MRS = -0.71 EQ5D Index, r = 0.74 EQ5D VAS, r =0.27 CES-D, r = -0.81	36 stroke participants

		Discriminant validity, assessed by correlating with the Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), National University Health System Aphasia Screening Test (NUHS-AST), and Boston Diagnostic Aphasia Examination Severity Rating Scale (BDAE Severity).	Correlation, r MMSE, r= 0.35 FAB, r = 0.53 NUHS-AST, r = 0.51 BDAE Severity, r =0.37	
	Hilari et al. 2003	Within-scale analyses Construct validity, assessed by correlating with the Frenchay Aphasia Screening Test (FAST), American Speech and Hearing Associaion Functional Assessment of Communication Skills for Adults (ASHA-FACS), Raven's Colored Progressive Matrices (RCPM), General Health Questionnaire (GHQ-12), Frenchay Activities Index (FAI), Social Support Survey (SSS).	Intercorrelations between subscale scores (r=0.10 to 0.47) and domain-total correlations (r = 0.38 to 0.58) Convergent validity (r = 0.55 to 0.67) Discriminant validity (r=0.02 to 0.27)	83 stroke participants
	Hilari et al. 2009	Convergent validity, assessed by correlating with BI, FAI, GHQ-12,	Overall (r= 0.36-0.70) Domains (r= 0.47-0.78))	87 stroke participants.
		Discriminant validity, assessed by correlating on the FAST	Overall (r= 0.26) Domains (r=0.03-0.40)	

SS-QOL	Chen. 2012	NDI	NDI	N/A
	Williams et al. 1999	Construct validity of Domains	SS-QOL scores were significantly linearly associated with corresponding scores of energies, family roles, mobility, mood, personality and self-care on other measures.	32 stroke patients
SS-QOL-12	Post et al. 2011	Criterion validity, assessed in comparison with SS-QOL (49 item).	The mean difference between scores on the SS-QOL 12- and 49-item measures were negligible, well within the limits of agreement (criterion) stated. This was true across domains and in overall scores for all 3 samples.	105 ischemic stroke participants
	Kerber et al. 2012	Validity of SS-QOL-12, assessed by correlating with the full-scale SS-QOL (49 item)	Correlation between the two tests was very high (intraclass correlation coefficient, 0.98)	45 ischemic stroke participants

AQoL. Assessment of Quality of Life; EQ-5D, EQ-5D-5L, EuroQoL 5-Dimensions Questionnaire; EQ-VAS, EuroQoL Visual analogue scale; (HUI2, Health Utility Index Mark 2; HUI3, Health Utility Index Mark 3;HSQuale, Haemorrhagic Stroke Quality of Life ; HRQOLISP-40, Health-Related Quality of Life in Stroke Patients 40-items; NEWSQOL, Newcastle Stroke-Specific Quality of Life Measure; PBSI, Preference-Based Stroke Index; SF-12, SF-6D, SF-36, Medical Outcomes Study Short-Form Health Survey (12 item, 6-dimensions, 36-item); SIS 2.0, 3.0, Stroke Impact Scale (Version 2.0, 3.0); SF-SIS, Short-Form Stroke Impact Scale; Stroke-PROM; Stroke-Patient Reported Outcome Measure, SAQOL-39, Stroke and Aphasia Quality of Life Scale-39; SS-QOL, 12-item Stroke-Specific Quality of Life Scale, N/A; Not Applicable, NDI; No data identified

Table 5. *Recommended measures considering clinical utility and psychometric properties.*

<table>
<tr><td colspan="6">Screening tools meeting selection criteria (n = 17)</td></tr>
<tr><td colspan="3">Generic HR-QOL tool (n = 6)</td><td colspan="3">Stroke-specific HR-QOL tool (n = 11)</td></tr>
<tr><td>Administration time ≤5 minutes (n=4)</td><td>Administration time 6-10 minutes (n=2)</td><td>Administration time ≥11 minutes (n=0)</td><td>Administration time ≤5 minutes (n= 1)</td><td>Administration time 6-10 minutes (n= 2)</td><td>Administration time ≥11 minutes (n=8)</td></tr>
<tr><td colspan="3">Tools excluded as they require a cost > £100 (n=1; HUI)</td><td colspan="3">Tools excluded as they require a cost > £100 (n=0)</td></tr>
<tr><td colspan="3">Tools excluded as they require specialist training (n=1; HUI)</td><td colspan="3">Tools excluded as they require specialist training (n=0)</td></tr>
<tr><td>Remaining tools with administration time ≤5 minutes (n=4)</td><td>Remaining tools with administration time 6-10 minutes (n=1)</td><td>Remaining tools with administration time ≥11 minutes (n=0)</td><td>Remaining tools with administration time ≤5 minutes (n=1)</td><td>Remaining tools with administration time 6-10 minutes (n=2)</td><td>Remaining tools with administration time ≥11 minutes (n=8)</td></tr>
<tr><td colspan="3">Tools excluded following lack of reliability data (n= 4; AQol; Eq-5D-5L;SF-6D)
Tools excluded following lack of validity data (n = 1; SF-36)</td><td colspan="3">Tools excluded following lack of reliability data (n= 3; PBSI; SF-SIS; SS-QOL-12)
Tools excluded following lack of validity data (n = 0)</td></tr>
<tr><td>Remaining tools with administration time ≤5 minutes (n=1; SF-12)</td><td>Remaining tools with administration time 6-10 minutes (n=0)</td><td>Remaining tools with administration time ≥11 minutes (n=0)</td><td>Remaining tools with administration time ≤5 minutes (n=0)</td><td>Remaining tools with administration time 6-10 minutes (n=1; Stroke-PROM)</td><td>Remaining tools with administration time ≥11 minutes (n= 6; HRQLISP-40; NEWSQOL ; SIS 2.0; SIS 3.0; SAQOL-39;SS-QOL)</td></tr>
<tr><td colspan="3">Tools excluded for unavailability of measure (n= 0)</td><td colspan="3">Tools excluded for unavailability of measure (n= 3; HRQOLISP-40; NEWSQOL; Stroke-PROM)</td></tr>
<tr><td colspan="3">Remaining tools with administration time ≤5 minutes (n=1; SF-12)</td><td colspan="3">Remaining tools with administration time ≥11 minutes (n=4; SIS 2.0; SIS 3.0; SAQOL-39; SS-QOL)</td></tr>
</table>

Table 6. *Domains covered by selected measures*

Measure	Physical function	Role function	Pain	Emotional wellbeing	Cognitive function	Communication	Social function	Recreation	Energy	General health	Overall Quality of Life	Comments
AQoL-4D	++	+	+	+	-	+	±	-	-	-	-	Other questions about a person's vision, relationship with others and sleep were included
EQ-5D-5L	++	-	+	+	-	-	-	-	-	+	-	Other domains include activities of self-care. A visual analogue scale (VAS) asks the person to rate their general health status.
HUI	++	-	+	+	+	+	-	-	-	-	-	HUI questionnaire can be categorised using two multi-attribute systems, HUI2 and HUI3 with its own domain classifications.
HSQuale	++	++	-	++	++	+	+	++	+	-	+	Other domains include questions about a person's general outlook and perception of themselves, relationships, impact of stroke on their work and financial status.
HRQOLISP-40	++	+	+	++	++	+	+	+	+	-	-	Other domains include questions about a person's soul/spirituality and religious faith. It also asks questions on the context of their surrounding environment and their access to support/health care.
NEWSQOL	++	-	++	++	++	++	-	-	+/++	-	-	Questions relating to fatigue on this scale are assumed to link to an 'Energy' domain. Other domains include mobility, self-care, vision, interpersonal relationships and sleep.
PBSI	++	+	-	+/++	+	+	-	+	-	+	-	Other domains include questions about a person's ability to drive, their rating of coping abilities with difficulties and their self-esteem.
SF-6D	+	+	+	±	-	-	+	-	+	-	-	Some but not all of the statements for the 'role limitation' domain include responses that provide insight to a person's emotional wellbeing.
SF-12	++	-	+	++	-	-	+	-	+	++	-	N/a
SF-36	++	++	++	++	-	-	++	-	++	++	-	N/a

SIS 2.0	++	+	-	++	++	++	+	++	-	±	-	Other domains include a person's ability to carry out daily activities, mobility at the home and in the community. A VAS asks the person to rate their recovery.
SIS 3.0	++	+	-	++	++	++	+	++	-	±	-	Other domains include a person's ability to carry out activities of daily living, ability to be mobile at the home and in the community. A VAS asks the person to rate their recovery.
SF-SIS	++	+	-	+	+	-	+	-	-	-	-	Includes specific questions about the strength of a person's most affected leg and the most affected hand in picking up a coin.
Stroke-PROM	++	-	-	++	++	++	++	-	-	+	-	Other questions include views about receiving treatment ('Therapeutic Domain')
SAQOL-39	++	-	-	+	++	++	++	+	++	-	-	Scores are categorized into 3 domains: physical, communication and psychosocial
SS-QOL	++	-	-	++	++	++	++	+	++	-	-	Other domains included family roles, self-care, work/productivity, personality and vision.
SS-QOL-12	+	-	-	+	+	+	+	+	+	-	-	Other domains included family roles, self-care, work/productivity, personality and vision.

AQoL. Assessment of Quality of Life; EQ-5D, EQ-5D-5L, EuroQoL 5-Dimensions Questionnaire; EQ-VAS, EuroQoL Visual analogue scale; (HUI2, Health Utility Index Mark 2; HUI3, Health Utility Index Mark 3;HSQuale, Haemorrhagic Stroke Quality of Life ; HRQOLISP-40, Health-Related Quality of Life in Stroke Patients 40-items; NEWSQOL, Newcastle Stroke-Specific Quality of Life Measure; PBSI, Preference-Based Stroke Index; SF-12, SF-6D, SF-36, Medical Outcomes Study Short-Form Health Survey (12 item, 6-dimensions, 36-item); SIS 2.0, 3.0, Stroke Impact Scale (Version 2.0, 3.0); SF-SIS, Short-Form Stroke Impact Scale; Stroke-PROM; Stroke-Patient Reported Outcome Measure, SAQOL-39, Stroke and Aphasia Quality of Life Scale-39; SS-QOL, 12-item Stroke-Specific Quality of Life Scale, ('-') , no coverage; ('+'), limited coverage (1 item); ('++'), noteworthy coverage (2 or more items), ('±'), coverage equivocal

Discussion

The objective of this paper was to evaluate HR-QOL measures among stroke survivors, based on clinical utility, psychometric properties and HR-QOL domain coverage, and in turn to provide recommendations for clinicians and researchers on the most suitable HR-QOL measures. Twenty-four studies were included in this systematic review, comprising 4469 stroke participants at different stages of stroke recovery worldwide. Most studies were of 'Fair' – 'Good' quality, with only one paper rated as 'Poor' quality. A total of 17 published HR-QOL measures were validated for stroke use.

To meet the purpose of this review, key findings compared the HR- QOL measures identified. In regard to clinical utility (administration time, training requirement, cost), six of seventeen scales scored adequately, with the SF-12 scoring the highest. Whilst the SF-12 is a shorter measure requiring approximately less than 5 minutes administration time, other measures require approximately more than 11 minutes to administer.

Moreover, reliability and validity data for HR-QOL measures were also gathered. Although validity was reported for most scales, only ten measures had data on reliability. Where reliability data was excluded, authors tended to acknowledge reliability based on previous research rather than report original analysis data. The available information on reliability and validity for these HR-QOL measures for stroke suggest are limited. More work needs to be carried out to thoroughly assess psychometric properties of these tools before they are recommended for clinical use. This indicates direction for future research to ensure reliability and validity data of a measure is based on original data.

Finally, each measure was evaluated based on their different ranges of HR-QOL domains coverage. The SF-12 provides the least coverage of the domains (six of eleven domains) in comparison to the other measures such as the SIS 3.0, which covers the most (eight of eleven domains). This variance in coverage is expected across measures, especially when taking into account the number of the questions and administration time.

Whilst assessing clinical utility, psychometric properties and HR-QOL domains coverage, a flow chart was formed to determine the most suitable measures for clinical and research settings. Five recommended measures were identified using this process, namely; the SF-12, SIS 2.0, SIS 3.0, SAQOL-39 and SS-QOL.

Amongst the recommended tools, the SF-12 is the only generic HR-QOL identified, which may also explain its reduced domain coverage, compared to the other stroke-specific recommended measures. For example, in comparison to the other measures, the SF-12 excludes questions regarding a person's cognitive functioning or communication abilities. However, in cases where a person does not experience cognitive or communicative difficulties post-stroke, the SF-12 may still be an appropriate clinical measure because of its succinct length in considering the wider aspects of assessment.

Amongst the stroke-specific recommended measures, some differences in its properties may contribute to judgement of the most suitable tool. All stroke-specific measures obtained similar clinical utility scores for their administration time (≥11 minutes) and coverage of HR-QOL domains. Whilst the SAQOL-39 has the least number of items and takes the shortest time (10-15 minutes), the SIS 2.0, SIS 3.0 and SS-QOL estimate an administration time of 15-20 minutes. In terms of domain coverage, both the SIS 2.0 and SIS 3.0 have an additional advantage of a visual analogue scale (VAS) for patients to rate their recovery. It should also be noted that the SIS 3.0 was developed as an improvement of the SIS 2.0 – while its domain coverage and administration time are similar to its predecessor, the SIS 3.0 consists of 59 items instead of 64 items on the SIS 2.0.

Ultimately, professionals should exercise clinical judgement in deciding the best tool for specific situations, considering its practical utility and relevant domains. Although the difference of administration time is minimal, clinicians, researchers and trialists should consider the length of clinical interviews and other assessment measures to prevent response burden in stroke participants. For example, one should consider a patient or participants' energy and attentional abilities when selecting an assessment tool or planning a session. This

is particularly important for post-stroke patients, who are likely to experience fatigue.

To date, there is only one comparable systematic review for HR-QOL measures within the stroke literature. In comparison to the review by Golomb, Vickrey and Hays (2001), the present review identified fewer HR-QOL measures, 17 in total, comparing to their 32. This is because Golomb and colleagues (2001) also reviewed measures of physical functioning (e.g. Barthel Activities of Daily Living Index; Functional Ambulation Classification), and mood (e.g. Beck Depression Inventory; Hospital Anxiety and Depression Scale), both of which assess different domains of well-being and were assumed by the authors to measure HR-QOL. Where Golomb and colleagues (2001) identified 1 stroke-specific measure of 32 measures, this review indicates an improvement in stroke-specific measures development across the years. Additionally, a review by Geyh, Cieza, Kollerits and Grimby (2007) used alternative frameworks of reference, such as the international classification of functioning (ICF) to compare HR-QOL measures. The ICF uses a different approach and concept in mapping measure/questionnaire items to category sets. Although ICF has its strengths, it has also been criticised for its lack of subjective dimensions of functioning and disability (Ueda & Okawa, 2003). Nevertheless, it is noted that there is yet to be a HR-QOL measure that meets all the HR-QOL domains listed by Golomb, Vickrey and Hays's (2001) . In comparison to existing literature, the present review provides an updated search of HR-QOL measures, which includes more stroke-specific tools. In addition to reporting psychometric properties and HR-QOL domain coverage, this review also measures clinical utility with methods established by Burton and Tyson's (2015a; 2015b) work on stroke cognition and mood screens to aid in clinical decision-making.

This review has several limitations. Firstly, the present study emphasised HR-QOL-specific measures and excluded other measures that may also influence a person's HR-QOL. It may be that a person's emotional, physical and functioning state and abilities can provide a better indication of a person's HR-QOL. Some of these specific measures (e.g. mood screens,

cognitive screens, performance-based assessments of physical abilities) may already be included in stroke rehabilitation assessments.

Moreover, when interpreting indices of clinical utility and HR-QOL domains, this review replicated methods from previous researches, specifically those of Burton and Tyson (2015a; 2015b) and Golomb, Vickrey and Hays (2001). However, it is noted that there may be other definitions and methods of assessing clinical utility and HR-QOL domains that are not included in the replicated frameworks. These were indicated in Table 6, whereby notes were taken when the measure evaluated other domains. Thus, the results of the content comparison of the measures in this review may only hold relative to the frame of methodology utilised.

Additionally, this review did not identify comprehensive information about the different modes of administration of the measures. It is clinically important to recognise the conceptual differences in using self-, interviewer- or proxy-administered HR-QOL measures and the impact this can have on outcomes. Future research could look to address this and offer a more comprehensive commentary on this aspect of scale usage.

Although not a primary aim, the present review identified nine of the seventeen measures as suitable for use with proxy administration. However, only one measure indicated the availability of a specific proxy version (EQ-5D-5L) and interview-administration version (HUI). In one study, data collected by proxy-administration was not included in the analysis (Kerber et al., 2012). Overall, clear information on proxy administration is scarce. This may significantly impact up to a one-third of stroke survivors with post-stroke communication difficulties such as aphasia, dysarthria or apraxia of speech, thus potentially affecting assessment outcomes (Wray & Clarke, 2017). Specific research on proxy responses for HR-QOL stroke measures have found moderate agreement between responses from patients and their proxies (Carod-Artal et al., 2009; Dorman et al., 1997; Williams et al., 2006), despite findings that proxies tend to report more dysfunction on certain domains (Williams et al.,

2006). Additionally, existing research show that interviewer-administered assessments of HR-QOL measures tend to elicit more positive scores on domains related to mental health when compared to self-administered assessments such as postal interviews (Caute et al., 2012). As such, future research would need to consider the importance of proxy respondents for stroke patients, particularly in developing HR-QOL measures. This should come with clear guidance, instruction or specific versions for proxy administrators to ensure that responses are reliable and valid. This calls for future studies to report on proxy-administered data, adding to the body of evidence and ensuring that people with post-stroke communicative difficulties are not excluded in HR-QOL research.

Finally, only 30% of the studies included for this review were co-rated for quality. This suggests that quality ratings provided may be subjected to bias by the author's interpretation. The final rating in each COSMIN domains required subjective interpretations from respondents. Furthermore, assessment of eligibility and quality ratings are influenced by the extent to which they answered the review's question.

Conclusions & recommendations

This paper presents a systematic review of existing HR-QOL measures used within the stroke population. It outlines information important to make informed decisions on which identified measures are most valid, reliable and suitable for use in clinical or research settings to measure HR-QOL. The review identifies the strengths and limitations of each HR-QOL measures and recognises the gaps in the domains assessed. It remains that no existing HR-QOL measure addresses all the HR-QOL domains specified by Golomb, Vickrey and Hays (2001). This provides an indication and direction for future development of new measures. The information synthesised and presented also highlights a need for more psychometric data in testing the reliability and validity of HR-QOL measures. It is hoped that with additional research, more recently developed measures can become widely used and openly available to clinicians. Lastly, although this review attempts to systematically present and narrow down findings to a few recommended measures, it is important to remember that there is no perfect assessment scale for stroke survivors – the choice of instrument will always depend on professional judgement about the properties of that scale and more importantly, the purpose of its testing in both clinical and research settings (MasIsaac et al., 2016).

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Informed consent

Not applicable.

Guarantor

JP

Contributorship

JP conceived the study, researched literature, analysed data and wrote the manuscript. KH acted as the second-rater in assessing eligibility and quality of the studies. NB and PB provided supervision throughout the process of this study and approved the final version of the manuscript.

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CHAPTER THREE: Bridging Chapter

This chapter provided a summary of the systematic review and leads into the rationale for the empirical paper.

Word Count: 311

Bridging Chapter

The systematic review in Chapter Two investigated the current HR-QOL measures that are used for stroke, and considered them in reference to their clinical utility, psychometric properties and HR-QOL domains covered. By incorporating established methods of assessing clinical utility and synthesizing psychometric information gathered, this review was able to form a flow-chart and thus allow for ease of decision-making by researchers and clinicians when choosing HR- QOL measures to employ. The review therefore contributed to the research of HR-QOL in stroke and concluded in calling for future research in the area to build on this body of work.

When inspecting the HR-QOL measures identified for Chapter Two with respect to their coverage of HR-QOL domains, it was observed that all of the seventeen identified measures included at least one question about a person's emotional wellbeing, or mood. This gives an indication of the importance of a mood to a person's HR-QOL following stroke. Given the high prevalence of post-stroke depression (PSD), post-stroke anxiety (PSA) and post-stroke emotionalism (PSE), it is of course unsurprising that it is strongly linked to HR-QOL. A study comparing participants with similar neurological impairment found that stroke participants who were later diagnosed with anxiety were reported to be more dependent and rated lower on HR-QOL domains than those who did not receive a post-stroke anxiety diagnosis (Chun et al., 2018).

Recent years have seen researchers and clinicians include HR-QOL as a useful outcome measure for stroke rehabilitation and post-stroke mood interventions. However, despite advancements in the field, there remains no clear consensus on the best available interventions for PSD, PSA nor PSE. Thus, the empirical paper of this portfolio presents a

network meta-analysis to review the available evidence for the treatment intervention of PSD, PSA and PSE, considering both pharmacological and non-pharmacological approaches.

CHAPTER FOUR: Empirical Paper

Psychological & Pharmacological Interventions for Post-Stroke Depression, Anxiety & Emotionalism: A Network Meta-Analysis of Current Evidence and Perspectives for New Research

Prepared for Rehabilitation Psychology Journal

(Author guidelines found as Appendix J)

Word Count: 6 240 (excluding figures).

9575 (including figures)

Psychological & Pharmacological Interventions for Post-Stroke Depression, Anxiety & Emotionalism: A Network Meta-Analysis of Current Evidence and Perspectives for New Research

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Abstract

Purpose: It is common after the traumatic event of a stroke for people to experience a wide range of changes, including in their mood. Post-stroke depression (PSD), anxiety (PSA) and emotionalism (PSE) are often observed in the months following a stroke and can play a large role in a person's rehabilitative outcome and quality of life. Yet, there is no consensus on the best way to treat these post-stroke mood disorders. This paper aims to provide an overarching view of current evidence-based treatments for mood disorders after stroke and to highlight research gaps.

Method: Electronic databases MEDLINE, PubMed, The Cochrane Database of Systematic Reviews, EMBASE and Database of Research in Stroke (DORIS) were searched to identify randomised controlled trials (RCTs) on treatment interventions for PSD, PSA and PSE domains. Network meta-analyses (NMA) were conducted on the evidence for each domain to synthesise the findings based on direct and indirect comparisons.

Findings: Twenty-three trials were included in the final NMA for PSD, followed by eleven for PSA and none for PSE. The NMA categorised the interventions with reference to the type of control group used, and calculated treatment estimates and rankings based on direct and inferred evidence.

Discussion and Conclusion: The paper presents the wide range of interventions available for PSD and PSA. It highlights the disproportionate focus of present research within each domain. There is paucity of replicated evidence in the area. Thus, the NMA was not able to provide confident predictions of treatment rankings for either of the domains.

Keywords: stroke, post-stroke depression, post-stroke anxiety, post-stroke emotionalism, intervention, treatment

Introduction

Stroke occurs when a blood clot, ruptured artery or ruptured blood vessel causes an interruption of blood flow to the brain (Lincoln, Kneebone, MacNiven & Morris, 2011). Blockages in a brain artery lead to ischemic stroke, which accounts for 87% of stroke cases (Puig, Brenna & Magnus, 2018). When this happens, brain blood flow can stop, leading to hypoperfusion in the affected area and potentially lethal neuronal injury, or cell death (Puig, Brenna & Magnus, 2018). In haemorrhagic strokes, a hydrostatic jet of blood emerging from a ruptured blood vessel can cause immediate destruction to neuronal tissue (Zille et al., 2017). Up to 25% of those affected by stroke die within a month (Wolfe, 2000), whereas those who survive can be left with brain damage and a myriad of consequences. Depending on lesion location and severity, stroke can cause chronic disabilities involving physical dysfunction (Rossini, Calautti, Pauri & Baron, 2003; Mayo et al., 1999), cognitive impairments (Sun, Tan & Yu, 2014) and speech and language difficulties (Brady et al., 2016), all of which have a profound impact on a person's daily functioning. Accordingly, stroke is the leading cause of disability in the UK (Wilkins et al., 2017).

The sudden and life-threatening onset of a stroke can be a frightening and traumatic experience. Its aftermath can be devastating for patients and their families (Hole, Stubbs, Roskell & Soundy, 2014), requiring a person to reorder their life, renegotiate social relationships and find ways to cope with newly acquired difficulties (Lewinter & Mikkelsen, 1995). It is therefore not surprising that psychological and emotional difficulties are common after stroke, affecting up to a third of stroke survivors (Burton & Tyson, 2014). Post-stroke emotional disturbances negatively impact a person's quality of life (Carod-Artal & Egido, 2009), and may become a factor in impeding rehabilitative progress and outcome (Kneebone,

2016). Post-stroke depression (PSD) is associated with poor functional recovery (Pohjasvaara et al., 2001), increased length of hospital stays, heightened risk of suicide (Pompili et al., 2015), eroded quality of life and increased mortality (Razmara, et al., 2017; Bartoli et al., 2013; House et al. 2001). There is far less research conducted on post-stroke anxiety (PSA) and post-stroke emotionalism (PSE) although some evidence associates PSA with poor social functioning, activities of daily living (Shimoda & Robinson, 1998) and quality of life (Burton et al., 2013).

Whilst recognising the complexity and myriad of emotional difficulties that people may experience after stroke, this paper focuses on the more commonly observed emotional and mood difficulties; PSD, PSA and PSE. Other emotional disturbances, post-stroke fatigue (Lerdal et al., 2009), aggression, and anger proneness (Rosa et al., 2016) are not discussed.

Post-Stroke Depression (PSD)

Approximately one third of stroke survivors will experience symptoms of post-stroke depression within the 12 months following a stroke (Lanctot et al., 2019). The complex, multifactorial and wide-ranging nature of PSD is reflected in the current literature. Work that emphasises the neurobiological variables and changes as the main factors associated with PSD (Villa, Ferrari & Moretti, 2018) is contrasted with other work suggesting that PSD may be a psychological, reactive response associated with sudden functional impairments (Taylor, Todman & Broomfield, 2011; Kim, 2016).

Of all the available treatments, pharmacological interventions have been the most researched strategy for PSD (Deng et al., 2017). In recent reviews and meta-analyses, antidepressants such as fluoxetine, sertraline, citalopram and nortriptyline have been shown to be effective in reducing depressive symptoms for stroke patients (Hackett et al., 2008; Kneebone & Lincoln, 2012; Xu et al., 2016; Deng et al., 2017). However, even when considering pharmacological interventions alone, stroke clinicians have difficulties deciding the most appropriate treatment from more than 40 different antidepressants (Sun et al., 2017). Sun et al. (2017) investigated this problem with a network meta-analysis, concluding that

paroxetine might be the best choice in starting treatment for PSD, whereas fluoxetine performs the worst in comparison. Nevertheless, choosing pharmacological interventions for PSD is problematic given the high rate of adverse events (Hackett et al., 2009) particularly to the gastrointestinal and central nervous systems (Hackett et al., 2008). Notably, randomised controlled trials studying the effects of fluoxetine on functional outcomes after stroke (FOCUS)(Dennis et al., 2019), found that fluoxetine does not improve functional outcomes and despite a reduction of PSD, an increment of frequency in bone fractures is also observed. This is echoed in other trials: Assessment of fluoxetine in stroke recovery trial (AFFINITY) (Grp, A.T.C., 2015) and efficacy of fluoxetine – a randomised controlled trial in stroke (EFFECTS)(Lundström et al., 2020), both similarly found fluoxetine did not improve functional outcomes, but increased adverse effects and risk of falls, bone fractures, epileptic seizures and hyponatraemia (Hankey et al., 2020; Lundström et al., 2020). This is particularly worrying, given that older people are at much higher risk of stroke. The high rate of adverse effects that anti-depressant medication can also promote noncompliance to treatment (Bhardwaj, Arumugam & Gambhir, 2018), and not all patients wish to take anti- depressant medicine to improve their mood.

Non-pharmacological interventions such as CBT have been shown comparable in efficacy to pharmacotherapy treating moderate-severe depression in the general population (DeRubeis et al., 2005), for patients with acquired brain injuries (Ponsford et al., 2016) and multiple sclerosis (Hind et al., 2014). Components of CBT such as motivational interviewing, work on grief, adjustment (Broomfield et al., 2011) and problem solving (Hackett et al., 2008) may be particularly useful in addressing the role of cognition and behaviour in PSD (Allida et al., 2020). A review found that in comparison to usual care, CBT had very low evidence in treating depression and often treatment effect was not sustained (Hackett et al., 2008). However, a more recent meta-analysis of 23 studies by Wang et al. (2018) found CBT to have positive effects in treatingPSD, providing supportive evidence for non-pharmacological interventions. Nevertheless, both these reviews acknowledged that the overarching evidence

for psychological interventions remain inconclusive.

Beyond pharmacological and psychological interventions for PSD, there is growing interest in alternative treatments. Non-invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) takes advantage of neuronal plasticity and reorganisation in exciting or inhibiting areas of a neuronal or brain activity to create temporary or long-lastingdesirable changes (Hallett, 2007; Miniussi, 206). High frequency rTMS on the left dorsolateral prefrontal cortex (DLPFC) has been found to benefit treatment-resistant depression (Slotema, Blom, Hoek & Sommer, 2010). Although rTMS and tDCS demonstrates promising efficacy for PSD in recent research and meta-analysis (Frey, Najib, Lily & Adcock, 2020; Shen et al., 2017; Bueno et al., 2011), further research and randomised controlled trials are needed (Bucur & Papagno, 2018). There is also emerging evidence for other interventions such as ecosystem-focused therapy, life review, music therapy, exercise and robotic-assisted neurorehabilitation in improving PSD (Baker et al., 2017; Hadidi et al., 2017).

Post-Stroke Anxiety (PSA)

Post-stroke anxiety disorders describe a person's difficulty with excessive anxiousness or worries (Kim, 2016). To categorise anxiety sub-types after stroke, Chun et al. (2018) differentiates post-stroke phobic and generalised anxiety, the former of which is associated with poorer recovery outcomes. Difficulties with anxiety can be manifested in a number of different ways and broadly include physical changes (e.g. shortness of breath), cognitive changes (e.g. fearful thoughts), and consequent behavioural responses (e.g. avoidance) (Knapp et al., 2017). PSA is estimated to affect between 18-25% of people after stroke, and is closely

linked with PSD (Campbell Burton et al., 2012; Kim, 2016). Although some studies propose a connection between PSA and lesion location, a recent meta-analysis found this inconclusive (Campbell Burton et al., 2012).

PSA has received comparably less research attention than PSD (Mitchell et al., 2017). Pharmacological studies are restricted to those investigating PSA with cooccurring depression (Kneebone & Jeffries, 2013), while a review (Campbell Burton et al., 2012) found that studies for psychological treatment of PSA did not provide sufficient information about the proportion of study participants no longer meeting their anxiety criteria, or the clinical significance of this decrease.

Behavioural and cognitive-behavioural psychotherapies are proven in the treatment of anxiety in the general population (Hall et al., 2016), and in older adults (Ayers, Sorrell, Thorp & Wetherell, 2007). Some authors propose for CBT to be successful for PSA with modified approaches that consider cognitive and communication problems (Lincoln & Flannaghan, 2003; Thomas et al., 2013; Kneebone & Jeffries, 2013). In the most comprehensive review to date, Knapp et al. (2017) found pharmacological therapies paroxetine and buspirone effective in treating anxiety after stroke, and that psychotherapy did not offer any significant benefits. However, there still remains a significant gap in evidence for treatment of PSA.

Post-Stroke Emotionalism (PSE)

Post-stroke emotionalism, otherwise known as emotional lability, emotional incontinence or pseudobulbar affect involves abnormal displays of emotion, usually uncontrollable outbursts of crying, occasionally laughter, not under normal personal control (Wilson, 1924; House et al., 1989). In the acute/subacute stages of stroke, prevalence of PSE varies from 6-34% (Kim, 2016). Gillespie et al. (2016)'s review found that PSE affects approximately 1 in 5 stroke survivors at the acute and post-acute phases, and 1 in 8 survivors beyond 6 months. Of the three mood disorders reviewed in this paper, studies of PSE tend to focus most on aetiological factors such as location of brain lesions (House et al., 1989)

although some research has considered psychological factors (Calvert, Knapp & House, 1998; Eccles, House & Knapp, 1999; McAleese et al., 2019). Kim (2016) reported that lesion location (in particular, the subcortical area) is associated with PSE only at the time of admission, whereas other factors such as functional status and social support are more strongly associated to PSE three months after the stroke.

Pathogenesis studies have considered the theoretical perspective of neuroanatomical lesions and neurotransmitter regulation on PSE (Kim, 2016). This might explain the emphasis of intervention studies focused on tricyclic antidepressants (e.g. imipramine) Selective Serotonin Reuptake Inhibitors (SSRI), (e.g. sertraline and citalopram), anticonvulsants (i.e. lamotrigine), dopamine precursors (e.g. levodopa) and NMDA receptor (glutamate and ion channel protein receptor) antagonists (e.g. dextromethorphan) (Imarhiagbe & Abidakun, 2018) for PSE. A recent Cochrane review by Allida, Patel and House (2019) concluded that antidepressants may be an effective PSE intervention, with no specific effect from one drug or class of drugs. However, researchers and clinicians cannot draw information on the effects of psychological therapy for PSE, with the exception of two case reports (Allida, Patel & House, 2019). To date, there are no controlled investigations of psychological therapies for PSE. This is despite the fact we know that a high proportion of stroke clinicians regularly utilize non-pharmacological approaches to treat PSE (Gillespie et al., 2020), thus further highlighting the existing gap and important need for research to better understand PSE and the behavioural interventions for it.

Rationale for this paper

The general scope of research and evidence for post-stroke mood interventions is unbalanced, with particular attention paid to PSD, and other common mood / emotional

problems following stroke still relatively neglected. Despite emerging evidence and support for non-pharmacological interventions in each of these conditions, particular emphasis has been drawn to pharmacological treatments. This paper intends to address this gap in literature by making head-to-head comparisons between pharmacological and non-pharmacological interventions for each of these post-stroke mood disorders using a network meta-analysis (NMA). A network meta-analysis will provide an advantage to a traditional meta-analysis, where all interventions that have been tested in randomized controlled trials (RCTs) can be simultaneously compared and their effects estimated relative to each other and to a common reference condition (e.g. waitlist) (Mayo-Wilson, 2016). Although there may be limitations due to the availability and scope of evidence within the existing literature, an NMA can nevertheless be useful in providing an overarching review of existing evidence and highlighting gaps in post-stroke mood research.

In comparison to NMAs carried out by Deng et al. (2017) and Sun et al., (2017), this paper is not limited to PSD nor pharmacological interventions. By conducting a network meta-analysis for PSD, PSA and PSE, for both pharmacological and non- pharmacological interventions, the present review gives researchers and clinicians an overarching view of the current evidence and scope of research conducted to evaluate post- stroke mood interventions. Employing an NMA also allows for computing a stepped ranking of treatment efficacy for each intervention, based on the available literature to date.

Method

Protocol and registration

This review is registered with PROSPERO: International prospective register of systematic reviews (ID: CRD42019141421). The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher, Liberati, Tetzlaff & Altman, 2009).

Search strategy

Electronic databases MEDLINE, PubMed, The Cochrane Database of Systematic Reviews, EMBASE and Database of Research in Stroke (DORIS) were searched from their inception to 2nd February 2020. The search used Boolean strategies to identify keywords and specific terms for the searches across each domain and database (Appendix A).

Eligibility Criteria

After the initial searches for articles were conducted on the electronic databases, all titles and abstracts were screened by one author (JP) for relevance to the research question. Following that, all articles were then further screened independently by two authors (JP & EH) against the eligibility criteria set for this systematic review.

Inclusion criteria for all three analyses (for PSD, PSA and PSE) comprised the following:

1) Studies published in the English language within a peer-reviewed journal;

2) Participants include adult stroke survivors over 18 years of age.

The exclusion criteria were as follows:

1) Studies that were not randomized clinical trials;

2) Less than 50% of the participants had suffered a stroke;

3) In mixed samples, where data from people with stroke could not be specifically extracted;

4) Studies specific to participants with transient ischemic attacks (TIA) and subarachnoid haemorrhage. This exclusion is because TIAs are defined by focal neurological symptoms that last for <24 hours (Easton et al., 2009). In contrast, stroke patients typically experience severe debilitating symptoms which require further rehabilitation treatment (Lam, Bloom & Kha, 2019). Although SAHs can be associated with stroke, it includes trauma resulting from head injuries, and may therefore be diagnosed and treated differently from a stroke (Chong, 2020). Exclusion of TIA and SAH participants from post-stroke studies and reviews have been noted within the literature (Hackett, Anderson, House & Xia, 2008; Sagen et al., 2009; Knapp et al., 2017).;

5) Interventions delivered to the caregivers of persons who had a stroke;

6) Studies where PSD/PSA/PSE was not listed as a primary outcome;

7) Studies where the intervention was categorized as Traditional Chinese Medicine (TCM). Due to the majority of research on TCM being published in Mandarin language, the inclusion of any TCM studies published in English will not provide a representative view of TCM.

This review included studies conducted in any setting (e.g. hospitals, community), using any outcome measures related to post-stroke depression, post-stroke anxiety and post-stroke emotionalism. The outcomes were conceptualized broadly to ensure that all eligible interventions were included. The inclusion criteria within the selected studies, as well as the mode of delivery for interventions (e.g. face-to-face, telephone) did not serve as exclusion criteria.

Data extraction & management

The primary author (JP) extracted demographic and methodological information for each selected study. The reviewer then extracted information on the study's design, participant characteristics, interventions, outcomes, and adverse events from each of the selected studies

to be included.

The primary outcome extracted was the overall efficacy of the interventions employed, measured by its effect size. Effect size was calculated using the mean difference of total score and standard deviation of the mood- rating scales used.

Where trials reported results from more than one outcome measure, the most commonly reported outcome measure (from the selected studies) was used for analysis. Tables 1, 2 and 3 describe the selected studies, including all the outcome measures used.

Effect size choice

Due to the fact that the studies used different scales, the treatment effect cannot be readily converted to a common measure (Morton et al., 2018). Therefore, the standardized mean difference (SMD) for each study was pooled across all the studies. The SMDs of each study were calculated using Hedges' *g* as a common metric, which was computed using this formula(Hedges & Olkin, 1985):

$$d\left(1-\frac{3}{4N-9}\right)$$

Where N is the total trial sample size.

Hedges'g helped reduce measurement error, taking into account between-scale correlation (Wei & Higgins, 2013, as cited in Mayo-Wilson et al., 2014).

Where multiple data time points were reported, the longest follow-up data was extracted.

Data analysis and synthesis

A frequentist random effects network meta-analysis (Dias, Sutton, Ades & Welton, 2013) was performed, using the statistical package 'netmeta' (https://cran.r-project.org/package=netmeta), which applies R programming language.

Where more than one type of treatment control group is used within the pool of studies, sub-networks were identified within each domain, which are differentiated by the type of control group used. These sub-networks were visualised using network plots, where the geometry of the treatment network comprising the included trials can be explored.

For each sub-network, a table of treatment estimates is presented. This includes firstly the direct data estimates (i.e. reported outcomes from articles included), and secondly the pooled estimates of treatment efficacy, which are inferred indirect treatment comparisons.

NMA allows for all treatments in the network to be considered for ranking in terms of their likely impact on treatment outcomes, based on both direct and inferred comparisons. This is done by computing the surface under the cumulative ranking (SUCRA) probabilities (Rücker, & Schwarzer, 2015). For a frequentist framework, the P-score, which is an analogue to the SUCRA, is based on frequentist point estimates and standard errors (Rücker & Schwarzer, 2015). The P-score "expresses the total efficacy or acceptability within each sub-network of every intervention relative to an imaginary intervention that is always the best, and without uncertainty on a continuous 0- 1 scale" (Chaimani et al;, 2013). Thus, a larger P-score indicates a more efficacious intervention. To interpret treatment ranking based on P-scores, a forest plot was produced for comparison. This allowed for further investigation of efficacy, taking into account confidence intervals for each treatment effect.

Consistency (i.e., indirect effects can be derived from differences in the corresponding direct effects) was assumed during modelling. The relative effect sizes were reported as mean differences along with 95% confidence intervals. Broader intervals reflect higher uncertainty about the estimated effect. Main effects were reported compared to the control conditions reported, used as the 'reference treatment' e.g. placebo as the reference treatment.

Heterogeneity assessment. Study heterogeneity was assessed using the I^2 statistic, whereby a score of more than 50% indicates moderate, and a score of 75% represents high levels of heterogeneity respectively (Higgins & Thompson, 2002). The random effects model takes into account between-study heterogeneity. Therefore, differences between studies are believed to be due, at least in part, to real differences in the underlying population (Shadish & Haddock, 1994).

Sensitivity analysis. This was undertaken in respect of the methodological quality (randomization process and blinding of outcome assessor) of the included studies. To aid this process, a criteria list and tick box format was created with the predefined methodological quality requirements.

Quality Assessment

All included articles were considered with regard to methodological quality. The Cochrane Collaboration's tool for assessment of the risk of bias (Sterne et al., 2019; Version 2) was used, as it is a common tool for assessing RCTs (Farrah, Young, Tunis & Zhao, 2019). This was further supplemented with selected items from the NICE quality appraisal checklist for quantitative intervention studies (NICE, 2012), given they capture other essential information for considering meta-analyses that are not covered in the Cochrane risk of bias tool. A list of the selected NICE quality appraisal items and its ratings can be found as Appendix E.

The Cochrane risk of bias tool and the NICE quality appraisal checklist is comprised of five domains each. The domains are rated on three levels ('high risk', 'some concerns' and 'low risk' on the Cochrane tool; '-'. '+' and '++' on the NICE checklist). The overall quality rating for each study was arrived as a mean of the agreed domain ratings for both the Cochrane risk of bias toll and the NICE quality appraisal checklist. The domain ratings for both tools and overall quality rating for each paper can be found as Appendix F.

Each study was assessed for quality by the primary author (JP), and a second-rater (EH) co-rated 30% of the articles, randomly selected to check for quality. For each domain on both the Cochrane risk of bias tool and the NICE quality appraisal checklist, where there were any inconsistencies in assessments between the two independent reviewers, this was discussed until a shared conclusion was agreed. There were minimal differences in ratings between the reviewers, which did not change the overall quality rating of the studies.

Results

Search and selection.

Overall, the search strategy yielded 2168 papers. Of these, twenty-five randomised controlled trials (fifty-six treatment arms) for PSD, eleven randomised controlled trials (ten treatment arms) for PSA and four randomised controlled trials (three treatment arms) for PSE met the inclusion criteria. The article identification and selection processes for each of these domains are presented in Figure 1.

Characteristics of studies and participants.

Post-Stroke Depression

From the twenty-five included trials, twenty were two-armed, and five were three-armed. The trials recruited patients from various settings, including 56% inpatient, 16% outpatient and 4% mixed, and 20% community settings, across thirteen countries. Pharmacological interventions were reported the most (8 studies), followed by psychological (individual and group) interventions, most of which focused on behaviour (6 studies). Three studies considered the efficacy of exercise on treating post-stroke depression. Other treatments included brain stimulation techniques, skill-based groups, music therapy and novel interventions such as educational and ecosystem focused therapy. Two trials (Andersen, 1994; Lauritzen, 1994) did not fit within the networks. For these studies, neither its treatment nor control conditions matched any study arms from the other papers. This meant that it was not possible to make direct nor indirect comparisons with other studies and were therefore excluded from further analyses. Details of the PSD studies are described in Table 1.

As can be seen in Figure 1, a large number of texts were not included due to the accessibility (n=60). For a number of these texts, the researcher was unable to access the publications in Chinese (n=28) and Japanese (n=1) journals. For the remaining articles (n=31),

full texts were not available within the database that the researcher had access to.

Post-Stroke Anxiety

From the eleven included trials, ten were two-armed, and one was three-armed. The trials recruited patients from various settings, including 45.5% inpatient, 19% outpatient and 36% community settings, across seven countries. Exercise/physical interventions were reported in three studies, as were psychological interventions (three studies). Other interventions included self-help techniques, muscular electrical stimulation and creative art therapy, and one study reported pharmacological interventions. One trial did not fit within the networks and was therefore excluded from further analyses (Karaiskos et al., 2012). Details of the PSA studies are described in Table 2.

Post-Stroke Emotionalism

Four PSE intervention trials were considered for network meta-analysis. These trials recruited a similar mix of patients from inpatient and outpatient settings, two of which were from the United Kingdom, one from Denmark and one from South Korea. Unfortunately, all four articles reported insufficient or inappropriate data needed for this meta-analysis (mean scores and standard deviation for outcome measures), thus a meta- analysis could not be performed. A description of these studies is reported in Table 3.

Figure 1. *PRISMA Flow chart of selected studies across the three mood domains.*

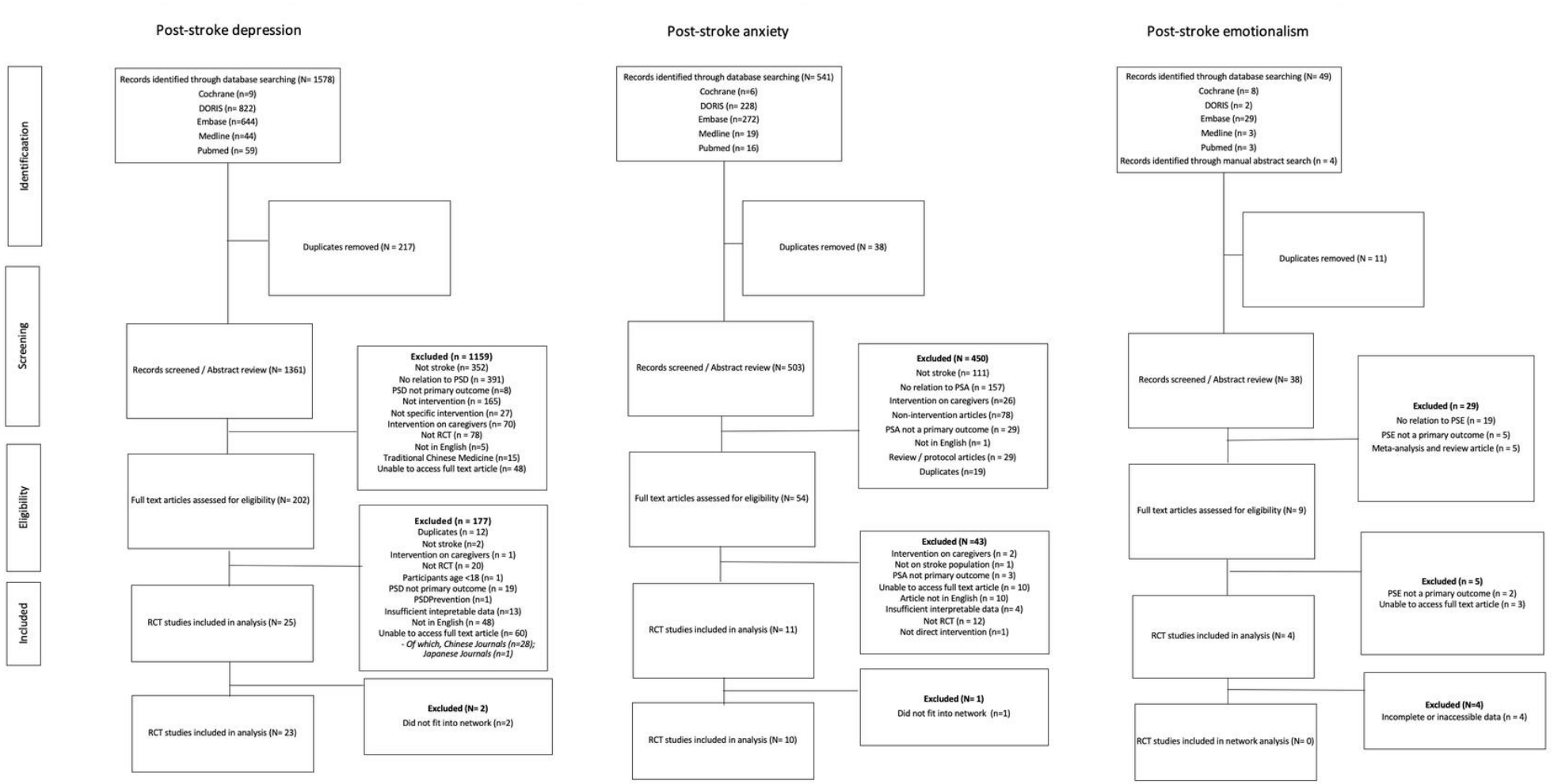


Table 1. *Description of PSD papers selected and included in network meta-analyses*

Study author, Year	Setting, Country	Stroke participants, N (mean age)	Intervention / control (N)	Diagnostic criteria (depression)	Outcome rating scale	Treatment duration	Quality Rating
Andersen 1994	Outpatient, Denmark	Subjects, N=33 (68.2) Control, N=33 (65.8)	Citalopram (33)/ Placebo (33)	DSM-III-R; HAMD (17 items)> 12	HAMD (17 items)	6 weeks	Low
Aidar et al., 2013	Community, Brazil	Subjects, N=15 (50.3) Control, N=13 (52.5)	Aquatic exercise (15)/ No intervention (13)	N/A	BDI	12 weeks	Moderate
Aidar et al., 2018	Community, Brazil	Subjects, N=19 (51.8) Control, N=17 (52.7)	Aquatic exercise (19)/ No intervention (17)	N/A	BDI	12 weeks	High
Cravello, Caltagirone & Spalletta, 2009	Hospital, Italy	Subjects, N= 25 (64.2) Control, N= 25 (65.9)	Venlafaxine, 75-100mg daily (25)/ Fluoxetine, 20-40mg daily (25)	Diagnosis of post-stroke major depressive-like episode, DSM-IV	HAMD	8 weeks	Low
Gao et al., 2017	Inpatient, China	Subjects, Citalopram, N=91 (66.0) Subjects, CBT, N=92 (64.9) Control, N=91 (67.2)	Citalopram,20 mg daily (91)/ Cognitive behavioural therapy, 2 hours weekly (92)/ Placebo (tablet and psychological Intervention) (91)	N/A	*HAMD, BDI, MES	3 months	Moderate

Golding, Kneebone & Fife-Shaw, 2016	Community, UK	Subjects, N=9 (67.8) Control, N=10 (62.4)	Self-help relaxation training, 20 minutes, 5 times a week (9)/ No intervention (10)	N/A	HADS-D	3 months	Moderate
Gu & Chang, 2017	Inpatient, South Korea	Subjects, N= 12 (58.1) Control, N=12 (58.3)	Repetitive Transcranial magnetic stimulation (rTMS) (12) / Placebo (12)	BDI >12 HAM-D17> 6	BDI *HAM-D	2 weeks	Low
Hoffmann, Ownsworth, Eames & Shum, 2015	Inpatient, Australia	Subjects, Coping skills, N= 11 (63.6) Subjects, Self-management, N= 12 (60.8) Control, N= 10 (57.0)	Coping skills (11)/ Self-management (12)/ Treatment as usual (10)	N/A	MADRS HADS	8 weeks	Low
Holmgren, Gosman-Hedstrom, Lindstrom & Wester, 2010	Inpatient, Sweden	Subjects, N= 13 (77.7) Control, N= 18 (79.2)	High-intensive exercise program (13)/ Education program control (15)	N/A	GDS	5 weeks	Moderate
Karaiskos et al., 2012	Outpatient, Greece	Subjects, Duloxetine,N= 20 (51.1) Subjects, Citalopram, N= 20 (54.3) Subjects, Sertraline, N= 20	Citalopram (20)/ Duloxetine (20)/ Sertraline (20)	DSM-IV	HAMD	12 weeks	Low

		(52.4)					
Kerr, McCann, Mackey & Wijeratne, 2017	Inpatient, Australia	Subjects, N= 18 (66.4), Control, N= 20 (69.9)	Motivational interviewing (18)/ Treatment as usual (69.9)	N/A	PHQ-9 *HADS	3 sessions	Moderate
Kim et al., 2010	Mixed, South Korea	Subjects, Low-rTMS, N= 6 (68.3), Subjects, High-rTMS, N= 6 (53.5), Control, N= 6 (66.8)	Low frequency rTMS (6)/ High frequency rTMS (6)/ Placebo (6)	N/A	BDI	2 weeks	Moderate
Kiosses et al., 2012	Inpatient, USA	Subjects, N= 12 (72.3) Control, N=12, (69.4)	Ecosystem Focused Therapy (12)/ Education on stroke and depression control (12)	PHQ-9 > 10 DSM-IV	HAM-D	12 weeks	High
Kirkness et al., 2017	Hospitals, USA	Subjects, Telephone behavioural therapy N=37 (61.7), Subjects, In-person behavioural therapy N=35 (58.5), Treatment as usual N=28 (60.7)	Behavioural therapy (telephone) (37)/ Behavioural therapy (in-person) (35)/ Treatment as usual (28)	GDS ≥ 11, Diagnostic Interview, Structured Hamilton, DSM-IV	HDRS	6 weeks	High
Lai et al., 2005	Community, USA	Subjects, N= 44 (68.5)	Exercise (44)/ Treatment as usual (49)	N/A	GDS	12 weeks	Low

		Control, N=49 (70.4)					
Lauritzen et al., 1994	Inpatient, Denmark	Subjects, N=10 (68.3) Control, N=10 (74.1)	Imipramine plus mianserin (10)/ Desipramine plus mianserin control (10)	HAMD (17 items) ≥ 15 MES	*HAMD (17 items) MES	6 weeks	Moderate
Majumdar & Morris, 2019	Outpatient, Wales	Subjects, N= 26 (65.3) Control, N=27 (60.0)	Acceptance and Commitment Therapy Group, 2 hours, weekly (26)/ Treatment as usual (27)	N/A	PHQ-9	4 weeks	High
Mitchell et al., 2009	Inpatient, USA	Subjects, N=44 (57) Control, N=48 (57)	Psychological-behavioural plus antidepressant (44)/ Treatment as usual, plus antidepressant (48)	GDS≥ 11 DISH DSM-IV	HDRS	8 weeks	High
Raffaele et al., 1996	N/A, Italy	Subjects, N=11 (69.5) Control, N=11 (70.4)	Trazodone (11)/ Placebo (11)	DSM-III-R	ZDS	45 days	High
Raglio et al., 2017	Inpatient, Italy	Subjects, N=19 (70.4) Control, N=19 (75.4)	Relational active music therapy (19)/ Treatment as usual (19)	N/A	HADS-D	6-8 weeks	Moderate
Robinson et al., 2000	Hospitals, USA & Argentina	Subjects, Fluoxetine N=23 (65)	Fluoxetine (23)/ Nortriptyline (16)/ Placebo (17)	DSM-IV, HAMD (28 items) ≥ 12	HAMD (28 items)	12 weeks	High

		Subjects, Nortriptyline N=16 (64) Control, N= 17 (73)					
Thomas et al., 2012	Outpatient / community, UK	Subjects, N= 43 (68.5) Control, N=46 (65.5)	Behavioural therapy (43)/ Treatment as usual (46)	SAD-Q ≥ 6 Visual analogue mood scale ('sad' items) ≥ 50	*SAD-Q Visual analogue mood scale ('sad' items)	3 months	Moderate
Thomas et al., 2019	Community, UK	Subjects, N=25 (62.6) Control, N=23 (68.8)	Behavioural activation therapy (25)/ Treatment as usual (23)	PHQ-9 ≥ 10 Visual analogue mood scale ('sad' items)≥ 50	*PHQ-9 SAD-Q Visual analogue mood scale ('sad' items)	4 months	Moderate
Wiart 2000	Inpatient, France	Subjects, N=16 (66.3) Control, N=15 (68.9)	Fluoxetine (16)/ Placebo (15)	ICD-10 MADRS≥ 19	MADRS	45 days	Low
Zhang et al., 2013	Inpatient, China	Subjects, N=48 (64.1) Control, N=49 (64.7)	Duloxetine (48)/ Treatment as usual (49)	DSM-IV HAMD-17	HAMD	12 weeks	Low

DSM-III/R, Diagnostic and Statistical Manual of Mental Disorders, 3rd edn., revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; HAMD, Hamilton Depression Scale, ICD, International Classification of Diseases; MADRS, Montgomery Asberg Depression Rating Scale; ZDS, Zung Depression Scale; BDI, Beck Depression Inventory; DASS-42, Depression, Anxiety Stress scale, 42-item; GDS-15, MES, Bech-Rafaelsen Melancholia Scale (MES); GDS-15, Geriatric Depression Scale, 15-item; HDRS, Hamilton Depression Rating Scale; MES,

*Melancholia Scale; WDI, Wakefield Depression Inventory; DISH, Diagnostic Interview and Structured Hamilton; SAD-Q, Stroke Aphasic Depression Questionnaire (10-item), MINI, Mini-International Neuropsychiatry Interview; Where multiple measures were used, * denotes the selected measure based on its frequency used in the selected articles.*

Table 2. *Description of PSA papers selected and included in network meta-analyses*

Study author, Year	Setting, Country	Stroke participants, N (mean age)	Intervention / control (N)	Diagnostic criteria (anxiety)	Outcome rating scale	Treatment duration	Quality Rating
Aidar et al., 2013	Community, Brazil	Subjects, N=15 (50.3) Control, N=13 (52.5)	Aquatic exercise (15)/ No intervention (13)	N/A	*IDATE (STAI) I (State) IDATE (STAI) II (Trait)	12 weeks	Moderate
Aidar et al., 2018	Community, Brazil	Subjects, N=19 (51.8) Control, N=17 (52.7)	Aquatic exercise (19)/ No intervention (17)	N/A	*IDATE (STAI) I (State) IDATE (STAI) II (Trait)	12 weeks	High
Golding, Kneebone & Fife-Shaw, 2016	Community, UK	Subjects, N=9 (67.8) Control, N=10 (62.4)	Self-help relaxation training, 20 minutes, 5 times a week (9)/ No intervention (10)	HADS-A ≥ 6	HADS-A	3 months	Low
Immink, Hillier & Petkov, 2014	Community Australia	Subjects, N= 10 (56.1) Control, N=10 (63.2)	Yoga intervention (11)/ No intervention (10)	N/A	*IDATE (STAI) I (State) IDATE (STAI) II (Trait)	10 weeks	Low
Karaiskos et al. 2012	Outpatient, Greece	Subjects, N= 20 (51.1)	Duloxetine, 60-12mg daily (20)/ Citalopram, 20-40mg daily (20)/	N/A	HAM-A	3 months	Low

		Control (Citalopram), N=20 (54.3), Control (Sertraline), N=20 (52.4)	Sertraline, 50-200mg daily (20)				
Kerr, McCann, Mackey & Wijeratne, 2017	Inpatient (multi-centre), Australia	Subjects, N= 18 (66.4) Control, N=20 (69.9)	Motivational interviewing, 30 minutes, 3 sessions (18)/ Treatment as usual (20)	N/A	HADS	3 days	Low
Kongkasuwan et al., 2016	Inpatient, Thailand	Subjects, N= 54 (67.1) Control, N=59 (65.5)	Creative art therapy, twice a week (54)/ Treatment as usual (59)	N/A	HADS	4 weeks	Moderate
Kotov, Isakova & Sheregeshev, 2020	Inpatient, Russia	Subjects, N= 50 (65.02) Control, N=50 (64.8)	Mechanotherapy, 30 minutes daily (50/ Treatment as usual (50)	N/A	BAS	2 weeks	Low
Majumdar & Morris, 2019	Outpatient, Wales	Subjects, N= 26 (65.3) Control, N=27 (60.0)	Acceptance and Commitment Therapy Group, 2 hours, weekly (26)/ Treatment as usual (27)	N/A	GAD-7	4 weeks	Low
Wu et al., 2012	Inpatient, China	Subjects, N= 60 (56.1) Control, N=60 (56.7)	Psychological intervention, 20 minutes, 5 times a week (60)/ Treatment as usual (60)	N/A	SCL-90	3 weeks	Low
Zeng et al., 2018	Inpatient, China	Subjects, N= 59 (67.92) Control, N= 53 (66.13)	Neuromuscular electrical stimulation (59)/ Treatment as usual (53)	N/A	HAM-A	12 days	Moderate

*HADS-A, Hospital Anxiety and Depression Scale – Anxiety subscale; IDATE I & II, Trace State Anxiety Inventory/ State-Trait Anxiety Inventory-STAI: Form Y; GAD-7, Generalized Anxiety Disorder-7 measure; SCL-90, Symptom Check List-90 item; HAMA, Hamilton Anxiety Scale; Where multiple measures were used, * denotes the selected measure based on its frequency used in the selected articles.*

Table 3. *Description of PSE papers selected, not included in network meta-analyses*

Study author, Year	Setting, Country	Stroke participants, N (mean age)	Intervention / control (N)	Diagnostic criteria	Outcome rating scale	Treatment duration	Quality Rating
Andersen 1993	Inpatient, Denmark	Subjects, N= 16, No Control Group	Citalopram, 10/20mg daily, Placebo	Lawson & Macleod semi-structured interview Qualitative clinical evaluation Frequency of crying scale Crying episode context scale Patient-recorded diary	Number of crying episodes	21 days	Low
Brown, Sloan & Pentland, 1998	Inpatient, Scotland	Subjects, N=9 (61.4) Controls, N=10 (63.7)	Fluoxetine, 20mg daily (9)/ Placebo (10)	DSM-III-R, History of emotionalism of at least 4 weeks	*Hamilton Rating Scale, Lawson and MacLeod rating scale	10 days	Low
Burns et al., 1999	Inpatient / Outpatient / Community, England	Subjects, N=11 (73.4) Controls, N=12 (67.6)	Sertraline, 50mg daily (11)/ Placebo (12)	Presence of lability of mood observed by the referring clinician	Lability Scale (House et al., 1989), CIBIC, *MADRS	8 weeks	Moderate
Choi-Kwon et al., 2006	Outpatient clinics, South Korea	Subjects, N=19 (58.41) Controls, N=12 (58.18)	Fluoxetine, 20mg daily (19)/ Placebo (32)	Presence of PSEI considered if patients exhibited excessive or inappropriate laughing (EIL), crying (EIC), or both, reported on ≥ 2 occasions by the patient or their relative	*VAS	3 months	Moderate

*CIBIC, Clinician's Interview-Based Impression of Change;MADRS, Montgomery and Asberg Depression Rating Scale; VAS, Visual Analogue Scale, Where multiple measures were used, * denotes the selected measure based on its frequency used in the selected articles and availability of interpretable data.*

Network groups

The interventions from the articles identified for this paper were not able to form a singular network within each mood domain, but instead three sub-networks were identified for PSD and two sub-networks for PSA. It was not possible to form a network for PSE interventions. These sub-networks are separated by means of the type of control group treatment, that is used as the reference group for each network. The geometrical relationships between the interventions are depicted in Figure 2, where a 'drug placebo' is the basis for PSD sub-network one (Figure 2a), 'treatment as usual' for PSD sub-network two (Figure 2b) and 'experimental placebo'(placebo or sham treatment) for PSD sub-network three (Figure 2c) is the reference control group. Similar cases can be seen with 'no intervention' for PSA sub-network one (Figure 2d) and 'treatment as usual' for PSA sub- network two (Figure 2e). The shaded areas in the figures indicate multi-arm studies between the treatments.

Figure 2. *Sub-network groups for PSD, & PSA*

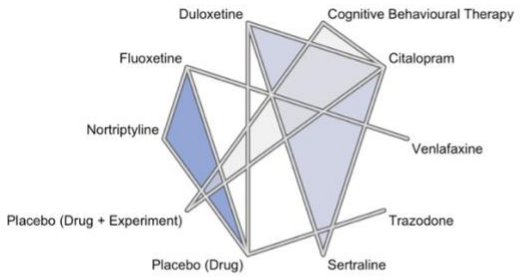


Figure 2a. PSD Sub-network one

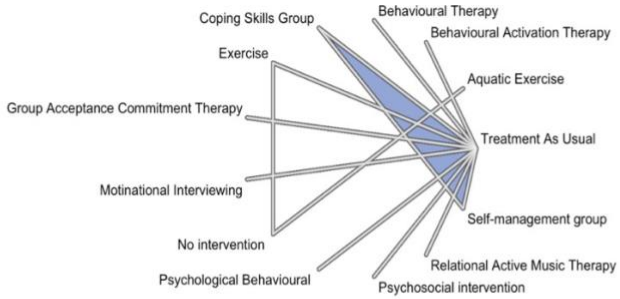


Figure 2b. PSD Sub-network two

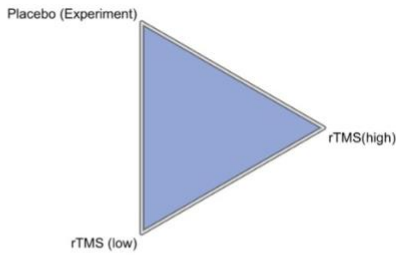


Figure 2c. PSD Sub-network three

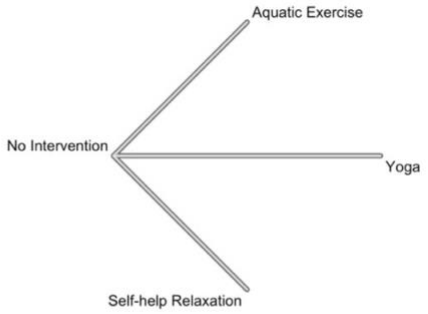


Figure 2d. PSA Sub-network one

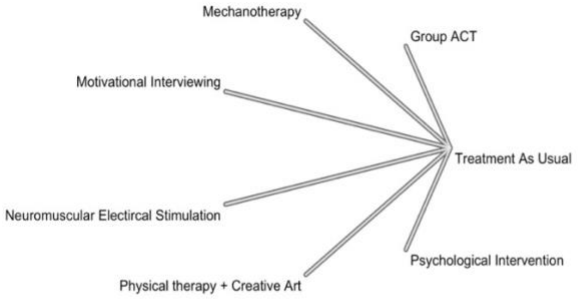


Figure 2e. PSA Sub-network two

It was not possible to fit interventions from Andersen (1994) and Lauritzen (1994) from the PSD studies, as well as Karaiskos et al. (2012) from PSA studies into any of the above networks. For these studies, neither its treatment nor control conditions matched any study arms from the other papers. Therefore, analyses of these studies were excluded.

Pairwise and network result

Post-Stroke Depression

Three sub-networks were identified for network meta-analysis of the post-stroke depression interventions. The first network consists of seven studies, comprising ten treatments and thirteen pairwise comparisons, with Placebo (Drug) conditions as the reference control. This network includes studies primarily evaluating pharmacological treatments, as well as CBT, which was the only psychological treatment that had been considered in a placebo- controlled trial. The results of pairwise comparisons and calculated standardized mean difference (SMD) based on a random effects model is shown in Table 4.

Table 4. *Pairwise comparisons based on the random effects model for PSD sub-network one*

Study	Treatment	Control	Standardized Mean Difference, SMD	95% Confidence Intervals	
				Lower	Upper
***Gao et al., 2017**	Citalopram	Placebo (Drug + Experiment)	0.0341	-2.0226	2.0908
***Gao et al., 2017**	Citalopram	CBT	0.0002	-2.0563	2.0567
***Gao et al., 2017**	CBT	Placebo (Drug + Experiment)	0.0339	-2.0227	2.0905
***Karaiskos, 2012**	Citalopram	Duloxetine	0.2950	-1.8342	2.4242
***Karaiskos, 2012**	Citalopram	Sertraline	-0.1762	-2.3048	1.9524
***Karaiskos, 2012**	Duloxetine	Sertraline	-0.4712	-2.6023	1.6599
Cravello, 2009	Fluoxetine	Venlafaxine	-1.7499	-3.8886	0.3888
***Robinson, 2000**	Fluoxetine	Nortriptyline	0.6844	-1.3555	2.7242
***Robinson, 2000**	Fluoxetine	Placebo (Drug)	-0.0519	-1.5903	1.4865
***Robinson, 2000**	Nortriptyline	Placebo (Drug)	-0.7363	-2.7761	1.3035
Raffaele 1996	Placebo (Drug)	Trazodone	1.2319	-1.0013	3.4651
Wiart, 2000	Fluoxetine	Placebo (Drug)	-0.0519	-1.5903	1.4865
Zhang, 2013	Duloxetine	Placebo (Drug)	-1.0393	-3.1191	1.0405

** signifies multi-arm studies, for which standard error was corrected*

Table 5. *Summary treatment estimates and credible intervals from network meta-analysis of treatment effects, PSD sub-network one.*

Citalopram	0.00 (-0.29; 0.29)	0.28 (-0.35; 0.90)	.	.	0.03 (-0.26; 0.32)	.	-0.16 (-0.78; 0.46)	.	.
0.00 (-0.29; 0.29)	Cognitive Behavioural Therapy	.	.	.	0.03 (-0.26; 0.32)	.	.	.	.
0.29 (-0.33; 0.92)	0.29 (-0.39; 0.98)	Duloxetine	.	.	.	-1.04(-1.46; -0.61)	-0.49 (-1.12; 0.14)	.	.
-0.63 (-1.56; 0.30)	-0.63 (-1.60; 0.34)	-0.93 (-1.61; -0.24)	Fluoxetine	0.81 (0.03; 1.60)	.	0.01 (-0.53; 0.55)	.	.	-1.75 (-2.40; -1.10)
0.02 (-1.03; 1.07)	0.02 (-1.07; 1.11)	-0.27 (-1.12; 0.57)	0.65 (-0.08; 1.38)	Nortriptyline	.	-0.61(-1.39; 0.18)	.	.	.
0.03 (-0.26; 0.32)	0.03 (-0.26; 0.32)	-0.26 (-0.95; 0.43)	0.67 (-0.31; 1.64)	0.01 (-1.08; 1.10)	Placebo (Drug + Experiment)	.	.	.	.
-0.74 (-1.50; 0.01)	-0.74 (-1.55; 0.06)	-1.04 (-1.46; -0.61)	-0.11 (-0.65; 0.43)	-0.77 (-1.50; -0.04)	-0.78(-1.59; 0.03)	Placebo (Drug)	.	1.23 (0.31; 2.15)	.
-0.18 (-0.80; 0.44)	-0.18 (-0.86; 0.51)	-0.47 (-1.10; 0.16)	0.46 (-0.48; 1.39)	-0.20 (-1.25; 0.86)	-0.21(-0.90; 0.48)	0.57 (-0.19; 1.33)	Sertraline	.	.
0.49 (-0.70; 1.67)	0.49 (-0.73; 1.71)	0.19 (-0.82; 1.20)	1.12 (0.05; 2.18)	0.47 (-0.71; 1.64)	0.45 (-0.77; 1.68)	1.23 (0.31; 2.15)	0.66 (-0.53; 1.85)	Trazodone	.
-2.38 (-3.52; -1.25)	-2.38 (-3.55; -1.21)	-2.68 (-3.63; -1.73)	-1.75 (-2.40; -1.10)	-2.40 (-3.38; -1.42)	-2.42(-3.59; -1.24)	-1.64 (-2.49; -0.79)	-2.21 (-3.34; -1.07)	-2.87 (-4.12; -1.62)	Venlafaxine

Table 5 reports a summary of direct and indirect treatment estimate results from the network meta-analysis. Treatment interventions are reported with outcomes of standardized mean differences (SMDs; 95% confidence intervals). Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment.

This table shows when two treatments have been directly compared against each other in the literature. This information is displayed in the upper- right triangle of the table, displaying the pooled effect sizes of the direct comparisons available in the network, as one would obtain from performing a conventional meta-analysis for each comparison.

The data in the boxes in the lower-left triangle of the table contains the indirect network meta-analysis effect sizes estimated for each comparison. This provides a calculated estimate of how two treatments may compare against each other, despite having not yet been compared to in existing research literature.

Overall, this table shows all the possible comparisons within this network in terms of its relative effectiveness (reported as estimated SMDs and confidence intervals) against the different interventions, whether as a product of a direct or indirect pooled estimate.

Table 6. *Treatment ranking efficacy of interventions from the first PSD subnetwork*

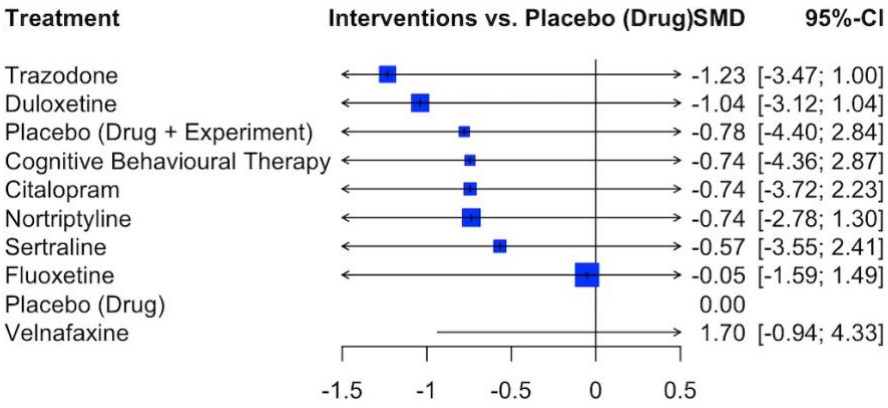
Intervention	P-score	N, appearances in the network
Trazodone	0.6889	1
Duloxetine	0.6674	3
Nortriptyline	0.5856	2
Placebo (Drug + Experiment)	0.5671	2
Citalopram	0.5640	4
Cognitive Behavioural Therapy	0.5576	2
Sertraline	0.5139	2
Fluoxetine	0.3999	4
Placebo (Drug)	0.3622	5
Venlafaxine	0.0935	1

Using frequentist modelling, the network meta-analysis calculated a prediction of treatment ranking using the data available from the selected studies. This was done using P-scores (measured from a score of 0-1, where a higher score indicates better efficacy) to measure the extent that one treatment is relatively better than the other, averaging over all competing treatments.

Within this network, Trazodone (P= 0.6889) ranked the highest, shortly followed by Duloxetine, at face value suggesting that these may be the most helpful treatments. Conversely, Venlafaxine ranked the lowest at P=0.0935, indicating that it may be the least efficacious of this network. However, these estimates should be interpreted with caution, taking into account the small number of studies and sample size of each intervention arm in forming this result. A network forest plot (Figure 3) is graphed against Placebo (Drug). This shows that several high-performing treatments have widely overlapping confidence intervals.

The network estimates presented assimilates data from both direct and indirect estimates. A visual depiction of this can be found as Appendix H, and a detailed evidence plot of direct and indirect estimates for this network can be found at Appendix G.

Figure 3. *Forest plot for PSD subnetwork one*



The second sub-network for PSD interventions consists of twelve studies, of which thirteen treatments are analysed with fourteen pairwise comparisons, with 'Treatment as Usual' (TAU) control as the reference. The results of pairwise comparisons and calculated effect size for each comparison are listed in Table 7.

Table 7. *Pairwise comparisons based on the random effects model for PSD sub-network two*

Study	Treatment	Control	Standardized Mean Difference, SMD	95% Confidence Intervals	
				Lower	Upper
Aidar, 2013	Aquatic Exercise	No Intervention	-0.4891	-0.9878	0.0096
Aidar, 2018	Aquatic Exercise	No Intervention	-0.2891	-0.9878	0.0096
***Hoffman, 2015**	Coping Skills Group	Self-management group	-0.3135	-1.1373	0.5103
***Hoffman, 2015**	Coping Skills Group	Treatment As Usual	-0.5877	-1.4633	0.2878
***Hoffman, 2015**	Self-management Group	Treatment As Usual	-0.2743	-1.1180	0.5695
Holmgren, 2010	Exercise	No Intervention	-0.2816	-0.9986	0.4354
Kerr, 2017	Motivational Interviewing	Treatment As Usual	-0.1021	-0.7654	0.5612
Kirkness, 2017	Psychosocial Intervention	Treatment As Usual	-0.1019	-0.5654	0.3616
Lai, 2005	Exercise	Treatment As Usual	-0.1444	-0.5521	0.2633
Majumdar, 2019	Group Acceptance Commitment Therapy	Treatment As Usual	-0.2077	-0.7477	0.3323
Mitchell, 2009	Psychological Behavioural	Treatment As Usual	0.0458	-0.3448	0.4364
Ragalio, 2017	Relational Active Music Therapy	Treatment As Usual	0.0409	-0.5951	0.6769
Thomas, 2012	Behavioural Therapy	Treatment As Usual	-0.4574	-0.8990	-0.0158
Thomas, 2019	Behavioural Activation Therapy	Treatment As Usual	-0.7027	-1.3520	-0.0534

** signifies multi-arm studies, for which standard error was corrected*

Table 8 reports a summary of direct and indirect treatment estimate results from the network meta-analysis.

Table 8. *Summary treatment estimates and credible intervals from network meta-analysis of treatment effects, PSD sub-network two.*

Aquatic Exercise	.	.	.	.	.	.	-0.49 (-0.99; 0.01)	.	.	.	.	.
0.35 (-0.81; 1.51)	Behavioural Activation Therapy	.	.	.	.	.	.	.	.	.	.	-0.70 (-1.35; -0.05)
0.11 (-0.95; 1.17)	-0.25 (-1.03; 0.54)	Behavioural Therapy	.	.	.	.	.	.	.	.	.	-0.46 (-0.90; -0.02)
0.24 (-1.07; 1.54)	-0.11 (-1.20; 0.98)	0.13 (-0.85; 1.11)	Coping Skills Group	.	.	.	.	.	.	.	-0.32 (-1.15; 0.50)	-0.58 (-1.45; 0.30)
-0.21 (-1.08; 0.67)	-0.56 (-1.33; 0.21)	-0.31 (-0.91; 0.29)	-0.44 (-1.41; 0.52)	Exercise	.	.	-0.28 (-1.00; 0.44)	.	.	.	.	-0.14 (-0.55; 0.26)
-0.14 (-1.25; 0.96)	-0.50 (-1.34; 0.35)	-0.25 (-0.95; 0.45)	-0.38 (-1.41; 0.65)	0.06 (-0.61; 0.74)	Group Acceptance Commitment Therapy	.	.	.	.	.	.	-0.21 (-0.75; 0.33)
-0.25 (-1.42; 0.92)	-0.60 (-1.53; 0.33)	-0.36 (-1.15; 0.44)	-0.49 (-1.58; 0.61)	-0.04 (-0.82; 0.74)	-0.11 (-0.96; 0.75)	Motivational Interviewing	.	.	.	.	.	-0.10 (-0.77; 0.56)
-0.49 (-0.99; 0.01)	-0.84 (-1.89; 0.21)	-0.59 (-1.53; 0.34)	-0.72 (-1.93; 0.48)	-0.28 (-1.00; 0.44)	-0.34 (-1.33; 0.64)	-0.24 (-1.30; 0.82)	No intervention	.	.	.	.	.
-0.40 (-1.44; 0.64)	-0.75 (-1.51; 0.01)	-0.50 (-1.09; 0.09)	-0.63 (-1.59; 0.33)	-0.19 (-0.75; 0.37)	-0.25 (-0.92; 0.41)	-0.15 (-0.92; 0.62)	0.09 (-0.82; 1.00)	Psychological Behavioural	.	.	.	0.05 (-0.34; 0.44)
-0.25 (-1.32; 0.82)	-0.60 (-1.40; 0.20)	-0.36 (-1.00; 0.28)	-0.49 (-1.48; 0.50)	-0.04 (-0.66; 0.57)	-0.11 (-0.82; 0.61)	-0.00 (-0.81; 0.81)	0.24 (-0.71; 1.19)	0.15 (-0.46; 0.75)	Psychosocial intervention	.	.	-0.10 (-0.57; 0.36)
-0.39 (-1.55; 0.76)	-0.74 (-1.65; 0.17)	-0.50 (-1.27; 0.28)	-0.63 (-1.71; 0.45)	-0.19 (-0.94; 0.57)	-0.25 (-1.08; 0.59)	-0.14 (-1.06; 0.78)	0.10 (-0.95; 1.14)	0.00 (-0.74; 0.75)	-0.14 (-0.93; 0.64)	Relational Active Music Therapy	.	0.04 (-0.60; 0.68)
-0.08 (-1.36; 1.20)	-0.43 (-1.49; 0.64)	-0.18 (-1.14; 0.77)	-0.31 (-1.14; 0.51)	0.13 (-0.81; 1.07)	0.07 (0.94; 1.07)	0.17 (-0.90; 1.25)	0.41 (-0.77; 1.59)	0.32 (-0.61; 1.25)	0.17 (-0.79; 1.14)	0.32 (-0.74; 1.37)	Self-management group	-0.28 (-1.13; 0.56)
-0.35 (-1.32; 0.61)	-0.70 (-1.35; -0.05)	-0.46 (-0.90; -0.02)	-0.59 (-1.46; 0.29)	-0.14 (-0.55; 0.26)	-0.21 (-0.75; 0.33)	-0.10 (-0.77; 0.56)	0.14 (-0.69; 0.96)	0.05 (-0.34; 0.44)	-0.10 (-0.57; 0.36)	0.04 (-0.60; 0.68)	-0.27 (-1.12; 0.57)	Treatment As Usual

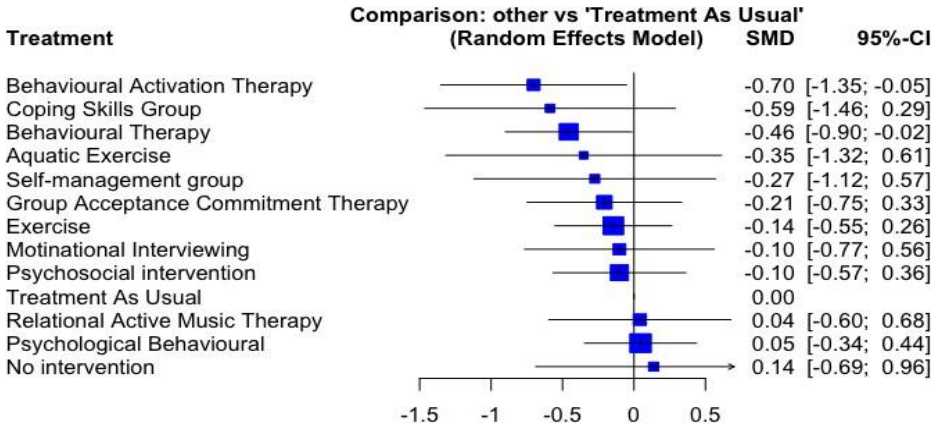
Table 9. *Treatment ranking for efficacy of interventions, PSD subnetwork two*

Intervention	P-score	N, number of appearances in the network
Behavioural Activation Therapy	0.8574	1
Coping Skills Group	0.7678	2
Behavioural Therapy	0.7407	1
Aquatic Exercise	0.6236	2
Self-management group	0.5525	2
Group Acceptance Commitment Therapy	0.5210	1
Exercise	0.4681	2
Motivational Interviewing	0.4266	1
Psychosocial intervention	0.4228	1
Relational Active Music Therapy	0.3067	1
Treatment As Usual	0.2987	10
Psychological Behavioural	0.2735	1
No intervention	0.2406	3

Frequentist treatment ranking was calculated using P-scores for prediction of efficacy of these treatments relative to each other (Table 9). Behaviour Activation Therapy (P= 0.8574) ranked the highest, a face value indicating that it may be the most helpful treatment. Conversely, 'No Intervention' ranked the lowest at P=0.2406, indicating that it may be the least efficacious of this network. Again, these estimates should be interpreted with caution, taking into account the number of studies and limited sample size of each intervention arm in forming this result. As seen in Table 9, most estimated treatment effects were derived from direct effects reported in a single study. Further, when a network forest plot (Figure 4) is graphed against 'Treatment As Usual', again there is evidence that all treatment have widely overlapping confidence intervals.

A detailed evidence plot of direct and indirect estimates for this network can be found at Appendix H.

Figure 4. *Forest plot, PSD subnetwork two*



The third sub-network for PSD interventions consists of two studies, of which four treatments are analysed with four pairwise comparisons, with ‘Placebo (Experiment)’ control as the reference. The results of pairwise comparisons and calculated effect size for each comparison are listed in Table 10. This network details the efficacy of low and high frequency rTMS interventions.. A ‘Placebo Experiment’ group describes a sham intervention treatment commonly used in TMS studies.

Table 10. *Pairwise comparisons based on the random effects model for PSD sub-network three*

Study	Treatment	Control	Standardized Mean Difference, SMD	95% Confidence Intervals	
				Lower	Upper
Gu2017	Placebo (Experiment)	rTMS(high)	2.0048	1.1918	2.8179
***Kim2010**	rTMS(low)	rTMS(high)	1.8244	0.6858	2.9629
***Kim2010**	Placebo (Experiment)	rTMS(low)	0.1805	-0.8810	1.2420
***Kim2010**	Placebo (Experiment)	rTMS (high)	2.0048	1.1918	2.8179

** signifies multi-arm studies, for which standard error was corrected*

Table 11 reports a summary of direct and indirect treatment estimate results from the network meta-analysis.

Table 11. *Summary treatment estimates and credible intervals from network meta-analysis of treatment effects, PSD sub-network three.*

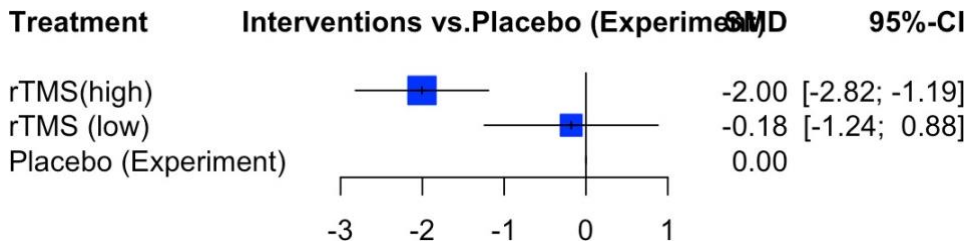
Placebo (Experiment)	0.02(-1.11; 1.15)	2.03 (1.22; 2.84)
0.18 (-0.88; 1.24)	rTMS (low)	1.56 (0.24; 2.87)
2.00 (1.19; 2.82)	1.82 (0.69; 2.96)	rTMS(high)

Frequentist treatment ranking was calculated using P-scores for prediction of efficacy of these treatments relative to each other. As shown in Table 12, rTMS (high), where the frequency is at 10Hz ranked the highest (P= 0.9996), indicating that it may be the most helpful treatment, compared to rTMS (low) (1 Hz), P=0.3157 and Placebo (Experiment), P=0.1847. This difference is depicted in a network forest plot (Figure 5), where rTMS (low) and rTMS (high) are graphed against Placebo (Experiment).

Table 12. *Treatment ranking for efficacy of interventions in PSD subnetwork three*

	P-score	N, number of appearances in the network
rTMS(high)	0.9996	3
rTMS (low)	0.3157	2
Placebo (Experiment)	0.1847	3

Figure 5. *Forest plot, PSD subnetwork three*



Post-Stroke Anxiety

Network meta-analysis of the post-stroke anxiety articles identified two sub-networks. The first network consists of four studies, comprising four treatments and pairwise comparisons, with 'No Interventions' condition as the reference control. The results of pairwise comparisons are shown in Table 13.

Table 13. *Pairwise comparisons based on the random effects model for PSA sub-network one*

Study	**Treatment**	**Control**	**Standardized Mean Difference, SMD**	**95% Confidence Intervals**	
				Lower	Upper
Aidar 2013	Aquatic Exercise	No Intervention	-0.4504	-0.9485	0.0477
Aidar 2018	Aquatic Exercise	No Intervention	-0.4504	-0.9485	0.0477
Golding 2016	No Intervention	Self-help relaxation	1.0292	0.0657	1.9927
Imink 2014	No Intervention	Yoga	0.6227	-0.2150	1.4604

Table 14 reports a summary of direct and indirect treatment estimate results from the network meta-analysis.

Table 14. *Summary treatment estimates and credible intervals from network meta-analysis of treatment effects, PSA sub-network one.*

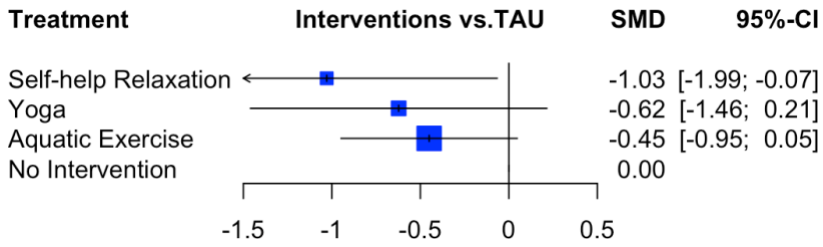
Aquatic Exercise	-0.45 (-0.95; 0.05)	.	.
-0.45 (-0.95; 0.05)	No Intervention	1.03 (0.07; 1.99)	0.62 (- 0.21; 1.46)
0.58 (- 0.51; 1.66)	1.03 (0.07; 1.99)	Self-help Relaxation	.
0.17 (- 0.80; 1.15)	0.62 (- 0.21; 1.46)	-0.41 (-1.68; 0.87)	Yoga

Table 15. *Treatment ranking for efficacy of treatments, PSA subnetwork one*

Intervention	**P-score**	**N, number of appearances in the network**
Self-help Relaxation	0.8559	1
Yoga	0.6097	1
Aquatic Exercise	0.4914	2
No Intervention	0.0430	4

Frequentist treatment ranking was calculated using P-scores for prediction of efficacy of these treatments relative to each other. Self-help relaxation ranked the highest (P= 0.8559), indicating that it may be the most helpful treatment, whereas ‘no intervention’ ranked the lowest (0.0430), as shown on Table 15. The treatment estimates are visualised in Figure 6, where a forest plot is graphed against ‘No Intervention’.

Figure 6. *Forest plot, PSA subnetwork one*



The second PSA subnetwork consists of six studies, comprising seven treatments and six pairwise comparisons, with ‘Treatment As Usual’ condition as the reference control. The results of pairwise comparisons shown in Table 16.

Table 16. *Pairwise comparisons based on the random effects model for PSA sub-network two*

Study	**Treatment**	**Control**	**Standardized Mean Difference, SMD**	**95% Confidence Intervals**	
				Lower	Upper
Kerr 2017	Motivational Interviewing	Treatment As Usual	0.0494	-0.5874	0.6862
Kongkasuwan 2016	Physical therapy + Creative Art	Treatment As Usual	-0.0239	-0.3930	0.3452
Kotov 2020	Mechanotherapy	Treatment As Usual	0.3481	-0.0468	0.7430
Majumdar 2019	Group ACT	Treatment As Usual	0.2952	-0.2463	0.8367
Wu 2012	Psychological Intervention	Treatment As Usual	2.4294	1.8412	3.0176
Zheng2018	Neuromuscular Electrical Stimulation	Treatment As Usual	-0.4686	-0.8447	-0.0925

Table 17 reports a summary of direct and indirect treatment estimate results from the network meta-analysis.

Table 17. *Summary treatment estimates and credible intervals from network meta-analysis of treatment effects, PSA sub-network two.*

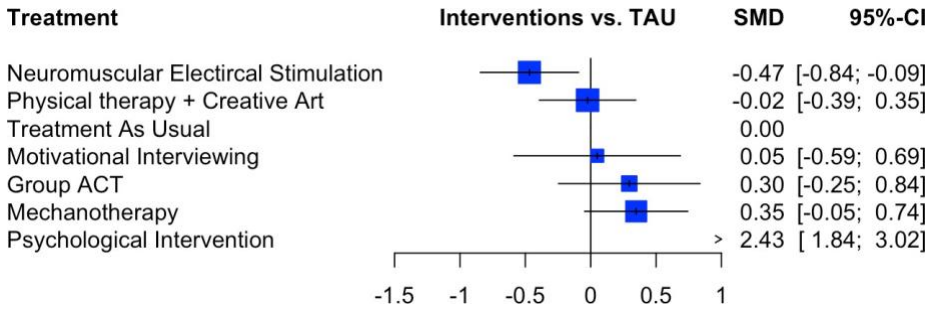
Group ACT	.	.	.	.	.	0.30 (- 0.25; 0.84)
-0.05 (- 0.72; 0.62)	Mechanotherapy	.	.	.	.	0.35 (- 0.05; 0.74)
0.25 (- 0.59; 1.08)	0.30 (-0.45; 1.05)	Motivational Interviewing	.	.	.	0.05 (- 0.59; 0.69)
0.76 (0.10; 1.42)	0.82 (0.27; 1.36)	0.52 (- 0.22; 1.26)	Neuromuscular Electrical Stimulation	.	.	-0.47 (-0.84; -0.09)
0.32 (- 0.34; 0.97)	0.37 (-0.17; 0.91)	0.07 (-0.66; 0.81)	-0.44 (-0.97; 0.08)	Physical therapy + Creative Art	.	-0.02 (- 0.39; 0.35)
-2.13 (-2.93; -1.33)	-2.08 (-2.79; -1.37)	-2.38 (-3.25; -1.51)	-2.90 (-3.60; -2.20)	-2.45 (-3.15; -1.76)	Psychological Intervention	2.43 (1.84; 3.02)
0.30 (- 0.25; 0.84)	0.35 (-0.05; 0.74)	0.05 (- 0.59; 0.69)	-0.47 (-0.84; -0.09)	-0.02 (- 0.39; 0.35)	2.43 (1.84; 3.02)	Treatment As Usual

Table 18. *Treatment ranking for efficacy of treatments, PSA subnetwork two*

	P-score	**N, number of appearances in the network**
Neuromuscular Electrical Stimulation	0.9742	1
Physical therapy + Creative Art	0.6530	1
Treatment As Usual	0.6388	6
Motivational Interviewing	0.5746	1
Group ACT	0.3613	1
Mechanotherapy	0.2980	1
Psychological Intervention	0.0000	1

Frequentist treatment ranking was calculated using P-scores for prediction of efficacy of these treatments relative to each other, neuromuscular electrical stimulation ranked the highest (P= 0.9742), indicating that it may be the most helpful treatment, whereas psychological intervention ranked the lowest (P= 0.000), as shown on Table 18. The relative treatment estimates are visualised in Figure 7, where a forest plot is graphed against 'Treatment As Usual'.

Figure 7. *Forest plot, PSA subnetwork two*



Tests of heterogeneity & publication bias

Within PSD sub-network one, tests of heterogeneity in this network were very high, I^2= 87.6%, confirming that a random-effects model is warranted. The heterogeneity between treatment designs reflects the actual inconsistency in this network and is highly significant (p=0.0015). This high degree of heterogeneity is not unexpected in an NMA, considering the variability of studies being compared in the network. The I^2 was unable to be calculated for PSD sub-networks two and three due to the small number of informative designs.

To assess publication bias of the network, a comparison-adjusted funnel plot was generated. Funnel plots for PSD sub-network group one and two can be found as Appendix I, showing no evidence of publication bias or small study effects. Additionally, Egger's Test statistic was available for PSD sub-network one (p=0.976) and two (p=0.8051), suggesting that funnel asymmetry is not present, indicating no publication bias.

Discussion

This multi-domain NMA provides an overarching view of the existing body of literature about the current treatment (pharmacological and non-pharmacological) of post-stroke mood disorders. First and foremost, a central finding was the disproportionate focus among the three mood domains. Whilst it is widely known that post-stroke depression makes up the majority of existing research, this was demonstrated through a systematic search in this paper. Initial searches for PSD papers returned 1578 articles, PSA with 541 articles and PSE with 49, and similar difference ratio was maintained at each step of the paper identification process. Although researchers have cited depression to be the most prevalent of the mood disorders after stroke (20%; Lanctot et al., 2019), the prevalence of anxiety (20-25%; Campbell Burton et al., 2013) and emotionalism (one in five survivors; Gillespie et al., 2018) after stroke remains significant. In fact, stroke clinicians have known that emotionalism tends to go under-recognised (Allida et al., 2019) and can be misdiagnosed for depression.

In the treatment of PSD, final network meta-analyses included twenty-three clinical trials, comprising seven different pharmacological interventions, five types of control groups, three group interventions (one based on a specific psychological model), three different psychological therapies, two exercise interventions, two rTMS interventions (low/high frequency), one music therapy, one motivational interviewing, and one CBT intervention. The wide-ranging variability of interventions reflects the multitude of approaches to PSD, which in turn highlights the many factors that affect a person's mood and provides stroke survivors and clinicians with many potential options for treatment. However, there is sparsity in evidence for these interventions. In the available literature, even the most frequently evaluated treatments for PSD, Citalopram and Fluoxetine, both appeared just four times within the network. Furthermore, psychological interventions are rarely considered against pharmacological interventions, and in only one case has CBT been considered in a placebo-controlled trial.

Without the availability of well researched, replicated and reported data to evidence these interventions, estimates of treatment effect and ranking that were performed in the network meta-analysis have to be interpreted with caution. Interventions that have stronger direct evidence from research (e.g. Citalopram and Fluoxetine) will produce more accurate predictions of indirect treatment estimates than those that are cited just once, using data from a small sample size.

The same discretion should be made – and perhaps even to a greater degree- when interpreting the network analysis results of PSA interventions. From the ten analysed trials, three types of exercise/physical interventions, three broad ranges of psychological interventions (one group), one intervention combining art and physical therapy, one mechanotherapy and one neuromuscular stimulation were compared and grouped on two types of control groups. No interventions studied the efficacy of pharmacological interventions on PSA in our review. Similar to the results found in the PSD analyses, current evidence in the literature covers a wide range of interventions, with few or no replicated studies.

Due to the unavailability of appropriate data, this paper could not review the evidence of PSE interventions in a network analysis. Unfortunately, the difficulty that exists with reviewing existing research for this domain echoes the comprehensive effort of Allida et al. (2019), who reported the lack of appropriately published data in emotionalism research. One potential drawback for PSE research at this stage is the absence of a standardised, reliable and valid tool to measure and outcome emotionalism. Although this paper did not analyse PSE data, the description of PSE studies included (Table 3) shows limitations in both diagnosing and rating

emotionalism. Many existing studies and clinical practice still rely on subjective ratings of crying or laughing frequency to determine PSE presence, or on the clinician (or researcher's) subjective impression of this mood disorder. The lack of a theoretically derived, validated outcome measure for PSE will continue to hamper the work of researchers to determine evidence- based treatments and hamper the efforts of clinicians to accurately detect and manage this commonly occurring disorder.

Overall, there exist many gaps and inconsistencies in the body of evidence considering psychological and emotional outcomes post-stroke, which is reflected in the limitations ofthis paper. In efforts to include the widest range of evidence available, we did not exclude trials based on the diagnostic criteria used or outcome measures reported, as other network meta-analyses on PSD have (Sun et al.,2017; Deng et al., 2017). This contributed to even more variability in the available data, not taking into account the variation arising from the use of different outcome measures of depression and anxiety. Other factors such as time since stroke, length of intervention and dose of medication may have added to the variability.

Further, this review was not able to replicate the results reported by the NMAs mentioned or the findings from Wang et al.'s (2018) meta-analysis, which provided promising results on the effects of CBT on PSD. Unfortunately, most of the articles cited in Wang et al. (2018)'s paper were unavailable for interpretation in the present analysis. Most of these trials were conducted in China, published in journals that could not be accessed, or reported in Mandarin language.

Although there appears to be a plethora of Traditional Chinese Medicine intervention studies relevant to post-stroke mood disorders, very few studies report their findings in English.

Moreover, of English-published papers reported by Wang et al. (2018) in their CBT for PSD review, we could not include the important seminal research of Lincoln and Flannaghan (2003), who studied CBT against a placebo intervention and 'treatment as usual' control and the work of Kootker et al. (2017) - who tested augmented CBT intervention for PSD. Both these studies published outcome data on median values, which is not interpretable in this analysis. Such drawbacks may be due to the methodological limitations of choosing a network meta- analysis approach, as well as the lack of interpretable data reported by the authors. For example, studies that reported outcomes based on median values and percentage of change could not be included in this network meta-analysis and this is an important point to consider, for researchers in the field going forward.

Additionally, the network meta-analysis reported here does not take into account reporting of adverse effects. This may be particularly important when talking about treatment efficacy of pharmacological interventions, whereby adverse effects may well have an impact on safety and a person's decision to adhere to the medication.

Conclusions and recommendations.

This paper presents a review of existing research on the interventions for PSD, PSA and PSE. Given the limitations discussed, the estimates and rankings reported in this paper can only indicate the efficacy of treatments presented with minimal confidence, and only in relation to each other. It is also noted that all of the treatment estimates for both PSD and PSA interventions are reported with wide ranges in their confidence intervals, again reflecting the large extent of variance when it comes to interpreting the data. Nevertheless, this work provides a framework for further wide-scale network comparisons in treatment of post-stroke depression, anxiety and emotionalism. As it currently exists, NMAs within this field focus primarily on pharmacological interventions (Qin et al., 2018, Sun et al., 2017), whereas one NMA included only one psychological intervention in its comparisons (Deng et al., 2017). Within stroke services, psychological therapies are often employed in treating these mood

disorders – however, this is poorly reflected in the current literature. Moreover, as discussed in this paper, even the most commonly reported (pharmacological) interventions are not well studied with respect to the most common mood domain (PSD).

There are several overarching recommendations that can be made in conclusion of this paper. First, it is hoped that additional research and future evidence on post-stroke mood intervention will continue to develop within the field. Additionally, standardised reporting of outcome measures will provide the necessary details for future reviews to be conducted successfully and conclusions to be drawn with more accuracy. The lack of a standard outcome measure of any sort currently, for PSE, is a good example. This paper recommends for future researchers that they report data that can be included in meta-analyses such as mean and standard deviation or standard error statistic of its outcomes, which is needed to calculate the SMD.

Stroke occurs to more than 100,000 people every year in England (Burton & Tyson, 2015). It is the fourth biggest cause of mortality in the UK and the second leading cause of death worldwide (Stroke Org, 2018). When such a traumatic and life-threatening occurrence can have a wide-ranging impact on our abilities and daily living, it is not surprising that it may have a profound impact on a person's mood. Given the prevalence of stroke and the corresponding prevalence of post-stroke mood disorders, it is vitally important to study the existing interventions to enable clinicians to treat these conditions in the safest and most efficacious way.

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CHAPTER FIVE: General discussion and critical review

This chapter summarises the findings from both the systematic review and the empirical paper. A critical appraisal of themes within the papers is presented in the context of relevant literature.

This thesis intended to explore the wide range of interventions currently employed in the treatment of depression, anxiety and emotionalism following stroke. Despite advances and progress in stroke research and practice, rehabilitation and treatment of these post-stroke mood disorders persists as a challenge worldwide. At present, NICE guidelines for managing post-stroke depression refer to the recommendations made for depression in adults with a chronic physical health problem and generalised anxiety disorder (NICE, 2013) suggesting a stepped-care approach considering psychological and pharmacological interventions, or both. This generalised approach towards mood disorders after stroke may be met with some difficulties. First, pharmacological interventions, which are commonly employed (Wannagat, Zielasek & Gaebel, 2013) cannot fully address the profound psychological, social and environmental impacts of a stroke, and the inherent adjustments necessary to the inevitable changes to life after it. This approach also does not take into the account the high rates of adverse effects from pharmacological interventions (Hackett et al., 2009), which is a particularly worrying factor for the stroke population, who are generally of older age. Additionally, there should be caution in given the increased risk of stroke recurrence associated with antidepressants (Jung, Chen & Chien, 2015; Biffi, Scotti & Corrao, 2017; Trajkova et al., 2019). Furthermore, recommendations for post-stroke anxiety and emotionalism - both of which show a high prevalence post-stroke – do not have specific associated treatment recommendations (Knapp et al., 2017;Gillespie et al., 2016).

Although literature related to the general treatment of depression and anxiety may inform the treatment of these presentations post-stroke, an associated evidence base for this population is lacking. This is largely known by clinicians and researchers in the field and is noted across reviews of all three post-stroke domains (Wang et al., 2018; Knapp et al., 2017; Allida et al.,

2020). The network meta-analysis in Chapter Four aimed to provide an overarching view of evidence-based treatments for mood disorders after stroke and to highlight gaps within this literature. In this pursuit, it attempted to synthesise the most researched interventions and, where possible, make multiple-treatment comparisons to indicate which interventions are most efficacious. A network meta-analysis is able to perform this by synthesising both direct (within-trial evidence of randomised groups) and indirect (estimations calculated between trials) comparisons of multiple interventions that may not have been compared in the same trial, thus maximising the use of available evidence (Molloy et al., 2018). This advantage of NMA has drawn attention from researchers, leading to a large increase of its use in the last decade (Lee, 2014). Within the stroke literature however, the focus of NMA studies has been solely on PSD (Sun et al., 2017; Deng et al., 2017; Qin et al., 2018), and they lean heavily on pharmacological research. To our knowledge, this thesis presents the first paper employing NMA methodology across multiple mood disorder / emotion disorder domains, and to consider both pharmacological and psychological interventions in tandem.

In considering the results, it must be reflected that the conclusions from the NMA broadly mirror those reported in the conventional MA's (Knapp et al., 2017; Allida et al., 2020). i.e. that a lack of stroke-specific treatment research hampers making clear clinical recommendations. More specifically, results from the network analyses were unable to draw firm conclusions of efficacious interventions across all domains. Treatment ranking was estimated based on a wide range of interventions across relatively few studies. Although there are indications pointing towards Trazodone, Behavioural Activation Therapy and high-frequency transcranial magnetic stimulation for PSD, as well as neuromuscular electrical stimulation and self-help relaxation interventions for PSA, these results should be interpreted with significant caution. Many of the indirect effects are based on direct effects obtained from single studies with small samples or research papers of relatively low quality. More high-quality trials investigating these existing interventions are badly needed, before definite clinical recommendations can be made. For example, the most researched intervention within

the largest network (sub-network one for PSD), relied on data from only three trials. For PSA, two networks were produced, but neither one compared interventions that were studied in more than two trials. And finally, for PSE, it was not possible to produce a network at all, reflecting the particular paucity of treatment research focused on this common sequela of stroke. Overall, the findings arising from the NMA emphasizes the particular scarcity of treatment research within this field – a scarcity that applied to both pharmacological and psychological treatments, and particularly studies considering such treatments in comparison - and further affirms the disproportionate focus of research across the three mood domains. This finding also highlights the need for researchers to make available valuable data from their studies in a format that allows subsequent synthesis, reporting statistical means and standard deviations / standard errors which will allow for its conversion to a standardised mean for comparison, improving accessibility for future research.

The importance of a strong evidence-base for the treatment of post-stroke mood disorders cannot be over emphasised. Stroke is a common clinical problem, impacting up to 230 people every day in the United Kingdom alone (NHS, 2020). Moreover, for acute ischemic stroke at least, survival rates are improving with the introduction of new reperfusion techniques (intravenous alteplase) (Anderson et al., 2019). As a result, more people than ever survive with ischemic stroke and accordingly live with the consequent mood effects we know from the epidemiology literature commonly arise. Approximately one third of stroke survivors will develop clinical depression, one quarter post-stroke anxiety and one fifth post-stroke emotionalism (Hackett et al., 2014; Knapp et al., 2020; Gillespie et al., 2016). It is known that if left untreated, PSD negatively impacts rehabilitation efforts, length of hospital stays,

functional outcome, mortality (Ahn et al., 2015; Gunal, Baskurt & Baskurt, 2019), and also stroke survivor quality of life.

Indeed, the particular importance of considering quality of life after stroke is considered in Chapter Two, where a comprehensive and updated review of HR-QOL measures used for people who have sustained a stroke, is presented. The review of HR-QOL measures in stroke replicated a methodology first adopted by Golomb, Vickrey and Hays (2001) nineteen years ago, but updated with the addition of reviewing the clinical utility of the measures using the framework outlined by Burton and Tyson (2015a; 2015b) in their stroke research. Interestingly, alongside physical functioning, emotional wellbeing is the only other domain (out of eleven) that was covered in all seventeen identified HR-QOL measures for stroke. As noted in the conclusion, whilst the review was able to offer recommendations in terms of the best available HR-QOL measures for researchers and clinicians, expert judgement needs to be employed when considering choice of measure.

Taken together, the systematic review and network meta-analysis provide a comprehensive review and synthesis of current research pertaining both to HR-QOL measurement in the stroke context, and to evidence-based treatment approaches (pharmacological and psychological) for the most common post-stroke mood disorders. Firstly, practical implications can be drawn from the findings of the systematic review of HR-QOL measures. Given the information synthesised in the review, the resulting flow-chart provides a simple tool for stroke clinicians and researches across the multidisciplinary team to evaluate the best suited measure that will meet a patient's needs. This will take into account the cost of the measure, the length of time available for assessment and the specific HR-QOL domains that may be specifically important for a person (i.e. someone who was affected physically from the stroke may be more suited to using a measure that takes into account a physical / functioning domain). Additionally, the network meta-analysis may encourage stroke clinicians to critically appraise the evidence for post-stroke mood interventions. Despite the common prescription of SSRIs and TCAs for PSD, PSA and PSE, it is noted in this paper that the

effectiveness of these interventions is not well proven and replicated. Observations of the current literature which includes non-psychological and non-pharmacological approaches to treat post-stroke mood disorders (i.e. exercise interventions reported for PSA) suggest that a holistic, multi-disciplinary approach may be beneficial to people who have experienced a stroke. This ties in with the recommendations for choosing HR-QOL measures, where it is important for clinicians to exercise their expert judgement specific to the person in need of HR-QOL assessment or post-stroke mood treatment.

However, both the systematic review presented in Chapter Two and the network meta-analysis presented in Chapter Four are not without limitations. First, the framework on which the systematic review of HR-QOL measures was performed is methodologically driven by existing work - which may be both a strength and a limitation. Where Burton and Tyson (20015a; 2015b) and Golomb, Vickrey and Hays (2001) have contributed a systematic methodology for assessing measures, the present work assimilates the strength of both approaches. This adds to research replicability, allowing for straightforward and direct comparisons between the reviews. However, this in turn means that the present review is bound to the same limitations of the prior, therefore not suggesting favourability of this methodology over others. Therefore, this methodology may be limited in terms of how much it advances in this area.

The network meta-analysis approach for post-stroke mood disorders may also be considered to have some limitations. Whilst it is an advancing method of research, the results from this present paper suggest that the scarcity and quality of existing RCTs available mean that it is unable to provide a meaningful analysis of treatment efficacy ranking. Previous NMAs conducted by Sun et al. (2017) and Qin et al. (2018) have only looked at antidepressant interventions, and Deng et al. (2017) was stringent in their criteria and only included studies reporting Hamilton Depression Rating Scale (HAMD) scores. In an attempt to capture a wide,

inclusive snapshot of current evidence, the present NMA employed loose inclusion criteria. This is reflected in the variability of interventions found, and the multiple sub-network groups that were categorised for PSD and PSA interventions, instead of a singular network. This factor, added to the unavailability of appropriate data for analysis, meant that analyses of indirect treatment estimates may be inaccurate.

Even within the scarcity of available evidence, there additionally appeared to be a distinct favourability to PSD research (in comparison to the other mood domains), and within that – favourability to pharmacological interventions, although even here it is fair to describe the state of research as limited. As discussed, the framework of other interventions were wide-ranging and variable. However, it is important to note that a large body of research on Traditional Chinese Medicine (TCM) is not included in the review. The practice of TCM is long-standing and is widely used across Asia (Liu, Ding & Wen, 2018). This covers a range of natural medication, acupuncture and physiotherapy interventions, most of which are adapted to current times and have reportedly few adverse effects (Tang, Liu & Ma, 2008; Liu, Ding & Wen, 2018). However, the majority of this research is published in the Mandarin language and Chinese journals, making it difficult to access. This is a common problem in trying to synthesise and compare research internationally, with the potential of missing novel, innovative or alternative efficacious treatments that are practised around the world.

Nonetheless, notwithstanding the above limitations, both the systematic review and network meta-analyses provide a comprehensive framework for future research. The systematic review drew on already-proven methodologies to replicate and provided an update of existing HR-QOL measures, where we can already see development of more stroke-specific HR- QOL measures in the field. However, as noted in Chapter Two, there still remains a gap in this field where no existing measure covered all HR-QOL domains. On the other hand, the

network meta-analyses provide an overarching view on the gaps in research and compares the existing literature across three post-stroke mood disorders. Although this paper was not able to confidently conclude on a best-available intervention for either of the domains, this encourages future triallists to replicate existing findings.

Worldwide, stroke is the second leading cause of death and the third leading cause of disability (Johnson, Onuma, Owolabi & Sachdev, 2016) and it commonly leaves a significant and long-lasting impact on a person's life, physical and/or psychological. This includes a range of significant mental health impacts. It is therefore unquestionable that improving mental health care for people who have suffered a stroke is and must remain a global priority. Across both the systematic review and network meta-analysis, the prevailing recommendation is for further quality research on stroke. In reporting outcomes for post-stroke mood interventions, or psychometric properties of HR-QOL measures, it is important to include appropriate and interpretable data. However, whilst there are many existing gaps in research focused on improving post-stroke mental health and quality of life care, there is at least some encouraging progress within this important field. This thesis portfolio adds to this gradually expanding body of work, highlighting the needs of future research for stroke mood interventions, and making recommendations based on an updated review of HR-QOL assessments.

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Informed consent

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Guarantor

JP

Contributorship

JP conceived the study, researched literature, analysed data and wrote the manuscript. EH acted as the second-rater in assessing eligibility and quality of the studies. NB and PB provided supervision throughout the process of this study and approved the final version of the manuscript.

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Appendix A: Search terms for all databases for Systematic Review

	Medline, via EBSCO	PsycINFO, via EBSCO	Embase, via Ovid
	(MM "Stroke+") OR (MM "Stroke, Lacunar") OR (MM "Stroke Rehabilitation")	(DE "Cerebrovascular Accidents" OR DE "Cognitive Rehabilitation") or stroke	stroke.mp. or cerebrovascular accident/
AND	((MM "Outcome Assessment (Health Care)+") OR "measure") OR (screen* or tool or measure* or questionnaire or scale)	"outcome assessment" or measure or tool or questionnaire or screen or scale	(questionnaire or measure* or screen* or tool or scale).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

AND	(MM "Quality of Life") OR "health-related quality of life"	(MM "Health Related Quality of Life")	health-related quality of life.mp. or *"quality of life"/
	844	54	2208

Appendix B: Journal of Clinical Psychology in Medical Settings – Instructions for Authors for Systematic Review

Instructions for Authors

General

In general, the journal follows the recommendations of the 2010 Publication Manual of the American Psychological Association (Sixth Edition), and it is suggested that contributors refer to this publication.

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The affiliation should comprise

- the department
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Key Words

- A list of 4–5 key words is to be provided directly below the abstract. Key words should express the precise content of the manuscript, as they are used for indexing purposes.

References

List references alphabetically at the end of the paper and refer to them in the text by name and year in parentheses. References should include (in this order):

- last names and initials of all authors,
- year published
- title of article
- name of publication
- volume number
- and inclusive pages

The style and punctuation of the references should conform to strict APA style and follow guidelines of the Publication Manual of the American Psychological Association, Sixth Edition – illustrated by the following examples:

- Journal Article

  Burns, J. W., & Katkin, E. S. (1993). Psychological, situational, and gender predictors of cardiovascular reactivity to stress: A multivariate approach. *Journal of Behavioral Medicine, 16,* 445–465.

- Book

  Ray, R. (2006): *Chronic Pain and Family: A Clinical Perspective.* New York: Springer.

- Contribution to a Book

  Bleiberg, J., Ciulla, R., & Katz, B. L. (1991). Psychological components of rehabilitation programs for brain–injured and spinal–cord–injured patients. In J. J. Sweet, R. H. Rozensky, & S. M. Tovian (Eds.), *Handbook of clinical psychology in medical settings* (pp. 375–400). New York: Plenum Press.

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If there is suspicion of misbehavior or alleged fraud the Journal and/or Publisher will carry out an investigation following COPE guidelines. If, after investigation, there are valid concerns, the author(s) concerned will be contacted under their given e-mail address and given an opportunity to address the issue. Depending on the situation, this may result in the Journal's and/or Publisher's implementation of the following measures, including, but not limited to:

- If the manuscript is still under consideration, it may be rejected and returned to the author.
- If the article has already been published online, depending on the nature and severity of the infraction:

  - an erratum/correction may be placed with the article

  - an expression of concern may be placed with the article

  - or in severe cases retraction of the article may occur.

The reason will be given in the published erratum/correction, expression of concern or retraction note. Please note that retraction means that the article is **maintained on the platform**, watermarked "retracted" and the explanation for the retraction is provided in a note linked to the watermarked article.

- The author's institution may be informed
- A notice of suspected transgression of ethical standards in the peer review system may be included as part of the author's and article's bibliographic record.

Fundamental errors

Authors have an obligation to correct mistakes once they discover a significant error or inaccuracy in their published article. The author(s) is/are requested to contact the journal and explain in what sense the error is impacting the article. A decision on how to correct the literature will depend on the nature of the error. This may be a correction or retraction. The retraction note should provide transparency which parts of the article are impacted by the error.

Suggesting / excluding reviewers

Authors are welcome to suggest suitable reviewers and/or request the exclusion of certain individuals when they submit their manuscripts. When suggesting reviewers, authors should make sure they are totally independent and not connected to the work in any way. It is strongly recommended to suggest a mix of reviewers from different countries and different institutions. When suggesting reviewers, the Corresponding Author must provide an institutional email address for each suggested reviewer, or, if this is not possible to include other means of verifying the identity such as a link to a personal homepage, a link to the publication record or a researcher or author ID in the submission letter. Please note that the Journal may not use the suggestions, but suggestions are appreciated and may help facilitate the peer review process.

Authorship principles

These guidelines describe authorship principles and good authorship practices to which prospective authors should adhere to.

Authorship clarified

The Journal and Publisher assume all authors agreed with the content and that all gave explicit consent to submit and that they obtained consent from the responsible authorities at the institute/organization where the work has been carried out, **before** the work is submitted.

The Publisher does not prescribe the kinds of contributions that warrant authorship. It is recommended that authors adhere to the guidelines for authorship that are applicable in their specific research field. In absence of specific guidelines it is recommended to adhere to the following guidelines*:

All authors whose names appear on the submission

1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

* Based on/adapted from:

ICMJE, Defining the Role of Authors and Contributors,

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018

Disclosures and declarations

All authors are requested to include information regarding sources of funding, financial or non-financial interests, study-specific approval by the appropriate ethics committee for research involving humans and/or animals, informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals (as appropriate).

The decision whether such information should be included is not only dependent on the scope of the journal, but also the scope of the article. Work submitted for publication may have implications for public health or general welfare and in those cases it is the responsibility of all authors to include the appropriate disclosures and declarations.

Data transparency

All authors are requested to make sure that all data and materials as well as software application or custom code support their published claims and comply with field standards. Please note that journals may have individual policies on

(sharing) research data in concordance with disciplinary norms and expectations. Please check the Instructions for Authors of the Journal that you are submitting to for specific instructions.

Role of the Corresponding Author

One author is assigned as Corresponding Author and acts on behalf of all co-authors and ensures that questions related to the accuracy or integrity of any part of the work are appropriately addressed.

The Corresponding Author is responsible for the following requirements:

- ensuring that all listed authors have approved the manuscript before submission, including the names and order of authors;
- managing all communication between the Journal and all co-authors, before and after publication;*
- providing transparency on re-use of material and mention any unpublished material (for example manuscripts in press) included in the manuscript in a cover letter to the Editor;
- making sure disclosures, declarations and transparency on data statements from all authors are included in the manuscript as appropriate (see above).

* The requirement of managing all communication between the journal and all co-authors during submission and proofing may be delegated to a Contact or Submitting Author. In this case please make sure the Corresponding Author is clearly indicated in the manuscript.

Author contributions

In absence of specific instructions and in research fields where it is possible to describe discrete efforts, the Publisher recommends authors to include contribution statements in the work that specifies the contribution of every author in order to promote transparency. These contributions should be listed at the separate title page.

Examples of such statement(s) are shown below:

• Free text:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [full name], [full name] and [full name]. The first draft of the manuscript was written by [full name] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Example: CRediT taxonomy:

• Conceptualization: [full name], ...; Methodology: [full name], ...; Formal analysis and investigation: [full name], ...; Writing - original draft preparation: [full name, ...]; Writing - review and editing: [full name], ...; Funding acquisition: [full name], ...; Resources: [full name], ...; Supervision: [full name],....

For **review articles** where discrete statements are less applicable a statement should be included who had the idea for the article, who performed the literature search and data analysis, and who drafted and/or critically revised the work.

For articles that are based primarily on the **student's dissertation or thesis**, it is recommended that the student is usually listed as principal author:

A Graduate Student's Guide to Determining Authorship Credit and Authorship Order, APA Science Student Council 2006

Affiliation

The primary affiliation for each author should be the institution where the majority of their work was done. If an author has subsequently moved, the current address may additionally be stated. Addresses will not be updated or changed after publication of the article.

Changes to authorship

Authors are strongly advised to ensure the correct author group, the Corresponding Author, and the order of authors at submission. Changes of authorship by adding or deleting authors, and/or changes in Corresponding Author, and/or changes in the sequence of authors are **not** accepted **after acceptance** of a manuscript.

- **Please note that author names will be published exactly as they appear on the accepted submission!**

Please make sure that the names of all authors are present and correctly spelled, and that addresses and affiliations are current.

Adding and/or deleting authors at revision stage are generally not permitted, but in some cases it may be warranted. Reasons for these changes in authorship should be explained. Approval of the change during revision is at the discretion of the Editor-in-Chief. Please note that journals may have individual policies on adding and/or deleting authors during revision stage.

Author identification

Authors are recommended to use their ORCID ID when submitting an article for consideration or acquire an ORCID ID via the submission process.

Deceased or incapacitated authors

For cases in which a co-author dies or is incapacitated during the writing, submission, or peer-review process, and the co-authors feel it is appropriate to include the author, co-authors should obtain approval from a (legal) representative which could be a direct relative.

Authorship issues or disputes

In the case of an authorship dispute during peer review or after acceptance and publication, the Journal will not be in a position to investigate or adjudicate. Authors will be asked to resolve the dispute themselves. If they are unable the Journal reserves the right to withdraw a manuscript from the editorial process or in case of a published paper raise the issue with the authors' institution(s) and abide by its guidelines.

Confidentiality

Authors should treat all communication with the Journal as confidential which includes correspondence with direct representatives from the Journal such as Editors-in-Chief and/or Handling Editors and reviewers' reports unless explicit consent has been received to share information.

Compliance with Ethical Standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Disclosure of potential conflicts of interest

Authors must disclose all relationships or interests that could influence or bias the work. Although an author may not feel there are conflicts, disclosure of relationships and interests affords a more transparent process, leading to an accurate and objective assessment of the work. Awareness of real or perceived conflicts of interests is a perspective to which the readers are entitled and is not meant to imply that a financial relationship with an organization that sponsored the research or compensation for consultancy work is inappropriate. Examples of potential conflicts of interests **that are directly or indirectly related to the research** may include but are not limited to the following:

- Research grants from funding agencies (please give the research funder and the grant number)
- Honoraria for speaking at symposia
- Financial support for attending symposia
- Financial support for educational programs
- Employment or consultation
- Support from a project sponsor
- Position on advisory board or board of directors or other type of management relationships
- Multiple affiliations
- Financial relationships, for example equity ownership or investment interest
- Intellectual property rights (e.g. patents, copyrights and royalties from such rights)
- Holdings of spouse and/or children that may have financial interest in the work

In addition, interests that go beyond financial interests and compensation (non-financial interests) that may be important to readers should be disclosed. These may include but are not limited to personal relationships or competing interests directly or indirectly tied to this research, or professional interests or personal beliefs that may influence your research.

The corresponding author collects the conflict of interest disclosure forms from all authors. In author collaborations where formal agreements for representation allow it, it is sufficient for the corresponding author to sign the disclosure form on behalf of all authors. Examples of forms can be found

here:

The corresponding author will include a summary statement **on the title page that is separate from their manuscript,** that reflects what is recorded in the potential conflict of interest disclosure form(s).

See below examples of disclosures:

Funding: This study was funded by X (grant number X).

Conflict of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z.

If no conflict exists, the authors should state:

Conflict of Interest: The authors declare that they have no conflict of interest.

Research involving human participants, their data or biological material

Ethics approval

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

Retrospective ethics approval

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

Ethics approval for retrospective studies

Although retrospective studies are conducted on already available data or biological material (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of a country. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

Ethics approval for case studies

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on **Informed Consent**.

Cell lines

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

Research Resource Identifiers (RRID)

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

Organism: *Filip1*$^{tm1a(KOMP)Wtsi}$ **RRID:MMRRC_055641-UCD**

Cell Line: RST307 cell line **RRID:CVCL_C321**

Antibody: Luciferase antibody DSHB Cat# LUC-3, **RRID:AB_2722109**

Plasmid: mRuby3 plasmid **RRID:Addgene_104005**

Software: ImageJ Version 1.2.4 **RRID:SCR_003070**

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

Clinical Trial Registration

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as "A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions" and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively registered' should be included as the last line of the manuscript abstract.

Purely observational trials will not require registration.

Standards of reporting

Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal's Instructions for Authors.

Checklists are available for a number of study designs, including:

Randomised trials (CONSORT) and Study protocols (SPIRIT)

Observational studies (STROBE)

Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P)

Diagnostic/prognostic studies (STARD) and (TRIPOD)

Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

Summary of requirements

The above should be summarized in a statement and placed in a **"Declarations"** section before the reference list under a heading of **'Ethics approval'**.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No ....).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

• This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

Exceptions where it is not necessary to obtain consent:

• Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

• Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant information regarding consent. Authors should provide the appropriate attribution for republished images.

Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered "informed". However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

Consent to Participate

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra

care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

Consent to Publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies. A consent to publish form can be found

here. (Download docx, 36 kB)

Summary of requirements

The above should be summarized in a statement and placed in a **"Declarations"** section under a heading of **"Consent to participate"** and/or **"Consent to publish"**. The Declarations section should be placed on a title page that is separate from the manuscript. Please use the title page as outlined in the Title Page section of these Instructions for Authors for providing the statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for **"Consent to participate"**:

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for **"Consent to publish"**:

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Images will be removed from publication if authors have not obtained informed consent or the paper may be removed and replaced with a notice explaining the reason for removal.

English Language Editing

For editors and reviewers to accurately assess the work presented in your manuscript you need to ensure the English language is of sufficient quality to be understood. If you need help with writing in English you should consider:

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- Visiting the English language tutorial which covers the common mistakes when writing in English.
- Using a professional language editing service where editors will improve the English to ensure that your meaning is clear and identify problems that require your review. Two such services are provided by our affiliates Nature Research Editing Service and American Journal Experts. Springer authors are entitled to a 10% discount on their first submission to either of these services, simply follow the links below.

English language tutorial

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Please note that the use of a language editing service is not a requirement for publication in this journal and does not imply or guarantee that the article will be selected for peer review or accepted.

If your manuscript is accepted it will be checked by our copyeditors for spelling and formal style before publication.

Appendix C: Quality Ratings for Systematic Review

Methodological quality of each study per questionnaire and measurement property. Studies marked with an asterisk (*) indicate co-rated quality assessment by an independent rater.

Study	Measure	Structural Validity	Internal Consistency	Cross cultural validity /Translation	Reliability	Measurement Error	Content Validity	Hypotheses Testing	Responsiveness	Overall
***Bohannon, Maljanian, Lee & Ahlquist (2004)**	SF-12	Fair	Excellent	N/A	Excellent	Fair	Poor	N/A	Good	Fair
***Buck et al. (2003)**	NEWSQOL	Poor	Excellent	N/A	Good	Poor	Good	Poor	Poor	Fair
Chen et al. (2012)	SS-QoL-12	Good	Poor	N/A	Poor	Poor	Excellent	Poor	Excellent	Fair
Chen et al. (2016)	EQ-5D-5L; EQ-VAS; SIS 3.0	Poor	Poor	N/A	Poor	Good	Good	Good	Good	Fair
Duncan et al. (1999)	SIS 2.0	Poor	Excellent	N/A	Poor	Poor	Good	Good	Good	Fair
Guo, Togher, Power & Koh (2016)	SAQOL-39	Poor	Excellent	N/A	Excellent	Poor	Poor	Good	Good	Fair
***Hamedani et al. (2001)**	HSQuale	Poor	Poor	N/A	Good	Good	Poor	Poor	Poor	Poor
Hilari, Byng, Lamping & Smith (2003)	SAQOL-39	Poor	Excellent	N/A	Good	Poor	Good	Excellent	Excellent	Good
Hilari et al. (2009)	SAQOL-39	Poor	Poor	N/A	Excellent	Poor	Good	Good	Good	Fair
***Hobart et al. (2009)**	SF-36	Poor	Poor	N/A	Poor	Poor	Good	Good	Good	Fair
Hunger et al. (2012)	EQ-5D; SIS 2.0	Poor	Poor	N/A	Excellent	Poor	Good	Excellent	Excellent	Fair

Kerber et al. 2013)	SSQOL	Poor	Excellent	N/A	Good	Poor	Good	N/A	Good	Fair
***Kwon et al. (2006)**	SIS	Excellent	Poor	N/A	Poor	Excellent	Excellent	Poor	Poor	Fair
Luo et al. (2015)	Stroke-PROM	Poor	Excellent	N/A	Poor	Good	Excellent	Good	Excellent	Good
MasIsaac et al. (2016)	SF-SIS	Poor	Excellent	Fair	N/A	Poor	Good	Excellent	Excellent	Fair
OjoOwolabi et al. (2010)	HRQOLISP-40	Poor	Excellent	Good	Poor	Poor	Poor	Good	Good	Fair
Pickard et al. (2005)	EQ-5D; SF-6D; HUI2; HUI3	Poor	Poor	N/A	Poor	Poor	Excellent	Excellent	Excellent	Fair
Possiant et al. (2003)	PBSI	Excellent	Excellent	N/A	Poor	Poor	Excellent	Excellent	Excellent	Good
Post et al. (2011)	Short SS-QoL	Poor	Excellent	N/A	Poor	Poor	Excellent	Excellent	Excellent	Fair
***Richardson et al. (2016)**	SIS 3.0	Poor	Excellent	N/A	Poor	Poor	Excellent	Excellent	Poor	Fair
***Silva et al. (2016)**	SS-QoL	Poor	Excellent	N/A	Good	Excellent	Good			Good
Strum et al. (2002)	AQoL	Poor	Poor	N/A	Poor	Poor	Excellent	Excellent	Excellent	Fair
***VincentOnabajo et al. (2013)**	HRQOLISP-40	Poor	Poor	N/A	Good	Good	Excellent	N/A	N/A	Fair
***Williams et al. (1999)**	SS-QOL	Poor	Excellent	N/A	Excellent	Good	Excellent	Poor	Poor	Fair

AQoL. Assessment of Quality of Life; EQ-5D, EQ-5D-5L, EuroQoL 5-Dimensions Questionnaire; EQ-VAS, EuroQoL Visual analogue scale; (HUI2, Health Utility Index Mark 2; HUI3, Health Utility Index Mark 3;HSQuale, Haemorrhagic Stroke Quality of Life ; HRQOLISP-40, Health-Related Quality of Life in Stroke Patients 40-items; NEWSQOL, Newcastle Stroke-Specific Quality of Life Measure; PBSI, Preference-Based Stroke Index; SF-12, SF-6D, SF-36, Medical Outcomes Study Short-Form Health Survey (12 item, 6-dimensions, 36-item); SIS 2.0, 3.0, Stroke Impact Scale (Version 2.0, 3.0); SF-SIS, Short-Form Stroke

Impact Scale; Stroke-PROM; Stroke-Patient Reported Outcome Measure, SAQOL-39, Stroke and Aphasia Quality of Life Scale-39; SS-QOL, 12-item Stroke-Specific Quality of Life Scale, NA; Not Available, *, Co-rated quality assessment

Appendix D: Search terms for all databases for Empirical Paper

MEDLINE via EBSCO Host:

	Depression	Anxiety	Emotionalism
	(MM "Stroke+") OR (MM "Stroke Rehabilitation") OR (MM "Stroke, Lacunar")		
AND	(MM "Depression") OR "depression" OR (MM "Depressive Disorder+") OR (MM "Depressive Disorder, Major")	(MM "Anxiety+") OR "anxiety" OR (MM "Anxiety Disorders+")	"post-stroke emotionalism" OR emotionalism OR "emotional lability" OR "pseudobulbar affect"
AND	(MM "Randomized Controlled Trial+") OR (MM "Randomized Controlled Trials as Topic") OR "randomised controlled trials"		
	49	18	3

PsycINFO via EBSCO Host:

	Depression	Anxiety	Emotionalism
	DE "Cerebrovascular Accidents" OR Stroke		
AND	MM "Major Depression" OR MM "Depression (Emotion)" OR	MM "Anxiety" OR MM "Anxiety Disorders" OR	MM "Emotional Instability" OR "emotional lability"

	depression OR "depressive disorder"	MM "Generalized Anxiety Disorder"	OR "emotionalism" OR "pseudobulbar affect"
AND	MM "Randomized Controlled Trials" OR MM "Randomized Clinical Trials"		
	0	0	0

Cochrane Library:

	Depression	Anxiety	Emotionalism
	MeSH descriptor: [Stroke] explode all trees		
AND	MeSH descriptor: [Depression] explode all trees	MeSH descriptor: [Anxiety] explode all trees	Emotionalism or “emotional lability” or “pseudobulbar affect”
AND	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees		
	9	6	5

EMBASE via Ovid:

	Depression	Anxiety	Emotionalism
	stroke.mp. or cerebrovascular accident/		
AND	depression/ or post-stroke depression/	anxiety.mp. or anxiety/ or anxiety disorder/	emotionalism.mp.

AND	randomised controlled trials.mp. or randomized controlled trial/		
	635	394	8

DORIS:

*All studies on DORIS are related to stroke.

	Depression	Anxiety	Emotionalism
Selected categories: - Mood disturbance - All treatment stages - All stroke types - Completed RCTs			
Search term:	Depress-	Anxi-	Emotional-
Psychological therapy	122	48	14 (0 results from 'emotionalism' and 'pseudobulbar affect')
Pharmacology	179	18	18 (2 results from 'emotionalism' and 0 'pseudobulbar affect'
Complementary medical therapy	64	13	5 (0 results from 'emotionalism'

			and ‘pseudobulbar affect’)
	365	79	37

Appendix E: NICE Quality appraisal checklist for Empirical Paper

1. Is the source population or source area well described?

    - Was the country (e.g. developed or non-developed, type of healthcare system), setting (primary schools, community centres etc.), location (urban, rural), population demographics etc. adequately described?

2. Is the eligible population or area representative of the source population or area?

    - Was the recruitment of individuals, clusters or areas well defined (e.g. advertisement, birth register)?
    - Was the eligible population representative of the source? Were important groups under-represented?

3. Do the selected participants or areas represent the eligible population?

    - Was the method of selection of participants from the eligible population well described?
    - What % of selected individuals or clusters agreed to participate? Were there any sources of bias?
    - Were the inclusion or exclusion criteria explicit and appropriate?

4. Were interventions (and comparisons) well described and appropriate?

    - Were interventions and comparisons described in sufficient detail (i.e. enough for study to be replicated)?
    - Were comparisons appropriate (e.g. usual practice rather than no intervention)?

5. Was the study sufficiently powered to detect an intervention effect (if one exists)?

    - A power of 0.8 (that is, it is likely to see an effect of a given size if one exists, 80% of the time) is the conventionally accepted standard.
    - Is a power calculation presented? If not, what is the expected effect size? Is the sample size adequate?

    For each item on the NICE checklist, 5 ratings are available:

++ Indicates that for that particular aspect of study design, the study has been designed or conducted in such a way as to minimise the risk of bias.

+ Indicates that either the answer to the checklist question is not clear from the way the study is reported, or that the study may not have addressed all potential sources of bias for that particular aspect of study design. Should be reserved for those aspects of the study design in which significant sources of bias may persist.

Not reported (NR) Should be reserved for those aspects in which the study under review fails to report how they have (or might have) been considered.

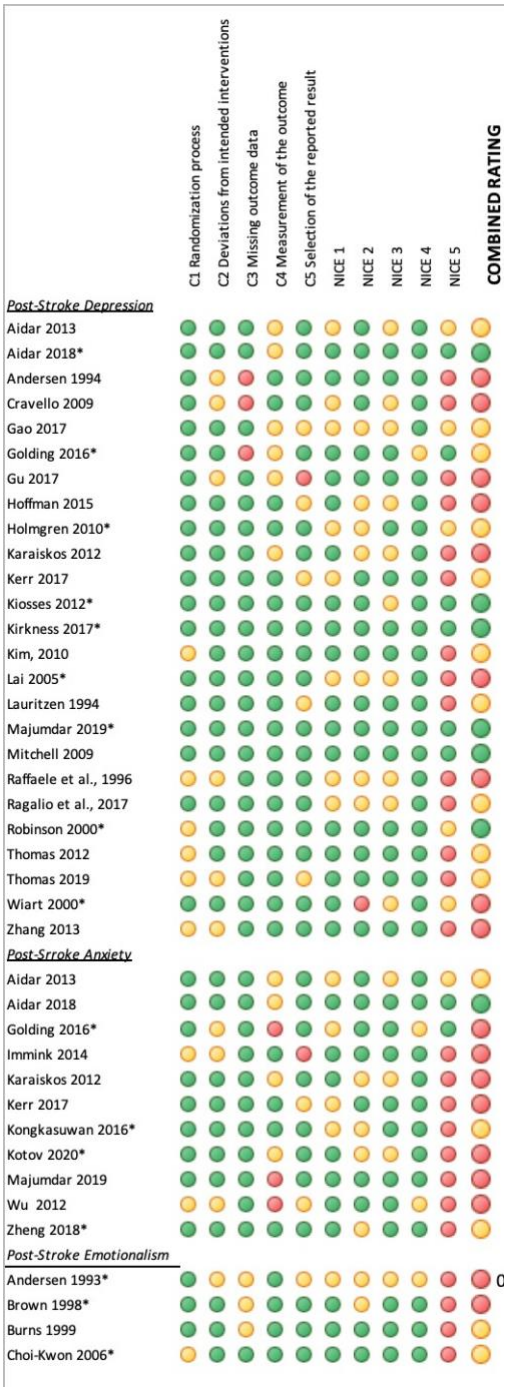
Not applicable (NA) Should be reserved for those study design aspects that are not applicable given the study design under review (for example, allocation concealment would not be applicable for case control studies).

The overall rating from the Cochrane tool and NICE appraisal checklist were merged, and studies were given a final rating of high, moderate, or low quality:

- High: All or most of the criteria, across both the NICE and Cochrane checklists, scored well, where they have not met criteria the conclusions were very unlikely to alter or not meeting criteria were unavoidable.
- Moderate: Some of the criteria across both the NICE and Cochrane checklists have scored well, and where they have not, or haven't been adequately described, the conclusions were unlikely to alter.
- Low: Few or no checklist criteria have been fulfilled across either the NICE or Cochrane checklists, and the conclusions were likely or very likely to alter.

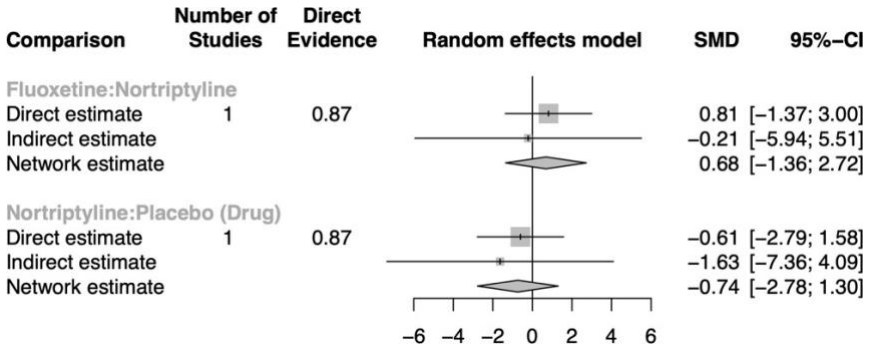
(Criteria were adapted from the NICE quality appraisal checklist for quantitative intervention studies, 2012).

Appendix F: Quality Ratings for Empirical Paper



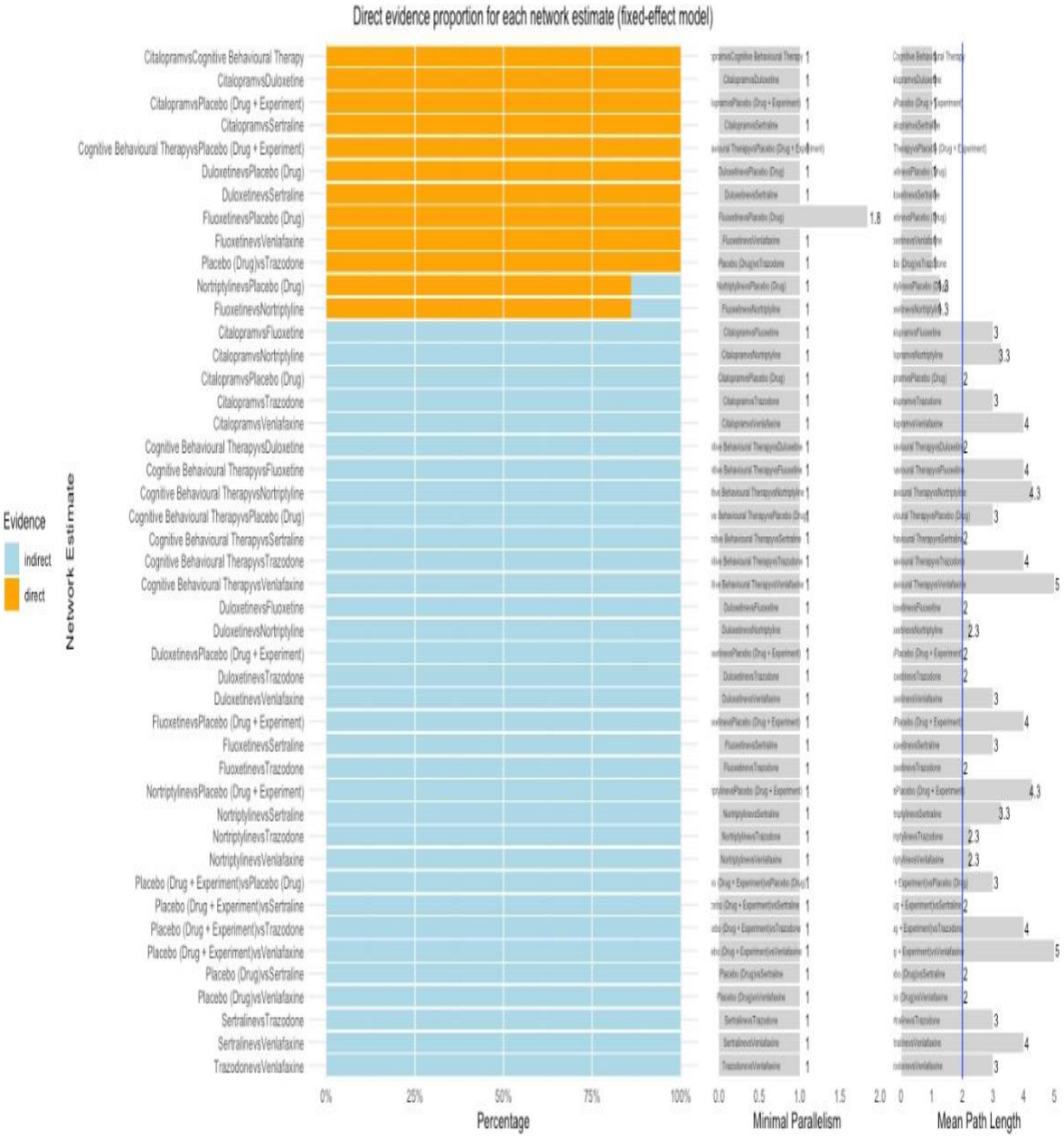
Ratings assigned using the Cochrane risk-of-bias tool for randomised trials (Sterne et al., 2019, Ver 2.) and the NICE quality appraisal checklist for quantitative intervention studies (NICE, 2012). "C1-C5" domains represent Domains 1-5 on the Cochrane tool, and "NICE 1-5" represent the selected items from the NICE checklist (Appendix A). "Combined rating" represents the overall rating from both tools. The rating codes are: red circles = high risk of bias on Cochrane tool, "-"/ Not Reported on NICE tool; yellow circles = some concerns on Cochrane tool, "+" on NICE tool; green circles = low risk of bias on Cochrane tool, "++" on NICE tool.

Appendix G: Forest plot of studies with direct and indirect evidence for PSD subnetwork one (Empirical Paper)

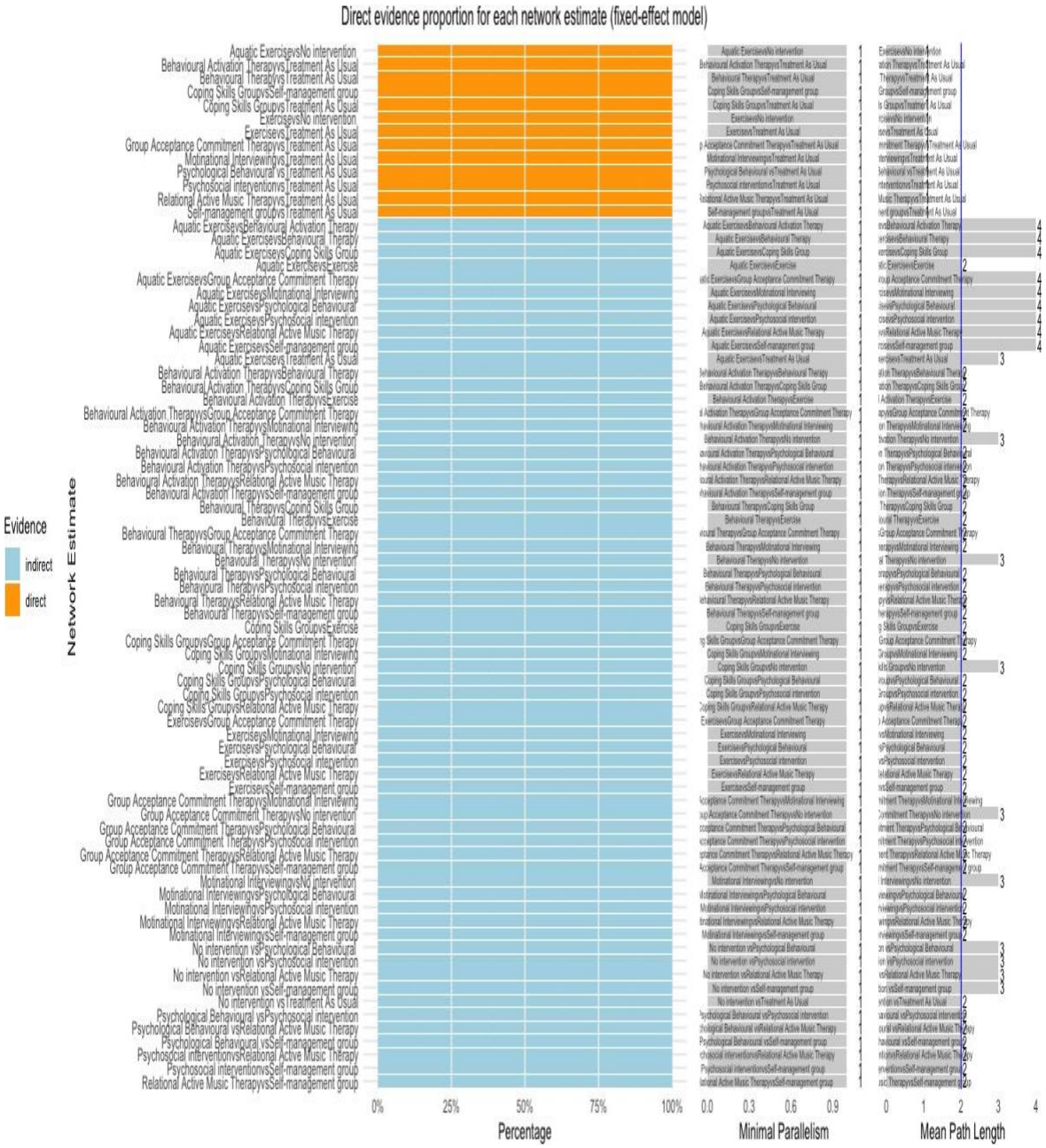


Appendix H: Direct and indirect evidence plots for PSD and PSA sub-networks (Empirical Paper)

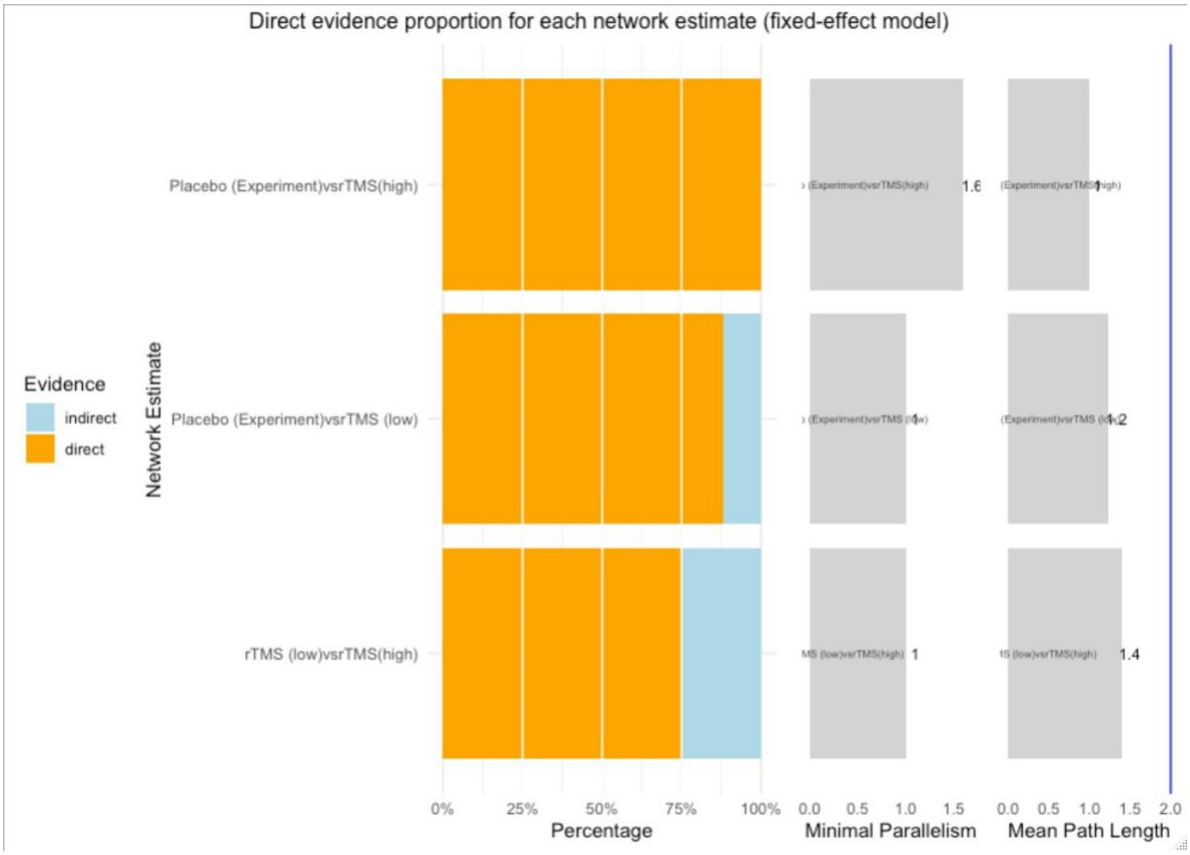
PSD sub-network one:



PSD sub-network two:



PSD sub-network three:



PSA Sub-network group two:

Appendix I: Funnel plots for publication bias for PSD and PSA subnetwork groups (Empirical Paper)

Funnel plot for PSD subnetwork one

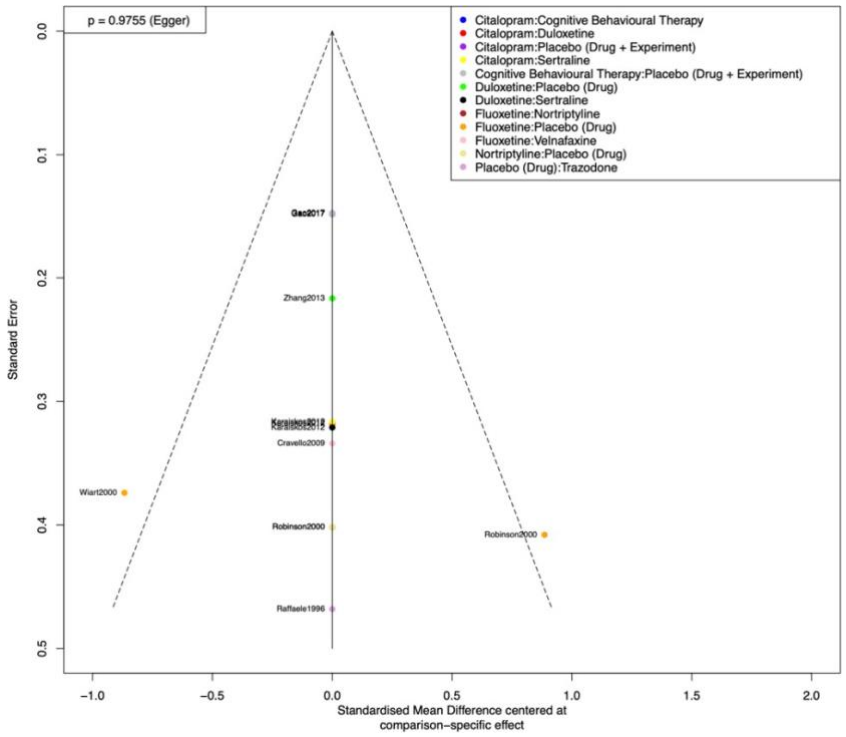


Figure 7. *Funnel plot, PSD subnetwork two*

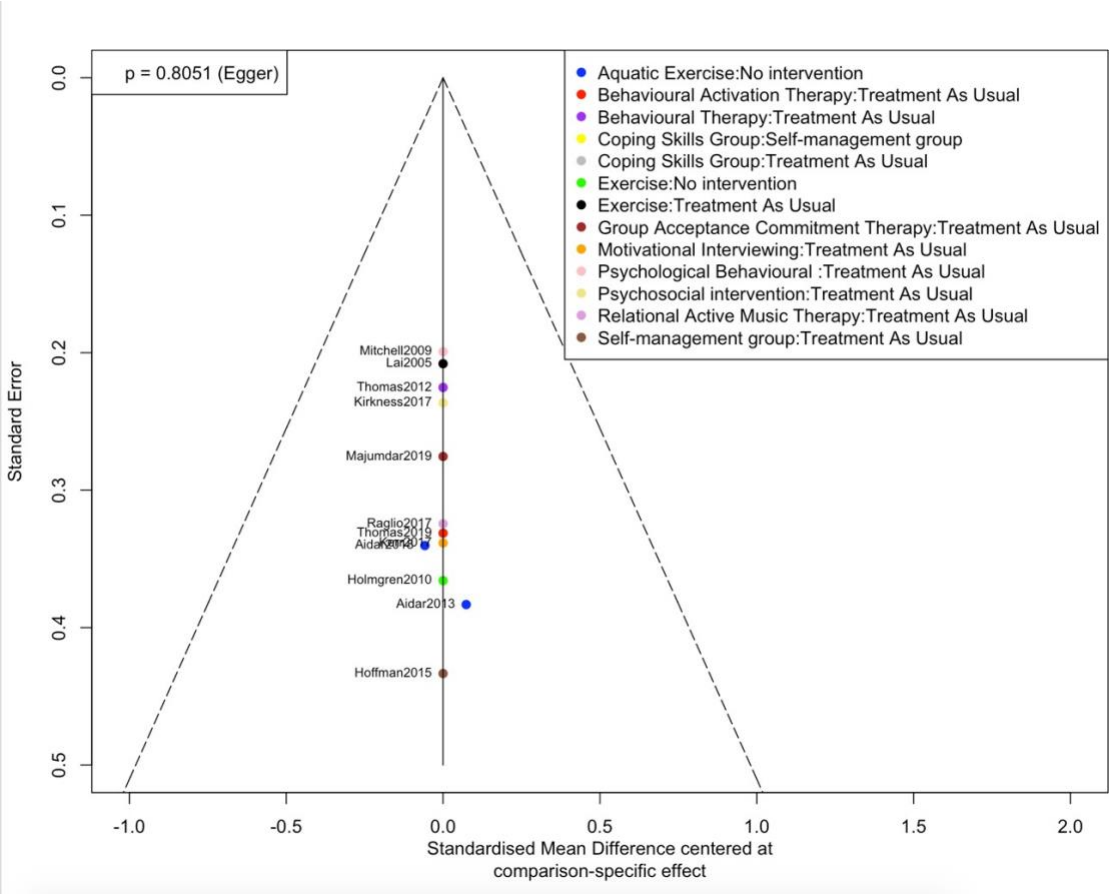
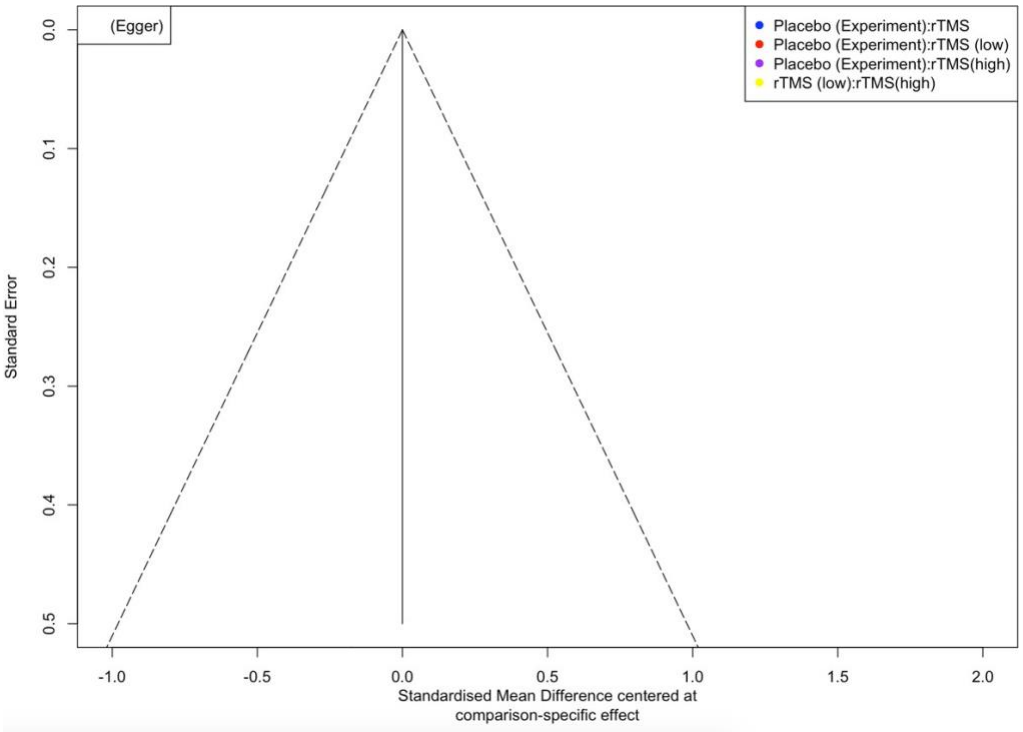
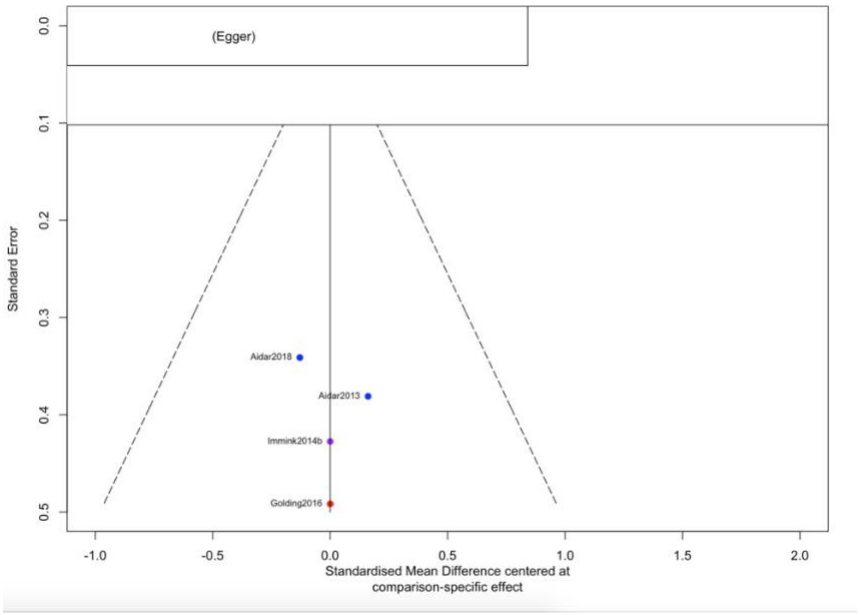


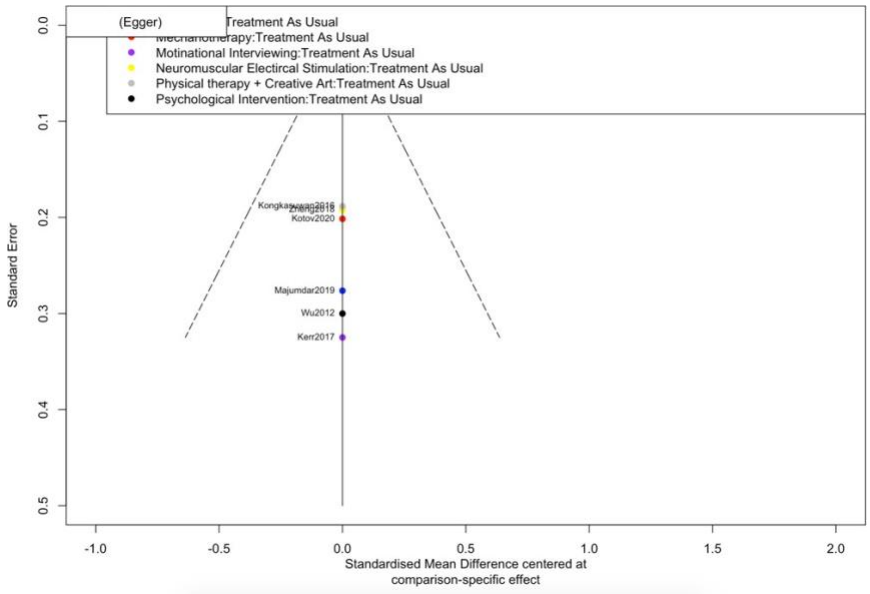
Figure 11. Funnel plot, PSD subnetwork three



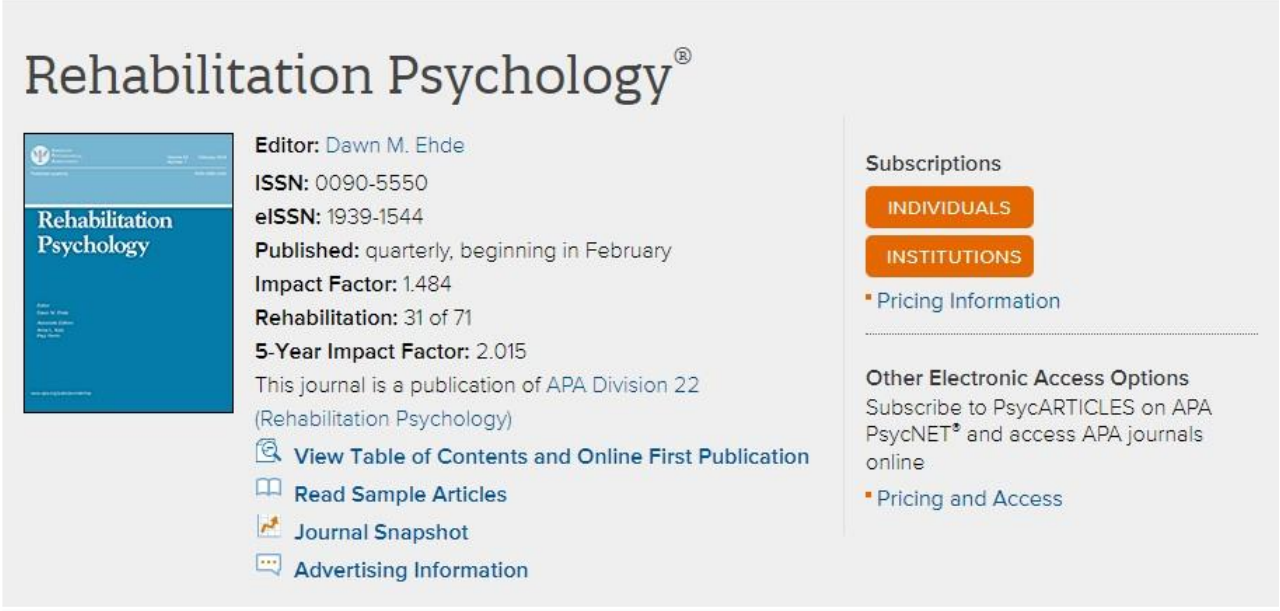
PSA funnel plots for sub-network one:



PSA funnel plots for sub-network two:



Appendix J: Journal of Rehabilitation Psychology – Instructions for Manuscript Submission (Empirical Paper)



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- a statement that the paper has been seen and approved by all authors

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- Research Method/Design - including the number and type of participants
- Results
- Conclusions/Implications

After the abstract, please supply up to five keywords.

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At the start of each paper the authors should provide 2-3 bullet points, with the header "Impact", that states what the current paper adds to the literature and one to two practice or policy implications the findings. This is not a statement of the conclusions, rather a thoughtful series of statements highlighting the novel contribution of the work and translation of the findings for practice or policy. This section should be no more than 200 words.

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It is important that readers have an accurate understanding of the data source the study is based on. Please include details in the Methods section as to the source of the data for this study.

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- **Authored Book:**
  Rogers, T. T., & McClelland, J. L. (2004). *Semantic cognition: A parallel distributed processing approach.* Cambridge, MA: MIT Press.
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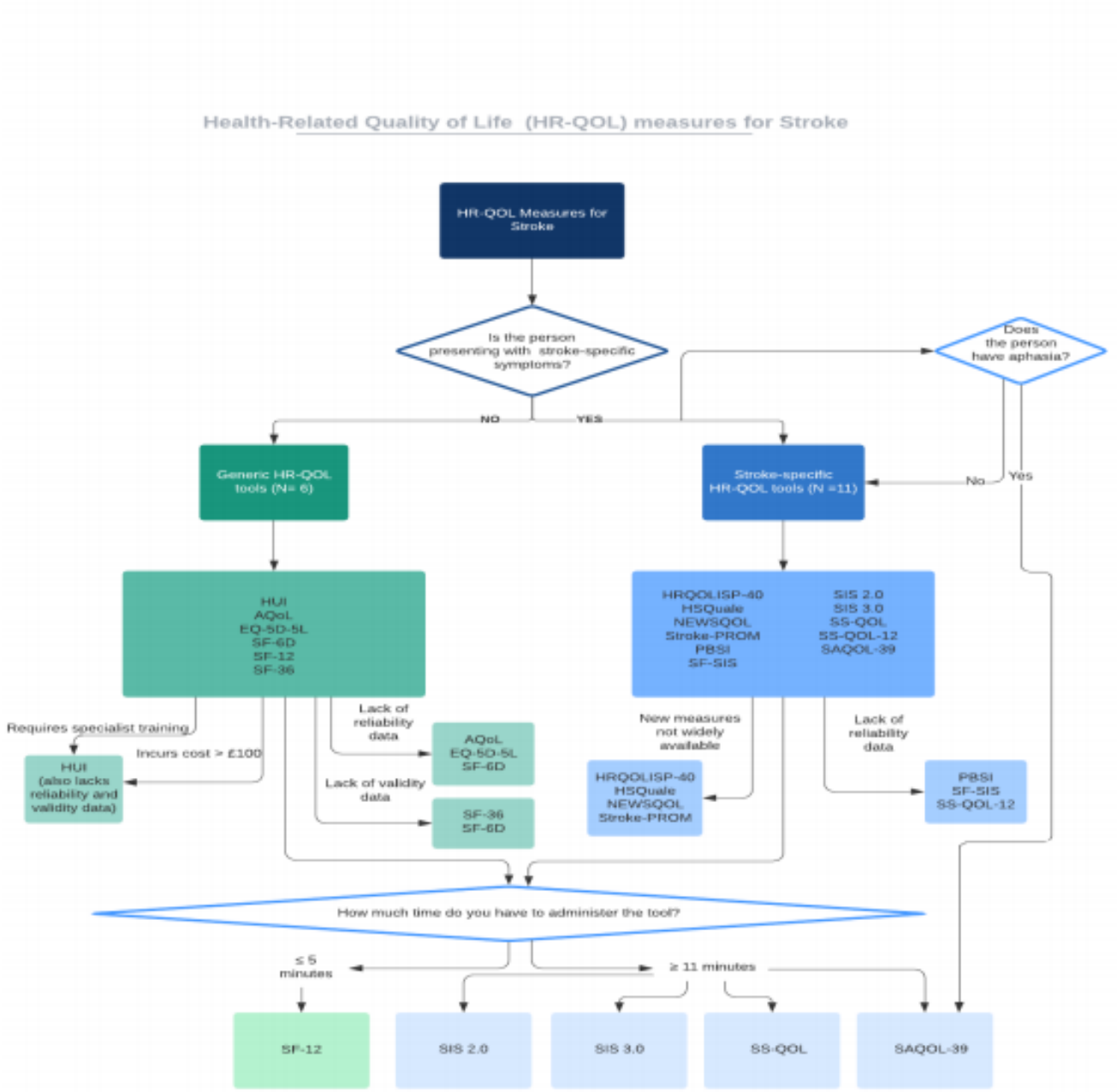
Appendix K: HR-QOL Flow chart for clinical and research use



Physical functioning	✓	✓	✓	✓	✓
Role function		✓	✓		
Pain	✓				
Emotional wellbeing	✓	✓	✓	✓	✓
Cognitive function		✓	✓	✓	✓
Communication		✓	✓	✓	✓
Social function	✓	✓	✓	✓	✓
Recreation		✓	✓	✓	✓
Energy	✓			✓	✓
General health	✓	✓	✓		
Overall quality of life					