Acute assessments in stroke care: clinical guidance on cognitive testing, patients' perceptions, and accuracy of diagnostic scoring systems

Dr David J McMahon M.Sci., MBChB, MRCGP

Thesis Submitted in fulfilment of the requirements for the degree of Doctor of Medicine

School of Cardiovascular and Metabolic Health, College of Medicine

University of Glasgow

Submitted 2023

Abstract

The thesis describes three complementary projects each of which were designed to allow me to develop differing research skills, comprising evidence synthesis, qualitative and quantitative techniques.

In the first project, I performed an analysis of clinical practice guidelines (CPGs) describing recommendations around cognitive assessment in stroke. I compared the content and strength of CPG recommendations. I found there to be limited guidance for clinicians around assessing cognition in stroke.

In the second project, I used qualitative techniques to assess interviews with thirteen stroke survivors. I considered the factors that influenced acceptability of cognitive assessments through the lens of the theory of acceptability (TFA). Using the TFA as a framework, this process yielded five themes that described the factors that influence acceptability of cognitive screening from the patient perspective. These were 1) participation motives; 2) trust in health professionals; 3) perceived risks of harm; 4) information provision; & 5) burden of testing.

In the final project, I assessed the diagnostic test accuracy of clinical scoring systems used to identify stroke. The scoring systems assessed were: ROSIER (Recognition of Stroke in the Emergency Room score) score, ABCD2 score, Dawson score and the DOT (Diagnosis of TIA) score. I described and compared sensitivity, specificity, area under the curve; and positive and negative predictive values for each of these assessment tools. I found that no tool was perfectly suited to stroke assessment, albeit the Dawson score had higher accuracy metrics than other tools.

In the discussion section I summarise the main issues and points arising from these three projects and consider overall conclusions and implications for future research. In particular, I explore how CPG development and validation of tests need to consider issues such as acceptability of the tool to the patients in whom the guidance or assessment is intended to be used. Finally, I offer a biography of myself, to explain why I chose the themes explored in this thesis; as well as providing context and clarity for the later areas of discussion. I will describe my progression into homelessness health care, and the relevant and inter-related issues of stroke and cognitive impairment within homeless people.

Summary of Thesis Chapters

In the introduction **Chapter one,** the definitions and descriptions of stroke and TIA are given. The rationale for this comprehensive overview of stroke is given at the beginning of this chapter and the purpose is to frame the understanding of all the subsequent content. To be able to contextualise the chapters which proceed, I felt that taking time to comprehensively cover stroke and TIA definitions and their aetiology is necessary. Stroke and TIA are framed according to their temporal evolution. The classical definition of stroke rests upon history and the elicited examination findings. This was the sole basis for diagnosis before the advent of radiological imaging, the situation of reliance on clinical assessment is one which persists in low- and middle-income countries where access to imaging is limited. Transient ischaemic attack (TIA) is a distinct entity from stroke, with the same features but with symptoms persisting no longer than a 24-hour period (or alternatively leading to earlier death). I will compare these time limited definitions to the more recent radiological based definitions, where TIA is described as "a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction".

To aid in diagnose and aetiological classification there are several schemes which can be employed, some of which rely on symptomatology, and others which rely upon medical investigation. As they are pertinent to the original research chapters, I will describe these classification schemes in detail in the Introduction. The well-known 'Oxford' or 'Bamford' classification of stroke employs a collection of initial symptoms; and the extent of those symptoms produce classifications that suggest the anatomical distribution of the stroke lesion including total anterior circulation syndrome (TAC); partial anterior circulation syndrome (PAC); lacunar syndrome (LAC); and posterior circulation syndrome (PCS). Another route for classification is that based upon the presumed aetiological origin of the disease, and within which several schemes exist; these are contingent on numerous investigations to generate their taxonomies. These include the (Trial of ORG 10172 in Acute Stroke Treatment) TOAST classification system, the (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: Dissection) ASCOD phenotyping system, and the Causative Classification System (CSS). In addition to these aetiological classification schemes, there are also tools which exist to aid diagnosis of stroke and TIA,

with the aim of distinguishing those conditions from stroke mimics. Again, as these tools are pertinent to one of the original research projects they are described in brief in the Introduction, with a more detailed exploration of the tools in the main body of work.

Given that themes of the research chapters major on cognition and cognitive testing, patient centred care, and clinical practice guidelines, I also offer an overview regarding each of these topics in the Introduction. This contextual information is further developed in the corresponding chapters and should enable a fuller understanding of this subsequent chapters and how these projects add to our understanding of the field of cognition and cognitive assessment in stroke.

Specifically addressing cognitive dysfunction is **Chapter two,** which provides a systematic review and synthesis I undertook to identify clinical practice guidelines (CPGs) pertaining to cognitive assessment in adult stroke survivors. Here the content of these guidelines, as well as the strength of evidence they were based on was reviewed. As well as looking at the recommendations, and the supporting evidence base, I employed the AGREE-II (appraisal of guidelines for research and evaluation) tool to describe the quality of the guidelines themselves. The AGREE-II tool is a means of looking at the guideline document itself and does not speak to the quality of evidence used within the guideline, nor the utility of the recommendations themselves. It is nonetheless an endeavour worth undertaking to ensure guideline reporting standards are followed and that guidance is produced to the expected high standards. The anticipation is that a CPG with a higher AGREE score will offer more trustworthy content and recommendations. Overall, my systematic search found eight relevant guidelines, of which seven were eligible. Their recommendations, and their relative strengths were then extracted and collated. These texts were then condensed and summarised to yield a final table of ‘global’ recommendations, as well as their respective AGREE-II quality rating. The purpose of this was to create a synthesis of all current CPG guidelines describing cognitive assessment in stroke in one readily accessible format that should be a useful resource for clinicians and researchers.

Using a discrete, but complementary, approach **Chapter three** considers the acceptability of post-stroke cognitive assessments from the viewpoint of stroke survivors. This balances the early focus which was primarily concerned with the clinician as the user of such assessments (Chapter two). The project took a qualitative approach, achieved by examining stroke survivor’s viewpoints and experiences. The interview content was

evaluated through the lens of the theory of acceptability (TFA), using a thematic qualitative study approach. The theory of acceptability can be considered one aspect of assessing whether the experience of assessment provided is suitably person centred. In recent years there has been much interest in, and efforts to define and improve, person-centred care. From a clinical perspective, person-centred care has been shown in many settings and contexts to confer benefits. Thus, following from this, many governmental, health and science agencies, as well as research funders attach greater importance to delivering person-centred healthcare.

Understanding the experience of in-hospital cognitive assessments as viewed by those assessed has, somewhat surprisingly, not been undertaken previously in a stroke population. The primary aim of the study was to examine the factors influencing acceptability of this testing. Semi-structured interviews with patients discharged from stroke services were utilised in the analysis. The interviews were partly structured to explore participants' experience of cognitive assessment i.e., what they recalled of the assessments, whether the assessment purpose was explained to them, and if so, how was it done, and finally what they themselves thought the purpose of the assessment was. I also sought to capture how participants reacted to the assessment, and the feelings it engendered at the time, as well as later once they had had the time to reflect upon the experience (if they did reflect on it). Interviews were audio recorded and transcribed verbatim. Five themes were identified that describe the factors that influence acceptability of cognitive screening from the participant perspective: 1) participation motives; 2) trust in health professionals; 3) perceived risks of harm; 4) information provision; 5) burden of testing. This study provides novel findings through the insight into the factors that affect acceptability of cognitive assessment in acute stroke through the lens of the TFA.

In the next original research project, I consider the issue of how to identify stroke in the first instance and this comprises the work presented in **Chapter four.** Here, I compared four schema diagnostic tools used to detect TIA and stroke. To achieve this, I utilised a diagnostic test accuracy study (DTA) approach. Two of the diagnostic tools reviewed are commonly and widely used clinical scoring tools which stratify risk and/or diagnosis of TIA or stroke, these are the ABCD2 score, and the ROSIER (Recognition of Stroke in the Emergency Room) score. The other two diagnostic tools have not achieved as much clinical traction but have been described in previous research, namely the DOT (Diagnosis of TIA) score and the tool described by Dawson et al. The ABCD2 was developed to assist

non-stroke specialists in determining which patients were at greatest risk of developing a stroke after a proven TIA, but it has also been utilised as a diagnostic tool, distinguishing TIA from conditions that mimic TIA. The ROSIER was developed to assist Emergency Department physicians or primary care physicians' to rapidly distinguish a TIA/stroke. The Dawson and the DOT tools were diagnostic in purpose, developed to assist non-specialists make the diagnosis of TIA with greater accuracy and thus reduce stroke mimic referrals to outpatient cerebrovascular services. I performed a direct comparison of the four tools' accuracy using the same patient data set and same reference standard for all four tools. My primary objective was to inform practicing clinicians of the accuracy of each tool in the hope that a tool with superior accuracy could be demonstrated, and to discuss how the results from these tools can be interpreted and implemented.

I described accuracy using metrics of sensitivity and specificity, positive and negative predictive values, likelihood ratios and area under the receiver operating characteristic (ROC) curve (AUC) in 165 patients. On comparative analysis of AUCs from the ROCs plotted for each clinical scoring system, the Dawson score had the greatest absolute accurately with an AUC of 0.73, followed by the ROSIER score at 0.68, the DOT score third at 0.63 with the ABCD2 score coming last at 0.60, albeit there was substantial uncertainty in all the estimates. Looking at sensitivity and specificity separately, the Dawson score's sensitivity was also superior to the other scores (97%) but it had the lowest specificity of any score (19%). Given the significance of missed strokes in terms of mortality and morbidity, achieving the fewest false negatives could be argued to have greatest clinical utility. From my findings, it is apparent that there is no currently available perfect tool to detect TIA or stroke, with all the available assessments possessing broadly similarly ranges of accuracy.

Notwithstanding these accuracy metrics, another essential concern is a tools' 'user friendliness' and feasibility in the situation in which it is usually applied. Long, complex, and difficult to use scales may not be feasible or acceptable to people with suspected stroke or to busy clinicians. Thus, even a perfectly discriminating scale, which is complex to administer, or requires laborious effort, would likely be difficult to adopt into widespread clinical use. This would be especially likely amongst non-stroke specialists, the very group who these tools are designed for.

Finally in **Chapter five,** the Discussion offers an overview of the preceding chapters. By examining the findings of all the three bodies of work in a cohesive manner and demonstrating their common thread I consider how the results of each of the chapters informs, and compliments the interpretation of the others. Furthermore, by considering the thesis findings as a whole, I hope to add value over and above that of the stand-alone data. By outlining the key messages that emerge from all three chapters, I endeavour to provide some novel aspects of insights into the field of stroke research.

Considering the various CPGs assessed in chapter two and the common key messages from the expert opinion advice i.e., the recommendation to use cognitive screening routinely and to assume some degree of cognitive impairment during stroke, this advice aligns with stroke survivor's expectations as detailed in chapter three. Reassuringly, if someone has sustained, or is suspected of having sustained a stroke or TIA, patients expect and indeed wish to undertake such assessments. Thus, there is a congruity between clinicians and patients about the need for these assessments and their importance. The recommendation to perform more testing if problems are identified however must be balanced against the distress and harm that some patients express at the experience of further, or repeated testing. Little is mentioned regarding aspects of acceptability of testing with regards to the patient in the CPG recommendations. However, acceptability can be manifest in many different ways and clinicians must be mindful of this. This theme of the discussion chapter, is illustrated in the case of one of the stroke survivor participants in chapter three, who noted mental fatigue, and this then resulted in the cessation of their active engagement with the assessment. This shows that while initially the assessment had been acceptable, this changed during the course of the assessment and emphasises the dynamic nature of acceptability and the need for a person-centred approach. This could mean the vague CPG statements about using standardised, validated tools for screening, while fulfilling the evidence base around cognitive testing, may not be useful for that individual patient and adjustments might need be undertaken due to patient preference or request, and may result (rightly) in non-standard tools being used. The CPG recommendation to adjust information sharing if a problem is identified, broadly aligns with patients wishes and expectations around having family and relatives present when they receive information, even in the absence of such problems being identified. Thus, how information is shared, and with whom is important, and a further recommendation to provide educational support around post stroke cognition was aligned with patients expectations. Much as acceptability in tools measuring cognition are crucial, it is also true to say that it would be a key metric for any

stroke or TIA diagnostic tool. Merely adding more items to a multi-item assessment in an attempt to achieve gains in diagnostic discrimination, as measured by sensitivity or specificity, could become a redundant course of action if it only increases the mental taxation and burden upon patients. Adding content to an assessment tool could thus reduce both acceptability and engagement with that assessment, and ultimately be counterproductive leading to consequential impacts upon the completion and accuracy of the tools.

To conclude this chapter, I outline a biography of myself, putting the motivation and findings of this thesis in the context of my research and clinical career. I consider future directions that research based on my findings could take. A research relevant theme, that I am passionate about, relates to health inequalities, (or sometimes termed the social determinants of health).

Table of Contents

Chapter one

Chapter two

Chapter three

Chapter four

Chapter five

List of Tables

List of Figures

List of Appendices

Impact of COVID-19 Pandemic

Impact upon the thesis & my MD program

The COVID-19 viral pandemic had substantial effects upon the design and conduct of my MD research program. The global nature of the pandemic had detrimental impacts upon my thesis related research and my MD programme of study. As I commenced my MD in early 2019, the pandemic was at its peak during the bulk of my study period.

Given the unprecedented pressures on the health system, and with a supervisory team and research Institute that encouraged supporting clinical services, I decided to re-join the NHS in a more substantial manner during the initial waves of the pandemic. I spent time working in the community COVID assessment centres where there was a need for experienced clinicians. I began working in these centres at their inception to support the NHS, and my fellow clinicians, in a manner that best utilised my generalist skills. I recognised that there was a pressing requirement for clinicians to assess COVID-19 patients in the community and safely divert them away from GP surgeries where they may have potentially infected other vulnerable patients. The COVID community hubs also helped manage the flow of appropriate patients onto secondary care for further review if this was indicated.

Although this work was full time clinical, I still applied the learning from my research to date. For example, I was able to draw upon the work describing test accuracy in terms of specificity and sensitivity within my MD program, when patients were presenting to the assessment centre. Many had questions about why their home antigen test had been negative and yet they had symptoms, and conversely some asked why their test had shown as positive when they didn't have any symptoms. I was able to discuss the basis of the scientific advice at the time in terms of test accuracy metrics, and then explain the evidence base behind the requirement to undergo polymerase chain reaction (PCR) antigen-antibody testing. Based on my MD study of diagnostic test theory, I felt more confident explaining the data on accuracy of the gold standard PCR test versus their rapid antigen home testing counterpart. I was also able to look at the very new COVID response documents and guidelines and critically appraise the evidence base on which conclusions and then recommendations were made. My work reviewing the CPGs for stroke and cognition, and the subsequent synthesis, was crucial to my ability to appraise and apply COVID guideline

recommendations. This in turn made it much easier to be able to discuss with patients and their families the rationale behind clinical practice and isolation rules.

The viral pandemic also had negative implications for my development as a researcher. One of the ways in which this became apparent was in the withdrawal of many of the university's Graduate School in-person teaching, workshops and classes. I had self-identified areas of knowledge and skill where I was hoping for formal teaching during my MD. This was especially true for both statistical analysis and qualitative research methods. I had intended to make use of the local teaching and training available in these areas. However, once the mandatory government remain at home regulations were enacted, in-person teaching courses were suspended and given the rapidity of their implementation remote teaching opportunities were not immediately available at the time I had hoped. Solutions were found through self-directed reading of online materials, reading of available library textbooks and handbooks, tutorials with my supervisors and online multi-media presentations. While I feel I gained the knowledge necessary, I missed the opportunity to discuss with tutors and discuss with other students.

The pandemic also had a detrimental impact upon my opportunities to submit and present at scientific conferences, and meetings. This had an unfavourable impact upon my ability to practice communicating science and receive in person feedback from leaders in the field. I also missed opportunities for networking and engaging with fellow MD and PhD students from other centres. Thus, as a result of the pandemic I was unable to get as much independent feedback to improve my research as I would have liked, both from professionals and peers. While there were indeed challenges during the peak of the pandemic, there were also some notable positive experiences, such as presenting an online poster to the European Geriatrics Medicine society virtually in 2020. The presentation allowed me to discuss my work around cognitive assessment guidelines. While not quite replicating the experience of in person conference interactions, this and other events demonstrated to me that many clinicians and academics had a genuine interest in the areas I was researching, and highlighted the need for further work in this field. I also took advantage of the annual virtual research meetings within the University to discuss my work, and to consider how it complemented other ongoing projects and also considered those speakers who challenged my own ideas and work, and how to utilise this in my own work.

I shall now move on to detail the specific impact the pandemic has had upon each chapter.

Impact on chapter two (Guideline review)

The COVID-19 pandemic did not have a direct impact upon the design nor the analysis and results construction of chapter two. Rather, it was the peer review process of the submitted manuscript that was affected, taking around one year from the original submission, through the editorial changes suggested by the reviewers to the final draft being accepted and published in the journal. This situation was not unique to me, and I know from conversations with colleagues and my supervisors that the first wave of covid saw a substantial increase in journal submissions with a decrease in availability of clinical academics to perform peer review.

Impact on chapter three (Qualitative study)

The qualitative study started with an experienced qualitative researcher conducting the first interviews, with a plan that I would take on the interviewing role. Due to the isolation and other restrictions mandated by the pandemic, my plans for conducting more patient interviews were not feasible, nor ethical given the significant risk such a face-to-face encounter could cause. It also meant that follow up with patients who had previously had their interviews was not possible either. The initial engagement and immersion in the qualitative methodological research process was challenging as I had had no prior experience or teaching in this method. In the absence of the training courses I had planned, I was then necessarily dependent upon one of my supervisors, Dr Katie Gallacher who helped to guide my initial foray into the analysis and assisted sense checking of the emerging data and themes.

Impact on chapter four (Test accuracy)

Perhaps the most marked effect of the COVID-19 pandemic unsurprisingly came during my 3rd and final project, which was a patient facing study. This work originally was designed as a study to identify and validate a biomarker of stroke and TIA in patients who had presented to stroke services. However, early during the pandemic both the scientific expertise, scientific equipment in the form high performance liquid chromatography equipment, and the physical laboratory space which had underpinned the core of this work

was re-purposed and subsumed into NHS clinical laboratory needs. This had been done with the intent of scaling up and improving COVID-19 testing at the time. The rapidly evolving situation meant it was not feasible for me to continue the laboratory base aspect of the project and instead, after discussions with my supervisory team, I took the project in a different direction to that which I intended. Thus, instead of validating a biomarker to aid in the accurate diagnosis of stroke or TIA, I pivoted to use the data already collected to assess the accuracy of clinical scoring systems used to aid in diagnosing stroke and TIA. However, while the method of research to explore diagnostic accuracy necessarily had to change, the spirit of it remained the same in essence. I was fortunate to have an immerse experience in this study, having been heavily involved in recruiting patients for the study at my local site, and then engaged with the adjudication panels to formulate consensus diagnosis. To ensure the maximal efficiency I drew on all pre-gathered information to allow me to compare the accuracy of these differing tools, however some signs and symptoms were not captured in the original data, and this inevitably meant that I had to then look at the clinical records of over 100 patients to obtain these myself.

Acknowledgements

The work presented in this thesis represents the product of several successful collaborations and completion would not have been possible without the valued contribution, advice and support of a number of colleagues.

I wish to thank my supervisors Dr Terry Quinn and Professor Jesse Dawson for the opportunity to undertake an M.D and to contribute actively to their fields of clinical practice and research. Dr Katie Gallacher has also been of great support during my qualitative methods section and the subsequent analysis. Having had little experience of this method, amidst a global pandemic and lockdown she provided much encouragement virtually. Professor Diane Dixon whose original work was the foundation for my subsequent endeavours must also be fully recognised as indispensable and essential having undertaken the interviews of patients. My supervisors support and advice, through the setbacks and tribulations was and remains humbly appreciated.

To my office roommate Bogna Drozdowska whose encouragement, coffee and discussions on the world at large in strange times kept me going when things got tough. I would also like to thank and acknowledge the Glasgow royal infirmary Stroke research nurse Ruth Graham, who every cheerful and dedicated again helped me so much on this journey.

It was a privilege to be able to carry out research in the historical setting of Glasgow Royal Infirmary where luminaries such as likes of Lister himself and John Macintyre practiced and changed the course of practice not only in Glasgow, but around the world. This has been a tradition I have been humbled to be part of with the modern-day Professors David Stott and Peter Langhorne providing much inspiration.

My sincere gratitude is also given to the David Cargill Trust who funded my thesis.

Lastly, I dedicate this thesis to my dear mother who had become ill during the height of the pandemic but who possesses a formidable will; and who has ever been a force of nature in my life, turned the known certainties upon their head; demonstrating that nothing is impossible, and that ‘fate’ is merely conjecture.

Hope springs eternal, a principle that has lit the path on the darker stretches of this journey.

Student contribution to the research presented

During the course of this MD I have undertaken several roles during each original research chapter which I shall outline below and detail my personal contribution.

In chapter two, which pertained to the work around the systematic review and analysis of CPGs on assessing stroke in cognition, I devised, drafted and also registered the protocol at the Centre for Open Science. I was responsible for designing and executing the search strategy. Working with my supervisors and a librarian, I devised the review search terms, and chose which databases to interrogate. I was also responsible the title screening and selection of relevant papers, extracting data, and quality assessing the included guidelines. In keeping with best practice, these steps were performed independently and in parallel by another clinician (Dr Clayton Micallef). This process then yielded eligible titles for our analysis against a modified PICAR (Population, clinical area, and characteristics) table that I produced. I performed analyses of variability between my data extraction and the other reviewer. As well as writing this project as a thesis chapter, I also drafted the manuscript for publication, addressed peer review comments and attended to copy editing.

In chapter three I performed the qualitative analysis of stroke survivors' experiences around undergoing cognitive assessments. A colleague, Professor Diane Dixon had undertaken all of the qualitative interviews with survivor's and made these audio transcripts available to me. I performed all aspects of coding and synthesis, both using a traditional 'pen and paper' approach, and also employing the qualitative analysis software NVivo. Along with my supervisor, Dr Gallacher, I was able to generate several iterations of themes that emerged from patients own experiences until a final agreed themes list was produced. I also plan to submit a research paper to an appropriate journal pertaining to this work in the near future and have drafted and submitted a manuscript.

Within chapter four, the test accuracy study, I was involved in several aspects of the parent study and took lead on the analyses presented here. Within my local site at the Glasgow Royal Infirmary, I was responsibility for recruitment of patients to the study. This necessarily involved me liaising with the treating teams to identify who might be eligible and suitable for inclusion, sharing participant information sheet and ensuring informed consent. Once recruited I obtained and processed urine and blood samples in the local Clinical Research Facility. As well as the baseline assessment, I coordinated and

performed follow-up visits, which included clinical assessment, medicines reconciliation and further blood and urine samples. I was also responsible for coordinating and contributing to the expert consensus panel on diagnosis. As part of this process, I collected and assessed medical notes, imaging and laboratory results for all the participating sites including from Glasgow and Manchester and Aberdeen. A series of both in person and online meetings were held to discuss cases to allow an agreed consensus final diagnosis (the reference standard).

Specifically, from my test accuracy study, I extracted relevant study data from case report forms from all participating sites and augmented with data on demographic, clinical, prescribing and investigations all taken from their medical notes. I also sought and recorded the diagnosis of the G.P and that of a specialist clinician from these. I performed all the test accuracy analyses, although once these had been performed Professor Dawson checked them to ensure they were accurate. I have also begun preparing a manuscript to have this study published in an appropriate journal of relevance within stroke.

Publications and presentations from this work

Parts of this work have been published in the following scientific journals, on which I am first author.

-Review of clinical practice guidelines relating to cognitive assessment in stroke. Published in Dec 2022 Journal of Disability and Rehabilitation (McMahon D, Micallef C, Quinn TJ**.)**

-The Acceptability of post-stroke cognitive testing through the lens of the theory of acceptability, a qualitative study. Journal of Cerebral Circulation & Cognitive Behaviour Published in. Dec 2023 (McMahon D, Dixon D, Quinn T, Gallacher KI.)

Also parts of this work was presented at scientific conferences where I was first author and also where I was not (denoted by *) at the UK Stroke forum Birmingham, UK Nov 2023:

-The Acceptability of post-stroke cognitive testing through the lens of the theory of acceptability, a qualitative study. Poster presentation (McMahon D, Dixon D, Quinn T, Gallacher KI.)

-Evaluating the performance of diagnostic instruments in people with suspected minor stroke and TIA*. Poster presentation **(Louvinia Wong, Alan Cameron, Craig Smith, Terry Quinn, David McMahon, Jesse Dawson)**

Author's Declaration

The work contained in this thesis is original research performed by me and carried out during my tenure as Clinical Research Fellow in the University of Glasgow within the Institute of Cardiovascular and Medical Sciences (ICAMs) from 2019-2021 based at the New Lister Building Campus.

All the studies reported herein have either been published or submitted to journals for consideration of publication. A list of these papers is included. All the work reported in this thesis was undertaken by me, with the assistance of a number of colleagues who are formally acknowledged. All the statistical analyses herein were performed by me, and the manuscript was written solely by me.

List of Abbreviations

AD……...Alzheimer's disease

AGREE-II ……...appraisal of guidelines for research and evaluation

AMSTAR……..…assessment of multiple systematic reviews

ASCOD .....

.....atherosclerosis; small-vessel disease; cardiac pathology; other causes; & dissection

AUC…….…….area under the curve

CPG…….…….....clinical practice guidelines

CSS ……..……..causative classification system

CT-A ……..……..……. CT angiography

CT ……..……... computer tomography

DTA ……..…… a diagnostic test accuracy study

DOT ……..……..…diagnosis of TIA

EBM……..evidence based medicine

EDTA ……..…….ethylenediaminetetraacetic acid

FN……....false negative

FP……..false positive

GP…….general practitioner

ICC ……..……intra-class correlation coefficient

ICH ……..…….intracerebral haemorrhage

IOM……. Institute of Medicine

LAC ……..……...… lacunar syndrome

MCI……mild cognitive impairment

MRA ……..…… MR angiography

MRC……Medical Research Council

MRI ……..…….. magnetic resonance imaging

NPV……...negative predictive value

PAC ……..……partial anterior circulation syndrome

PCR ……..……. polymerase chain reaction

PCS ……..……. posterior circulation syndrome

PICAR ……..……..population, clinical area, and characteristics

PICO ……..…… population, intervention, control, and outcomes

PFO…… patent foramen ovale

PPV…….positive predictive value

QUADAS……..quality assessment of diagnostic accuracy studies

RCT…… randomized controlled trial

ROC ……receiver operating characteristic

ROSIER ……...recognition of stroke in the emergency room score

SAH ……..subarachnoid haemorrhage

SIGN……..the Scottish intercollegiate guideline network

SST ……. short synacthen test

SWAT ……... study within a trial

TA……..thematic analysis

TAC ……..total anterior circulation syndrome

TFA ……theoretical framework of acceptability

TIA ……..transient ischaemic attack

TriMethS …….trimethylamine derivative

TOAST …….trial of ORG 10172 in acute stroke treatment

TOM……...theory of the mind

US…….ultrasound

US-D ……..… ultrasound-duplex

US-TCD ……..transcranial doppler ultrasound

XRA…… x-ray angiography

Chapter one

Introduction: Stroke, Patient-centredness; Cognition and Clinical Practice Guidelines

1.1

Stroke definitions

For a thesis with a focus on stroke and related disease, it seems prudent to begin with a series of definitions. These have changed with time and advances in medical science.

1.2

Traditional medical definition of stroke

The traditional medical definition of stroke is clinical, that is a definition based on both history and elicited examination findings. Accordingly, the deficit and its location within the central nervous system is characterized and the stroke defined as *acute onset of focal neurological function loss secondary to either infarction or haemorrhage* [1,2].

Transient ischaemic attack (TIA), is a similar syndrome but distinct from stroke, having the same basic definition but with the symptoms persisting no longer than a 24-hour period (or leading to earlier death). These definitions pre-dated the emergence of radiological imaging which has changed the way in which clinicians define these two entities and revolutionized both their diagnoses [3] and the potential for immediate treatments such as mechanical thrombectomy [4-6] and thrombolysis [7,8].

1.3

Contemporary definition derived from radiology

In a clinical context where access to neuroimaging is the norm, a more contemporaneous definition of stroke has been proposed, that of '*an acute episode of focal dysfunction of the central nervous system lasting longer than 24 hours, or of any duration if imaging computer tomography (CT) or magnetic resonance imaging (MRI) and/or post mortem evidence demonstrates focal infarction or haemorrhage anatomically relevant to the patients symptoms*' [2].

The TIA definition has similarly been modernized with its re-definition as "*a focal dysfunction of less than 24 hours duration and with the absence of imaging evidence of a corresponding intracerebral infarction*' [2].

1.4

Subtyping strokes

The following sections give definitions of the subtypes of stroke which arise as a result of the pathological mechanisms that result in these. Also given is a definition of the pathological mechanisms which give rise to Transient ischaemic attack (TIA).

1.4.1
Ischaemic stroke

Within the clinical syndrome of stroke, there is the potential to further classify. The usual process is to first subtype by pathology, as this has immediate implications for treatment and prognosis, further classification by aetiology or clinical presentation can then be achieved. Aetiological classification of ischaemic stroke is described later in this chapter and in the test accuracy chapter.

In terms of a pathological classification, ischaemic stroke, where there is a disturbance of supply of oxygenated blood to brain tissue, is defined by the American Heart Association as an episode of "*neurological dysfunction caused by focal cerebral, spinal, or retinal infarction*." [2] This is in the presence of clinical findings and, or radiological or pathological objective evidence of stroke. Within ischaemic stroke the episode of neurological dysfunction is caused by focal cerebral, spinal, or retinal infarction.

This is however not the whole picture, with the shift to a structural, rather than purely clinical, diagnosis of stroke requiring a critical reappraisal of the terms "silent stroke" and "silent infarction." The development of the concept of silent cerebral infarction reflects the recognition that brain abnormalities, consistent with ischemic injury, can be identified pathologically or on neuroimaging in patients without a history of stroke or TIA. No standard or commonly accepted definition for silent infarction exists, partly because of a

lack of a clear consensus regarding what is meant by “silence.” “Silence” depends on one’s vantage point and may differ between the patient and physician. Patients may not be aware that some prior constellation of symptoms was related to an imaged abnormality, or they may not have been evaluated for it at the time so that a diagnosis of stroke was never made. Therefore, currently one definition of silent infarct can be *imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion*.

1.4.2
Haemorrhagic stroke

Second in frequency to ischaemic stroke is haemorrhagic stroke. Haemorrhages in the central nervous system are classified as stroke if they are nontraumatic, are caused by a vascular event, and result in injury [2]. In contrast, traumatic haemorrhages should not be characterized as stroke. Within the haemorrhagic stroke diagnosis category are Intracerebral Haemorrhage (ICH), subarachnoid haemorrhage (SAH) which is inclusive of both aneurysmal and non-aneurysmal origins of haemorrhage, and finally intraventricular haemorrhage (IVH), which can be primary or secondary.

ICH is defined as a focal collection of blood within the brain parenchyma itself, this blood may extend into the ventricular system. In contrast, SAH arises from bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord). Finally, IVH is considered a subtype of ICH and while isolated primary IVH is common among premature infants it is less common in adults. Therefore, although distinguishing haemorrhagic from ischaemic stroke is relatively straightforward, further work is needed to subtype the haemorrhage, and a number of issues must be considered, including traumatic injury or secondary causes of bleeding.

Haemorrhagic stroke can be further classified according to the anatomical site or presumed aetiology. The most common sites of intracerebral haemorrhage are supratentorial (85–95%), including deep (50–75%) and lobar (25–40%). The leading causes of haemorrhagic stroke are given as hypertension (30–60%), cerebral amyloid angiopathy (10–30%), anticoagulation (1–20%), and vascular structural lesions (3–8%); with the cause being undetermined in about 5–20% of cases [1]. This however belies the fact that in many cases of haemorrhagic stroke there are multiple pathologies contributing to its pathogenesis. For

example, possessing an already structurally weakened blood vessel from amyloid deposit contributes to dysfunction of both endothelium and extracellular matrix. Ultimately this results in fibrinoid necrosis and weakening of the vessel wall with consequent rupture into the brain parenchyma [9]. Anti-coagulation medication can, in this context, also play a significant role [10].

1.4.3

Transient ischaemic Attack (TIA)

The definitions of TIA, both time based, and tissue (imaging) based, are given above. While the time based definition describes symptoms lasting less than 24 hours, most TIAs have a duration of less than 60 minutes, and usually less than 30 minutes. To complicate matters further, up to 50% of TIAs lasting minutes can still result in radiological sequelae seen on diffusion weighted magnetic resonance imaging. Consequently, this has prompted a move by some to shift from a timing based definition to a tissue-based (imaging) diagnosis instead, thereby making an arbitrary time constrained definition redundant. The operationalisation and implementation of the tissue based definition is however highly dependent on timely access to radiological imaging, and is set against persisting barriers to such radiology services even in the most developed and wealthy of healthcare systems [11]. Thus, practically at the present time, TIA remains primarily a clinical diagnosis and the time based definition is still commonly employed in practice.

The definition of TIA that was used in the 1975 report was universally cited until the beginning of the 21st century, when data accumulated that prompted redefinition. These data fell into two categories: duration of TIAs and imaging findings [2] The new data ignited controversy, which remains to the present day, pertaining to redefining the duration of TIAs and the need for incorporating brain and vascular imaging data into the definition. Thus in 2002, a new definition was proffered: "*A TIA is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction*". This was updated again in 2009, as "*transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction*".

The underlying pathophysiology of TIA shares many features with stroke; simply they result from localized decrease of cerebral perfusion. TIA can result from “either embolism into a cerebral artery (cardiac in origin, or the great proximal vessels, extra cranial or intracranial arteries, commonly affected by atherosclerosis), or in-situ occlusion of small perforating arteries”. It is supposed that symptoms spontaneously resolve by thrombosis or embolus lysis or distal passage of the occluding determinant. Another theorized potential mechanism of symptom resolution is via compensatory collateral circulation restoration and thus perfusion into the ischaemic region.

1.5

Classification of stroke

There are two main methods for classifying strokes one being the use of symptomatology, and the other based upon aetiology (within which exists several distinct classification schemes). The later classifications are more contemporary than the clinical schema and are inherently conditional upon radiology, and other investigation results.

1.6

Symptomatology classifications

The clinical stroke syndromes which encompass total anterior circulation syndrome, partial anterior circulation syndrome, lacunar syndrome, and posterior circulation syndrome are ascribed based on the patient’s symptoms and physical examination [12]. This scheme is widely known as the ‘Oxford’ classification of stroke.

Total anterior circulation stroke (TAC) patients have a combination of two new higher cerebral dysfunction such as dysphasia, dyscalculia, or a visuospatial disorder, a homonymous visual field defect; and ipsilateral motor and/or sensory deficit of at least two areas of the face, arm, and leg. If their consciousness is impaired and formal testing of higher cerebral function or the visual fields is not possible, a deficit is then assumed.

Partial anterior circulation stroke (PAC) manifests with only two of the three TAC syndrome components, i.e., with higher cerebral dysfunctions alone, or with motor/sensory deficits and a single higher cerebral impairment.

Lacunar stroke (LAC) patients present with syndromes of a pure motor stroke, pure sensory stroke, sensory-motor stroke, or with ataxic hemiparesis or the ‘clumsy hand dysarthria’ presentation. In contrast, anterior circulation stroke patients may exhibit more localised symptoms, for example confined to one limb, or to the face and hand but not to the whole arm.

Posterior circulation strokes (POC) often present with the following features: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit; disorder of conjugate eye movement; cerebellar dysfunction without ipsilateral long-tract deficit; or an isolated homonymous visual field defect.

If neuroimaging is available these classifications can be refined, for example the TACS (total anterior circulation stroke) becomes a TACI (total anterior circulation infarct) when combining radiological images that confirm ischaemia and clinical features. Likewise, the PACS becomes PACI (partial anterior circulation infarct), POCS becomes POCI (posterior circulation infarct), and LACS becomes LACI (lacunar infarct).

The Oxford system can be used even if no neuroimaging has been performed to define pathology. Thus in environments where radiological imaging access is poor or limited this scheme has obvious advantages [13].

1.7

Why we continue use the oxford classification: prognostication

As well as having clinical utility in describing stroke, in the absence of radiological information, the Oxford classification has clear prognostic value as well. The four groups have differences in natural history as well as significant differences in mortality and morbidity. These differences can be used to guide treatment and therapies. Within the TACI group good functional outcomes are much fewer and mortality is higher [14]. As a result, only a small proportion with this form of stroke are alive and living at home after one year. The mortality and disability associated with a TACI is both from the stroke but also the consequences of the stroke. More than twice as many deaths are due to the complications of immobility rather than as a direct neurological sequelae of the infarct.

Within the PACI group an early recurrent stroke is more likely than any other group, highlighting the need for aggressive secondary prevention. Those in the POCI group are at risk of a recurrent stroke later in the first year after the index event, but have the best chance of a good functional outcome. Finally, despite the small anatomical size of the infarcts in the LACI group, many of these patients continue to have substantial neurological deficits. Epidemiological studies have confirmed the theory regarding the Oxford stroke categories and outcome. For example in one large series, the TACI group had a significantly higher mortality, morbidity (as per disability scales), length of hospital stay, and complications (respiratory tract infection and seizures) as compared to the other three groups which were all similar at the different time points [15]. Thus these classifications are still routinely used to provide prognostic value for both clinicians and patients.

1.8

Aetiological definition

Another system for classification is based upon the aetiological origin of the disease. Within this system several approaches exist, these systems are distinct in some aspects of their approach, but all rely on comprehensive investigations to produce their taxonomies.

Mechanistically or aetiologically, ischaemic stroke can be caused by an embolism from the heart, artery-to-artery embolism, and in-situ small vessel disease. Aetiological ischaemic stroke subtypes can thus be classified according to the (trial of ORG 10172 in acute stroke treatment) TOAST classification system [16], the (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: Dissection) the (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: Dissection) ASCOD phenotyping system [17], and the Causative Classification System (CSS) [18]. However, even when applied robustly with access to appropriate investigations around one third of ischaemic strokes remain of undetermined cause (i.e., cryptogenic origin) [19].

In the following text, I shall describe in detail each of the aforementioned aetiological classification schema providing a comprehensive description of their processes and how to utilize them to classify a stroke. Comprehensive descriptions are given here, as the subsequent chapters do not give additional details on this aspect of classification. As will be seen in the following descriptions there are many common processes, assessments and

investigations with which these schemes approach a clinical stroke presentation. However, subtle differences in relative weighting, and how to arrive at a particular conclusion are seen with uncertainty being managed differently within each taxonomy.

These approaches rely very heavily on modern medical investigations and imaging, the provision of which can vary greatly in different parts of the globe. Its noteworthy that all have some manner of category of undefined/un-classifiable diagnosis even in circumstances were all investigations possible have been undertaken but do not provide definitive results.

1.8.1
Trial of ORG 10172 in acute stroke treatment classification system (TOAST)

One such aetiological taxonomy system is the (trial of ORG 10172 in acute stroke treatment) TOAST criteria, which assigns ischaemic strokes into five categories [16].

The first category is that of cardio-embolic arterial occlusions which are presumed to arise secondary to an embolus originating in the heart. To be considered valid at least one cardiac source for an embolus must be identified for a possible or probable diagnosis of cardioembolic stroke to be given. In addition, the clinical and vascular imaging findings must not be consistent with those depicted for large-artery atherosclerosis. Finally, some form of evidence of a previous TIA or stroke in more than one vascular territory or a systemic embolism likewise supports a clinical diagnosis of cardiogenic stroke. A stroke in a patient with a medium-risk cardiac source of embolism and no other cause of stroke is classified as a possible cardioembolic stroke, contingent upon potential large-artery atherosclerotic sources of thrombosis or embolism being eliminated.

The second category is that of large artery atherosclerosis, which is derived from a combination of both clinical and radiological findings. If a greater than 50% occlusion or stenosis is demonstrated in a major artery supplying the brain in the presence of an anatomically corresponding region with clinical findings such as aphasia, neglect, restricted motor involvement, or brain stem cerebellar dysfunction then a large artery atherosclerosis diagnosis can be given. Likewise, within an imaging context, supportive

radiological evidence of either cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts which are greater than 1.5 cm in diameter on CT or MRI are deemed to be of potential large-artery atherosclerotic origin, although may also represent cardioembolic. Supportive evidence provided by other modalities such as duplex imaging or that of definite arteriography of a stenosis of greater than 50% of an appropriate intracranial or extracranial artery is also a prerequisite for classification of this category of stroke.

Similarly, within the small-artery occlusion category (lacune class) patients must exhibit one of the traditional clinical lacunar syndromes, but not demonstrate evidence of cerebral cortical dysfunction. The existence of a past medical history of the traditional risk factors of either diabetes mellitus or hypertension strengthens the clinical diagnosis within this category. Within the radiological sphere, a normal CT or MRI examination may be obtained, or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm and corresponding to the symptoms may be seen on imaging.

Fourthly within the TOAST taxonomy is the category of 'other determined aetiology'. This diverse group of causes includes patients with less common reasons for a stroke, for example in those who have hypercoagulable states, in those with haematological disorders, and also those individuals with nonatherosclerotic vasculopathies. This category is mandated to have both dual clinical, and radiological (either a CT or MRI) findings of an acute ischemic stroke, regardless of the size or location of the identified lesion. Diagnostic studies such as blood investigations or arteriography should reveal one of these unusual causes of stroke. Finally for completion, cardiac sources of embolism as well as large-artery atherosclerosis sources of stroke should be excluded by other studies.

TOAST concludes with the 'Stroke of undetermined aetiology' classification. This label is arrived at when the cause of a stroke cannot be determined with any degree of confidence despite an extensive and appropriate evaluation. It is also applicable in those patients where no cause is found as a sequela of only a cursory evaluation. This group also includes those patients with two, or more potential causes of stroke, thus making it impossible for the clinician to determine a single final diagnosis with confidence. For example, a patient with a medium-risk cardiac source of embolism, such as atrial fibrillation who also has a stenotic vascular lesion in the correct arterial distribution would be classified as having a stroke of undetermined aetiology.

1.8.2

The A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: Dissection (ASCOD) classification system

An alternative aetiological classification is the (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: Dissection) ASCOD phenotyping system or taxonomy approach [17,20] . In this method strokes are phenotyped using the following coding method. The letter ‘A’ is designated for atherosclerosis; ‘S’ is designated for small-vessel disease; ‘C’ is designated for cardiac pathology, while ‘O’ represents other causes. It should be noted that the original ASCO classification was updated and augmented with the addition of the further ‘D’ category which signified dissection. This was done in recognition of the fact that arterial dissection is a frequent cause of stroke with differing risk factors and natural history to large vessel atherosclerosis.

The ASCOD phenotyping system functions whereby a measure of likelihood is assigned with respect to a causal relationship for every potential disease causing a stroke. Thus, a ‘1’ is assigned for a potentially causal, ‘2’ is assigned for a causality is uncertain, ‘3’ is assigned for unlikely causality but the disease is present, ‘0’ is assigned when there is an absence of disease, and a ‘9’ is assigned when an insufficient workup has taken place to be able to rule out the disease. In contrast to some of the other classifications which are more rigid and unequivocal in their singular categorization protocol approaches the ASCOD phenotyping system grades the causality of all the diseases present in any given patient.

Within the ASCOD phenotyping system nomenclature a ‘1’ for atherothrombotic stroke (A) is assigned if an ipsilateral atherosclerotic stenosis of between 50 to 99% in an intra-cranial or extracranial artery supplying the ischaemic field is identified. Further, a ‘1’ is also assigned if an ipsilateral atherosclerotic stenosis of less than 50% in an intra-cranial or extracranial artery with an endoluminal thrombus supplying the ischaemic field is found. Likewise, ‘1’ is also assigned where a mobile thrombus in the aortic arch is evident on investigation. Moreover, where an ipsilateral arterial occlusion in an intra-cranial or extracranial artery with some form of corroboration of an underlying atherosclerotic plaque supplying the ischemic field is denoted a ‘1’ is assigned too. Beneath this highest grade of evidence, are the ‘2’ or ‘3’ categories, with ‘uncertain’ and ‘causal link unlikely but disease present’ being represented respectively. Where a ‘0’ is assigned, it thus rules out atherosclerosis and this is confirmed by a negative extracranial arterial stenosis

investigation (which is inclusive of one, or several diagnostic tests namely these may be: Ultrasound-Duplex (US-D), CT angiography (CTA), MR angiography (MRA), x-ray angiography (XRA), or a post-mortem examination providing negative findings. An ‘0’ assignment is also applicable when an aortic arch atheroma is demonstrated as being absent on trans-oesophageal echo which is specifically tasked with assessing the aortic arch, or can be arrived at by specific aortic arch CTA assessment. Finally, a ‘9’ is allocated representing incomplete workup when investigations have not been conducted to a sufficient confidence to allow diagnosis, i.e., when US-Duplex, US-TCD or CTA, or MRA, or XRA or a post-mortem examination have not been performed. The minimum permitted workup is extra- and intracranial assessment of cerebral arteries with a maximum workup also including a transoesophageal assessment of the aortic arch (or a default CTA of the aortic arch).

Within the small-vessel disease phenotype (S) a ‘1’ assignment of causality grade requires a combination of a lacunar infarction specifically showing a small deep infarct of less than 1.5cm (within the perforator branch territory) on MRI-Diffusion weighted Imaging (or on a default CT) in a brain area corresponding to the symptoms. Additionally, at least one of the following criteria must also be met, these are: the existence of one or several small deep older infarct(s) of lacunar nature in other territories; severe (confluent – Fazekas III) leukoaraiosis; presence of cerebral microbleeds, or severe dilatation of perivascular spaces (‘état criblé’). Furthermore, additional or repeated, recent (which is defined as occurring within the preceding month) TIAs attributable to the same territory as the index infarct also qualify. Similarly, to atherothrombosis causes where lesser grades of evidence than ‘1’ exist, then a ‘2’ can be assigned to suggest that the ‘causal link is uncertain’, and a ‘3’ can be assigned where ‘causal link unlikely but disease present’. Where no disease is detected a ‘0’ is assigned representing a negative MRI with the relevant sequences (T2, FLAIR, GRE, DWI) finding and no appropriate clinical syndrome suggestive of a deep branch artery stroke. Where workup is incomplete ‘a 9’ is ascribed and indicates no MRI (or CT) was performed.

Within the cardiac origin phenotype (C) of ASCOD, cardiogenic stroke can be defined as the following; acute, or recent, and older bi-hemispheric or supra- and infratentorial territorial or cortical ischaemic lesions. Signs of systemic embolism are made with the detection of at least one of the following potential causes: mitral stenosis (with a surface area of less than 1.5 cm squared); the presence of a mechanical valve; the occurrence of a

myocardial infarction within 4 weeks of the preceding index cerebral infarction or a mural thromboses in one of the left cardiac cavities. Other potential causes which are valid for a '1' include: an aneurysm of the left ventricle; a history of, or the presence of documented atrial fibrillation (this is irrespectively of whether it is paroxysmal (but present for over 60 seconds duration) or if it is persistent or permanent atrial fibrillation or with flutter); this can be with or without the presence of a left atrial thrombus on spontaneous echocardiogram. A score of '1' is also valid in the presence of atrial disease and a dilated or hypertrophic cardiomyopathy; a left ventricle ejection fraction of less than 35%; the presence of endocarditis or an intracardiac mass being identified are also legitimate findings within this class. Lastly, a patent foramen ovale (PFO) with a thrombus in situ; a PFO and concomitant pulmonary embolism or a proximal deep vein thrombosis (DVT) preceding the index cerebral infarction and the cardiac pathologies with single, or without obvious cerebral ischemic lesion are ascribed a '1' as well. As with the A and S categories' where the level is not sufficient to support this high level of confidence but there is some evidence present then a '2' or '3' can be assigned for uncertain, and unlikely categories respectively. A '0' is allocated when a cardiac source of embolism has been ruled out at a minimum by a negative Electrocardiogram (ECG) and an examination by a cardiologist. On the other hand, a cardiac source can be excluded definitively by a battery including negative ECG, negative cardiac monitoring i.e., 24-hour Holter ECG/long-term ECG recording (implantable device, trans telephonic ECG, loop recorder) and negative transoesophageal echocardiogram (TOE) examining for atrium, valvular and septal abnormalities. Furthermore, a negative TOE for PFO, and an assessment of the left ventricle, a negative cardiac CT/MRI, a negative abdominal CT/MRI (searching for an old or simultaneous subdiaphragmatic visceral infarction) also garner a '0' for work up by absence of disease. Finally, a '9' for incomplete work up is assigned were at a minimum an ECG and examination by a trained cardiologist has been undertaken, but without any cardiac imaging having been performed.

Causality grades for 'other causes' (O) the next phenotype, which may be assigned a '1' include dolichoectasia with complicated aneurysm; a proven polycythaemia vera or thrombocythaemia with platelets above 800,000/mm, systemic lupus; disseminated intravascular coagulation; antiphospholipid antibody syndrome (of greater than 100 GPL units of anticardiolipin antibody, or lupus anticoagulant), Fabry's disease, a co-existing meningitis, sickle cell disease and a ruptured intracranial aneurysm with or without vasospasm of the artery supplying the infarcted area. Also inclusive of these is severe

hyperhomocysteinaemia, Horton's disease, and other cerebral inflammatory or infectious angiitis, as well as Moyamoya disease. Where there exists less firm evidence, similar to other categories again a '2' or '3' within the ASCOD phenotyping system is assigned to reflect this reduced certainty. While a '0' is ascribed to cases where a cause has been proven as negative. This is achieved by undertaking cerebrospinal fluid testing, assessing markers of haemostasis, performing cerebral arterial imaging, excluding a family history of inherited disease, inflammatory marker testing (both erythrocyte sedimentation rate and C-reactive protein being negative), haematological testing (i.e. platelets, leucocytes, and eosinophilic counts, as well as haematocrit all being unremarkable), and undertaking specific specialized tests according to the suspected disease (e.g., genetic testing and retinal angiography for Susac's syndrome) with all of these being negative. A '9' is given for incomplete work up where it is impossible to reasonably exclude other causes based on the best available diagnostic tests and an account of a stroke-specific history.

The latter additional category is Dissection (D) and represents the final aetiological phenotype within the taxonomy. Here where a '1' has been assigned it necessarily mandates that an arterial dissection is confirmed as shown by direct demonstration (i.e., evidence of a mural haematoma, the presence of a hypersignal on FAT-saturated MRI or at post-mortem, or on a time-of-flight angiography using MRA). In lieu of these investigations the dissection may correspondingly be demonstrated on CT scanning via axial sections that show both enlargement of the arterial wall by the haematoma along with concurrent narrowing of the lumen. It may also be shown on echocardiography which visualises a hypoechoic arterial wall with narrowing of the lumen and sudden enlargement of the carotid or vertebral (V2) artery diameter. Lastly a '1' may also be assigned when an arterial dissection is shown by indirect demonstration, or by less sensitive or less specific diagnostic tests (only long arterial stenosis beyond the carotid bifurcation, or in V2, V3 or V4 without demonstration of arterial wall haematoma on X-ray angiography, and or echography and/or CTA and/or MRA) or the presence of an equivocal US with recanalization during follow-up. As with the other phenotypical classes, where there are lower degrees of evidence then these are assigned either a '2' or '3'. Where no dissection is detected or suspected as determined by a negative FAT-saturated MRI of suspected artery or on a good quality, normal X-ray angiography (it should be noted that too early FAT-saturated MRI performed within 3 days of symptom onset can be falsely negative and thus should be repeated to ensure validity). If there is no clinical suspicion of dissection, the patient can be classified as such with a '0' assuming that good-quality extra- or

intracranial cerebral artery and cardiac evaluations have been adequately performed. Where a '9', or incomplete workup is assigned is applicable when patients are aged less than 60 years of age, and have no evidence of either A1, A2, S1, C1, or O1 category, in addition no FAT-saturated MRI has been performed on the extra- or intracranial artery supplying the ischaemic field and no X-ray angiography has been performed (all of the incomplete investigations must have been performed within 15 days of symptom onset).

1.8.3

The Causative Classification of Stroke System

The Causative Classification of Stroke System (CCS) is the final codification which like preceding schemes aims to classify stroke, by aetiology. It does so by incorporating clinical, epidemiological (quantitative primary stroke risk estimates), and diagnostic data to determine stroke subtype into 5 major categories [18]. These categories consist of large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, and undetermined causes. The undetermined group is further sub-divided into four types: cryptogenic embolism, other cryptogenic, incomplete evaluation, and unclassified categories.

In the CCS, each aetiologic class is categorized based on the weight of evidence as "evident," "probable," or "possible". A mechanism is deemed "evident" only if the available data indicate that it is the sole potential mechanism conforming to one of the aetiologic groupings. When there are greater than one "evident" stroke mechanisms, the system assigns a "probable" stroke mechanism based on specific characteristics that make one mechanism more probable than the others. In the absence of any "evident" cause, a search is made for "possible" mechanisms that carry a lower or less-well defined risk for stroke.

Within large artery atherosclerosis an 'evident' label is assigned when either an occlusive, or stenotic lesion of equal to, or greater than a 50% diameter reduction, or less than a 50% diameter reduction with plaque ulceration or thrombosis is found. This is true also if a plaque with less than or equal to 50% diameter reduction that is seated at the site of the origin of the penetrating artery supplying the region of an acute lacunar infarct vascular disease is judged to be due to atherosclerosis in the clinically relevant extracranial or intracranial arteries. Likewise, if there is no acute infarction in vascular territories other

than in stenotic or occluded arteries it is found to be ‘evident’. The ‘probable’ level of confidence is assigned in the following three situations. In a prior history of one or more transient monocular blindness (TMB) episodes, TIA, or stroke from the territory of index artery affected by atherosclerosis within the month preceding the index stroke. This is true also if there is evidence of thrombosis, near-occlusive stenosis or non-chronic complete occlusion judged to be due to atherosclerosis in the clinically relevant extracranial or intracranial arteries (except for the vertebral arteries). ‘Probable’ is also designated in the presence of ipsilateral and unilateral acute internal watershed infarctions or multiple, temporally separated infarctions exclusively within the territory of the affected artery demonstrated on radiological imaging. Last of all, ‘possible’ confidence is allocated where an atherosclerotic plaque protruding into the lumen and causing mild stenosis (of less than 50%) in the absence of any detectable plaque ulceration or thrombosis is identified in a clinically relevant extracranial or intracranial artery. A prior history of two or more TMB, TIA, or stroke from the territory of index artery affected by atherosclerosis, with at least one event within the last month must also be co-present to qualify.

In the highest confidence in Cardio-aortic embolism as the aetiology, ‘evident’ is assigned where there are high risk cardiac source(s) of cerebral embolism. While for ‘probable’ confidence there must be evidence of systemic embolism, or evidence of multiple acute infarctions that have occurred temporally close together. These must be within both right and left anterior or both anterior and posterior circulations in the absence of non-embolic occlusion or near occlusive stenosis of all the relevant vessels. Other diseases that can cause multifocal ischaemic brain injury such as the vasculitides, vasculopathies, and haemostatic or hemodynamic disturbances must also have been excluded. Finally, ‘possible’ is assigned in the presence of a cardiac condition with a low or uncertain primary risk of cerebral embolism.

Small artery occlusion is ‘evident’ if imaging evidence of a single and clinically relevant acute infarction (less than 20 mm at greatest diameter) is found within the territory of basal or brainstem penetrating arteries; in conjunction with the absence of any focal pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasospasm, etc.). ‘Probable’ confidence is arrived at in the presence of stereotypic lacunar transient ischemic attacks within the last week, or in the presence of a lacunar syndrome. Finally, ‘possible’ is assigned to a classical lacunar syndrome in the absence of imaging that is sensitive enough to detect small infarctions.

Within the other ‘uncommon causes’ category, the presence of a specific disease process that involves clinically appropriate brain arteries garners ‘evident’ confidence, while ‘probable’ is given when a specific disease process that has occurred in a clear and close temporal or spatial relationship to the onset of brain infarction such as arterial dissection, cardiac or arterial surgery, or cardiovascular interventions. ‘Possible’ confidence is assigned for evidence of other causes in the absence of complete diagnostic investigation.

Undetermined causes have two main subsets contained within it. One subset is that of unknown cryptogenic embolism which display angiographic evidence of abrupt cut-off consistent with a blood clot within otherwise angiographically normal looking intracranial arteries, or imaging evidence of complete recanalization of previously occluded artery. The presence of multiple acute infarctions that have occurred in a closely related temporal manner without detectable abnormality in the relevant vessels also falls under this class.

The other classes include other cryptogenic causes in which those cases do not fulfil the criteria for cryptogenic embolism or where there is incomplete evaluation in which the absence of diagnostic tests that, in the examiner`s judgment, mean it is therefore not possible to uncover the underlying aetiology.

The unclassified category in this taxonomy means in the presence of one or more possible or evident mechanisms where there is either probable evidence for each, or no probable evidence to be able to establish a single cause then it is assigned to the unclassified.

1.9

Diagnostic systems

The various international stroke guidelines such as from the European Stroke Organization (ESO) [21], the American Heart Association (AHA)[22], National Institutes of health and social Care Excellence (NICE) {, #58} and Canadian guidelines [23], all make clear reference to the need for, and expectation of, the use of, radiological imaging and other investigations beyond history and examination to make a diagnosis of stroke. A comprehensive ‘work-up’ is integral to assist in diagnosis and aid in patient management. However, it is clear from the classification taxonomies described previously, that there are many instances where despite an extensive battery of investigations, including all of the recommended tests, a definitive diagnosis of stroke or TIA can still be difficult.

To support diagnosis and target utilization of radiological and other finite health resources to those in greatest need, clinical scoring tools have been developed and employed. These tools are discussed in more detail within the fourth chapter and so I shall merely list them here, with a more detailed description contained in the subsequent chapter. Of the various tools available I will focus on four exemplars these are the ROSIER [24] or recognition of stroke in the emergency room tool, the ABCD2 or ‘age’, ‘blood pressure’ ‘clinical features and ‘duration of symptoms’ tool [25], the DOT score, an acronym of ‘Diagnosis of TIA’ score [26], and lastly the Dawson score which was similarly developed to assist in accurate TIA detection [27].

1.10

Stroke mimics

As well as differentiating between stroke types, and subtypes, clinicians must also contend with entities which can give the appearance of stroke or ‘mimic’ of it, despite it not truly being such. The presence of these ‘stroke mimics’ is one of the reasons for the continued interest in stroke diagnostic tools.

It is known that up to 60% of TIA clinic referrals are in fact not confirmed as cerebrovascular [28]. Within the ER environment the prevalence of alternative diagnoses mistaken as stroke can range from 1% to 30% of all of strokes assessed and referred for further opinion [29]. Other studies have noted that the frequency of stroke mimics is variable across settings and depends where the diagnosis is made but mimics can account for 20–50% of cases of acute suspected stroke depending if the patients are evaluated by the emergency personal or stroke physicians [30]. Thus, the heterogeneity of clinical referral methods and arrays of diagnostic pathway chosen all influence this 'final' confirmed or refuted diagnosis.

Common mimics include migraine with aura, seizures, cardiogenic syncope and functional or anxiety related phenomena [28]. Up to 20% of patients referred with possible TIA instead have a migrainous aura mimic, representing the most common form of mimic. When this condition arises without headache or as an imperceivable headache the ensuing diagnostic difficulty of discerning it from TIA is formidable [31]. Seizures as another mimic of TIAs are a further challenge especially so in older patients [32]. On the one hand generalized seizures typically are often uncomplicated to discern from TIAs, but partial seizures which may present with a hemiparesis, or language disorder present a diagnostic conundrum.

Cardiogenic syncope arises from a transient loss of arterial tone, and thus loss of consciousness with normally rapid resolution upon recumbency. This transient cerebral hypoperfusion is usually the result of a reflex (vasovagal) syncope whereby a rapid reduction in both heart rate and blood pressure is brought about by enhanced para-sympathetic nervous system activation, and parallel reduced sympathetic nervous system activity. This causes blood vessel dilatation and thus reduced blood pressure and also a reduction in both the heart rate (negative chronotropic effect) and contractility (negative inotropic effect) leading to a decrease in cardiac output that is significant enough to result in a loss of consciousness. Other causes within this category include both postural hypotension and carotid sinus hypersensitivity. Non-benign causes of syncope are manifested in the cardiac arrhythmias.

Lastly functional disorders, and disorders related to anxiety mimicking stroke, have been cited as representing as many as 6-7% of all referrals [33] [34] . The cardinal feature of these functional and anxiety origin mimics is it being of "sudden onset or on waking" and

“symptoms may be stereotyped and recurrent and may be accompanied by panic, pain or physical injury at the time of onset. There may be dissociative or multiple symptoms…” Discrepancy between symptoms and physical examination, or indeed between examination and observations, can also be indicators of this. This patient population tend to be younger patients who lack the conventional (cardio) vascular risk factors that are more typically found in older patients with proven cerebral vascular disease.

The aforementioned diagnoses are not all of the possible stroke and TIA mimics, and instead merely represent the most common, and demonstrate the range of conditions which can be mistaken for TIA and stroke and thus muddy the diagnostic waters. What they readily demonstrate, is that definitive TIA diagnosis from stroke mimics, even armed with all possible available investigations, a clear history and thorough clinical examination, it is not always such a straightforward matter. For the non-specialist, and in time pressured acute situations, accurate diagnosis can be even more formidable. This is one of the arguments supporting the increased use of the diagnostic tools described previously.

The need to find ways to improve discrimination of stroke and stroke mimic by non-stroke specialist clinicians is clearly of importance given the fact that in some series more than half of TIA clinic referrals are in fact not TIA. This inevitably leads to finite medical resources designed for TIA and stroke patients being consumed by patients with other pathologies, and potentially denies true TIA and stroke presentations from being able to access this resource. This can also result in patients being erroneously placed under the care of stroke physicians rather than by those potentially best placed to treat them such as cardiologists in cardiac origin aetiologies, seizures from a neurological origin rather than secondary to a stroke, and finally in those with a migraine presentation (the majority of which are usually managed by primary care physicians [35] [36]).

This does of course practically have the implication that stroke physicians are managing conditions outside of their speciality. While this may feel uncomfortable for some stroke physicians, it could be argued from a patient perspective that they are content that they have been investigated for a stroke or TIA, been reassured by the appropriate specialist to rule this out, and commenced on appropriately treatment by that physician. Whilst not the intended pathway, as long as a stroke or TIA has been excluded and the patient is being managed safely and is satisfied, it could be argued that this is still acceptable.

The diagnostic tools such as DOT [26] and ROSIER [24] can be useful in aiding diagnosis but are imperfect, as are all current means of contemporary stroke diagnosis, with the 'in-between' and grey zones often ultimately only resolved by expert consensus.

Notwithstanding these issues of contemporary practice, it is clear that efforts to ensure the validity of these tools in current stroke populations are still required. Further it is worth noting that some previous studies on these tools are over a decade old now.

1.11

Stroke classifications and their importance in clinical practice

Having discussed stroke, and its definitions and classifications in depth, it is worth now exploring just why these are so important, and to understand the rationale for using these tools. Stroke is the subject of this thesis, and each chapter in turn examines an aspect of stroke, albeit each project contained approaches to stroke from a differing vantage point. Thus, it is clearly prudent to describe and explain stroke and the taxonomies used. By having a firm grasp of the nomenclature and aetiologies of stroke it consequently informs the understanding of subsequent chapters by contextualising the subject matter.

The importance of stroke classification is first apparent when considering the patient group of interest in my review of clinical practice guidelines pertaining to cognition. It is helpful to consider the various types and anatomical classification of stroke lesions when considering cognitive dysfunction and cognitive testing. For example, a lacunar stroke causing hemi-paresis might result in a patient being unable to complete written assessments, whereas a dominant hemisphere cortical lesion may impact on ability to respond appropriately to assessment questions. This heterogeneity inherent in stroke is a recurring theme in this thesis and suggests that a one size fits all approach, or singular recommendation about how to clinically assess cognition, is neither good practice nor advisable.

For the work exploring patients experiences of cognitive assessments it is again important to be cognisant of stroke, and the various classifications and aetiologies. When considering

the qualitative results, having a knowledge of stroke definitions and classifications gives us a lens through which to view these results, i.e. do the types of stroke seem to influence patients answers or experiences. For example, in patients with intact cognition but upper limb motor dysfunction, 'pen and paper' assessments could result in complex feelings or emotions. When considering stroke survivors' memories of information sharing around assessment, it is worth bearing in mind that certain strokes can have an impact on memory and recall. As speech can so often be affected by stroke, classification systems that identify those likely to have communication issues provide a useful lens for considering cognitive test performance and experience. Thus, we can assess the intersection between quantitative and categorical classification of stroke and qualitative experiential data provided by stroke survivors themselves. This draws together the second and third chapters which provide cognitive assessment from the clinicians' point of view in the CPG work, and then cognitive assessment from the patient point of view in the qualitative work.

Finally, considering the multitude of definitions and aetiologies used to define stroke (all of which still do not delineate the entire spectrum of stroke), gives a useful lens through which to interpret the final research chapter looking at diagnostic tools. Understanding the underlying principle behind these tools, and why certain components of those tools are employed, necessarily requires an understanding of stroke aetiology and classifications.

1.12

Cognition and cognitive impairment

Cognition or 'thinking', and its underlying existential nature, mechanism and genesis have been a topic of debate among philosophers and scholars throughout recorded time. Indeed, it remains a contemporary polemic today [37]. It is far beyond the scope of this work to seek to philosophise about the theories of cognition, or even attempt to describe it better than the notable contributions already given by luminaries in the field such as those of Descartes, who had a profound impact on Western thinking during the European Renaissance regarding the nature of cognition or consciousness.

His most famous proposition was the influential Cognito argument oft quoted 'I am thinking, therefore I exist,' or, 'ego cogito, ergo sum,' in its Latin form. In this argument he advances the very notion of thinking, and the act of doubting one's own existence,

means that they necessarily do exist [38] [39]. This ability imbues us our intrinsic properties as human beings or as ‘thinking things’. This indelible mark in philosophy too permeates into society at large with much of our self-worth, our value and sense of self bound up in how we are able to think.

As an introduction to cognition for this thesis, I will focus on more tangible and quantifiable components of cognition, and in particular major on current definitions for dysfunction or impairment. Having defined the context, I shall then cover the aspects of cognitive assessment from a clinical practice perspective.

Given the ongoing debate around what cognition itself is, it is therefore not surprising that cognitive impairment is an area of considerable academic discussion. Within the literature there is a high degree of heterogeneity surrounding nomenclature, diagnosis, natural history and current practices in clinical diagnoses [40] [41].

A variety of cognitive syndromes have been described that can be seen in stroke survivors, and these diagnostic labels are used commonly in clinical practice. Although described as discrete entities, there is often overlap between these syndromes and, as with stroke, precision diagnosis is not always possible.

On the one hand the World Health Organisation (WHO) International Classification of Diseases for Mortality and Morbidity Statistics, 11th Revision (ICD-11) defines mild cognitive impairment (MCI) or ‘6D71 Mild neurocognitive disorder’ as being ‘characterized by mild impairment in one or more cognitive domains relative to that expected given the individual’s age and general premorbid level of cognitive functioning, and which represents a decline from the individual’s previous level of functioning’ [42]. Diagnosis is based on reports from the patient, informant, or clinical observation, and is accompanied by objective evidence of impairment by quantified clinical assessment or standardized cognitive testing. The cognitive impairment is not severe enough to significantly interfere with an individual’s ability to perform activities related to personal, family, social, educational, occupational functioning or other important functional areas. The cognitive impairment is also not attributable to normal aging and may be static, progressive, or may resolve depending on the underlying cause or treatment. Cognitive impairment may be attributable to an underlying acquired disease of the nervous system, a trauma, an infection or other disease process affecting the brain, use of specific substances

or medications, nutritional deficiency or exposure to toxins, or the aetiology may be undetermined. The impairment should not be related to substance intoxication or withdrawal.

On the other hand, and other end of the cognitive spectrum, Dementia is usually operationalised as ‘an acquired loss of cognition in multiple cognitive domains sufficiently severe to affect social or occupational function’. Dementia is a syndrome associated with more than one neuropathology, the commenest being Alzheimer disease (6D80 Dementia due to Alzheimer disease) [42], and cerebrovascular pathology [43], both of which can co-exist. In contrast to the ICD, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), does not use the terms dementia or MCI, preferring instead to use major and minor neurocognitive disorder.

It is important to bear in mind that both MCI and dementia are labels used to describe chronic cognitive disorders, and are typically of an insidious onset. This is in contrast, and quite different, to the syndrome of delirium, which the WHO ICD-11 characterizes as ‘a disturbance of attention, orientation, and awareness that develops within a short period of time, typically presenting as significant confusion or global neurocognitive impairment, with transient symptoms that may fluctuate depending on the underlying causal condition or aetiology’ [42]. Delirium (6D70 Delirium) often includes disturbance of behaviour and emotion, and may include impairment in multiple cognitive domains. A disturbance of the sleep-wake cycle, including reduced arousal of acute onset or total sleep loss with reversal of the sleep-wake cycle, may also be present. Delirium may be caused by the direct physiological effects of a medical condition not classified under mental, behavioural or neurodevelopmental disorders, by the direct physiological effects of a substance or medication, including withdrawal, or by multiple or unknown etiological factors. In spite of it being an acute disorder of attention and cognition first described more than 2500 years ago, delirium remains frequently unrecognised and incompletely understood [44].

Delirium can be envisaged as an acute brain failure, not dissimilar to heart failure, and is a multifactorial syndrome which may develop acutely in response to noxious insults like sepsis or major surgery, or indeed subsequent to a stroke. Further by conceptualising the idea of a ‘cognitive reserve’ which is where the brain possesses resilience to external factors, and where this is overwhelmed in delirium, it may point to an already vulnerable

brain possessing a diminished reserve capacity. In this context a brain with greater reserve might better withstand these noxious stimuli and be less prone to delirium.

The importance of delirium as a result of stroke is clear, a recent systematic review estimated the incidence of delirium at around 25% in acute stroke [45]. While this acute brain failure can often resolve, numerous papers point to ongoing chronic cognitive impairments on the spectrum from MCI, up to that of dementia, in patients in the post stroke phase [46] [47].

1.13

Cognitive assessment

At its simplest cognitive assessment involves ‘dividing the aspects of cognition up into separate discrete entities and then assessing each domain. This includes the higher cortical functions: particularly memory, attention, orientation, language, executive function (planning activities), praxis (sequencing of activities) and visuospatial skills [48] [49] [50].

1.13.1

General approach to assessment

Rather than consider neuropsychological theory, my reading around cognitive assessment in stroke was more practical and applied. An approach that is more typical in a clinician interaction between a patient and professional.

Cognitive assessment serves the purpose of separating out those patients in whom a firm clinical diagnosis can be made, from those who require further and more comprehensive investigation [51]. In the text below I will consider the formal, comprehensive neuropsychiatric assessment. This is a level of assessment that would not be suited to primary care or screening. Rather, it is included to highlight the complexity and potential work involved in cognitive assessment. This is important context for understanding the implications of the guideline and qualitative chapters.

As is common in clinical medicine, the history forms an integral part of the examination, and the ability to respond to conversational cues is as significant a part of the examination as any formal assessment. Furthermore, it is vital to remain cognisant that the perspective of a reliable informant is essential, as memory disturbance and impaired insight into cognitive difficulties may be present [52]. Therefore in the following discourse, I will first cover the history component before moving onto specific aspects of examination and potential clinical presentations. Given the nature of the cognitive assessment it is often appropriate to blend aspects of the history taking, with immediate confirmation via specific examination. Practiced examiners habitually weave their assessment adeptly into a relaxed conversation putting a patient at ease. Many of the following tests described in this section below can be modified and incorporated to suit an individualised style of assessment.

1.13.2

Memory

First looking at the memory as a domain of cognition, a useful framework for analysing memory complaints divides memory into several distinct domains with differing brain regions involved in these functions [51]. Episodic memory (personally experienced events) comprising anterograde (newly encountered information) or retrograde (past events) components. Neuroanatomically, memory is dependent on the hippocampal–diencephalic system. A second important system involves memory for word meaning and general knowledge (semantic memory), the key neural substrate in this instance being the anterior temporal lobe. Working memory refers only to the very specific and limited capacity which allows for information retention for only a few seconds. The brain regions responsible for working memory are the dorsolateral prefrontal cortex regions.

In the history, deficits in episodic, anterograde memory loss can be suggested by the following: forgetting recent personal and family events (appointments, social occasions), losing items around the home, repetitive questioning, an inability to follow and/or remember plots of movies or television shows, the deterioration of message taking skills, or an increasing reliance on lists to aid memory. In a likewise fashion retrograde memory loss may manifest as deficits of memory of significant past events (jobs, past homes, major news items), getting lost, or presenting with poor topographical sense (route finding). Memory loss and learning deficiencies out of proportion to other cognitive domain disturbance is recognized as the amnesic syndrome. Patients suffering from the "amnesic

syndrome" exhibit five general symptoms: (a) Premorbid levels of intellectual function such as language are maintained except in cases where an associated dementia is present, (b) Immediate memory function appears intact with patients exhibiting normal scores on memory span and showing typical recency effects, (c) Retrograde amnesia is present in varying degrees, (d) Anterograde amnesia with performance on conventional long term memory tests usually at least two standard deviations below the norm, (e) A degree of residual learning capability is exhibited but this is restricted to memory tasks which do not require the patient to access the memory of a specific personal event [53]. For example, patients can learn a novel motor skill whilst being totally unable to recollect the circumstances under which they learnt it. Generally speaking, in the majority of neurodegenerative conditions both anterograde and retrograde memory loss occur simultaneously, such as in Alzheimer's disease [54] or as secondary to a head injury. However, there are some exceptions seen in clinical practice.

Relatively pure anterograde amnesia may be seen when there is hippocampal damage, which is particularly associated with herpes simplex encephalitis, tumours of the focal temporal lobe, or indeed from infarction resulting from stroke. Another example is the Korsakoff syndrome, being characterized by confabulation, memory loss, and gait abnormalities that are often irreversible and results if not treated adequately [55]. Pure anterograde amnesia might manifest itself as either grandiose or delusional, but more often involves the mis-ordering and fusion of real memories which end up being retrieved out of context. A transient amnesic syndrome with pronounced anterograde, and variable retrograde, amnesia is seen in transient global amnesia (TGA).Transient global amnesia (TGA) is a clinical syndrome characterized by the sudden onset of anterograde amnesia, accompanied by repetitive questioning, sometimes with a retrograde component, lasting up to 24 hours, without compromise of other neurologic functions [56], while repeated brief episodes of memory loss are suggestive of transient epileptic amnesia (TEA). Transient epileptic amnesia (TEA) is itself a sub-type of mesial temporal lobe epilepsy, with amnesic seizures [57] and is characterized by recurrent episodes of amnesia. Lapses in concentration and attention (losing your train of thought, wandering into a room and forgetting the purpose of the visit), are common and increase with age, depression, and anxiety [58]. Such symptoms are much more evident to patients than to family members.

Dissociative amnesia is a disorder characterized by retrospectively reported memory gaps [59]. These gaps involve an inability to recall personal information, usually of a traumatic

or stressful nature. Dissociative amnesia most commonly occurs in the presence of other psychiatric conditions, particularly in those patients with personality disorders [59,60].

Patients with semantic memory breakdown typically complain of loss of words. Vocabulary diminishes and such patients may substitute bland words like “thing”. There is a parallel impairment in appreciating the meaning of individual words which first involves words which are infrequently encountered or unusual. Word finding difficulty is common in both anxiety [61] and aging [62], but this is variable and not associated with impaired comprehension. This is in stark contrast to the anomia seen in semantic dementia (SD). SD designates a progressive cognitive and language deficit, primarily involving comprehension of words and related semantic processing [63]. People living with SD lose the meaning of words, usually nouns, but retain fluency, phonology, and syntax. SD is progressive and associated with atrophy of the anterior temporal lobe, usually on the left.

Memory may be tested by directing some specific questions about the person’s journey to the hospital, or recent events on the ward during the conversation. Recalling a name and address, or the names of three items, is also common practice, however proper care at the start must be taken to ensure proper registration of the items, or the results may be confusing or misleading. Poor registration, (itself usually a feature of poor attention or executive dysfunction) may invalidate the results of recall or recognition which test episodic memory, and it is also true that free recall is harder than recognition of an item from a list. Some diagnostic challenges arise when testing in the hearing or visually impaired and this situation may necessitate the use of written instructions, in large print, and the wearing of their spectacles if needed. Anterograde non-verbal memory may be measured by asking a subject to copy, and later recall, geometric shapes, or alternatively, if it is possible to hide several objects around the room at random, and then ask the patient to search for them several minutes later. This is generally an easy task, and the inability to perform well is a convincing sign of memory impairment. When attempting to test retrograde memory without an informant, famous events, recent sporting results, or the names of recent US presidents can all be deployed to look for weakness. More remote autobiographical memory assessment necessitates corroboration, and even then, it may be relatively preserved in the initial stages of Alzheimer’s disease.

By simply asking both the patient and their informant to give an overall memory rating (for example, out of 10) a helpful insight is gleaned. Seldomly, if ever, will a truly amnestic

patient give themselves scores such as 0 or 1, although their informant might. The converse is often found in those who forget primarily because of anxiety or depression.

In people with dementia, the most common variant is Alzheimer disease, from a memory point of view onset is usually insidious with impairment typically reported as the initial presenting complaint [42]. The characteristic course is a slow but steady decline from a previous level of cognitive functioning with impairment(s) in additional cognitive domains (such as executive function, attention, language, social cognition and judgment, psychomotor speed, visuoperceptual or visuospatial abilities) with disease progression.

The frequency of dementia is said to be up to one in three people over 80 years of age and 70% of people over 90 years of age [64]. Most dementias are progressive degenerative diseases and thus, the symptoms and features of certain other psychiatric disorders, may become less noticeable as dementia progresses. However, more commonly, neurodegenerative conditions, such as Alzheimer's disease (AD), actually cause or aggravate underlying neuropsychiatric symptoms, increasing both the disability and disease burden.

Depression is a condition centrally focussed on depressive mood and loss of interest or pleasure over a period of weeks and accompanied by a number of associated symptoms such as anhedonia, inactivity, anxiety, loss of appetite, sleep disturbances, agitation, and fatigue. However, many patients also complain of difficulties thinking, concentrating, and making decisions and often have difficulty performing tasks that require a high level of attention. This can result in depression being mistaken for an early symptom of dementia in older adults, so called depressive pseudo dementia. This coupled with the fact that many depressed older adults do not exhibit the classical depressive symptoms seen in early and midlife underscores that depressive mood is a symptom, that can be difficult to discern, and distinguish from cognitive syndromes [64,65].

Cognitive screening tests, such as the Mini-Mental State Examination (MMSE) [66], may have some utility in differentiating pseudo dementia (which may be amenable to treatment) from Alzheimer Disease, depending on the performance on the test items and the observed attitude toward taking the test [67]. Pseudo dementia tends be associated with a decline in verbal fluency rather than a decline in delayed recall, which is different from AD [64]. However, often more detailed neuropsychological assessment is required to differentiate

mood disorder from dementia. Indeed, even for assessment of the person with suspected cognitive decline and no concomitant mood disorder, the MMSE has well recognised limitations.[64,68].

1.13.3

Language

Moving onto another key domain, that of language, in the history, the majority of language deficits will usually be revealed, particularly where poor fluency, prosody, agrammatism and articulation are involved. Evidence of word finding impairments and paraphasic errors are also usually quick to become apparent. Vigilant noting and documenting of several examples of a patient's errors is frequently helpful to subsequent clinicians. However, it is vital to remain mindful that a relatively fluent history may mask quite significant naming and single word comprehension deficits, and it is therefore important to assess language formally and routinely with infrequently encountered words.

The testing of language measuring the degree of anomia (or naming) is useful as an overall index of the severity of a language deficit, and is a prominent feature in virtually all post-stroke aphasic patients, in moderate stage Alzheimer's disease, as well as semantic dementia. Naming ability requires the integration of visual, semantic, and phonological aspects of item knowledge. There is a notable frequency effect, and rather than using common items to test the patient, such as a pen or watch, it may be more informative to ask about a 'winder', 'nib', 'cufflinks', or a 'stethoscope'. Phonemic paraphasias (for example, "baby flitter" for "baby sitter"), and semantic paraphasias ("clock" for "watch", or "apple" for "orange") may also be seen, and are reflective of pathology in Broca's area and the posterior perisylvian region, respectively. Broad superordinate responses, such as "animal", may be given in response to pictures of and enquiring what it is, for example, a camel. Progressive semantic memory impairment is classically seen in semantic dementia. Posterior lesions, particularly of the angular gyrus, can produce quite pronounced anomia for visually recognised objects, and may be associated with alexia.

It is useful to assess language comprehension in a graded manner, starting with simple and then more complex instructions. Difficulty with comprehension can often (incorrectly) be assumed to be secondary to a hearing impairment and accordingly complaints of

difficulties using the telephone, or withdrawal from group conversations, may prompt subtle clues to the presence of language difficulties. Using several commonly found items (such as a coin, key, or pen), and asking the patient to point to each one in turn in order to assess single word comprehension is valuable. There is however an element of frequency effect, and if this test proves too easy, then trying more difficult items around the room is advisable. In terms of sentence comprehension, this can be tested with several common items in order to devise syntactically complex commands. For example, by instructing the patient to, "touch the pen, and then the watch", with subsequent follow up carried out by more difficult sentences such as "touch the watch, after touching the keys and the pen". As an alternative to these it might be useful to ask the patient "If the lion ate the tiger, who remained?" being cognisant that syntactic ability is suggestive of lesions of Broca's area, or the anterior insular region. Furthermore, these lesions are classically accompanied by phonological errors and poor repetition. When thinking about conceptual comprehension (that is, understanding) this can also be assessed using the same objects, for example, "which of these items is used for recording the passage of time?". Equally, "which bird flies mainly at night and hoots?" can be asked, with this type of naming to definition helping to exclude a visual deficit, while actively accessing the patient's semantic store.

Practically assessing language repetition can be achieved by using a series of words and sentences of increasing complexity. Repetition of "hippopotamus" followed by enquiry as to the nature of the animal, assesses phonological, articulatory, and semantic processing simultaneously. Additional useful words for repetition which may be used are "aubergine", "emerald", and "perimeter" while careful listening by the examiner is employed to detect phonemic paraphasias. Sentence repetition can be assessed by using the phrase, "No ifs, ands or buts", which is more difficult to repeat than its alternative, "The orchestra played and the audience applauded".

While reading deficits and a failure to comprehend are usually accompanied by an inability to read aloud, the reverse is not necessarily true, and this can be tested either by writing a simple command such as "Close your eyes" or simply improvising by using a few phrases from a nearby book or newspaper. If a reading deficit is identified, this should be characterised further. Those patients with a so-called pure alexia exhibit the phenomenon of letter-by-letter reading, with frequent errors in letter identification. Neglect dyslexia, which is typically seen following a right hemisphere injury, is usually confined to the initial part of a word and can take the form of either omissions or substitutions (for

example, “land” for “island”, and “fish” for “dish”). Where the difficulty is in reading words with irregular spelling (for example, “suite”, “cellist”, “dough”) this can portend a breakdown in the linkage of words to their underlying semantic meanings and is one of the signs of semantic dementia.

Writing, is more susceptible to disruption than reading, as it involves coordination between both central (spelling) and more peripheral (letter formation) components. Central dysgraphias affect both written and oral spelling and these syndromes are analogous to those seen in the acquired dyslexias, and can be similarly tested. Predominantly where there is preserved oral spelling in the face of written spelling impairment it suggests a writing dyspraxia or neglect dysgraphia aetiology. The former results in effortful, and often illegible, writing with frequent errors in the shape or orientation of letters, with copying also being abnormal. A mixed central and peripheral dysgraphia exhibited by spelling errors that tend to be phonologically plausible is normally seen in corticobasal degeneration. Neglect dysgraphia is characterised by misspelling of the initial part of words, and is most frequently associated with other non-dominant parietal lobe deficits of visuospatial ability and perceptual functions.

In acalculia, which is the inability to read, write, and comprehend numbers, (but is not identically analogous to an inability to perform arithmetical calculations which is termed anarithmetrica. Simple calculations are sufficient for the majority of test purposes, that being said a comprehensive assessment of this skill requires the patient to write numbers to dictation accurately, to copy numbers accurately and to be able to read those numbers aloud also. The patient should also be asked to perform oral arithmetic, written calculation, and finally be tested in their ability to reason arithmetically (for example, “If someone buys two items costing £1.64, and one costing 75p how much change would be received from tendering a £5 note?”).

1.13.4

Executive function

Within executive function impairments (concerning frontal lobe function) this ordinarily involve errors of planning, judgement, problem solving, impulse control, and abstract reasoning. Although executive function is generally believed to be a (dorsolateral) frontal lobe function, this set of skills is likely more widely distributed in the brain. Head injury is a common cause of impaired executive function, as is Alzheimer's disease, even in the initial stages. It is imperative to be aware that the majority of the frontal lobe is composed of subcortical white matter, and the leucodystrophies [69], demyelination, and vascular pathologies, can all cause executive dysfunction. Similarly basal ganglia disorders may also impair these skills. Progressive supranuclear palsy (PSP). is a relatively uncommon neurological disorder that affects movement, gait, balance, speech, swallowing, vision, eye movements, mood, behaviour, and cognition being a leading example of neurodegenerative condition with predominant dysexecutive cognitive presentation [70].

Executive function testing encompasses a broad range of skills that are comprised of "executive abilities" and so as a consequence, if deficits are suspected, then the testing of this ability in a number of different ways to characterise it more precisely must be undertaken. Inclusive of this is letter and category verbal fluency assessments, and it should constitute part of the core cognitive evaluation, with a poor performance of both being indicative of executive dysfunction. To assess this suitably patients are asked to produce as many words as possible starting with a particular letter of the alphabet (F, A, and S being the commonly used letters), with proper names, and the generation of exemplars from a single stem (for example, pot, pots, potter) being impermissible. Category fluency assessment can be performed by asking for as many animals as they someone can list within one minute. It would be expected that a young adult could produce 20 animals, with 15 animals considered low average, and less than 10 being demonstrative of impairment. On the subject of letter fluency, which usually proves more difficult (a score of 15 words per letter is rated as normal), and subjects with either subcortical or frontal pathology score poorly on both measures, but particularly badly on letter fluency. In contrast to these more restricted pathologies, patients with semantic deficits, such as semantic dementia or Alzheimer's disease, have more pronounced impairment for categories, but if refinements are required to better discriminate then categories of dogs for example, can be introduced.

Next when assessing impulsivity, which is thought to reflect a failure of response inhibition, and thus is characterised as inferior frontal pathology it can be assessed using the “Go-No-Go task” [71].

This is whereby the examiner instructs the patient to tap once in response to a single tap, and to withhold a response for two taps. Furthermore, it can be made more challenging by changing the initial rule after several trials (for example, “tap once when I tap twice, and not at all when I tap once”). Here the ability to alternate task, and the inhibition of inappropriate, or perseverative, responses can also be assessed by asking the patient to copy a short sequence of alternating squares and triangles, and then to continue across the page. Perseveration in drawing one or other of the shapes may be seen in frontal lobe deficits, however, the test is relatively insensitive. Further clinical examples of perseveration might manifest as palilalia or palilogia which are characterised by the repetition of sounds or words, respectively, while the repetition of whatever is heard is known as echolalia.

The cognitive estimates examination may prompt improbable responses in patients with frontal or executive dysfunction, and whilst it is not a formal test (with defined scoring parameters), it can be performed at the bedside by asking, for example, the height of the statue of liberty, the population of New York, or the speed of a typical racehorse.

Inferential reasoning might be assessed by asking questions about the similarity between two conceptually similar objects like simple pairs such as “apples and oranges” or “desk and chair” usually being tested first, followed by more abstract pairs such as “love and hate” or “sculpture and symphony”. Patients typically answer, quite concretely, that the two objects are “different” or “not similar” instead of forming an abstract concept to link the pair. This very often persists in spite of suggestion to consider other ways in which the items are alike. Equally, the testing of proverb meanings which measures a similar skill, can be employed, however it is highly dependent upon the pre-morbid educational ability and cultural background of the patient.

Attention can be tested in a several ways including serial 7s, digit span, spelling “world” backwards, and recitation of the months of the year in reverse order. While serial 7s is frequently employed, it is often performed incorrectly by older adults, and by those with

impaired attention. As a comparatively pure test of attention, the digit span test, is reliant on working memory, but is nonspecific, and can be impaired in several aetiologies (however it should remain normal in the amnesic syndrome (i.e., Korsakoff's syndrome or medial temporal lobe damage). By starting with three digits, and ensuring that they are spoken individually by the patient and not clustered together (in the way that one might recite a telephone number), this can be achieved (i.e., 3-7-2-5 and not 37-25, etc.). A normal digit span is considered to be 6±1, depending on age and general intellectual ability, with 5 being considered normal in older adults, or the intellectually impaired. Reverse span is usually one less than forward span. When executing this test, it is helpful to write out the numbers to be used before starting.

1.13.5

Praxis

Another aspect of cognition is praxis, or the ability to perform a desired movement with a body part. Therefore, apraxia arises if there is impairment despite intact sensory and motor function. Although a number of classes, such as limb kinetic, ideomotor, and ideational, exist, these labels are rarely used in routine clinical practice. It is more helpful to describe the apraxia by region (orobuccal or limb), and to provide a description of impaired performance, recording both spatial and sequencing errors on several different types of tasks. Orobuccal apraxia is closely associated with lesions of the left inferior frontal lobe and the insula, and commonly accompanies the aphasia caused by lesions of Broca's area. Progressive isolated limb apraxia is virtually diagnostic of corticobasal degeneration.

When actually assessing apraxia, imitation of gestures, both meaningful (for example, wave, salute, hitch-hiking sign) and meaningless (body and non-body oriented hand positions) should both be tested to command. This can be achieved by the use of imagined objects (comb your hair, brush your teeth, carve a loaf of bread), with the actual use of the object generally eliciting better performance than when it is mimed. This being typical of so-called ideomotor apraxia. Orobuccal movements can be specifically tested by giving instructions such as "blow out a candle", "stick out your tongue", or "lick your lips".
A sequencing task such as the Luria three step command (fist, edge, palm), or the alternating hand movements test, completes the assessment of apraxia. This latter is performed, after demonstration, with arms outstretched, and alternately opening and closing the fingers of each hand, such that one hand opens as the other hand closes in a fist.

Dressing apraxia is easily tested by having the patient put on clothing that has been turned inside out.

1.13.6

Visuospatial

The Visuospatial ability domain is where information from the visual cortex is directed towards the temporal or parietal cortex via one of two neural streams. The dorsal ("where") stream links visual information with spatial position and orientation in the parietal lobe, whereas the ventral ("what") stream links this information to the store of semantic knowledge in the temporal lobes. Where this system is impaired, in visual neglect for example, it can produce a characteristic failure to groom one half of the body, or to eat only half a plate of food.

Visual hallucinations usually suggest an organic cause and are prominent in dementia with Lewy bodies. Lewy body dementia results from the formation of Lewy bodies, which contain aggregates of the misfolded protein, α-synuclein. These deposit in areas of the nervous system and brain, leading to neuronal cell death and causing the clinically apparent symptoms [72]. Visual hallucinations also arise in acute confusional states (such as delirium) [73]. Additionally, formed visual hallucinations may also be seen in the absence of cognitive impairment, such as in Charles Bonnet syndrome (CBS). This phenomenon is characterized by complex visual hallucinations in people with visual impairment. [74]

In visuospatial neglect of personal and extra personal space (usually arising from lesions in the right hemisphere located in the inferior parietal or prefrontal regions) deficits can be exposed by either simultaneous bilateral sensory or visual stimulation. Alternatively, it can be unmasked by having the patient bisect lines of variable length, or using the 'Letter and star' cancellation tasks which is similar, but a more formal assessment of the same skill. Those patients with an object centred neglect fail to copy one side of an object, and neglect dyslexics may not read the beginning of a line or, of a single word. Patients being assessed who have anosognosia reject that they are hemiplegic or can even deny that the affected limb belongs to them at all.

Constructional apraxias are best considered as visuospatial, rather than motor apraxia. They are relatively easy to assess by asking the patient to copy three dimensional shapes such as a wire cube, producing two interlocking pentagons, or constructing a clock-face with numbers. Left sided lesions tend to produce over-simplification in copying ability, whereas right sided lesions can result in aberrant spatial relationships between the constituent figure components.

Visual object agnosias may precipitate object recognition failure, despite the patient having adequate perception. Those with apperceptive visual agnosia usually have normal basic visual functions but fail on additional complex tasks affecting object identification and naming. They do however, retain the ability to name objects to description, or by touch, signifying a preserved underlying semantic representation of that object. This phenomenon is illustrated within those patients with widespread, bilateral occipitotemporal infarction. In cases of associative visual agnosia, the deficit reflects a disruption of accumulated semantic knowledge, and involves all of the modalities accessing this information, with lesions of the anterior left temporal lobe being highly archetypal. To assess for these syndromes, it is necessary to assess object naming and description, along with tactile naming, naming unseen objects to description, and the ability to provide semantic information about those unnamed items in addition.

Those patients affected with prosopagnosias cannot recognise familiar faces, and it is often the case that other clues, such as their gait, voice or distinctive clothing are used to aid identification. These deficits result from an inferior occipitotemporal lesion. The deficit may not be wholly discriminating to just faces, and often fine grained identification within categories may also be impaired (for example, recognising makes of car, or types of flowers). Patients are generally able to characterise individual facial features, and since the underlying (semantic) knowledge associated with a particular person is not disrupted, the ability to produce attributes of the face in question, (if it is named) is preserved. Furthermore, prosopagnosia is often associated with field defects, achromatopsia or pure alexia. In delusional misidentification syndromes such as the Capgras syndrome patients are convinced that an impostor, who looks identical, has replaced a close relative [75], and is frequently found in those suffering dementia and schizophrenia.

Testing colour processing can reveal deficits such as achromatopsia (which is the loss of colour discrimination) after medial occipitotemporal damage, subsequent to left posterior

cerebral artery infarction. Colour agnosia impairs tasks requiring retrieval of colour information i.e. “What colour is a banana?”. While colour anomia can be assessed simply by asking the patient “What colour is this?”.

1.13.7

Social cognition

When considering someone’s behaviour the volunteering of inappropriate social behaviour is seldom, if ever, elicited from the history given by the patient, and on occasion, might lead the clinician to wonder whether the informant was referring to someone else altogether [51]. Direct questioning about conflict at work or with interpersonal relationships, or involvement with law enforcement agencies, may be helpful in determining the degree of insight. Informants may mention embarrassing social behaviour, changes in food preference (in particular sweet foods), or inappropriate sexual behaviour (especially when interviewed alone).

The ability to empathise and judge the emotional state of others is disrupted in the fronto-temporal syndromes. A history of apathy or poor motivation is a common feature of Alzheimer’s disease, fronto-temporal and subcortical dementias, but is not a particularly discriminatory finding, while impulsiveness, teased out on questioning, or being volunteered, may be a marker of impaired inhibition, reflecting an inferior frontal lobe function lesion.

At its heart, social cognition describes the skills and behaviours of those higher-order cognitive processes that individuals require to be able to interpret the behaviours of others, and which allows a person to process and understand social information in order to respond appropriately in everyday interactions [76,77]. Social cognition is also inclusive of the theory of mind (ToM), that is the intrinsic ability to recognise other people’s mental states so as to understand and predict their behaviour, emotion recognition, empathy, moral judgments and the understanding of social norms [78,79].

The theory of mind itself is comprised of both the Cognitive ToM which is the ability to make inferences about the thoughts, intentions and beliefs of another individual and affective ToM which refers to the ability to make inferences about what another individual

is feeling. Several tools have been developed to measure ToM such as the Reading the Mind in the Eyes (RME) [80] and Faux Pas stories (a verbal story based test that requires participants to make ToM inferences from short interactions involving social norms violations and non-social norm violations) [81].

In response to criticism of these existing tools, the Edinburgh Social Cognition Test (ESCoT) has been specifically devised to, for the first time, explicitly measure both cognitive and affective ToM in the same test [82]. The ESCoT consists of 11 dynamic, cartoon-style social interactions (each approximately 30 seconds long) and containing one practice interaction, five interactions involve a social norm violation and five interactions that do not involve social norm violations. Each animation has a different context and specific questions relating to that context. Participants are then asked to describe what had occurred in the interaction and then asked one question to assess each of the four subtests of social cognition. Analysis found that participants performance was not predicted by measures of verbal comprehension and perceptual reasoning, in contrast to other established tests of TOM, and thus may offer another method of measuring both cognitive ToM and affective ToM within the same test for clinician and patient if preferred.

1.13.8

Orientation

When considering orientation, which is usually assessed to time, place and person, it must be borne in mind that impairments in this domain are not particularly discriminating, and further that intact orientation does not exclude a significant memory disorder (particularly if an informant has concerns about the patient's memory). The most useful aspect of orientation is to time, and this should include asking the time of day. It is also true that many 'normal' people do not know the exact date, and therefore being incorrect by two days or less, is considered within the spectrum of normal when scoring orientation formally in a test. Additionally, time intervals are often poorly observed by patients with: delirium, moderate to severe dementia, and in those suffering from amnesic syndrome, and so this is readily tested by merely enquiring about the length of time spent in hospital for example. Likewise, place should be also be confirmed, by asking what the name of the actual building is (for example, the outpatient clinic), rather than the name of the hospital, as this often demonstrate a lack of awareness of location. Although since there are often visual and contextual cues present, this is less sensitive than orientation to time. Coming

onto the person aspect of orientation (name, age, and date of birth), true disorientation to name is unusual and only seen in psychogenic amnesia while in the aphasic patients, a mistaken label of "confusion" is frequently applied because they either fail to comprehend the question, or produce the wrong answer (though if given a choice, they can typically pick out their own name).

1.13.9
Assessing function

Considering how someone copes with the basic and extended activities of daily living (ADL) is also key to the cognitive interview [83] [84]. The ability to organise finances, use home appliances, to drive safely, and organise medication regimens are higher order ADLs which are usually impaired earlier in disease than the more commonly assessed skills such as cooking, walking, personal hygiene, and continence. This is an area in which a reliable informant, who knows the patients well, is essential [85].

1.13.10
Mood

The focussed evaluation of mood, specifically within the context of a cognition assessment is a vital undertaking given the impact mood can have upon cognition and performance in cognitive assessments.

This assessment can be difficult given the complex and nuanced interrelationship between mood and cognition [86], and despite cognitive deficits in the context of mood disorders having been studied extensively [87]. Indeed, emotion has a substantial influence on the cognitive processes in humans, including perception, attention, learning, memory, reasoning, and problem solving [88]. Emotion has a particularly strong influence on attention, especially modulating the selectivity of attention as well as motivating action and behaviour. This attentional and executive control is intimately linked to learning processes, as intrinsically limited attentional capacities are better focused on relevant information.

Emotion also facilitates encoding and helps retrieval of information efficiently. However, the effects of emotion on learning and memory are not always univalent, as studies have

reported that emotion can either enhance or impair learning and long-term memory retention, depending on a range of factors.

Bearing this in mind, in general, unipolar and bipolar patients have both shown impaired performance in tests of attention, executive function, and memory function [87] [89,90]. It had also been demonstrated that greater cognitive dysfunction is often associated with greater mood symptom severity, with cognitive deficits still persisting during the euthymic or remitted states.

The relationship between impaired cognition and mood is further complicated by the subset of older adults who present for the first time to a practitioner with complaints of mood (often depression) and who subsequently develop Alzheimer's Disease (AD) [91]. Indeed, some evidence has confirmed that cognitive decline might develop in conjunction with mood disorders, with the number of depressive symptoms in participants at baseline being predictive of increased risk of developing AD [92].

This association between depression and poorer cognitive performance was confirmed further in the UK biobank community-based study of middle to early old age participants, with bipolar disorder and depression patients, being found to have lower performances on cognitive testing, such as those examining visuospatial memory [93].

Considering the associations between cognitive function and depression using the Mini-Mental State Examination (MMSE) [66] , and the short Geriatric Depression Scale GDS [94] one group demonstrated that MMSE score was significantly negatively correlated with the depression scale. Thereby indicating that lower cognitive functioning is associated with more depressive symptoms, and so underscoring the importance of recognising depressive pseudo-dementia. If this presentation is recognised it may be amenable to therapy and so not only improve quality of life but also improve objective cognitive scores on testing [95,96].

The emergence of a mood disorder in later life is often, though not exclusively, indicative of organic disease, and this is particularly so in the form of a neurodegenerative pathology [97]. However, mood disorders can also emerge from several neuro-inflammatory processes as well as from cerebrovascular disease [98]. The inflammation hypothesis proposes that immune dysregulation influences vulnerability to, and the development of

later life mood disorder [99]. It posits that people with depression across the entire adult lifespan can exhibit elevated levels of pro-inflammatory cytokines including C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor (TNF) alpha and lower anti-inflammatory cytokine levels [100]. These biomarkers themselves are associated with depression severity, suicide risk, and refractory responses in geriatric blood samples [101]. Other studies have established that pro-inflammatory cytokines are associated with worse cognitive function in executive processes, memory, and processing and motor speed domains [102].

Cerebral small vessel disease (CSVD) aetiologies are postulated to contribute to mood disorder in various ways. These implicate leakage from the blood-brain barrier and dysfunction of cerebral autoregulation, neurovascular coupling, and capillary blood flow dysfunction thereby causing cerebral perfusion deficits and hypoxia, triggering inflammation and neuronal death [103]. Moreover hypertension, atherosclerosis, and diabetes themselves all directly contribute to CSVD and result in the thickening of the penetrating small arteries, fibrosis of the vessel wall, and depletion of vascular smooth muscle cells thereby producing vascular remodelling. The “vascular depression hypothesis” [104] posits that CSVD may predispose, precipitate, or perpetuate later life depression. This process likely begins in adulthood, as midlife cerebrovascular burden predicts increased depression severity over time.

So in summary while routine questioning should include enquiry about sleep patterns, appetite changes, anhedonia, energy or “spirits”, and any changes in libido the complexities of accurate diagnosis of mood disorders, and need for a judicious work up becomes apparent.

1.13.11
Driving

When considering driving in the context of a cognitive assessment, the finding of an initial mild cognitive impairment does not necessarily preclude driving, nonetheless it should prompt discussion around driving ability [51]. In general, informants are usually attentive of changes in driving skill, and their anxieties should be taken into account. Impairments in visuospatial ability (for example, copying the wire cube, pentagons, drawing a clock face)

are reliable indicators of increased driving hazard. In extreme circumstances, where poor insight conflicts with safety, keys are sometimes concealed, or cars are disabled, moved or sold by the patient's relatives. Likewise, the licensing authority can be notified (by either informants or clinician), and referral for an independent driving assessment may be necessary.

1.14

Definitions of healthcare intervention(s) & patient centred care

Healthcare intervention(s)

In the chapters on guidelines, the qualitative interviews and the work around test accuracy, a recurring theme is around assessment as a complex intervention. When considering patient care and their experience of healthcare interventions, it is necessary to first define and discuss the concept of health care interventions.

1.14.1

Healthcare intervention definitions

A healthcare intervention is defined by the World Health Organization as "... 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" [105]. Thus, from this multi-component definition it is clear that healthcare interventions are intricate and inter-connected, and not easily disentangled from the other components of health. "Complex interventions are "built up from a number of components, which may act both independently and interdependently" [106].

One metric of assessing an intervention's complexity might be on the basis of the number of components within the intervention (and the interactions between those components); actions required from participants; actions required from those delivering the intervention; organisational levels the intervention is targeting; and outcome measures employed [107]. Many interventions delivered within the stroke rehabilitation services can be considered complex, though some are more complex than others existing on a spectrum of complexity.

As well as the due consideration to the complexity of a healthcare intervention, another key metric by which to assess any intervention is by its acceptability to the patients(s) who the intervention is designed for. Indeed, the UK Medical Research Council has updated the definition of a complex intervention as "hav[ing] a number of interacting components, that require new behaviours by those delivering or receiving the intervention or have a variety of outcomes" [108]. This updated guidance states within the framework of actions for intervention development to "Involve stakeholders throughout the development process"

and articulates “Many groups of people are likely to have a stake in the proposed intervention: the intervention may be aimed at patients or the public, or they may be expected to use the intervention; practitioners may deliver the intervention in a range of settings, … and users, policy makers or tax payers may pay for the intervention”. It makes clear that identifying stakeholder priorities is a key undertaking and advises “Coproduction rather than consultation is likely to be important when buy-in is needed from a set of stakeholders to facilitate the feasibility, acceptability and engagement with the intervention”. This updated MRC guidance, much like its preceding iterations, does not offer a means for measuring acceptability. Accordingly, despite being an area of priority as set out by the MRC, there remains a gap on how acceptability is measured.

1.14.2

Definitions of acceptability

Despite acceptability gaining momentum in the literature and being recognised as an important strategic goal for funders, policy makers and wider stakeholder in designing, implementing, monitoring and assessing healthcare systems and policy interventions, there is still a lack of a comprehensive definition and conceptual framework of acceptability [109,110]. In one paper the authors define acceptability in the public health context as “a multi-construct concept describing nonlinear cumulative combination in parts or in whole of expected and experienced degree of healthcare from patient, provider or healthcare systems and policy perspectives in a given context”. They produce a conceptual framework based on five essential features: (1) context, (2) basic theories, (3) dependent variables, (4) independent variables and (5) applications of acceptability in public health [109].

In another conceptualisation of acceptability (of health care interventions), the definition used is: “… a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention”. The description goes on to identify that “the theoretical framework of acceptability (TFA) consists of seven component constructs: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy” [110]. This is the framework which I shall employ later on in this thesis, when considering stroke survivors’ experiences

of undergoing cognitive assessment. Thus, I will now discuss why acceptability of interventions, and patient centred care are so important and give an insight into why these topics are given such prominence by funders and policy makers.

1.14.3

Patient centred care, what is it?

Patient or person-centred care and the seminal influence these concepts have had in healthcare can be traced back to 1969 when Balint first proposed his paradigm shift [111]. Here in his discussion of the possibilities of patient centred care, he posited a move away from the traditional 'illness-orientated medicine'. This describes when a person who happens to have a disease was merely seen as a heart failure or stroke patient, and their individuality was considered, if considered at all, in a very biomedical approach. He starkly contrasted this with his so-called 'patient-centred medicine', where a doctor should seek to not only discover localizable illness or illnesses, but they should scrutinize the whole person in order to form an 'overall diagnosis'. Necessarily this should include everything that the doctor knows and understands about their patient, in a holistic fashion, considering the person as a unique human-being distinct from others with the same pathology.

Around 2,500 years ago the father of modern medicine, Hippocrates, stated 'it is more important to know what sort of person has a disease than to know what sort of disease a person has' [112]. Given this insightful observation, some ask why it is only within recent decades that person-centred approaches have come to the fore, and specifically how healthcare systems could be adapted to meet the individual needs of patients and carers.

Unlike at the inception of the NHS when people were delighted to receive free medical care and 'doctor knows best' todays patients wish to be treated as individuals whose uniqueness in values, family, social context, preferences and knowledge are recognized as being of crucial importance when deciding how to manage their medical care. Person-centred care means treating patients as individuals and as equal partners in the business of healing. This approach should be personalised, coordinated, and enabling. It is not a medical model, and should be regarded as multidisciplinary, recognising that a person may

need more than one profession's input. This shift to patient centredness is true in both Scotland, the rest of the UK [113] [114], and indeed in the EU [115].

There are many definitions and dimensions of person-centred care. In the Healthcare Quality Strategy for NHS Scotland, the concept is described it as: "Mutually beneficial partnerships between patients, their families and those delivering healthcare services which respect individual needs and values, and which demonstrate compassion, continuity, clear communication and shared decision making." It is, perhaps possible to describe person-centred care more simply. Fundamentally, the person-centred approach means asking not, "What's the matter with you?", but, "What matters to you?" It means finding out who is important to the person and working with them, and their loved ones, to support their care. It means providing the information people need to be fully involved in decision making, ensuring that services are, as far as possible, organised around their needs, and enabling them to be involved in their care at the level they choose [116].

It is my hope that I have made the concept of acceptability to patients, and its close relationship with patient-centred care readily seen, while demonstrating that these remain distinct concepts but with many common constituents. Indeed trust is central from individual relationships between patient and health provider, to trust in whole health care systems i.e. spanning both micro to macro interactions [117] [118] [119].

If something is made or offered in an acceptable manner for patients, it is highly likely that this, at least in part, ensures it is patient centred. Communication problems in health care may arise as a result of healthcare providers focusing on diseases and their management, rather than people, their lives and their health problems.

Patient-centred approaches to care delivery in the patient encounter are increasingly advocated by consumers and clinicians and incorporated into training for healthcare providers. However, the impact of these interventions directly on clinical encounters and indirectly on patient satisfaction, healthcare behaviour and health status has not been adequately evaluated [120].

1.14.4

Patient centred care improves outcomes

The principles of person-centred, rather than service-centric clinician driven, approaches are known to improve health outcomes. The advantages of involving patients as individuals and as partners in the processes of recovery through a provision of care that is personalised, coordinated, and enabling are well established [121]. Patient adherence to therapy and treatment regime is enhanced with this approach [122] [123]. Patient-centred care has been shown to be associated with decreased utilization of health care services and lower total annual charges [124]. This might reflect trust in their clinician partner and many mean that patients don't 'shop around' for a second opinion, or indeed by following their clinician partner's recommendations they should have less need for unscheduled or other medical reviews and treatments. Patient-centred care approaches also shorten hospital stay and maintain functional performance in patients hospitalized for worsening chronic heart failure, without increasing risk for readmission or jeopardizing patients' health-related quality of life at six month follow up [125]. Again, within primary care settings patient-centred care, and co-creation of care, were associated positively with satisfaction with care and the physical and social well-being of patients with multi-morbidity in the primary care setting [126].

1.14.5

Treatment burden

Another aspect of acceptability to be considered briefly is that of the concept of treatment burden. It is beyond the scope of this work to extensively discuss this area in detail, however its worth considering within this section given the synergy it has with acceptability. Simply, treatment burden is 'the workload of healthcare experienced by those with chronic conditions and the consequent impact that this has upon their well-being' [127] [128,129].

Treatment burden can negatively impact on quality of life of patients and their adherence to treatments. Within treatment burden, patient capacity is defined as 'the ability to manage health problems and follow treatments'. A previous study around treatment burden in stroke survivors has identified that the 'workload of healthcare' and the 'endurance of care

deficiencies' can contribute to treatment burden post stroke. The study also identified several factors that affect patient capacity: personal attributes and skills; physical and cognitive abilities; support network; financial status; life workload, and environment [130].

The consideration of acceptability through a person-centered care approach seeks to minimize treatment burden by tailoring treatment regimens to the realities of the daily lives of individual patients and their particular goals by engaging in Minimally Disruptive Medicine [131]. By considering treatment burden in clinical practice, a clinician would be cognisant of patient distress, prompting partnership development with the patient, working together to agree upon treatment strategies that are both effective and acceptable for the patient and their caregiver [132].

Treatment burden and acceptability are therefore closely aligned concepts, with acceptability likely to be higher with lower levels of treatment burden.

1.15

Lack of primary research around acceptability within healthcare

While there is a growing interest, and importance attached to acceptability of healthcare interventions, the de novo primary research around the acceptability of healthcare interventions in patients is sparse [110]. While there have been a limited number of studies looking at the acceptability of interventions within healthcare, for example research describing perinatal depression in woman [133-136], given the heterogeneity of methods, disparities in tests employed and the varied reporting strategies, drawing reliable results and conclusions remains challenging [137].

This is also true within stroke [138] with evidence aggregation being similarly problematic due to inconsistency in method and diverse assessment regimes. As a further caveat, many of the tools used to quantify acceptability assess a treatment-specific expectation, therefore limiting their comparability between different conditions. Within stroke a recent Cochrane review assessed the evidence for telerehabilitation services and looked at patient satisfaction as a secondary outcome, The review included 22 trials of n=1937 patients but the review authors were unable to draw conclusions due to study heterogeneity, limited information and insufficient evidence [139]. This serves to underscore the current problems in the field around standardised nomenclature, methods and guidance on reporting.

I hope I have made apparent the association between patient centred approaches, and their benefits, and how this relates to cognitive assessment within stroke. Any assessment undertaken on someone must be acceptable to them, and by understanding the benefits of ensuring acceptability, I hope to persuade clinicians of the potential outcome benefits. It also speaks to the use of a tool to not only discriminate on cognitive issues but be seen by the patient as acceptable to them, and necessarily be patient centred by involving them in a shared approach about its purpose, the results and possible implications.

1.16

What are Clinical practice guidelines

Clinical practice guidelines are documents written and produced by professional bodies and organizations such as: governments, medical colleges, statutory bodies and academic partners. They are created with the aim of providing clear directions around clinical management in line with evidence-based medicine for clinicians about patient care [140].

For example, within Scotland, the Scottish Intercollegiate Guideline Network (SIGN) is one of the main bodies tasked with creating clinical guidance. SIGN states that “CPGs are able to enhance clinician and patient decision making by clearly describing and appraising the scientific evidence and reasoning (the likely benefits and harms) behind clinical recommendations, making them relevant to the individual patient encounter” [141]. Further SIGN states “The link between a set of guidelines and the scientific evidence must be explicit, and scientific and clinical evidence should take precedence over expert judgement”. While in the main body of this thesis, I consider CPGs in relation to assessing cognition specifically during a stroke, it is important to be mindful of the more general processes of CPG development and that there remain contentious issues regarding CPGs [140].

With the rapid advances in medical, biomedical and health services CPGs have a vital role to play in reducing uncertainty by establishing standards of care backed by robust scientific evidence. Indeed, CPGs are now ubiquitous in many healthcare systems, with the Guidelines International Network (GIN) database currently listing more than 3,700 guidelines from 39 countries [142]. While the aims of CPG are laudable, there remain a number of challenges when developing guidelines including anxieties around a lack of transparent methodological practices, difficulty reconciling conflicting guidelines, and potential for conflicts of interest.

During a guideline’s development process, normally a panel of experts formulate recommendation questions that guide the retrieval of evidence used to inform the recommendations [143]. Typically, the final guideline will contain a description of the methods of guideline development, a summary of the supporting evidence, and a justification of the panel's decisions accompany the recommendations. To be able to use guidelines optimally, clinicians must understand the implications of the recommendations,

assess the trustworthiness of the development process, and evaluate the extent to which the recommendations are applicable to the patients in their practice settings. Helpful recommendations are clear and actionable, and explicitly specify whether they are strong or weak, are appropriate for all patients, or are dependent on individual patients' circumstances and values. Rigorous guidelines and recommendations are informed by appropriately conducted; up-to-date systematic reviews that consider outcomes important to patients. Because judgments are involved in the interpretation of the evidence and the process of moving from evidence to recommendations, useful guidelines necessarily consider all relevant factors that have a bearing in a clinical decision making and crucially are not influenced by conflicts of interest.

1.16.1

Why understanding CPGs are vital

While the importance of systemic reviews that systematically identify, assess, and summarize the current available evidence on a clinical topic are not in dispute, a criticism of many CPGs and their processes has been the lack of a substantial and rigorous methodological approach, as well as poor adherence to transparent reporting practices [144]. It is clear then, that a critical methodological quality issue in any CPG development is how best to describe the strength of the evidence underpinning any recommendations it offers.

As the stakeholders who will use guideline content, it is important for clinicians to understand the process of guideline development, and to be familiar with the resources used to assess guidelines [140]. To ensure this, clinicians must know the commonly used systems for creating guideline recommendations and for evaluating guideline quality. Critical assessment of evidence, including guideline recommendations, could be considered a core clinical skill, as much as history taking, or physically examining a patient. An understanding of CPGs should not be considered the preserve of academia. Given they are written for use in the clinic sphere, CPGS are very much ‘working’ documents intended to have practical utility.

1.16.2

CPG evidence assurance methods

To date there have been various approaches to grading evidence to inform CPG recommendations. These have been developed with the intent of offering standardized methods of evaluation. These are discussed below.

1.16.3

American College of Cardiology and American Heart Association Grading

The method employed by the American College of Cardiology and the American Heart Association (ACC/AHA) uses the letters A, B, and C to indicate the quality of evidence for a given treatment [145]. The letter A indicates that the data were derived from multiple randomized clinical trials or meta-analyses; the letter B indicates that the data were derived from one randomized trial or from nonrandomized studies; and the letter C indicates that the data were derived from expert opinions, case studies, or standards of care. These classifications are then divided into levels I, II, and III. Level I indicate that a consensus based on clinical evidence and expert opinions has found that the treatment is useful and effective. Level II is applied when there is conflicting evidence or differences of opinion, and it is further divided into levels IIa (in favour of the treatment) and IIb (the evidence and/or opinions are less well established). Level III indicates that the treatment is not useful or effective, and that, in some cases, it may even be harmful.

1.16.4

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

Another approach with global traction is that proposed by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) working group, which sets out to create more-direct language regarding the strength of recommendations (“strong” or “weak” instead of letters and numbers) and the quality of recommendations (high, moderate, or low) [146]. This system allows clinicians to evaluate more effectively the quality of clinical evidence and the applicability of current recommendations to the care of their patients.

GRADE offers a systematic and transparent approach for rating the certainty of evidence in systematic reviews and clinical practice guidelines, and for developing and determining the strength of clinical practice recommendations [147] [148]. While use of GRADE in systematic reviews is currently mandated by only a few journals, it is becoming a *de facto* standard for high-quality systematic reviews [146]. GRADE has been adopted by more than 100 organisations worldwide, including SIGN, the Cochrane Collaboration, WHO, and the UK National Institute for Health and Clinical Excellence (NICE). Within GRADE, the initial phases consist of selection of the topics and settings of interest, formulating population, intervention, comparator, outcomes (PICO) questions. Patients or population to which the question applies Intervention (or diagnostic test, exposure, risk factor, etc.) being considered in relation to these patients, Comparison(s) to be made between those receiving the intervention and another group who do not receive the intervention and Outcome(s) to be used to establish the size of any effect caused by the intervention. When prioritising outcomes the focus is on patient-important outcomes. The next stage involves systematically summarising the evidence base by conducting or updating a systematic review. This is followed by an assessment of the certainty of evidence, and for guidelines only, issuing recommendations and rating their strength, which requires consideration of multiple factors. This last step is omitted in systematic reviews. Finally, the systematic review or guideline undergoes peer review, is published, and disseminated, and, when necessary, updated accordingly.

1.16.5

Scottish Intercollegiate Guideline Network (SIGN) CPG methodology

Within the Scottish context it is appropriate for us to consider SIGN, as it serves as a significant resource of guidelines which are expected to be considered when providing care in Scotland.

Since 2012 SIGN has committed to following the principles of the GRADE methodology, as per the description in the Journal of Clinical Epidemiology (JCE) series on GRADE [148]. However, there are certain aspects of the SIGN approach that are not mandated by GRADE and will be described here. The SIGN 50, CPG methodology handbook is a 'living' publication, continually revised to reflect contemporary developments in methodology, and thus its definitive version is published on the SIGN website.

A factor likely to influence a practitioner's decision to implement a CPG recommendation is the degree of confidence in that recommendation, i.e. how certain they are that following the recommendation will produce the expected improvement in outcome for their patients, as well as encompassing other issues such as patient preferences and the availability of resources to support the use of the intervention. SIGN guidance considers both the overall quality of the supporting evidence, and the other contextual factors that might influence the strength of the recommendation.

SIGN also have a clear approach to addressing patient issues in the literature search incorporating the patient's perspective from the beginning of the development process. One of the methods employed is to conduct a specific search on patient issues in advance of the first meeting of the guideline development group. This search is designed to cover both quantitative and qualitative evidence and is not limited to specific study designs or sources of literature. The scope is deliberately as broad and inclusive as possible, encompassing the entire condition under consideration. The results of this search are presented to the guideline development group to inform the setting of key questions.

To define the key questions that comprise a SIGN guideline, the development groups break down the guideline remit into a series of structured key questions using the PICO format.

The next step in the guideline development process is to examine the body of evidence associated with each specific key question. Therefore, the guideline development group has to consider both the overall quality of the supporting evidence and the other factors that might influence the strength of the recommendation.

SIGN expects each recommendation to be based on a systematic review of the literature, and where a systematic review already exists, the guideline development group is provided with the complete review plus an evidence table summarising any more recent studies. Where there are multiple existing reviews, an evidence table summarising the findings of all existing reviews, is then provided. In considering the studies that may inform the guideline, methodological quality assessment is done in the following manner [149]. The SIGN checklist for systematic reviews is based on the AMSTAR tool [150], while that for RCTs is based on an internal project carried out in 1997. Checklists for observational studies are based on the MERGE (Method for Evaluating Research and Guideline Evidence) checklists developed by the New South Wales Department of Health [151], and the checklist for diagnostic accuracy studies is based on the QUADAS programme [152]. With this approach a degree of standardization is offered.

At this juncture the guideline development group are aware of how much evidence there is (or is not) available to answer their questions. While deliberation is likely to occur about some issues, there exists a framework of basic rules for identifying and appraising the evidence. In some instances, the best available evidence may be limited to expert opinion.

While a newcomer to the field of evidence-based guidelines may wonder what place opinion has in applying evidence, we need to consider the basic definition of evidence-based medicine (EBM). In a landmark book on EBM, David Sackett and his co-authors defined: "…the integration of best research evidence with clinical expertise and patient values" [153]. Thus, evidence has to be weighted with clinical wisdom and patient values and not created in a sterile vacuum. Accordingly clinical expertise and patient values, amongst other things, must be applied for that evidence to arrive at a recommendation that is in line with the published science, is practical to deliver, and takes account of patient preferences. A recommendation, in other words, must be both likely to be implemented and be acceptable to patients.

SIGN then makes recommendations with strength based on the work of the GRADE group in terms of Strong versus weak, which in the SIGN implementation of GRADE, is known as ‘conditional’ recommendations. On the one hand a strong recommendation is made where: there is evidence is of high quality, estimates of the effect of an intervention are precise (i.e. there is a high degree of certainty that effects will be achieved in practice), there are few downsides of the therapy and there is a high degree of acceptance among patients. On the other hand, a conditional recommendation is made where the evidence base has weaknesses in it, where there is a degree of doubt about the size of the effect that can be expected in practice. Where there is a need to balance the upsides and downsides of the therapy and there are likely to be varying degrees of acceptance among patients.

1.17

Concern around CPGS

Despite all the efforts of guideline producing bodies and guideline methodologists, a large body of literature suggests that there are still problems with CPGs. The most notable issue, that has attracted considerable attention in medical and lay press, is the effect of financial or other conflicts of interest in CPGs. [154,155] [156] [157] Financial relationships between CPG development organizations and biomedical companies are common but infrequently disclosed in guidelines. In this situation, recommendations influenced by opinions, experience, and expertise have questionable credibility, since some CPG development committees may be self-serving and this may ultimately compromise the guideline validity. Given that full transparency and disclosure is considered an integral factor in CPG production, it is disappointing to note that adequate rigour of development, editorial independence and stake-holder engagement (i.e. with patients) was seen in less than half of CPGs [158] when assessed a decade ago. The situation may not have improved ad there is persisting evidence of lack of transparency and poor stakeholder or patient involvement in CPG production [159].

1.18

Concluding remarks

I hope that in this introduction I have demonstrated the rationale for having a precise and comprehensive understand of stroke and TIA; in terms of their definitions, aetiological classifications, and clinical presentations. These definitions serve as a solid foundation by which to consider the following chapters or original research in this thesis.

Given that a central theme, alongside stroke has been on cognition it is also right that some time is taken to initially consider cognition, what it is and what its components might look like. This is to ensure a full appreciation of the work that then follows in chapter two and chapter three. For this reason, I have described in detail aspects of the comprehensive

cognitive assessment. Although as a General Practitioner I would not usually perform such a detailed assessment as described in this chapter, an appreciation of what this assessment involves helped me contextualise the guideline content. For example, one recommendation states “In aphasia use a validated cognitive tool in conjunction with speech and language therapist”. Through understanding the neuro-anatomy of language, I can appreciate what type of stroke can result in aphasia, and, given the complexity of assessment, why the use of speech and language therapist is needed.

Within the work considering stroke survivors’ experiences of cognitive assessment, the understanding of aetiologies and classifications is again germane. While patients’ experiences are inherently subjective, it is still important to consider common stroke related factors when reflecting upon their experiences. Emotions and memory are integral parts of our experiences as human beings, but they are also neuropsychological processes that can be impacted upon by stroke. This is not to detract from the experience of those who contributed their view, but it is useful to be mindful that certain types of stroke are more likely than others to impact upon memory and potentially influence recollection of the assessment process and information giving around it.

Being aware of the common aetiologies and natural histories of stroke can be invaluable in thinking about the generalizability of the subjects included in my research. For example, using the Oxford classification, one would not expect many TACS to be included in a study of stroke survivors at home, since a return home is rare in this severe stroke.

For the chapter concerning stroke and TIA clinical scoring tools, an understanding of stroke aetiologies and classifications it is again readily apparent. By their very definition, these clinical schema are composed of symptoms, signs and investigations. The appreciation of the components of stroke clinical and aetiological classification schemes allows for an assessment of ‘face validity’ and can facilitate a review across the different tools to understand features common to all tool and why some features might be unique to one tool only.

Stroke mimics as already outlined present a diagnostic challenge and result in many non-stroke referrals to stroke services. Appreciation of the complexity of stroke definitions and classifications gives some insight into why making the initial diagnosis is difficult. In this context, the benefits of accurate diagnostic tools are apparent and any aid which can more

precisely discriminate between a true stroke or TIA and its mimic, is a practical and worthwhile tool.

A theme that I will return to throughout the thesis is the need to understand the experience of assessment from the patient perspective. In this regard, cognitive and other assessments can be considered as exemplars of 'complex' interventions. In this Introduction, I have described definitions and theories of complex interventions and then used this as a basis to discuss issues around acceptability of treatment.

Finally, an understanding of CPGs and the current practices in their development and formation is necessary to cover at this juncture before we look more closely at the original research chapters which follow. This is particularly true when considering how we assess CPGs, how they relate to patient acceptability and how these are incorporated together.

Chapter two

Review of clinical practice guidelines relating to cognitive assessment in stroke

2.1

Introduction

Having taken the time to fully appreciate the current definitions of cognition, and its clinical assessment this chapter will now focus on clinical practice guidelines in relation to cognitive assessment for those patients who had sustained a cerebellar vascular insult or stroke.

2.1.1

Association between stroke and cognitive dysfunction

Stroke and cognitive decline are positively associated with advancing age [160] [161]. They often co-exist with a bi -directional relationship. Stroke is associated with a spectrum of cognitive issues, often labelled using the umbrella term ‘vascular cognitive impairment’. Post-stroke cognitive impairments are highly prevalent with estimates suggesting important impairments in almost one in four stroke survivors [162].

Despite this, our understanding of best practice in managing stroke related cognitive deficits is limited and as a result there is considerable variation in practice [163]. Cognitive problems can manifest at all stages of the stroke journey, from pre-stroke cognitive impairment, through acute cognitive issues including delirium [164], to medium and longer term cognitive issues, including overt dementia [165,166].

The importance of post stroke cognition to stroke survivors themselves is clear [167]. In stroke research, priority setting projects indicate that improving the management of cognitive impairment is consistently voted the most important factor by stakeholders including stroke survivors and their care-givers, both in Scotland and internationally [168,169]. However this might not be universal, given a Swedish study did not find this theme to be the number one priority [170].

The first step in managing stroke related cognitive problems is assessment and diagnosis. However, there is currently no consensus agreement on the optimal approach to cognitive

assessment. Cognitive assessment can be defined, as described in the Introduction, '[the] examination of higher cortical functions, particularly memory, attention, orientation, language, executive function (planning activities), and praxis (sequencing of activities)' [171-174]. The visuospatial domain of cognition may also be tested (as described in chapter one), and is highly relevant in stroke care [175].

2.1.2

Clinical practice guidelines relating to cognition

To facilitate structured cognitive assessment, there are a wide variety of tools available [176,177], ranging from very short screening tools, through to longer multidomain assessments and then tools that attempt to give a diagnostic formulation. Some assessments focus on cognitive impairment through psychometric assessments, whereas others assess cognition through functional activities There are further levels of variation as these cognitive assessments can be delivered in person, by questionnaire [178] , by video call [179] or using other IT platforms [180] . With this myriad of examination and testing options, clinicians may struggle to choose the optimal cognitive assessment [181].

In this context of an important clinical problem and multiple potential management options, clinicians rightly look to clinical practice guidelines (CPGs) to inform the care they offer. The expectation is that management decisions aligned with CPG recommendations will be evidence based and appropriate. Important stroke-cognitive assessment themes where clinicians and policy makers may seek guidance include the timing of cognitive assessment, the approach to cognitive assessment, the training and expertise required and how to communicate and use results of these assessments.

However, Guidelines are not a panacea, and the possession of a CPG label is not a guarantee of quality. Indeed, there has been recent concern about biases and other limitations in certain high-profile CPGs [182-184]. Therefore, as with any collection of applied research data, there are methods available for critical appraisal of a CPG's content. The development of the Appraisal of Guidelines for Research and Evaluation 2nd version (AGREE-II) provides a suitable yardstick to judge CPG quality [158,184].

Various international bodies and professional societies produce guidelines and the recommendations included may differ across countries, healthcare systems or professional groups. As methods for the collation, synthesis and critical appraisal of guideline content are now available, a potential useful application would be to use these methods in exploring the topic of cognitive assessment in stroke.

2.2

Materials & Methods

These are discussed in the following sections below.

2.2.1

Aim and research questions

My primary aim was to identify, compare and appraise all of the relevant English language CPGs, with content pertaining to cognitive assessment in stroke survivors.

I wanted to specifically compare their recommendations about how to perform the cognitive assessment of stroke survivors, and look for consensus or areas of disagreement. I also sought to assess the quality of those CPGs, using the AGREE-II tool. In addition, I wished to review the evidence base that informed the recommendations contained within these CPGs. Finally, I wanted to collate guidance pertaining to the important clinical questions of: how to assess cognition in stroke, who should perform the assessment, when to assess and how to use the results of the cognitive assessment.

2.2.2

Search strategy

I searched various, multidisciplinary electronic databases: Medline (OVID), Embase (OVID), and CINAHL (EBSCO) & PsycInfo (EBSCO) and both the Scottish Intercollegiate Guideline network (SIGN) and National Institute of Clinical and Healthcare Excellence (NICE) websites from March 2008 to March 2021[185].

I supplemented our literature search by liaising with international topic experts. I hand searched the websites of relevant specialist societies and guideline producers: American Heart association (AHA), European Stroke organization (ESO), Stroke Foundation (Australia & New Zealand). I also contacted relevant professional associations: British Psychological Society, British Neuropsychological Society (BNS), Royal College of Occupational Therapists, Council of Occupational Therapists for European Countries and the stroke psychology special interest group of the World Federation for Neuro Rehabilitation (OPSYRIS – Organisation for Psychological Research in Stroke). The full search strategy and syntax can be found in appendix materials as Appendix A: Clinical practice guideline search strategy.

2.2.3

Inclusion/exclusion criteria

I formulated our inclusion criteria using the ‘PICAR’ approach recommended for guideline reviews (modified from the traditional PICO for clinical question framing and focussing on Population, Intervention, Comparator, Attributes and Recommendations) [186].

I limited inclusion to English language guidance and publication within our search time window. Where more than one guideline was produced on the same topic by the same organisation, I selected the most recent publication. If a guideline was described as needing updated by the host organisation, but no update was available, and the guidance remained in the public domain then I included the CPG.

With respect to the Australian & New Zealand guidelines of 2017, which are subsequently referred to as the Australian Stroke Foundation guidelines, these have since moved to a

living guidelines model. This move was after this systematic review and analysis had been conducted. However, despite this and chapter 5 rehabilitation being updated on 28/07/2023 (v 10.1) the text does not differ from the text published on 21/11/2019 (v 5.4) with respect to the recommendations. That is within the practical points section being identical “All stroke survivors should be screened for cognitive and perceptual deficits by a trained person (e.g. neuropsychologist, occupational therapist or speech pathologist) using validated and reliable screening tools, ideally prior to discharge from hospital. Stroke survivors identified during screening as having cognitive deficits should be referred for comprehensive clinical neuropsychological investigations” [187].

2.2.4

Data extraction

Both reviewers extracted all relevant information from CPGs into a bespoke extraction form created using an Excel spreadsheet (Microsoft® Excel® for Microsoft 365 MSO (Version 2207 Build 16.0.15427.20182Version, Microsoft 2023). The following general and topic specific guideline information was extracted: publisher of the guideline, country of origin, target population, method of evidence collation, method of evidence grading, method of evidence synthesis, evidence base for the recommendation(s) as well as the recommendations.

I also pre-defined four specific areas of particular interest, namely around cognitive test to be used, timing of assessment, training required and how to use the resulting data (table 1). The extracted elements were compared to ensure both reviewers had consistent data. The master list of all verbatim extractions is available in Appendix D: All CPGs original verbatim recommendations**.**

I followed best practice in systematic review and evidence synthesis, As there is no specific protocol or guidance for CPG synthesis I used the Preferred Reporting Items in Systematic Review and Meta-Analysis (PRISMA) checklist where appropriate [188]. I registered our protocol at the Centre for Open Science [185]. The PRISMA statement can be found in Appendix B: The PRISMA 2020 statement- an updated guideline for reporting systematic reviews.

All aspects of the conduct of the review (title selection, data extraction and quality assessment) involved two researchers (DM, CM) working independently and continually comparing results. Both are clinicians and both are trained in systematic review but neither had any conflicts of interests with the CPGs reviewed. Consensus was reached through discussion with recourse to a third rater (TQ) where needed to resolve disagreement.

Table 1: PICAR Inclusion criteria for the review

PICAR element	Study specific criteria
Population, Clinical area & characteristics	Adults (>18 years old) with history of stroke, regardless of pre-existing cognitive status. Assessment could be performed in any clinical setting. Clinical Practice Guidelines will be categorised by setting and timing on the stroke pathway, defined as: Hyper-acute stroke (First 48 hours) Acute stroke (First month) Rehabilitation Outpatient Community Research
Interventions	A global cognitive assessment strategy including screening tools and tools for assessment of delirium (but not including single domain specific tools designed for a specific purpose i.e., aphasia tools).
Comparators	No direct comparators.
Attributes of CPGs	**Language:** English language or has English language version. **Publication regions:** Any. **Version:** Only the latest versions of CPGs are to be included. **Age:** From 2008-2019 inclusive ensuring only up to date practice is captured. **Development strategies**: Evidence Based Medicine approach with synthesis of published literature and other information sources and explicit evaluation of the quality of the supporting data. **Rating of evidence**: Employs a systemic way of evaluating the given evidence for recommendations. **Scope:** CPGs assessing cognition in adult patients with stroke disease. **Recommendations:** Reports on ≥1 recommendations of interest.
Recommendation characteristics	**Interventions**: Recommendations must explicitly discuss ≥1 assessment of interest. **Comparators:** Recommendations do not require to compare against cognitive testing in other groups i.e., non-stoke patients. **Confidence level:** Must describe how bias has been assessed and reduced where possible.
	Clinical considerations of interest **How to assess:** Which cognitive assessment to use. **When to assess:** Assessed by timing and setting. **Who should assess:** Which professionals should undertake these assessments and what training is required. **How to use assessments:** How should cognitive assessment inform care pathways and how should they be communicated to patients and families.

2.2.5
Quality assessment

I used the AGREE II tool to assess the quality of included guidelines [189].The AGREE-II consists of 23 items arranged into six domains: scope and purpose (three items), stakeholder involvement (three items), rigour of development (eight items), clarity of presentation (three items), applicability (four items), and editorial independence (two items) [190-192]. The AGREE-II check list can be found at Appendix C: AGREE-II Reporting Checklist.

All guidelines with recommendations on cognitive assessment in stroke were assessed at the level of each AGREE-II domain item using a seven-point scale and transferring the results to a standardized form based on the AGREE template. The scoring system was ordinal with a score of 1 (strongly disagree) to 7 (strongly agree). A combined AGREE-II domain result was calculated using an aggregated score using:

$(Obtained\ score - minimum\ possible\ score)/\ (Maximum\ possible\ score - minimum\ possible\ score)\ x100\%.$

This was done as per the AGREE II user's manuals instructions, and each domain had the same weighting [191].

Judgements on each guideline's overall quality were made by employing a standardized scoring rubric. Guidelines were of 'high quality' if they adequately addressed at least four of the six AGREE II domains, including the 'Rigour of Development' domain. To be considered as having adequately addressed a domain, a calculated AGREE-II result threshold of 50% or more had to be attained. If two or more domains were adequately addressed (or three domains except for 'Rigour of Development') CPGs were graded 'moderate quality'. CPGs where only one, or no domains reached the 50% result were of 'low' overall quality. There is currently no consensus on scoring AGREE-II data. As the topic CPGs could inform clinical practice, I prioritised the 'Rigour of Development' domain, believing that all clinical guidance should be as evidence based as was practically possible. For the same reasons, I set a high threshold for the label of 'high quality' by mandating that at least four domains be adequately addressed. My approach followed usual practice in other reviews of guidelines [193]. When interpreting AGREE-II, one should

remember that the scoring relates to the quality and reporting of the published CPG document rather than the evidence underlying the recommendations [190].

Recognising the potential for variation in AGREE-II assessments, it is recommended that all domains are assessed by at least two independent reviewers, then as an aggregate, scores are compared using the intra-class correlation coefficient (ICC). [189,194], where values less than 0.5, between 0.51-0.75, between 0.76-0.9, and greater than 0.91 are indicative of poor, moderate, good, and excellent reliability, respectively [189]. Where disagreement remained following discussion (indicated by an ICC score of less than 0.5) a third rater (TQ) made the final judgement.

2.2.6

Data synthesis

I developed matrices of guideline recommendations to facilitate systematically comparing, categorizing, and summarizing the content across, and within CPGs. Although the wording in each guideline differed, there were commonalities across the actions recommended. To allow an easily understood readily accessible summary of the guideline content, I combined and condensed the recommendations. Full text of each recommendation was copied verbatim, creating a long list of free text statements. This list was then assessed independently by DM and TQ, where recommendations suggested a common action, these were combined, and a summary text was created. This was done in an iterative process with comparison and discussion of the independent summaries.

In this manner, I adopted a thematic approach to the summary texts using a recursive method of familiarizing myself with the text summaries and identifying items of potential commonality [195]. I then generated initial codes before, searching for additional common themes. We then reviewed all the potential themes before agreeing, defining and naming them. The final condensed table of recommendations was developed using this approach. For example, using this approach ‘A full understanding of the patient's cognitive strengths and weaknesses should be an integral part of the rehabilitation plan’ from the SIGN 2010 CPG was considered equivalent to the first part of the Australian 2017 CPG recommendation ‘All stroke survivors should be screened for cognitive and perceptual deficits by a trained person (e.g. neuropsychologist, occupational therapist or speech pathologist) using validated and reliable screening tools, ideally prior to discharge from

hospital’. These were combined and simplified into the synthesised recommendation ‘Cognitive screening should be routine’.

The process continued until no more recommendations could be combined. I present these summary descriptions in data matrices, where recommendations are cross classified with guidelines and overall quality of evidence of the guideline.

The domain level quality of each guideline was collated and incorporated within a stacked polar chart. I had planned to covert the statements regarding the evidence supporting each recommendation into a standardised rubric to allow easy comparison however as all recommendations relied upon expert opinion only, I described this as a narrative instead.

2.3

Results

Figure 1: PRISMA flow diagram

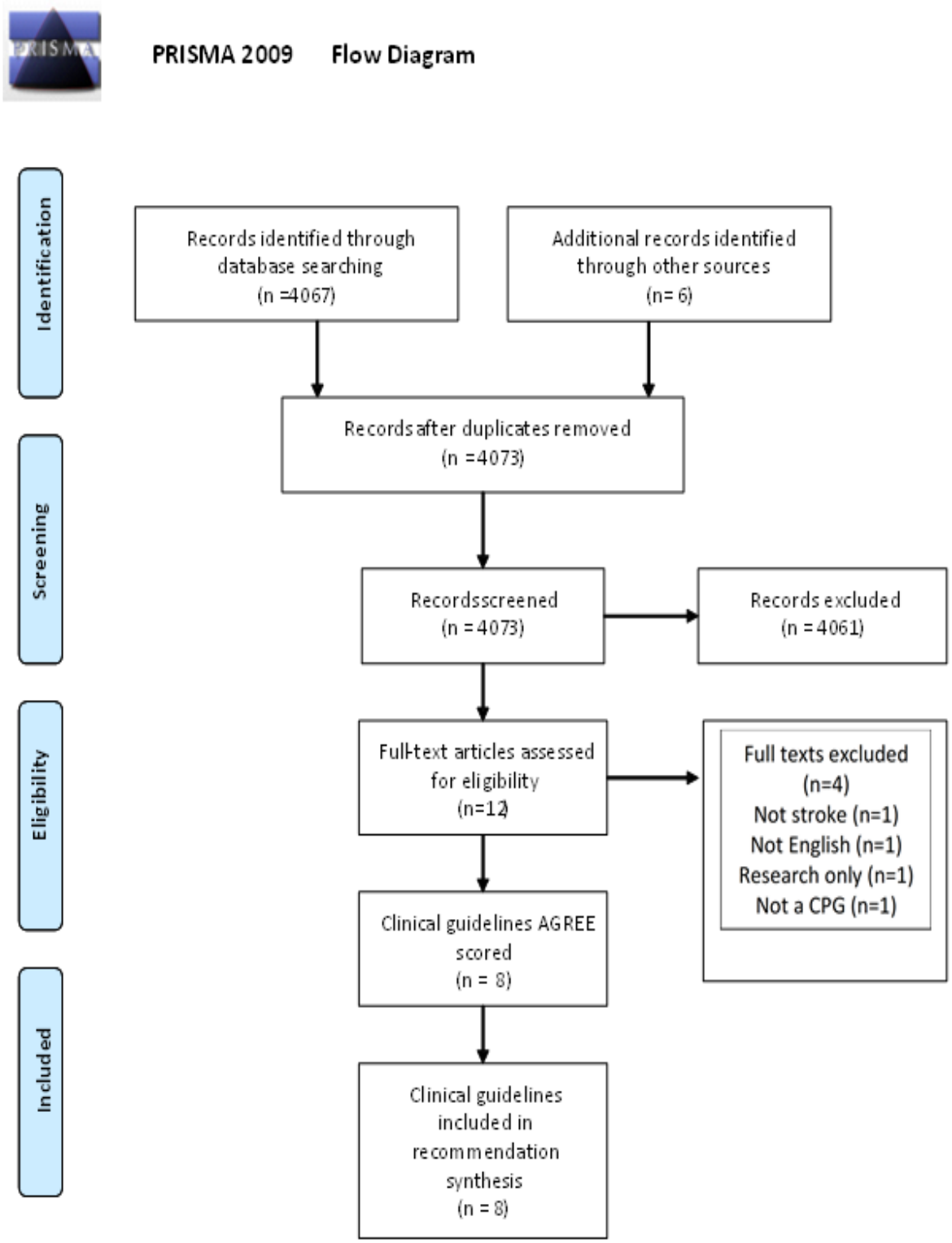


Table 2: Data extraction clinical practice guidelines

Characteristics of CPGs	RCP' 16	SIGN 118	SIGN 119	NICE 162	IHF'10	ASF'17	CSBP'19	AHA'16
Hyper-acute stroke (First 48 hours)	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Acute stroke (First month)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Rehabilitation of stroke	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outpatient stroke	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Community stroke	No	Yes	No	No	Yes	Yes	Yes	Yes
Where CPG published	UK	Scotland	Scotland	England & Wales	ROI	Australia & New Zealand	Canada	USA
Transparent method of evidence synthesis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Systematic rating of the evidence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Utilizes Evidence Based Medicine with transparent appraisal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Assess all regardless of pre-existing cognitive status	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Comment on optimal testing approach	Yes	No	No	No	No	No	Yes	Yes

Which professional is best placed to perform the assessment	**No**	**Yes**	**No**	**No**	**No**	**Yes**	**Yes**	**No**
Timing of assessment	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
How to use the assessment data	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**

Figure 2: AGREE-II scores of stroke Clinical Practice Guidelines

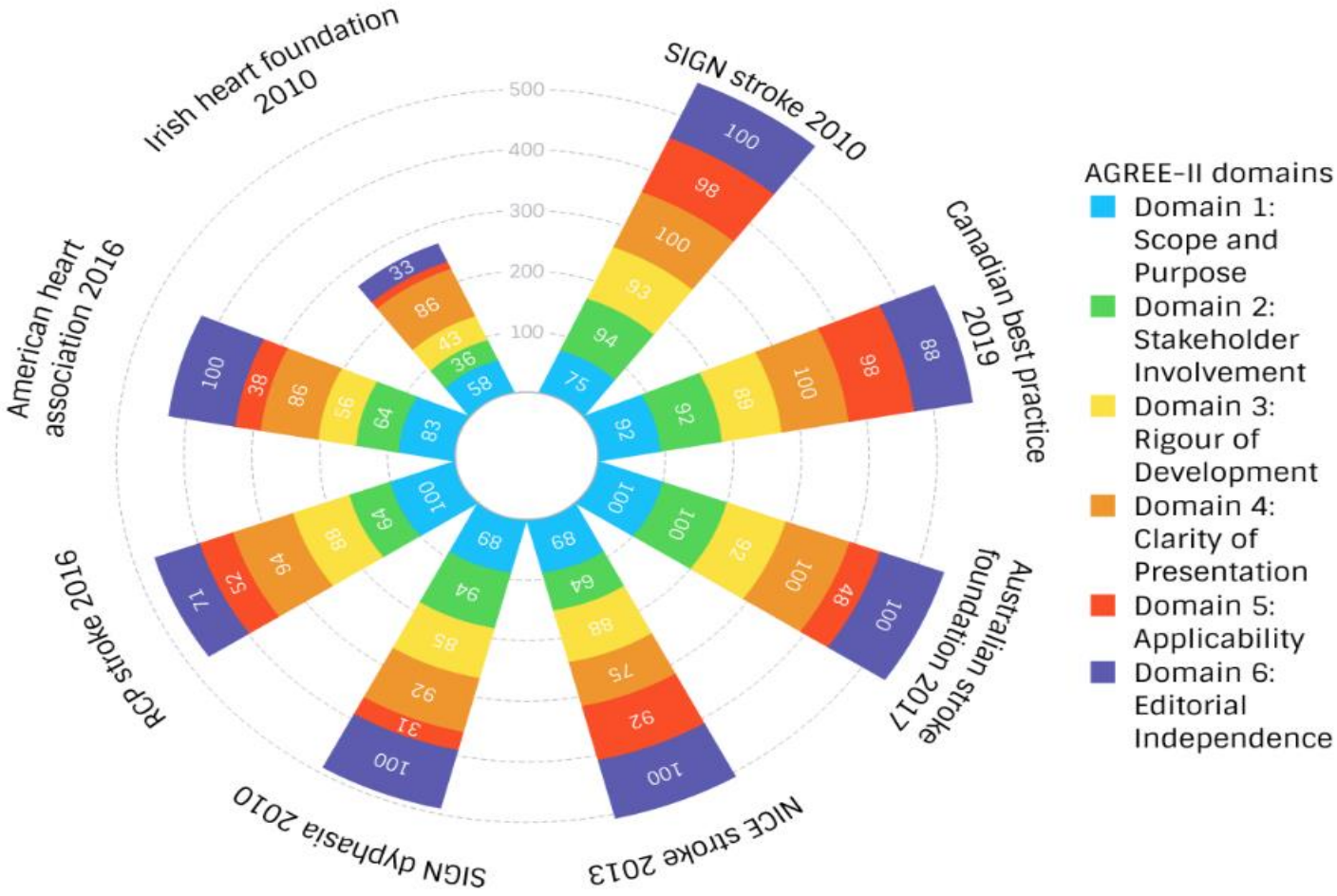


Table 3: AGREE-II scores of stroke Clinical Practice Guidelines

Clinical Practice Guideline	Rigour of development (%)	Number of domains ≥ 50%
RCP Stroke 2016	88	6
SIGN Stroke 2010	93	6
SIGN Dysphagia 2010	85	5
American Heart Association 2016	56	5
Irish Heart Foundation 2010	85	2
NICE Stroke 2013	88	6
Australian Stroke Foundation 2017	92	5
Canadian Stroke Best Practice 2019	89	6

2.3.1
Summary of CPGs

The following is a brief summary of each of the included CPGs and their recommendations as they relate to assessing cognition in stroke survivors.

The RCP is ‘an independent patient centred and clinically led organization, that drives improvement in the diagnosis of disease, the care of individual patients and the health of the whole population both in the UK and across the globe’. Within the UK Royal College of Physician’s (RCP) CPG on stroke, there is a specific section considering how to assess cognition, it recommends using a validated tool in conjunction with speech and language input in aphasic patients [196]. It also recommends assuming that all acute strokes survivors have (or are at risk of) having a cognitive impairment and that cognitive screening should be routine. Coming to when to perform these assessments, it suggests undertaking acute screening and if patients are not improving, then a more detailed cognitive assessment should be undertaken. Assessment should also be considered at the point of discharge or transfer. Further, it recommends a detailed assessment if someone is returning to cognitively demanding tasks. With respect to how to use the results of cognitive assessments it recommends using cognitive assessments to guide treatment, and the involvement of a (neuro)psychologist if severe/persisting problems continue. Finally, it also advises considering compensatory or adaptive techniques if cognitive problems are persisting.

The Scottish Intercollegiate Guideline Network (SIGN) ‘collaborate [s] with a network of clinicians, other health and social care professionals, patient organisations and individuals to develop evidence-based guidelines’. It does this ‘to improve the quality of health care for patients in Scotland by reducing variation in practice and outcome, through the development and dissemination of national clinical guidelines’. The SIGN stroke CPG 118 offers recommendations on who should perform assessments, and advocates assuming all acute strokes survivors have (or are at risk of) cognitive impairment, and thus cognitive screening should be routine in all [197]. Coming to the issue of when to perform assessments it endorses doing so if stroke survivors are returning to cognitively demanding tasks and at that juncture to undertake a detailed assessment.

Another relevant publication from SIGN is the more specific dysphagia CPG (119). This also endorses routine cognitive screening in strokes survivors [198]. Moreover, if cognitive issues are identified, then it recommends adjusting information sharing accordingly in light of the deficits, when considering how to use these assessments and their results.

The Australian Stroke Foundation CPG similarly recommends an assumption that all acute stroke survivors have (or are at risk of) cognitive impairment and that cognitive screening should be routine for these patients, with a further direction to involve a (neuro)psychologist if severe and or persisting cognitive problems are identified [187]. The Stroke Foundation is 'a national charity that partners with the community to prevent, treat and beat stroke. The association describes itself thus: 'We stand alongside stroke survivors and their families, healthcare professionals and researchers... We are the voice of stroke in Australia and we work to raise awareness of the risk factors, signs of stroke and promote healthy lifestyles, improve treatment for stroke to save lives and reduce disability, improve life after stroke for survivors and encourage and facilitate stroke research'.

The Heart and Stroke Foundation of Canada is 'a volunteer-based health charity, [it] leads in eliminating heart disease and stroke and reducing their impact through the advancement of research and its application, [and] the promotion of healthy living and advocacy'. The Canadian stroke CPG makes several recommendations in terms of how to assess cognition. It recommends using a validated tool for cognitive screening, and that this should cover assessment of both ADL and IADL within the cognitive assessment [23]. These assessments should be performed in all acute strokes survivors that have (or those are at risk of) cognitive impairment, and that cognitive screening should be undertaken routinely. It endorses performing reassessment at the point of discharge, or of transfer. Further it advises (neuro)psychology input if there is are severe/persisting cognitive problems, as well as screening for depression if cognitive impairment is suspected. It also recommends 'consider[ing] compensatory or adaptive techniques if cognitive problems persist.

The National Institute for Clinical Excellence (NICE) was legally established in 1999 to provide 'expert[ize] in evidence-based best practice and value for money'. NICE clinical guidelines cover the NHS in England, Wales and Northern Ireland aiming to 'help practitioners and commissioners get the best care to patients, fast, while ensuring value for

the taxpayer by producing useful and usable guidance for health and care practitioners, [as well as] developing recommendations that focus on what matters most and drive innovation into the hands of health and care practitioners [and] encouraging the uptake of best practice to improve outcomes for everyone. The NICE stroke CPG recommends assuming that all acute strokes have (or are at risk of) cognitive impairment, and that cognitive screening should be routinely undertaken. Much like other CPG authors it states that if cognitive issues are identified, then information sharing must be adapted accordingly. The other recommendations that NICE make relates to providing educational materials around post stroke cognition available to patients and their carers.

The Irish Stroke Foundation describe themselves: 'We work with stroke and heart patients and their loved ones to make sure their voices are heard (we are) the national charity for the prevention of heart disease and stroke in Ireland, our work involves influencing Government policy for improved patient care and the prevention of premature death from heart conditions and stroke'. The Irish stroke CPG recommends assuming all acute strokes have (or are at risk of) cognitive impairment and that cognitive screening should be routine [199]. It further recommends if patients are returning to cognitively demanding tasks then a detailed assessment should be undertaken.

The American Heart Association (AHA) and American Stroke Association (ASA) publish 'medical guidelines and scientific statements on various cardiovascular disease and stroke topics. [The] AHA/ASA volunteer scientists and healthcare professionals write the statements. The statements are supported by scientific studies published in recognized journals and have a rigorous review and approval process. Scientific statements generally include a review of data available on a specific subject, an evaluation on its relationship to overall cardiovascular disease science, and often an AHA/ASA position on the basis of that evaluation'. The AHA/ASA stroke CPG recommends routine cognitive screening in all strokes survivors and to use these cognitive assessments to guide treatment [200].

Table 4: Stroke Clinical Practice Guideline recommendations and strength of evidence

	Royal College Physicians, UK 2016	SIGN, Scotland (Stroke) 2010	SIGN, Scotland (Dysphagia) 2010	Australian Stroke Foundation 2017	Canadian Stroke 2019	NICE, UK 2013	Irish Heart Foundation 2010	AHA/ASA 2016
How to assess cognition in stroke								
Use a validated tool for cognitive screening								
In aphasia use a validated cognitive tool in conjunction with SLT								
Include assessment of ADL and IADL in cognitive assessment								
Who to assess for cognitive issues in stroke								
Assume all acute strokes have (or are at risk of) cognitive impairment								
Cognitive screening should be routine								
When to assess for cognitive issues in stroke								

If not improving, perform more detailed cognitive assessment								
At point of discharge or transfer reassess cognition								
If returning to cognitively demanding tasks perform detailed assessment								
How to use results of cognitive assessments in stroke								
Use cognitive assessments to guide treatment								
Involve a (neuro)psychologist if severe/persisting problems								
If cognitive issues identified, adjust information sharing accordingly								
If cognitive impairment suspected screen for depression								
Provide educational materials around post stroke cognition								

If persisting cognitive problems, consider compensatory or adaptive techniques								
Intraclass correlation								
	0.78	0.67	0.83	0.76	0.57	0.74	0.88	0.95

Key:

High quality guideline recommendation	
Moderate quality guideline recommendation	

2.3.2

AGREE-II assessment of CPGs

My search yielded eight eligible CPGs (Figure 1), offering 27 recommendations regarding cognitive assessment in stroke. I was able to condense these, in concert with TQ, into 14 common recommendations: three describing assessments; three describing assessment timing; two describing who to assess and six describing how the assessment should be used (table 3).

I also found four recent documents that were relevant to our question but did not completely meet our inclusion criteria: a guidance document from the Chinese Society of Geriatrics on cerebrovascular small vessel disease; a European Stroke Organisation (ESO) White Paper on cognitive impairment in cerebrovascular disease; ESO-Karolinska recommendations on cognitive assessment in stroke trials and Norwegian Directorate of Health Guidelines on stroke It is also worth considering that an ESO guideline on Post Stroke Cognitive Impairment had been in production and due for release in late 2021, after my peer review submission.

Seven CPGs were of high quality including the Royal College of Physicians (RCP), SIGN (two guidelines), Australian Stroke Foundation, Canadian best practice, American Heart Association and NICE. The Irish heart foundation CPG was judged to be of moderate quality (Figure 2).

All the included CPGS achieved greater than 50% scores in the Scope and Purpose domain. Seven CPGS achieved greater than 50% in Stakeholder Involvement and Rigour of Development. All CPGS achieved greater than 50% in Clarity of Presentation. Three CPGs achieved greater than 50% in Applicability. Seven CPGs achieved greater than 50% for Editorial Independence. The greatest variation between CPGs seen was within the Stakeholder and Applicability domains.

The strength of evidence that underpinned all the recommendations was based on expert opinion and the wording of the recommendations was created by the guideline

development groups. Where primary evidence was used to inform the CPGs, NICE guidance used indirect evidence from a Cochrane review [201] and the Canadian guidance document was partly based on test accuracy [202,203] and epidemiological studies [204]. In most other instances the guideline content was based on expert opinion.

2.4

Discussion

Despite the crucial importance of cognitive impairment in stroke, in this review of English language guidelines, I found a limited number of CPGs offering recommendations with reference to cognitive assessment in stroke care settings. By comparison recommendations pertaining to medical management and physiological monitoring during stroke featured substantially in all the national guidelines assessed. The UK national stroke audit (Sentinel Stroke National Audit Programme (SSNAP)) [205] highlights the possible disparity between 'psychological' and 'medical' aspects of stroke care. Across England, Wales and Northern Ireland the availability of access to a clinical psychologist has the lowest audit compliance of any criterion (just 12 of the 169 UK stroke centres included meet this criterion).

The CPGs which were included were generally of high quality when assessed using the AGREE-II tool, albeit there was variation across guidelines and across individual domains of the quality assessment. However, this high quality of is not synonymous with clinically useful guidance. AGREE was developed with the explicit intention of improving the comprehensiveness, completeness, and transparency of reporting in practice guidelines documents. The AGREE-II checklists are used to assess the process and content of CPGs not the evidence used to publish them. A guideline that concludes 'more research is needed' could score highly using the AGREE-II tool but fail to be of much use in clinical practice.

Where guidance had been offered in our eligible CPGs, there was consensus that post stroke cognitive impairment was a common disorder and that it should be assessed as part of routine clinical care. I had pre-specified important clinical questions for planning stroke cognitive assessment with the aim of using the CPGs to answer them. While the guidelines provided content on these themes, the recommendations were often highly generic rather than explicit and detailed and so there was little which could be implemented by clinicians. As an example of this vagueness, only one CPG named a preferred assessment tool to use to detect cognitive issues i.e. the Montreal Cognitive Assessment (MOCA). Some of the others recommended using a "validated tool" (an undefined concept), while other CPGs provided no elaboration whatsoever and a few others gave tables or appendices of various possible assessments in their supplementary data. The vague nature of guidance offered was not unique to any one country or guideline producing body, rather it was common issue to all the guidelines I assessed.

Underpinning all the relevant recommendations was a lack of high-quality study trial evidence, and in its place a reliance upon expert consensus instead. To be clear this is not a criticism of the CPGs, as on the important matter of post stroke cognitive assessment clinical trials are generally lacking, and this situation is not unique to post stoke cognitive assessment alone either. Other important aspects of stroke care such as the management of aphasia often rely on expert consensus as definitive original research studies are limited, albeit the situation is slowly improving with important new trials being recently completed or that are ongoing [206]. In the context of a rapidly evolving evidence base, CPGs need to promptly incorporate new data. I noted that during my searches some guideline producers are moving to a 'living' guideline approach. This is an approach whereby the evidence is scanned regularly, and recommendations updated as soon as required by the new research in an effort to ensure the highest validity.

Despite the critical importance of cognition in clinical practice, stroke guidelines are not alone in offering vague recommendations about cognitive assessment. Even in those conditions with a perceived 'cognitive focus' such as dementia and delirium the guideline bodies i.e. SIGN [207], NICE [208] and the RCP [209] are all equivocal in their recommendations about which cognitive assessment should be used by the clinician [207].

Unlike in stroke, lack of primary research is less of a challenge, as systematic reviews and meta-analyses of various cognitive screening tests are available [210,211].
It should be born in mind however that the availability of a CPG with clear, evidence-based and useful recommendation is not a guarantee of its implementation. There are well described practitioner barriers to clinician engagement with guidelines. A full discussion of the various barriers and facilitators to implementation is beyond the scope of this chapter, but important factors to consider include: time, access and ease of understanding the guidance and supporting evidence [212] [213]. In this sense, more systematic reviews of CPGs, with summaries and critique of the CPG content, may help clinicians make sense of contentious areas of practice.

The CPG recommendations I have included were all based on expert opinion, which within many guidelines rating schemes is often considered the lowest form of evidence. Using randomised methods to inform practice in use of a test strategy is uncommon, although novel research designs are emerging. While there are examples of both systematic reviews and meta-analyses of the properties of cognitive tests in stroke [181], the classical test accuracy paradigm of comparing a test to a 'gold' or reference standard is only partly helpful in clinical practice. More sophisticated methods involving comparative test accuracy; test-treatment-outcomes and incorporation of user experience are needed if the next iterations of guidelines are to offer more concrete and purposeful recommendations [214].

While more evidence is always to be welcomed by the clinician perhaps it is not for any CPG to mandate a particular protocol towards cognitive assessment. The choice of approach to assessing cognition will vary, fittingly, based on the person to be assessed, the particular clinical question to be answered and the resources available. A degree of clinical judgement will always be required, and CPGs should function as a source of guidance rather than be seen as a standardised operating procedure. However, few would argue against the need for more primary research on cognitive assessment in stroke so that clinicians can adjust their approach in a patient centred manner cognisant of the evidence-base to their chosen approach.

2.5

European Stroke Organisation (ESO) CPG

The recent joint European Stroke Organisation (ESO) and European Academy of Neurology (EAN) guidelines on post-stroke cognitive impairment (PSCI) provide recent evidence based CPG recommendations on this [215]. This GRADE produced CGP found no evidence regarding routine cognitive screening following stroke, but recognized the importance of targeted cognitive assessment. Of the three PICO questions it framed, 1. Does cognitive screening increase the detection of later cognitive syndromes in clinical practice; 2. Does cognitive screening change subsequent care pathways; and 3.does cognitive screening translate into health economic benefits. They found relatively few papers that assessed whether cognitive screening made a difference to patient care pathways or outcomes, and no trials that described outcomes relating to diagnosis or the components of stroke care. As a consequence they recommended 'Due to a lack of relevant trials in patients with stroke, there is continued uncertainty over the benefits and risks of routine cognitive screening to improve stroke care on an quality of evidence rated as Very low. Likewise describing the accuracy of the various available cognitive screening tests, they found no clear superior approach to testing and nor was there much evidence on the use of prediction tools for post-stroke cognition. This recent ESO CPG perhaps not surprisingly underscores many of the same issues that I encountered when reviewing the guidelines about clinical assessment of cognition in stroke. The prevailing use of low grade/ weak strength recommendations in CPGs despite robust processes for guideline development. Correspondingly, the reason this is the case is that there are few high quality primary research studies, or corresponding systemic reviews upon which to base these recommendations. Set against this backdrop no recommendation could be of particularly high strength or confidently very specific. This CPG also found no clear superior cognitive screening test approach echoing my findings.

2.6

Strengths and limitations

My search strategy was robust and with iterative steps, ensuring as much relevant literature was captured as possible. I followed best practice in evidence synthesis, with all steps performed independently by at least two trained assessors. While neither of the assessors were experienced guideline producers, as consumers of guidelines in clinical practice both had a working understanding of what fellow clinicians need from CPGs. I used various approaches to data visualisation, taking data that exist across several axes and creating an easy to understand at a glance synthesis suitable for clinicians, researchers and policy makers alike.

Some weakness of this work includes only capturing English language CPGs. Thus, the guidelines have an Australasia, North American, UK and Ireland focus. I suspect guidelines from other countries, especially low- and middle-income countries may look quite different. I limited our review to only one aspect of the management of cognition in stroke, namely assessment. A scoping of the literature suggests that a review of treatment options in post-stroke cognitive impairment may be equally limited by a lack of primary research. To aid data visualisation and summarising of the CPG text, I collated and condensed recommendations. In doing this I tried to preserve the meaning and nuance of the original text, but it is possible some information could have been lost. Some CPGs included in our synthesis were described as out of date by the host organisations. In the absence of any new version of these materials I still included these CPGs in our review.

2.7

Implications for practice, policy and research

The motivation for this review was the perceived inconsistency in clinical approach to cognitive assessment in stroke. The review of guidelines does not suggest a preferred

strategy to cognitive assessment. There are a multitude of cognitive assessment tools, and it is unclear currently which one is best; this is an area that could benefit from greater standardisation [216]. The current lack of consensus among CPGs highlights the uncertainty in the clinician community. While it may not be possible or appropriate to give prescriptive guidance on the choice of cognitive assessment, recommendations on timing of assessment, training of assessors and modifications to assessment strategies for patient groups could inform clinical pathways and ultimately improve patient care. In addition to standardising care, CPGs have an important role in bench marking best practice and clear guidelines around cognitive assessment may help improve the visibility, and raise standards in cognitive assessment. A useful next step would be to ask the clinical stroke community what they would want to see in future CPGs around cognitive assessment.

The AGREE tool results suggest that guidelines in the stroke cognition space are produced to a high quality. Although there is still scope to ensure further stakeholder involvement in production and greater consideration of the barriers and facilitators of implementation of the guidance given that these were the domains with the greatest variability across the CPGs. In line with other quality assessment tools, there may be an argument for adding a further domain to AGREE to allow assessment of clinical relevance of the guidance. By developing a "clinical recommendation" quality assessment domain it might be possible not only to drive up reporting standards in clinical guidelines, but to also begin to comment on the inherent clinical utility of the guidelines recommendations.

2.8

Conclusions

While over the last decades stroke care has advanced hugely, it remains the case that some elements of stroke care are better considered and better evidenced than others. Explicit guidance on hyperacute stroke therapy, underpinned by robust primary research has transformed stroke care and patient outcomes. At present the assessment of cognition in

stroke is lacking useful guidance, however this partly reflects the availability of original research in this area. Where recommendations are available, the guidelines tend to be of high quality but may lack clinical utility. Given the myriad of stroke cognitive presentations, clinician variation in management and differences in healthcare settings prescriptive guidance on the exact approach to cognitive testing may not be suitable. Clinical guidelines are just that, guidance and are not a substitute for clinical judgement or consideration of patient preferences. However, further primary research on cognitive assessment would allow the next iterations of guidelines to offer a stronger evidence base that could hopefully improve the approach to assessment. The recent ESO guideline makes clear that this remains a current gap in the landscape.

Chapter three

The acceptability of post-stroke cognitive testing through the lens of the theory of acceptability, a qualitative study

3.1

Introduction

Having looked at cognitive assessment from a clinician perspective now we turn to it from the patients' perspective in this chapter, and consider their vista in this work. I shall do this using a thematic analysis of data from interviews with stroke survivors.

3.1.1

Cognition impairments after stroke

As has already been outlined in prior chapters cognitive impairments post stroke (PSCI) are common and by some metrics reported to affect approximately 30% - 60% of people in the first year after stroke [165]. Despite the huge morbidity and ongoing lifelong impacts on patients, the optimal way of assessing and managing these conditions remains unclear. This can partly be explained by the underlying mechanisms of post-stroke cognitive impairment being incompletely understood, but which are known to include structural, biological, behavioural, and social factors [217].

Having spent the preceding chapter considering cognitive assessment from a clinician centric stance, now I consider it from the stroke survivors' optic. It is important to be mindful that priority setting exercises within stroke research indicate that improving the management of cognitive impairments is consistently conveyed by stroke survivors themselves (and their caregivers) in Scotland, and also in the wider UK as imperative to them [168,218].

In this context, many CPGs recommend screening for cognitive issues following a stroke [197,217,219]. This is due to both the high prevalence of cognitive deficits in stroke survivors and also their potential impact on rehabilitation, hospital stay, quality of life and

mortality [176]. On the other hand cognition and memory (and its sufficient assessment) are recognised as being vital to stroke patients themselves [167] [220,221]. The acceptability of cognitive assessments in stroke remains less researched than other aspects of stroke assessment, as recently demonstrated by the ESO CPG [21]. Yet consideration of the patient experience, and using this to inform practice is now considered best practice [222], and is in alignment with the recent shift in healthcare systems towards person-centred healthcare globally from Europe, Australia and the United states [223] [224] [225].

3.1.2

Person-centred healthcare and acceptability

As previously described (person-centred care) or patient centred care involves treating participants as individuals and as partners in the business of their healing [121]. It is the provision of care that is personalised, coordinated, and enabling. Person-centred care has been shown in many settings and contexts to enhance adherence to treatment plans [122] [123], improve health outcomes and increase participant satisfaction with healthcare services [124] [125], therefore consideration of person-centred care is now a priority for professional societies and policy makers in many countries including the UK and elsewhere in Europe [113] [114] [115].

Enhancing the acceptability of interventions and healthcare more generally is a key part of delivering person-centred healthcare. Alongside the drive towards person-centred healthcare, there has been an increasing interest in how to more clearly define acceptability of healthcare interventions [226] [110], as until recently, ‘acceptability’ was a commonly used term that lacked a precise definition.

Acceptability as a medical concept and as an integral part of healthcare has evolved since the earlier descriptions in the 1960s. Acceptability is not an objective entity, rather it is a complex subjective experience(s) likely influenced by many factors. Acceptability can be thought of as encompassing user satisfaction with a service, which is often considered a valid assessment of service quality in its own right [227]. In addition, acceptability

encompasses the services' conformity to the wishes, desires and expectations of those service users and relevant members of their families.

The inherent complexity of the concept of acceptability is reflected in Sekhon et al's theoretical framework of acceptability (TFA), which was designed to address a lack of theoretical foundation to the concept of acceptability in the healthcare setting [110]. They analysed systematic reviews that define and theorise acceptability of healthcare interventions and using the principles of inductive and deductive reasoning, and synthesising these they created a conceptual framework and middle-range theory. Thus, they define acceptability as the content, context and quality of care received from the patient's perspective and from the perspective of healthcare providers, whereby low acceptability may have an impact on the overall effectiveness of the intervention.

Having developed two versions of a framework to understand acceptability [110], the initial constructs described in version 1 were revised iteratively to reduced overlap between themes and create version 2. The final theoretical framework of acceptability (version 2) consists of seven constructs that influence the acceptability of interventions: 1) Affective attitude, defined as how an individual feels about taking part in an intervention; 2) Burden, the perceived amount of effort that is required to participate in the intervention with a focus on any associated 'work' (e.g. time, expense, or cognitive effort); 3) Perceived effectiveness of the intervention, defined as the extent to which the intervention is perceived as likely to achieve its purpose; 4) Ethicality, the extent to which the intervention has good fit with an individual's value system; 5) Intervention coherence, the extent to which the participant understands the intervention and how it works; 6) Opportunity costs, the extent to which benefits, profits, or values must be given up to engage in an intervention; 7) Self-efficacy, the participant's confidence that they can perform the behaviour(s) required to participate in the intervention

Whilst there is a growing interest around the acceptability of screening tools in healthcare settings, there is a lack of robust and generalizable research on the topic across many clinical fields, not just in stroke [110,226].

In this vista of few landmarks, other studies have used the theoretical framework of acceptability to understand patients' perspectives around the acceptability of interventions, for example one study directly compared anticipated and experienced acceptability in a population receiving a text message-based intervention to encourage medication adherence in people with type 2 diabetes [228]. Here a survey to ascertain the acceptability of messages to people with type 2 diabetes to help manage their condition found the mean scores for behaviour change techniques (BCT) had an overall acceptability median rating of 3.49. The authors reported this as being 'over the midpoint' of the acceptability scale they employed.

While another study used a methodological approach more similar to the approach outlined in this chapter, employing qualitative interviews which then underwent inductive thematic analysis [229]. This yielded six themes that they subsequently mapped onto six of the seven TFA constructs. Taken together the authors found that nurse-delivered reviews were acceptable to patients with inflammatory rheumatological conditions.

3.2

Aim and research questions

In this study I sought to use the theoretical framework of acceptability (TFA) developed be Sekhon et al as a structure to understand the experience of in-hospital cognitive assessments from the perspective of stroke survivors [226].

Using the TFA, as a previously developed and robust tool designed to assess what influences acceptability, I apply it here as a framework to understand what factors make cognitive assessment either acceptable or unacceptable to stroke survivors. This was to give voice to stroke survivors themselves about what makes a complex healthcare intervention, in this case cognitive assessment, acceptable to them. The framework analysis approach I used is detailed in the following sections below.

3.3

Methods

I describe the methods of this study in the following section which comprised of who was eligible to be recruited, how they were recruited and the methods of data gathering and analysis.

3.3.1
Eligibility

This study involved analysis of interviews with stroke survivors. Adult stroke patients admitted to hospital in Greater Glasgow and Clyde were included if they were over 18 years and were able to provide informed consent. Those with severe aphasia, those unable to speak English, or who were too unwell to participate were excluded. There was no set upper age limit. Only those under investigation for the clinical suspicion of stroke were included, therefore people admitted to stroke wards with primary non-stroke diagnoses were excluded. Eligibility was inclusive of all strokes i.e. both ischaemic and haemorrhagic stroke types. Recruitment was terminated when it was felt that data saturation was achieved, which I defined as when no new themes emerged from the data and interviews from further participants were unlikely to generate new themes or novel data.

3.3.2
Ethics

The study was approved by the Proportionate Review Sub-Committee of the Northeast - York Research Ethics Committee and ethics approval had been obtained for all participant sites (REC number 16/NE/0178) V1.0 10/05/16.

3.3.3
Interviews

Sampling was sequential, with a two-stage consent process. At point of discharge from hospital, either just before discharge or at early follow-up, eligible stroke survivors were approached by the clinical team regarding the study. Written consent was sought to allow the qualitative interviewer to contact them and provide a more detailed description of the study. If after this second contact the person was still keen to participate, a convenient time was organised to take written consent and to conduct the interview at the survivor's home or other chosen interview venue.

The semi-structured interviews were all conducted within one to three weeks of discharge from hospital. This was the case for all participants. The interview schedule is available for review in appendix E: Interview schedule. The interviews took place from May 2017 to March 2019. Interviews explored the participant's experience of cognitive assessment. The TFA was not used to create the interview topic guide but rather was used in the analysis. Instead, a template of questions was used, such as 'when were you asked cognitive questions', 'what questions/assessment was used', 'was the purpose of the assessment or results explained to you'. We also sought to capture how they reacted to the assessment, and how it made them feel at the time with the focus on the acceptability during the inpatient assessments. Each participant was interviewed once, and some had family members in attendance during the interviews.

Interviews were audio recorded and then transcribed verbatim by a third-party company ‘Small Biz Transcripts’ (9 Valleyfield, Milton of Campsie, Glasgow G66 8HN). This was then checked by two typists. I then reviewed theses final transcript drafts against the audio files to verify them authenticity and fidelity. I then used the patient’s case record to find out their age, sex, length of stay and stroke type.

3.3.4

Analysis

A mixture of both inductive and deductive methods were used in the analysis [230] [231]. Given the paucity of studies in the field I determined that utilising the TFA as an existing theory in the literature, would help contextual results but not restrict or obscure what stroke survivors themselves said. Emerging data was used inductively to yield codes, while the TFA was deductively considered to reflect how the ‘bottom up data’ might align with TFA [232].

Prior to the analyses, I adapted an initial template framework based on the TFA. This framework was continually adapted and refined as analysis progressed to truly reflect the emerging data, i.e. the data created their own themes and were not forced into any existing categories of the TFA.

The Framework Method was developed by researchers, Jane Ritchie and Liz Spencer, at the Qualitative Research Unit at the National Centre for Social Research in the United Kingdom [233] [234]. Its defining feature is its matrix output: rows (cases), columns (codes) and ‘cells’ of summarised data, providing a structure into which the researcher can systematically reduce the data, in order to analyse it by case and by code.

It arrives at these output codes as analytical output by going through the five stages. The first stage is the familiarisation with the interview were becoming acquainted with the whole interview using the audio recording and/or transcript and any notes that were

recorded by the interviewer is a vital stage in interpretation. Integral to this is having a good quality audio recording which should, ideally, be a *verbatim* (word for word) transcription of the interview is needed. This process then allows for coding to be undertaken**,** applying a paraphrase or label (a 'code') that describes what is interpreted in the passage as important.

The next stage is identifying a working analytical framework, which occurs after coding the first few transcripts, all researchers involved compare the labels they have applied and agree on a set of codes to apply to all following transcripts. Sometimes codes can be grouped together into categories (i.e. such as in a tree diagram). This forms a working analytical frame, which likely will undergo several iterations

Once this stage is complete the data is then charted into the framework matrix. Cognisant that qualitative data are capacious data management and summarizing is crucial and yields a matrix spreadsheet where the data are 'charted' into a matrix. Charting involves summarizing the data by category from each transcript, being mindful of the need to strike a balance between reducing the data on the one hand and retaining fidelity to the original meanings.

The next stage is mapping were by using the previous charting and summarization matrix, the researcher can start grouping both themes and research participants. Themes can be grouped into higher level categories. While research participants can be grouped into higher level typologies based on their similarities and then the researcher can analyze how those typologies and categories interrelate, and begin to map linkages between them.

The final stage is interpreting the data using a gradual approach that characterises the differences between the data and which may well generate typologies, the interrogation of theoretical concepts (such as those emerging from the data) or indeed the mapping of connections between categories to explore relationships and/or causality which may have emerge during the analysis.

Here in this framework Method that, unlike quantitative research where data collection and data analysis are strictly sequential and mutually exclusive stages of the research process, there is to a greater or lesser extent depending on the project, an ongoing interplay between data collection, analysis, and the theory development [234].

Consequently data were coded using the framework described above, and then the resulting codes were connected to identify the main themes from the data. These broad themes were then further clustered into overarching themes. The theoretical framework of acceptability (TFA) was continually and iteratively used as a tool for the interpretation of the themes; only those components of the theoretical framework of acceptability that showed concordance with the data were used. No components of the TFA were discordant with the emergent data. In this iterative process DM coded and analyzed the transcripts several times with a second, experienced qualitative researcher KG. The qualitative analysis program NVivo 12 (2018) was used simultaneously, as well as a 'pen & paper' approach, to analysis the transcripts and distil codes and themes from the transcripts as described above. As a final quality assurance step to sense check the coding, the draft results were shared with DD for review and comment. Some of the manual coding process is included in Appendix F: Manual coding process. Recruitment was stopped to allow a first pass analysis. After the first analysis it was felt that data saturation was achieved as no new themes were emerging and interviews from further participants was unlikely to change this.

Finally, when the ultimate consensus themes emerged as a quality assurance measure, I then began to map these back onto the TFA framework. I achieved this by looking for each construct or constructs which had the best fit to the data arising from the analysis. I carefully compared each construct and its definitions and essence to ensure the fidelity of that construct to each theme. I did this until each theme and construct had been optimally matched to its TFA. Thus, each theme was naturally aligned and allocated to their synonymatic TFA correspondent. This was achieved by me reviewing each theme in a continuous manner and iteratively identifying its closet TFA construct based on the natural data and careful consideration of the nucleus of each TFA.

3.3.5

Diagrammatic illustrations

I used Venngage Inc infographics to create a visual mind map of the major themes which emerged from the data and the associated sub themes using colour to denote these differences, and also their relationships to underscore what emerged from the analysis and attempt to show their linkages.

I again employed Venngage Inc to produce an infographic which demonstrated how these novel themes of acceptability were yielded from the analysis; and their alignment relationship to the TFA, and its constituent parts. Here, I was mapped my theme findings as they naturally aligned within the TFA, but also demonstrate their overlap and intersectionality between the TFA spheres themselves, and also between the themes themselves.

I also captured some of the socio-economic and geographic characteristics of participants using their post codes to cross reference with the Scottish index of multiple deprivation (SIMD) [235] and assign a deprivation score. The SIMD is a relative measure of deprivation across 6,976 small areas (called data zones) [236]. Areas identified as ‘deprived’ can relate to people having a low income, but it can also mean having fewer resources or opportunities across seven domains including: income, employment, education, health, access to services, crime and housing. SIMD ranks data zones from most deprived (ranked 1) to least deprived (ranked 6,976). Scotland is divided into 6,505. Data Zones each containing around 350 households and a mean population of 800 people [237]. This visualisation helped to better understand this sample and examine if there was a spread of Social-economic status.

As a data visualisation, I created a modified map taken from the Scottish Index of Multiple Deprivation website [235]. To this I overlaid the participants locality so as to give a degree

of socio-economic and health context to each participant, but without identifying their individual details. This is to demonstrate the contexts in which their lived experiences are forged and emanate from, as it is highly likely relevant in understanding their experiential circumstances.

3.4

Results

Table 5: Demographic data table of Participants & stroke characteristics

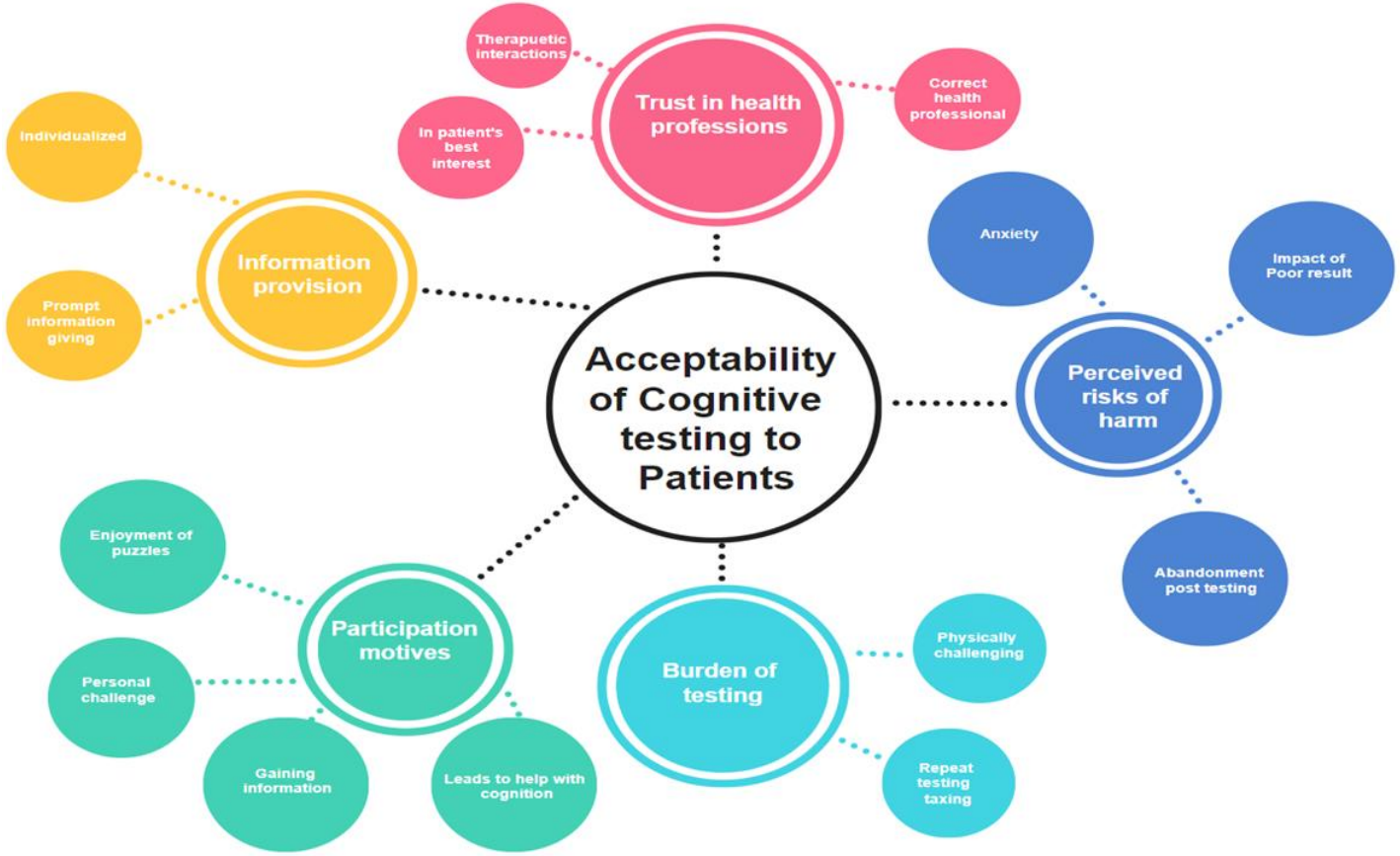
Participant	Sex	Age at event	Decile (SIMD)	Stroke syndrome at time of recruitment
1	**M**	**79**	**9**	**Left occipital lobe infarct**
2	**M**	**84**	**10**	**Left lacunar infarct**
3	**M**	**81**	**1**	**Left hemisphere infarct**
4	**F**	**73**	**2**	**Multi-focal posterior circulation infarct**
5	**M**	**81**	**2**	**Right lacunar infarct**
6	**F**	**75**	**6**	**Right hemisphere infarct**
7	**M**	**78**	**1**	**Frontal lobe infarct**
8	**M**	**62**	**9**	**Left hemisphere infarct**
9	**F**	**79**	**2**	**TIA**
10	**M**	**75**	**7**	**Right hemisphere infarct**
11	**F**	**63**	**10**	**Left lacunar infarct**
12	**M**	**63**	**7**	**Left hemisphere infarct**
13	**F**	**76**	**1**	***Clinically suspicion stroke but after full investigation diagnosis *Probable seizure***

Thirteen participants were interviewed. Interviews lasted between 16 and 57 minutes with the median length being 23 minutes and the Interquartile Range (IQR) being 16minutes, and so exhibiting a range of 41 minutes. These were calculated from a data set of 23, 36, 32, 21, 16, 23, 19, 20, 42, 21, 25, 57 and 37 minute interviews. If an interview lasted greater than 30 seconds, it was rounded up to the nearest whole minute i.e. 4:28 was recorded as 4 minutes long and an interview of 6:34 was recorded as 7 minutes long. After the consensus coding themes arrived at by KG and myself, the final codes where shared with DD the interviewer who reviewed the code findings to ensure fidelity to the interviews.

Demographic characteristics of the cohort are reported in Table 5, while in Figure 6. a map describing the geo-social and economic 'landscape' of the participants is given. Where this SMID shows areas with deeper red it indicates data zones of highest deprivation. Those areas with deeper blue denote the most affluent data zone communities. This figure helps us to visualise the spread of socioeconomic status in the sample and the geographical spread within the locality (Greater Glasgow and Clyde).

Five themes were identified that describe the factors that influence acceptability of cognitive screening from the patient perspective: 1) participation motives; 2) trust in health professionals; 3) perceived risks of harm; 4) information provision; 5) burden of testing. These will be described in turn. The themes are described individually, but there was substantial cross-over of component concepts.

Figure 3: Scheme of Acceptability of cognitive testing to participants-A graphical representation of themes and subthemes



3.4.1
Summary of main findings

Five themes and fourteen subthemes arose from the data. The five themes were: trust in health professionals, information provision, participation motives, the perceived risk of harm that assessment would have for those stroke survivors and burden of testing.

Through stroke survivors' own voices, it was clear that trust in health professionals was a fundamental facilitator of the acceptability of cognitive assessments. Survivors spoke about their trust that the correct professional was administering and scoring the cognitive assessment, with all survivors concurring that anyone within the multi-disciplinary team (MDT) was able to reflect on the results and implications to them, whether or not it was an occupational therapist, physiotherapist, psychologist, nurse or member of the medical team. Trust was enhanced by participants believing that the cognitive assessments were in their own best interests, and this helped them engage with the process. The relationship between the health professional and stroke survivor endowed a therapeutic benefit beyond just the perfunctory nature of the assessment and likely enhanced their acceptability also.

The participants expressed motives for taking part in testing which influenced acceptability for them. These included it furnishing themselves, and health professionals, with more information about their cognitive state and their stroke, 'knowing' was important to them. Once this information had been obtained stroke survivors wanted it to be used to provide support with their cognition needs, if these were indeed identified. For others the assessment was viewed as a 'puzzle' which they enjoyed tackling and solving. It could be that assessments provided them with a timely distraction to occupy their time. Lastly, overcoming a personal challenge or successfully undertaking and completing an assessment was also a motive for participation.

Stroke survivors spoke about issues around the perceived risks of harm of performing cognitive assessment. One issue was the anxiety that stroke survivors would experience if they received a poor result with some wondering if this may signify a significant memory deficit or even 'dementia'. Participants reported this as having a potential impact on both

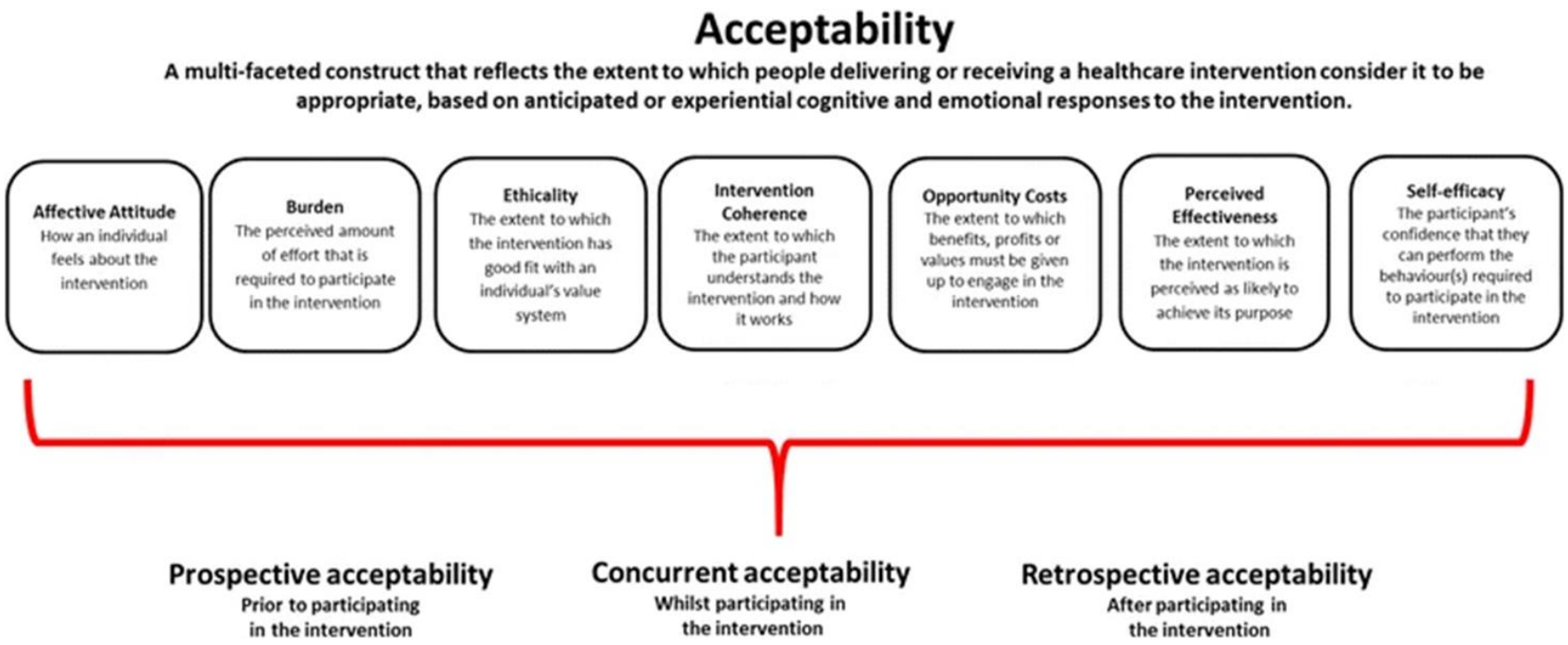
rehabilitation and mood. Another was the sense of abandonment, with the concern that if after testing they received a poor result or a deficit was discovered, they would then not have the support they felt they needed.

Participants were concerned about the burden of testing. This included the physically demands of being able to participate in cognitive assessments, especially with the written and drawing elements, a particular issue for stroke survivors with post-stroke issues such as hemiplegia, or pre-existing functional impairments. The other aspect they raised was the mental taxation that repeated assessment had upon them, and how this negatively impacted upon the assessments' acceptability and so their engagement with assessment.

Information provision was an important theme. Participants reported the need for prompt information giving to them soon after the assessment had been conducted. They also emphasized the need for individualized information provision.

Below in each main theme, I have provided quotes which support. Also included are further sub themes within the main theme, shown in italics, and above example quotes supporting it. It should be noted that sub themes may not be applicable to all the quotes and are therefore shown only were this is the case.

Figure 4: The theoretical framework of acceptability (TFA), and its seven constructs



3.4.2

Participation Motives

Participants expressed a range of motives which contributed to their perception of acceptability of cognitive assessment. Some participants described concerns about their own cognitive gaps and deficits and hoped and/or were motived by the belief that help could be provided for them if they participated in testing and these deficits were identified (see Figure 3: Scheme of Acceptability of cognitive testing to participants).

Lead to help with their cognition

> ***"I feel as though my memory's no' as sharp now. I… you know, I… that. So I want… I want all the help that you can give me"*** ***Participant 2***

Most participants displayed an understanding of the purpose of the cognitive screening, to identify issues, and also had an understanding that this would be beneficial in terms of grading the severity of their stroke related deficits. Thus their motive was an understanding of the healthcare team's motives for testing. Patients thought this assessment would assist in planning how stroke treatments generally would proceed for them in a tailored way.

The concept of cognitive assessment as a 'test' which looks at the brain and how it works, and how the stroke might have affected these workings, was almost universal in participant responses, see Figure 2. Thus, cognitive testing was rationalised as part of the battery of assessments that should be expected for all stroke patients in hospital.

Gaining information

"I thought it was part of their job, and they are trying to find out what was wrong with me...to see how far on I was, because...there's different degrees" Participant 3

Some viewed it as part of the routine treatments with little difference to the other parts of stroke care. This prevalence of view of it as a routine and expected part of stroke care was universal. One participant even liked it to a blood pressure or glycaemic check, such was the routineness that pervaded our cohort.

"But I thought, 'well, it's just one of the things they do,' like coming every couple of hours to take your blood pressure..." Participant 9

Some individuals likened participating in testing to a game or puzzle. Their prior experiences of participating in such puzzles and amusements was cited as a reason to engage or not engage with the testing, with familiarity and liking puzzles a motivating factor to participate. For these people it was a source of entertainment in hospital at a time when other activities could be limited. .

Enjoyment of puzzles

"I was quite enjoying it. Pass the time" Participant 4

Some people directly cited cognitive testing as a personal challenge in which to test themselves. It was something they could engage with, and taking part in the process brought satisfaction, allowing them to draw on their prior skills and experiences to meet the challenge. See Figure 2 under the sphere of participants' motives.

Personal challenge

> ***"And I told them… if you go tae an exam, read the paper, turn it over, and she says, "How do you know that?" I says, "I got taught that many years ago."***
>
> ***Participant 5***

3.4.3

Trust in health professionals

Relationships and trust were a major theme that many participants relayed as influencing their participation in testing. All those asked had an understanding that the cognitive testing had been performed by the correct and appropriately trained individuals (See the trust in healthcare professions sphere Figure 2.) There was an implicit trust that this assessment was for their own benefit.

In patients best interests

> ***"I knew, I knew they were doing it for my own good, so I jist answered them"***
>
> ***Participant 4***

Individuals trusted that the assessments being carried out were in their own best interests, and that the aim of seeking to identify any cognitive limitations or deficit was in order to help them. There were no concerns about using the assessments for harmful purposes or that the staff had anything other than the patients' best interests at heart.

Participants displayed an awareness that the occupational therapist played a central role in performing cognitive assessment, rather than it being a medical or nursing task, although many noted nursing encouragement during assessments. This in turn inspired confidence and trust in the occupational therapist. In one participant this seemed to come at the expense of trust in the medical staff, who were felt not to assess cognition or be interested in cognition, to any degree. This comment was in contrast to all other participants however who did not comment negatively on who carried out the assessments.

"…Medical people didn't seem to ask any questions in [cognition]…." Participant 1

Correct health professional

"I felt as though it was helping me… and then the nurses were encouraging me. Well, it was the physios .and I felt as though they were encouraging me, you know "
Participant 5

However, participants displayed mixed views about who could interpret the test results for them and who could explain the results comprehensively. One felt that the stroke consultant was better qualified than other staff, with the sense that other staff could not give an overall accurate assessment, and that when discussing matters with other members of the team, issues around diagnosis and prognosis were less clear.

Correct health professional

"Different folk were telling us different things… ..that wasn't right. But I, if you speak to the consultant, you expect the whole picture" Participant 8

Many people described a therapeutic benefit merely from their interactions with clinical staff. The sense they were being listened to, monitored, watched, assessed and "checked on" gave a sense of reassurance and peace of mind. This was beyond the mere utility of the assessments themselves and suggested that the interactions and a sense of curiosity about the individual patient provided a beneficial effect, underlying the complexity of healthcare interventions of this nature.

Therapeutic interactions

"It makes me feel better tae if they're asking me questions. And you feel more, 'Well, they're interested in how you're feeling." Participant 12

3.4.4

Perceived risks of harm

One participant spoke of their sense of abandonment post testing, particularly upon discharge from hospital. They had believed that once a problem was identified by the testing process, this would subsequently be acted upon. They went to express frustration and issues around broken trust/lack of community support and about how they had to be pro-active themselves in approaching organizations and allied health professionals for more information and support. There was also a perception of limited communication from stroke services to community services about them and/or for them. For those with identified cognitive deficits there was a sense that once discharged as medically (physically) fit, little afterthought was given to cognitive aspects.

Abandonment post testing

> ***"The ..test about memory flagged up..my memory's not very good. So they haven't said.. you should do regular memory check-ups. So I'm kind of left on my own to deal with.."*** ***Participant 1***

Participants reported that repeat testing could induce acute anxiety and made them feel worried, and that the number of times they were asked the same questions provoked fear. Their perception being that the more professionals asked repeated questions, the more the participants' answers were 'wrong' and/or indicative of a major issue and thus elicited fear and distress. These factors are illustrated within Figure 2 Perceived risks of harm sphere. A key issue arising was the potential impact that a diagnosis of poor memory could have upon the participant and the subsequent detrimental effects on mood and rehabilitation engagement.

Impact of poor cognitive result

> ***"Oh, I'd be very upset if they told me that. [had a poor memory test score] really would. I'd be hoping that they could do something about it…"***
>
> ***Participant 6***

> ***""I'd be kinda worried if they say there's a problem wi' my memory 'cause I've got a, I would start thinking that I'm in the first stage o' dementia. That would worry me a lot"*** ***Participant 4***

Anxiety of testing

> ***"The more they kinda asked it, you know, the more concerned I was getting…What was wrong wi' me…"***
>
> ***Participant 12***

3.4.5

Information provision

One participant reported a paucity of information around the cognitive assessment they underwent and went on to demonstrate a good understanding of the purpose of testing, despite reporting poor information provision from health services. They reported that they had worked in a high functioning managerial position previously and had a high educational status.

Most people reported wishing to know the results of any memory test performed and the implications from the person who tested them. Most felt that face-to-face discussion of test results would be the best forum, particularly if a poor result was obtained (Figure 2). Most participants wanted results of all tests and their implications explained to them clearly and

in a timely fashion. Most did not express a view upon who should give the information specifically, although one participant did feel it should be a nurse or doctor. Most others seemed to value timely feedback, with a few wishing to have immediate feedback. The same participant with the view about feedback coming from a nurse or doctor also thought that their family should be alongside them as they received the results.

Individualised information giving

"After I turned off the recorder, the interviewee said it would have been useful to have information about what each aspect of the test was tapping into, and the consequences of that. So, for example, whether it was looking at visual systems, or whether it was looking at memory systems. And what kind of coping strategies, mechanisms, might be available, if problems are found. And what particular scores might mean on each of those different types of assessments"

**** patient spoke to interviewer after interview stopped and written capture of their comments then made into tape***

Participant 1 *

"*Did anybody explain why you are being asked that?*

Yeah, they did, in actual fact. You know, they are trying tae find a benchmark.."

Participant 2

Prompt information giving

"*Aye, right then and there, I'd like to know, uh-huh."*

Participant 4

And which person would you prefer to do that,

"I wouldn't mind if it would be a doctor or a nurse. I don't think the physio, but I think a doctor or a nurse could do that with you"

Participant 12

3.4.6

Burden of testing

While most participants were content to participate in the process of testing and reported its benefits, some did identify burden of testing as an obstacle to their participation. One participant described initially enjoying testing but that it had become taxing and burdensome with repeated testing during their inpatient stay, and this had impacted upon their engagement with the process. This served to illustrate the risks of test fatigue, if too much is undertaken too quickly or without time for the participant to have adequate rest between assessments. This had a direct affect upon their engagement with the testing procedures and so likely influenced the results of the test. (See Figure 2. Burden of testing sphere). This concept of burden was distinct from the perceived harms of testing where participants might experience worry or anxiety and reflects instead the cognitive load burden placed upon participants to engage with the process.

Repeat testing taxing

> ***"So, the first paper I got was… circles and ovals and . But the second one I got.. didn't bother looking at it, I just… I just started circling them, you know?... I didn't bother concentrating on."***
>
> ***Participant 5***

Another participant spoke about their physical difficulty when it came to completing some of the tasks that required hand co-ordination and dexterity and cited this as a significant issue in terms of their engagement. Being unable to use their arm and unable to write presented a physical burden for this participant in contrast to the mental burden the other patient highlighted.

Physically challenging

Oh yes, you can't write. I mean I'm bad enough just now with my hands, because my arm's actually hopeless, you know, to use. My hand's okay, I can use that, but I can't write, I can't, you know."   ***Participant 13***

3.5

TFA construct mapping of the 5 emergent themes

By undertaking a review for analogous themes, I was then able to map these across to their corresponding TFA construct. This allowed the 5 themes in total to be mapped across to its analogous TFA but did mean however there were themes which arose which had more than one TFA analogue. This situation was true of the participation motives which fitted with both TFA affective attitude and ethicality. Another theme where this occurred was that of information provision whereby it mapped to both TFA intervention coherence and perceived effectiveness constructs. It was also the case that within the theme of burden of testing this likewise aligned to both the TFA burden and self-efficacy constructs. Finally, in the theme of Trust in health professionals this mapped onto the affective attitude construct of the TFA while the perceived risks of harm them mapped to the opportunity costs TFA construct.

Thus, while no data fell outside of the TFA frame, some TFAs constructs fitted with more than one theme analogue from the data emerged. As well as mapping each theme onto its respective TFA construct in Figure 5. I have included some quotes from participants.

Figure 5: Emergent themes mapped onto the theoretical framework of acceptability: A graphical representation of TFA, main themes with selected quotes influencing acceptability.

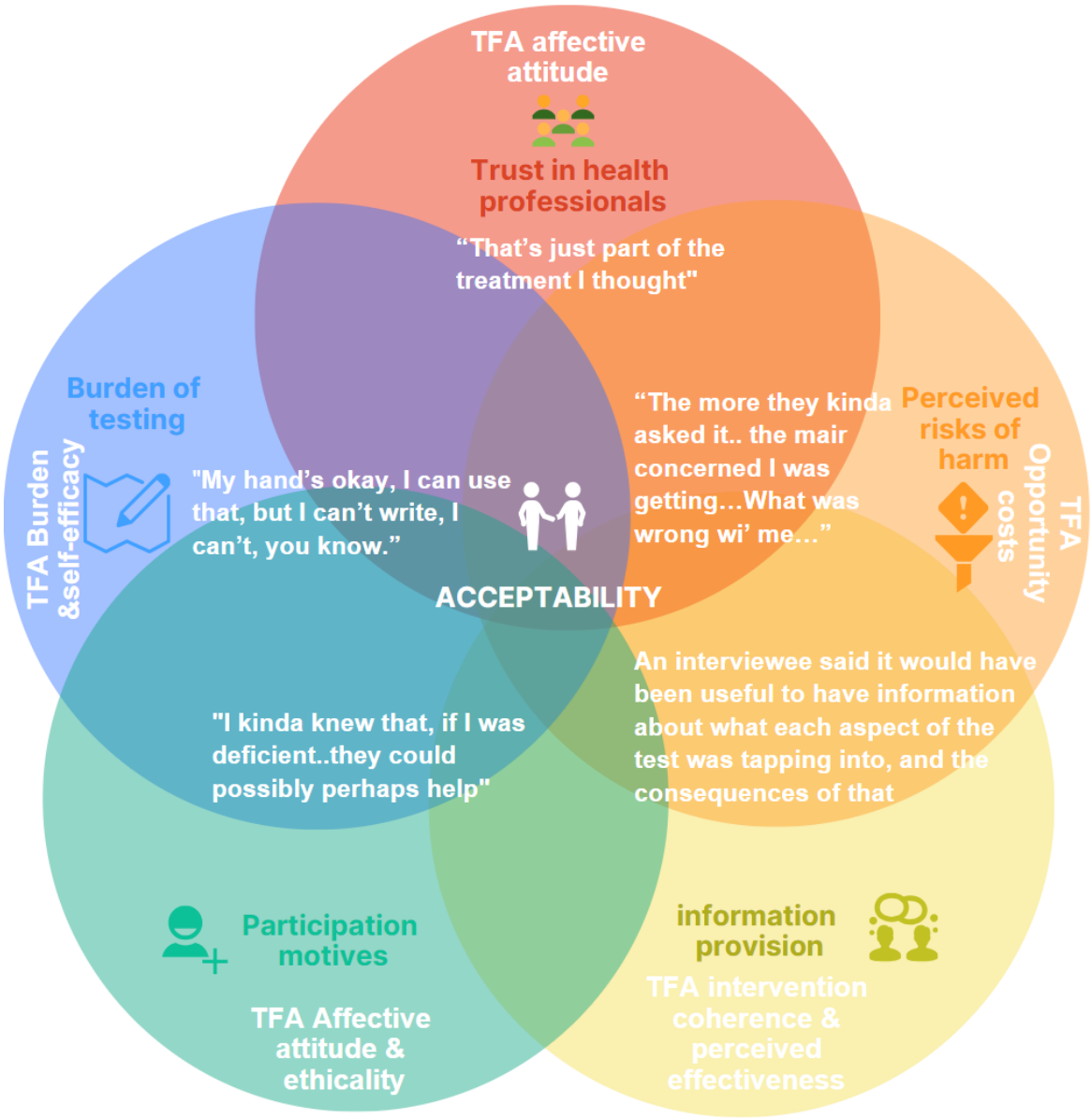
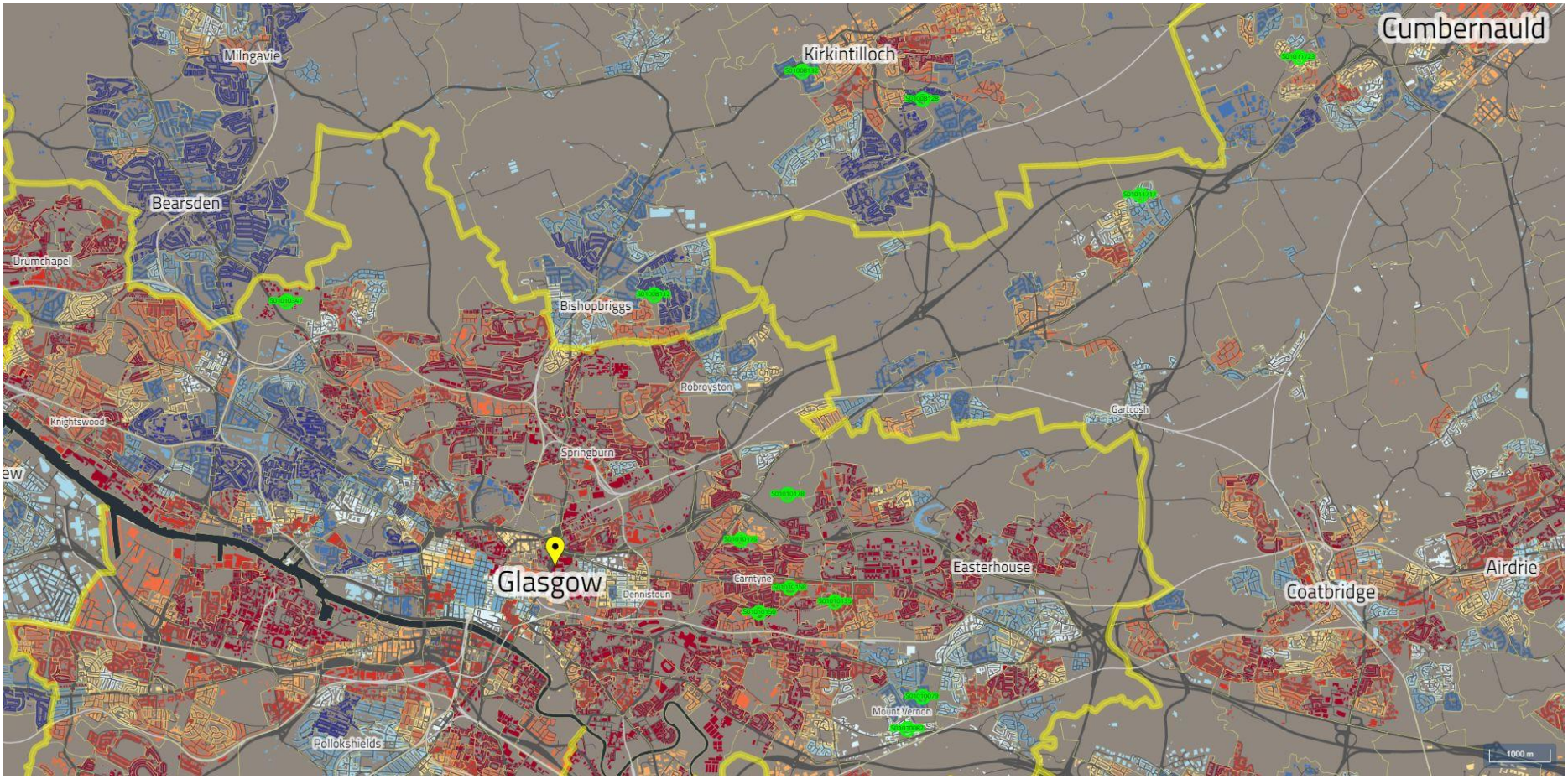


Figure 6: Scottish Index of Multiple Deprivation geographical distribution and socio-economic context [236]:***Data zone locations of participants with Glasgow royal infirmary identified by the yellow marker, with the reddest areas those with most deprivation and the bluer areas having least deprivation & Local authorities' boundaries are delineated in yellow***



3.6

Discussion

To my knowledge, this study is one of only two to date to explore the perception of cognitive assessment in stroke survivors admitted to hospital, and the only one employing the TFA specifically to evaluate the acceptability of such cognitive assessment. I have found five major themes that influenced acceptability: participation motives; trust in health professionals; perceived risk of harm; information provision and burden of testing. Taken together these 5 themes contain the essential components that stroke survivors name as needed for acceptability- that is of a trustworthy professional taking account of their individuality to deliver an assessment, and explanation of the results of that assessment, in a manner they personally find acceptable and which aids in their diagnosis, and which minimises potential burden and harms.

I decided to seek only the patient perspective as this can be overlooked, in preference to the clinician's viewpoint. I wished to know how clinicians' interventions impacted upon the patient, beyond the clinical utility of that intervention. Interventions following stroke are usually complex, specific and multi-faceted, and while for clinicians providing them, they may seem routine occurrences, patients may have a quite different and alternative view.

3.6.1

Specific findings related to the research question

Most participants expected and engaged with cognitive assessment. Indeed, it was stated as being as routine measure like a blood pressure assessment by one participant. However, patients wished to have information provision regarding their tests and results, and this should be understood and respected by clinical staff.

A key consideration was the impact that a diagnosis of poor memory can have upon stroke survivors and how this could have a detrimental impact on mood and rehabilitation engagement. Frequent testing was associated with perceived burden and could provoke

anxiety. The need to have a benchmark of cognitive status may have to be weighed against the need and frequency of testing. Guidelines tend to focus on the benefits of cognitive testing and little attention, or content is devoted to the potential for harm. While this was something a few participants spoke of, it should be a consideration by clinicians going forward to build and maintain therapeutic relationships.

3.6.2

Results in context of previous literature

To date only one other paper examined the experiences of stroke survivors who had underwent cognitive assessment during an acute stroke care admission [238]. Although not specifically examining the acceptability of cognitive assessment they employed a reflexive thematic qualitative analysis of 26 patients and found '3 key phases of [the] assessment'. These were pre-assessment: containing lack of explanation and considering the assessment useless. During the assessment: emotional responses, perception of purpose of the assessment, perception of cognitive deficits, confidence in cognitive function, and person administering assessments style. Lastly within post assessment they found feedback can impact self-confidence and efficacy, and that non-tailored feedback and clinical jargon were unhelpful. Thus, they give stroke survivors a voice, as well as a summary of some quantitative items such as the participants NIHSS and cognitive tool used and score for the whole sample. However, despite these metrics being summarised in tabular form it did not discuss how stroke survivors cognitive score or recorded NIHSS impacted or modulated their qualitative responses. These interviews were also conducted seven months after discharge, and it could be that memory recall after such a lag is poor. This study, notwithstanding these issues, and being cognisant that acceptability was not explicitly explored within patients experiences of post stroke cognitive assessment, has delivered some common messages. Their finding of the impact of a lack of explanation about the purpose of the assessment provides corroboration of my findings that tailored information given is crucial, that being as much or as little information as stroke survivors wish. Most of our participants seemed to understand the purpose of the assessments, in contrast to this study, perhaps because of the lack of explanation for the rationale of assessment that those stroke survivors spoke. Again, anxiety over testing emerged. Interactions with the health professionals administering the assessment was also mentioned as important, with positive relationships coming from 'patience and gentle' clinicians. Vague feedback and jargon

were criticised too in a clear preference for person centred tailored information giving which is individualized. Further that study also did not specifically evaluate what made the cognitive test employed acceptable or not to participants. This work presented here has evaluated acceptability, but did not specifically ask for patients to reflect on how their cognition had changed since their stroke as it was focused on what made those assessments acceptable at the time.

Similarly some previous work on post stroke dementia screening employing qualitative interview and analysis found that seeking a timely diagnosis, anxiety around a positive result and worry about possible impact on recovery all affected the acceptability of screening [239].

Most prior research on the acceptability of cognitive testing, had primarily been in small studies in non-stroke populations [240] [241]. A Canadian study of people with brain metastases undergoing treatment reported that 92% found the cognitive screening to be 'only mildly or not at all inconvenient' [241]. A German study exploring patient reported acceptability of cognitive screening pre- and postoperatively in people with brain tumour concluded testing was 'well accepted by the participants' [240]. They reported that 90% in the pre-treatment group rated the screening process as 'easy' or 'medium'; with a further 90% rating it as 'not burdensome'. Within the post-treatment group, 79% found it 'easy' or 'medium'; while 91% found it 'non-burdensome'. As this study sought to quantify acceptability using survey metrics, rather than explore the experience of testing qualitatively, the findings cannot be directly compared with these results. However, the message that patients are accepting of cognitive testing is congruent with my results.

A pilot study examining the acceptability of four cognitive tests for Australian Aboriginal people found that it was generally welcomed as a positive experience being liken to 'playing a game' and 'a good challenge which were some of the comments echoed by the stroke survivor stroke during analysis, and despite the obvious differences between the populations studied [242].

In a U.S study describing the acceptability of dementia screening in primary care settings, patients were interviewed using the Dementia Screening and Perceived Harms questionnaire, a 58-item survey that takes 8–12 minutes to administer [243]. The study authors reported that the acceptability and participation of other screening programs, as well as subjective memory complaints were associated with enhanced acceptable of

dementia screening. In this study, stroke survivors similarly demonstrated enthusiasm to have their subjective cognitive symptoms assessed.

In another study that explored the views of people living with multiple sclerosis on cognitive testing one subject remarked “If such tests are just standard, people wouldn’t be scared off…it is incredibly relevant, just as relevant as a blood sample…” [244]. This sentiment was echoed in this study too with one participant expressing the same sentiment.

A recent Swedish study with 18 participants describing older persons' experiences of a cognitive assessment scheme, mirrored my findings regarding some participant concern about abandonment with an ‘abnormal’ test result [245]. The need for trust in the screening process and patient-centred care are also important findings in both this study and from this data.

Thus, across a heterogeneity of study populations, screening tools and methods of data analysis there are findings that generally align with the theme findings from my study. Cognitive testing is seen as a routine part of healthcare, which is especially valued by those with concerns over cognitive symptoms. However, there is some potential for burden and harm if testing and disclosure of results is not handled well.

3.6.3
Strengths and Limitations

This study had a number of strengths, the population included almost equal male and female participants, from affluent and deprived social-economic contexts. There was no geographical clustering within Greater Glasgow and Clyde. A related strength was the limited exclusion criteria employed, allowing those with any level of physical disability and those with a degree of reduced cognition to take part.

However, it is likely that the more physically disabled, and those with more severe cognitive post-stroke deficits, were still under represented. By the very nature of the consent process self-selection bias is likely to be present, despite our inclusive approach. Thus, the participants in this study may have a more favourable attitude to cognitive testing than those stroke survivors who declined to participate.

The short time from discharge to interview of participants (3 weeks or less) is likely to have aided participant recollection of events. Furthermore, as interviews were conducted within the participants own home environment rather than a healthcare setting, and not by with a member of the clinical team, courtesy bias is less likely to be a factor. The multi-disciplinary nature of the research team including a psychologist, two GPs and a stroke consultant should be viewed as a strength, as all assessed the themes for face validity. Check coding by a second researcher further enhanced rigour of the study. The mix of inductive and deductive methods allowed examination of data through the lens of the theoretical framework of acceptability while ensuring that findings truly arose from the data. Further by then sense checking each emergent theme back into its respective TFA construct(s) I was able to further validate the data.

The study also had a number of other limitations. It could be considered a weakness that the interviewer was not the person undertaking the coding. As the individual performing the coding, I ensured that I immersed myself in the data to become familiar with it by reading and rereading transcripts and listening to each interview also. The small number of participants could be viewed as a limitation. However, in the qualitative research field, this number of participants is accepted as sufficient when exploration rather than generalization is the intention. The included participants had ischaemic events as the stroke aetiology, those with ICH were not deliberately excluded but our inclusion and exclusion would have favoured milder stroke severities. There is no obvious reason why acceptability of cognitive testing would differ between stroke pathologies, independent of severity, but nonetheless the lack of ICH in the sample is a limitation.

Another potential limitation of this study was that, due to the nature of our ethical approval only limited clinical and demographic details could be collected, with data pertaining to participants age and postcode and type of stroke collected, but other characteristics such as survivors' ethnicity, occupation, educational status, and information on premorbid cognition not available. It could well be that the educational status and belief systems of survivors influenced their answers. Similarly, severity of stroke, as rated on the NIHSS scale for example, and which cognitive assessments had been undertaken were not known. Details around the cognitive assessments performed were drawn from the interview only and we were not able to assess medical case-records to ascertain which tests were administered and when. Patients had to have capacity to consent to the study to be eligible, and so while not explicitly excluding those with pre-stroke cognitive impairment(s) or an

intercurrent delirium, it is likely that practically neither were significant enough in this cohort as all survivors were able to give informed consent.

It should be noted that the only other recent study in the field around this area also did not provide information on stroke severity or name of cognitive assessment tool used or score of cognitive assessment.

While the theoretical framework of acceptability has been useful as a lens to consider factors of acceptability, it could be argued that some constructs remain nebulous, and contain overlap. Although the methods used followed best practice there is an inherent interpretation and subjectivity to the coding and classification. However, human thoughts and feelings are complex concepts, and will never fit rigidly into defined boxes. Thus, in these subjective matters, themes could legitimately be arranged and interpreted differently. I represent the findings as I saw them, summarising and visualising the participants' perspectives as they represented them to me.

3.6.4
Recommendations for current practice and future research

Further studies of stroke survivors could examine the acceptability of different assessment tools, and how to communicate those tools in terms of the information that patients want, and in what form they wish this information and when. The timing of assessments and how they may influence participation is also a key area where further work could broaden our understanding.

There was an almost universal view that results should be explained, and their implications made clear to participants. This however must be carefully weighed against the fact that as a participant's clinical courses improve so might their score, and thus rather than being a static fixed measurement, it might well vary along with their course. Therefore explanation of this, as well as the associated implications may be required. This could make it difficult for the practitioner to divulge the information in a meaningful way; and perhaps is itself an area that merits discussion at the outset of testing.

The need to have a benchmark of cognitive status may have to be weighed against the potential for negative patient consequence and perceptions. Clinicians may have to consider this when deciding on the need and frequency of cognitive testing, as well as the type of test employed. As with the use of any test designed to answer a clinical question, be it a blood test or imaging test, the potential harms or pitfalls of cognitive testing need to be carefully considered. Therefore, timing and repetition of assessments must be carefully considered given the risk of harm to the participants.

In this way a tailored approach about ensuring the participants results are shared with them in the manner they wish, with or without other family members also being present as per the participants wishes. This must of course also be an accurate and transparent account of what the results mean and the around the need for further testing, being mindful about the possible evolution of results and implications going forward.

Likewise, when considering the burden testing brings it is important to be mindful of both cognitive and physical components. In this manner an assessment must be patient centred, and acceptable, for the reasons that both the participants themselves outline, but also because of the previous discourse around the benefits of patient-centred approaches for both patients and clinicians.

Necessarily given that future CPGs, as discussed the in preceding chapter, will likely only emphasis healthcare interventions even more emphatically as requiring to be patient centred and acceptable, this work suggests from a ‘bottom up from the patient’ and ‘top down from expert review panel’ that patient centred care is here to stay, that it is vital, and that all practitioners should be utilizing it in partnership with their patients.

3.7

Conclusion

This novel qualitative work, the first to utilize the TFA as a framework analysis in a stroke survivor cohort, provides insight into the factors that affect acceptability of cognitive screening during hospital admission with stroke. Acceptability was explored through the theoretical framework of acceptability which I found to be a useful framework. These findings can aid clinicians and policy makers in implementing acceptable cognitive assessment procedures in acute stroke care. The data suggest that clinical teams should be confident that stroke survivors expect this testing and understand the rationale for it. However, they should determine for themselves how much information the patient wants about the test and results, if any, through dialogue, information provision and actively listening. Clearly the increasing importance of, and necessity to undertaken stakeholder (patient) engagement is an area which is likely to only increase in prominence going forward, be it around other actual shop floor healthcare interventions and the CPG development process that makes recommendation about these. Thus, while this represents a useful insight into acceptability of a specific health care intervention in a stroke patient population both a validation of the factors of acceptability remains to be arrived at, as does how generalizable this might be to other complex health care interventions such as speech and language therapy post stroke for example.

Chapter four

Comparing the accuracy of TIA and stroke clinical recognition systems

4.1

Introduction

In the previous chapters I considered clinical practice guidelines around a specific aspect of stroke assessment, namely cognition, and the patient experience of assessment. In both these endeavours, the importance of understanding the accuracy of the test was a major theme. In this chapter I will explore test accuracy using a clinically applied example around diagnosis of stroke and transient ischemic attack (TIA).

The diagnosis of stroke and TIA can be difficult. A high proportion of people referred to specialist services have a mimic diagnosis. Brain imaging can help confirm the diagnosis, but even Magnetic Resonance Imaging (MRI) does not offer perfect diagnostic accuracy [246]. In a meta-analysis of emergency department studies describing diagnosis of TIA and stroke, TIA was misdiagnosed in 24%–60% of cases [247], this was also true for stroke (at the initial diagnosis stage) where 8.7% of cases were misdiagnosed. Therefore, the utility of improving, or indeed validating tools, in current stroke populations to benchmark their accuracy and ability to aid diagnosis are readily seen. Some well-known tools were developed over a decade ago but still serve as an additional armament in the clinicians' diagnostician battery.

Here I shall describe the test accuracy of various tools using the same reference standard, and same sample to directly compare commonly employed tools, as well as two lesser-known research tools which were produced with the express aim of improving TIA diagnosis accuracy.

To be able to interpret the resulting data, it is first necessary to understand these tools and their respective development and validation processes. This will then allow for the consideration of each head to head in this section.

4.2

Clinical scoring tools

There are various multi-item tools that have been developed to aid assessment of stroke and TIA. After scoping the literature, we chose those stroke and TIA scales that are commonly employed in clinical practice and can be used to improve diagnosis.

Given that the recruitment of patients in our sample was either from the acute stroke units, or from TIA fast track clinics, the use of clinical tools for physicians rather than tools for emergency medicine technicians or para-medics were chosen as from these routes patients had been referred to a stroke specialist either by an emergency medicine physicians or a general practitioner.

Additionally, when deciding which clinical tools to include, some tools are specifically intended for pre-hospital use rather than within hospital, and some tools are for different professions, which make them less appropriate for this study. Moreover, many of the prehospital clinical tools have specific items which were not easily obtainable from the clinical notes, or could not be ascertained with certainty or with the granularity required (for example timing of administration), further making them unsuitable for comparison.

Thus, when deciding which scoring systems to use, and after review of several sets of clinical notes to scope the information that could be obtained, certain assessments were judged not suitable for this study. For example, some items from the Cincinnati prehospital stroke scale (CPSS) were not documented around exam findings in medical records, meaning it would not be possible to calculate and include these items i.e. arm drift. [248]. The Los Angeles Prehospital Stroke Scale (LAPSS) was ruled out as it was not clear from clinical notes if patient were bedridden and/or a wheelchair user at time of assessment, as well as hand grip being unknown from most [249]. This was also the case for excluding the Melbourne Ambulance Stroke Scale (MASS) [250].

The Ontario Prehospital Stroke Screening Tool (OPSST) on the other hand required symptom(s) to have had a clear onset within 120 minutes, which was not the case for all of our cohort [251].

Within the Medic Prehospital Assessment for Code Stroke (MedPACS) gaze preference was not systematically /recorded within the clinical notes [252] thus making it unsuitable. The PreHospital Ambulance Stroke Test (PreHAST) tool again had items such as gaze/eye position unknown, and a tool specific item where the patient is told “close your eyes! Grip your hand” which was not available for our cohort [253] and thus similarly both of these tools were discounted.

The Newcastle FAST test whilst being simple, and having few items, was designed for acute use in patients referred to either the acute stroke unit by their primary care physician, or via emergency room physicians (where a stroke had not been identified by attending ambulance staff) [254]. This again, was not appropriate for our cohort. A large proportion of participants had already been recruited from the fast track TIA clinic at outpatients, and not at such a hyperacute stage, or had already been admitted to a stroke unit with their symptoms.

My scoping suggested, two tools that are commonly used in stroke care in the UK, the ABCD2 score [255] [256], and the ROSIER (Recognition of Stroke in the Emergency Room score) score [24,257]. In addition to these two widely employed clinical tools, there were two tools designed specifically to facilitate diagnosis of suspected TIA, the Dawson [27], and the DOT (Diagnosis of TIA) score [26]. These two scoring systems are not routinely clinically utilized at present but are worthy of further investigation as they were developed for clinical use and have reported accuracy similarly to the ROSIER scale.

These four tools will be described in turn, as each was developed with a differing purpose and intended application. The ABCD2 was developed as a risk stratification aid and diagnostic utility was descried later. The ROSIER was developed to assist Emergency Department (ED) physicians rapidly diagnosis TIA/stroke [258]. Both the Dawson score and the DOT score were developed as diagnostic tools to assist non-specialists in various settings make the diagnosis of TIA with greater accuracy.

Analogously, and for comparison when looking at other clinical tools and their respectively accuracy the Wells score when used in suspected pulmonary embolism (PE) demonstrated an area under the ROC curve of the 0.74, which was similar in the original, modified and simplified decision rule [259]. Similarly when the Wells score was used for the risk of deep venous thrombosis in trauma patients it yielded a sensitivity of 100 %, a specificity of 36 %, a PPV 9 % and a NPV of 100 % at a cut off of one [260].

The Patient Health Questionnaire (PHQ) which is used for depression screening was found to have a sensitivity of 88% and a specificity of 88% for major depression in its original study[261], with a subsequent validation study finding a slightly higher specificity at 91% and lower sensitivity of 74% at the same cut-off of 10 points[262].

4.2.1
ABCD2 score

The ABCD2 [25,255] was developed with the aim of assisting non-stroke specialists in determining which patients would go on to develop stroke after sustaining a TIA and so direct finite resources and potentially risky interventions at those most in need [25] [263].

Necessarily, the ABCD based tools start from a point where a patient has had a suspected or confirmed TIA. The ABCD2 score was derived from a unification of the ABCD score [255] and the California score [264], both having been validated scores to aid diagnosis in separate UK and US populations. The ABCD2 score [25,255] produces a summed total, stratifying the risk of subsequent stroke.

As well as a risk stratification tool, others have examined the utility of ABCD2 as a diagnostic tool that can differentiate cerebrovascular disease from mimics [265]. For example, in a UK outpatient clinic, ABCD2 scores were retrospectively derived for 3646 acute patients presenting to the service of which 1769 had a non-cerebrovascular diagnosis. The authors found a positive association between increasing ABCD2 score and cerebrovascular diagnosis ($P<0.001$), and higher ABCD2 score being associated with vascular lesions on brain imaging ($P<0.001$). Having an ABCD2 dichotomized at 0 to 2 gave a positive predictive value of 0.74 for non-cerebrovascular diagnosis and 0.93 for negative imaging; corresponding sensitivity was 52.6% and specificity 82.8%. Receiver operating characteristic curve analysis yielded a reasonable accuracy rate of 0.745 (AUC).

In another study in North Dublin, Ireland, the ABCD2 score was used to distinguish TIA/stroke events from non-cerebrovascular events [266]. They found that the ABCD2 score displayed good performance in distinguishing confirmed TIA from non-cerebrovascular events (with an AUC 0.68) They demonstrated that a ABCD2 score of equal to or greater than 4 correlated to a 60.3% sensitivity and 64.6% specificity for

discriminating TIA from non-cerebrovascular events. A score of equal to or greater than 6 had 16.8% sensitivity and 93.8% specificity to discriminate TIA from non-cerebrovascular events.

4.2.2
ROSIER score

The ROSIER or Recognition of Stroke in the Emergency Room score [24] was developed with the aim of aiding Emergency Department (ED) clinicians' (non-stroke specialists) in differentiation of common stroke mimics from true strokes

In a 9-month prospective validation study of the ROSIER tool, conducted within an ED in Newcastle, England, all patients aged 18 years or older with suspected stroke or TIA and who were assessed by ED physicians were included. Patients were enrolled between Nov 1st, 2002, and July 31st, 2003, with a total of 160 participants. The ROSIER pro forma was completed by ED physicians during the initial clinical assessment and prior to imaging, however with no knowledge of the final diagnosis. All patients who underwent the ROSIER scoring were referred to the acute stroke unit, irrespective of the ROSIER score that was recorded. Of these 160 patients 88 had stroke, 13 of 26 had TIA with symptoms or signs and 59 had a non-stroke diagnosis. In the prospective validation phase at a cut-point of +1 (i.e. being positive for stroke) the ROSIER scale had a Sensitivity of 93%, a Specificity of 83%, a PPV of 90 % and a NPV 88%.

The ROSIER scale incorrectly diagnosed 17 of 160 or around 10% of all patients. These included 10 false positives and 7 false negatives of the validated cases in the prospective validation phase. The false positive group included functional disorders (n=3), brain tumour (n=2), complex migraine (n=1), seizure (n=1), worsening dementia (n=1), alcohol intoxication (n=1), and dislocated jaw (n=1). The false-negative group included posterior circulation infarction (n=5) and lacunar infarction (n=2).

A subsequent validation study in a large Irish ED demonstrated of fifty consecutive patients admitted to the ED suspected of stroke, and after having a ROSIER completed showed that forty-seven patients (94%) had a ROSIER score of ≥1 indicating likely presence of a stroke [267]. Of these 44 patients (94% sensitivity) had stroke later confirmed on investigation.

Two patients with stroke were found to have had a ROSIER score of 0 i.e. not a likely stroke (FN=2), one was admitted unconscious with a large primary intracerebral haemorrhage (n=1) and was wrongly scored and the second had a cerebellar infarct (n=1) with no weakness, speech or visual field defects. Three patients were falsely identified (FP=3) with stroke; two who were scored 1 (n=2); and a third who scored 3 (n=1). This yielded a specificity of 90% with the Positive predictive value for the ROSIER calculated at 94% however the authors could not derive a negative predictive value due to the small study numbers.

A more recent Italian validation study was able to show of 539 participants who were enrolled in a prospective observational study, carried out in the ED of a major Milan teaching hospital. The ROSIER scale correctly identified 414 patients with stroke and 91 without, thus showing 97.6% sensitivity, 90.1% specificity, 97.5% positive predictive value, and 82.7% negative predictive value [257]. These patients had been admitted with neurological symptoms and underwent an Italian language ROSIER that had been approved by the original ROSIER developer.

There were 10 false negatives (FN): brain haemorrhage (n=1) and right hemisphere TIA (n=1) both scoring 0, 2 posterior ischemic strokes (patients who experienced dizziness only, without other signs and symptoms) (n=2), and 1 left hemisphere TIA (n=1) all scoring 0. Finally, there were 4 posterior symptomless TIAs (n=4), and 1 TIA (with mental confusion) (n=1) which scored −1 on ROSIER. Five patients were falsely positive (FP), one of which had dysarthria (n=1), one had visual disturbance from carbamazepine iatrogenic effect (n=1), another had 7th cranial nerve deficit after trauma (n=1), and two had paraesthesia in the right arm (n=2). The authors calculated the Italian ROSIER scale as having an AUC of 0.87.

4.2.3
DOT score

The Diagnosis of TIA (DOT) score is a web and mobile app based diagnostic tool which aims to delineate both cerebral and retinal TIAs [26].

The development cohort for the score was a subset of TIA clinic patients studied retrospectively from a TIA database. All patients had been referred to the 'Monday to Friday TIA clinics' of Gloucestershire Royal Hospital (GRH), England between April 2010 and May 2012. Referrals were accepted from ED, General Practitioners (GPs), paramedics, and other sources such as ophthalmology.

The team collected data included demographic information, past medical history, a detailed history of the suspected stroke, examination findings, ABCD2 scores, results of investigations (blood tests, ECG, same day carotid duplex ultrasounds, same day CT brain scans) and final diagnosis. The diagnosis was made by consultant stroke physicians with at least 7 years of stroke experience. Patients were classified as TIA, minor stroke or mimic. They produced discrete binary variables codes from the histories that were expected to predict or refute stroke or TIA, such as "unilateral weakness". Preliminary univariate analysis was used to identify predictive variables and then stepwise multiple logistic regression employed using the backwards elimination method to select the optimal model. The final diagnostic score was derived from the coefficients of the final model.

The optimal cut point for the score was calculated at 0.297 using the Youden Index and -0.547 using the cost of misclassification method. This cut point (0.547) was the one used in the final score. Patients with a DOT score of equal to or greater than 0.297 (probability of TIA > 57.4 %) were classified as "Probable TIA" with those between -0.547 and 0.297 classified as "Possible TIA" and those with a DOT score of < - 0.547 (probability of TIA < 36.7 %) were classed as "TIA unlikely".

The final model n=525 had seventeen predictors and had an AUC of 0.89 (95 % CI: 0.86–0.92). When tested on a validation cohort enrolled between January and August 2013 drawn from the same service, the AUC for DOTS was 0.89 (0.86–0.92). The sensitivity and specificity of the DOT score were 89 % (CI: 84 %–93 %) and 76 % (CI: 70%–81 %) respectively. The diagnostic accuracy measures of DOT yielded a positive predictive value of 75 %, and negative predictive value of 89 %.

The DOTs group then subsequently constructed a web-based calculator and smartphone application designed to calculate the probability of outcome and to present the result as “probable TIA”, “possible TIA” or “TIA unlikely”.

The DOT score was also externally validated in a Chinese population [268]. They found it to have relatively good calibration and discrimination to identify TIA in a Chinese population by enrolling 500 patients with transient neurological symptoms. They compared the TIA mimic group against patients with true TIA and calculated an area under the curve (AUC) of 0.728 for the DOT score, with a sensitivity of 70.3% and specificity of 62.9%, respectively. They did however recommend further validations are needed in multiple centres with larger samples in China.

4.2.4
Dawson score

This clinical scoring system was developed with the ambition of reducing the number of non-cerebrovascular referrals to a fast-track TIA service [27]. It was developed in Glasgow, Scotland.

The development cohort included 3230 referrals, primarily from GPs (>95%) to the fast-track TIA clinic. Baseline demographic data, presenting complaint, relevant examination findings and diagnosis and management plans were prospectively recorded at the time of clinic review and data entered into an electronic database. Data was held for all patients who attended the clinic between March 1992 and January 2005.

Sufficient data were available for 3216 patients, of whom 2215 (69%) had a diagnosis of TIA or minor stroke. First, univariate analysis was used to identify variables predictive of diagnosis. Logistic regression models were used to identify independently discriminatory variables. Stepwise selection procedures (both forward and backward) were employed to identify significant explanatory variables using Akaike’s Information Criterion yielding nine clinically useful predictive variables, these were: history of stroke or TIA, headache, diplopia, loss of consciousness/pre-syncope, seizure, speech abnormalities, unilateral limb weakness, upper motor neuron facial weakness and age.

Prospective validation of the diagnostic tool was then undertaken, and data collected prospectively on all referrals to the Fast Track TIA clinic were gathered from October 2005 to June 2006. Receiver operating characteristic curves (ROC) were used to determine optimal cut-off scores; and sensitivity, specificity and positive and negative predictive values were calculated. ROC curves identified a score of >6.1 as the optimal cut-off for prediction of a cerebrovascular diagnosis. This accurately identified 84% of cerebrovascular diagnoses and 60% of non-cerebrovascular diagnoses with a positive predictive value (PPV) of 82% and negative predictive value (NPV) of 62%. With an adjustment to reflect the greater significance of missing true cerebrovascular patients (a 2:1 cost ratio), an optimal cut-off score of >5.4 was then used. This yielded a sensitivity of 93% and a specificity 34% with PPV 68%, NPV 76%.

Table 6: Composite table of all clinical scoring tools

ABCD2 score	Age >60	BP > 140/90	Unilateral weakness	Speech disturbance without weakness	10-59 minutes	>60 minutes	History of diabetes
*	1	1	2	1	1	2	1

ROSIER Score	Loss of consciousness or syncope	Seizure activity	Asymmetric facial weakness	Asymmetric leg weakness	Asymmetric arm weakness	Speech disturbance	Visual field defect
*	**-1**	**-1**	**1**	**1**	**1**	**1**	**1**

≤0: Stroke unlikely >0: Stroke possible (cut point at 1)

DOT Score	Age	History hyper-tension	Atrial fibrillation (AF or pAF)	Dys-phasia	Unilateral facial weakness	Unilateral weakness arm/leg	Uni-lateral sensory loss	Visual loss one eye	Visual loss both eyes	Diplo-pia	Homon-nymous Hemi-anopia	Visual aura	Ataxia	Head ache	Amnesia	Loss of consciousness/ near LOC	Tingling & numbness
**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Not possible to calculate DOT score manually done via online calculator ** (cut point at 70 %)

Dawson Score	History of stroke or TIA	Headache	Diplopia	LOC/Pre-syncope	Seizure	Speech abnormalities	Unilateral limb weakness	UMN facial weakness	Age *0.04
Point* if present	Yes 0.5 No 0	No 0.5 Yes 0	Yes 1.2 No 0	Yes 0 No 1.1	Yes 0 No 1.6	Yes 1.3 No 0	Yes 1.7 No 0	Yes 0.6 No 0	Add age * 0.04

If total score >6.1, classify as TIA For '2:1 cost ratio >5.4, classify as TIA (cut point 5.4)

- ***Point if present***

4.3

Comparing the scores

While all of these tools can plausibly be used to aid diagnosis, they differ in the items used for assessment, and also in their scoring methodology. For example, the Dawson score employs a 2:1 cost of misclassification adjustment scheme, thereby reducing the risk of missed TIA, or false positives. DOTs endeavours to be more accurate and inclusive of retinal and posterior circulation events.

The impetus to develop more posterior circulation event sensitive tools was in response to criticism that existing tools such as the ABCD2 [255]and the FAST tool [269] are weighted towards anterior circulation events at the expense of posterior events [266,270].

Similarly, a recent Italian ROSIER validation study found that the majority of false negatives were in post circulation events i.e. in 6 of the 10 false negatives: (including 2 posterior ischemic strokes 4 posterior TIAs)[257], which was similar to the original validation study FP rate [24].

With differing tools available, and no consensus or guideline to suggest a preferred approach, clinicians may be left unsure which tool, if any, they should employ in practice. Indirect comparisons of the diagnostic data from the tools is only partly helpful as the original studies differed substantially in their method and setting. The ideal would be to compare multiple tools in a single dataset to allow direct comparisons.

4.4

Aim and research questions

In this study my primary aim was to compare the four clinical scoring tools against each other using data derived from a TIA/stroke referral cohort. My goal was to inform practicing clinicians of the accuracy of each tool against each other, to identify if any one tool had superior sensitivity and specificity. Further I endeavoured to do this against a common reference standard given previous studies have used varying reference standards making direct comparison problematic. Finally, it is worth mentioning that some of the studies underpinning current approaches are over a decade old now and I sought to confirm their generalizability and relevance to contemporary stroke settings and patients.

4.5

Methods

I created a comparative diagnostic test accuracy study and followed best practice in conduct and reporting [271]. This accuracy study was conducted fully in line with the STARD reporting guidance [272]. This work represents a study within a trial (SWAT) design. The parent trial was the ‘TriMethS’ study. This was a Chief Scientist Office of Scotland funded study looking at the potential efficacy of a stroke biomarker (a trimethylamine derivative) to aid in diagnosis of suspected minor stroke or TIA. Funding for this study had been granted by the Chief Scientist Office of Scotland, grant ID TCS/17/06.

The research ethics committee number of the original study is 17/WS/0252 and was sponsored by NHS Greater Glasgow and Clyde, this analysis was a part of the main study. The approvals for the main study were sufficient to allow this secondary analyses of the data. The protocol for the ‘TriMethS’ study can be found at Appendix G: TriMethS’ protocol (derivative).

A comparative test accuracy study required a cohort with a mix of stroke/TIA diagnoses and mimics, detailed phenotyping of participants and robust, consensus diagnosis. This made TriMethS an ideal substrate for this study as it had all the necessary components, albeit certain data had to be manually extracted or derived.

The TriMethS study database included information on presenting symptoms, cardiovascular risk factors and investigation findings. These data were used to derive ABCD2, ROSIER, DOT and Dawson scores. Where it was necessary to augment the information collected in the study case report forms, I reviewed the clinical records and relevant data. The original study data, including the consensus diagnosis adjudication, were collected prior to all the index test(s) being derived i.e., prior to ROSIER, DOT and Dawson score calculation.

Within the Glasgow royal infirmary site, I recruited patients to the TriMethS study. I liaised with the treating teams to identify those eligible and I provided them with a participant information sheet as well as obtaining written informed consent. Initial consent at the first visit was permitted and if recruited, I then obtained their demographic data,

ABCD2 score, brain and vascular imaging, drug therapies and cardiac investigations from their medical notes also recording the diagnosis of the GP (if available) and that of the specialist clinician. Additionally, I obtained their MRI report as well as urine and blood sample for bio-banking.

I also performed follow up visits where patients came back to the clinical research institute assessing patients for any recurrence of stroke and vascular events. I also then assessed their functional outcome as per the modified ranking scale and also recorded the medications they were taking at that time. In addition, and I also requested a further urine sample at that point. The pro forma sheet for this visit can be found at Appendix H: TriMethS' protocol (TriMethSylamine derivative) final follow up preform.

As part of the initial in-study classification, suspected TIA was defined as transient symptoms and stratified as possible, probable, or definite TIA by a referring clinician. While minor stroke was defined in out-patients as residual symptoms or symptoms lasting more than 24 hours felt to be possibly, probably, or definitely due to stroke by a referring clinician but in whom they had not been referred for in-patient assessment. For the purposes of in-patients, minor stroke was defined as ambulant patients with a NIH Stroke Scale Score (NIHSS) of equal to or less than 4 [273].

4.5.1
Reference standard

The reference standard employed was the adjudicated final diagnosis derived from consensus agreement between two senior stroke Physicians (JD, CS), DM a primary care physician and two senior doctors in training (AZ & AC) with review of the clinical history, radiological imaging, and discussion regarding diagnosis in a retrospective fashion to determine the final diagnosis. Consensus was independent of clinical scores such as ABCD2 and based solely on review of the clinical history, imaging and other investigations. Where agreement was not reached initially by independent assessment and discussion, a record of cases where disagreement existed was kept. A mixture of in person meeting and virtual meeting were held and through discussion disagreement cases were resolved by repeated review and discussion, until consensus was reached. Thus, all participants in TriMethS had a reference standard, consensus, clinical diagnosis.

I was involved in all adjudication and reference standard setting cases. At this point in determining final diagnosis the ABCD2 score was known for patients. I had not calculated the ABCD2 myself. It had already been calculated for the original trial (and was one of the index tests later used). However, the reference standard was derived before the results of the other index tests were calculated and known i.e. before the ROSIER, DOT and Dawson score. Thus, I was not fully masked to the ABCD2 score items, but was not aware of the total score at time of adjudication.

I then calculated the index tests myself at a later point after the adjudication work has been carried out for the original study. Thus, the reference standard had been calculated with the expectation of being used for a purpose other than for the use of describing data accuracy as used in this study.

4.5.2
Inclusion & exclusion criteria

Inclusion criteria to the parent study was, being aged at least 18 years old and having been referred to a stroke service with suspected TIA or minor stroke within 48 hours of onset of symptoms and able to provide informed consent. The exclusion criteria were those patients with a previous diagnosis of a structural brain disease (with the exception of TIA or stroke) and/or having frailty or other illness likely to lead to death within 3 months.

4.5.3
Participant identification & consent

Participants were identified by the clinical team during attendance at stroke services. They were asked if they were willing to be approached by a researcher. If so, they were given a participant information sheet. Informed consent was then obtained. Given the acute nature of the study, patients were permitted to consent at the initial visit, without mandating a minimum 24-hours to read participant information materials. Incorporating this delay would lead to potential out-patient participants needing to return for additional visits for consent and study assessments.

Adults felt not to have capacity to consent were not approached. Recruitment was performed in a consecutive manner.

4.5.4

Population

Two NHS Greater Glasgow and Clyde (NHS GGC) hospitals, in whom I had full access to case notes were used for this SWAT (study within a trial). Both are University teaching hospitals, serving a large urban and suburban cohort. Within Glasgow city' administrative boundaries there are high concentrations of deprivation [236]. Both provide secondary stroke services, with the QUEH also providing several tertiary services to the west of Scotland as the largest acute inpatient hospital in Scotland. In the study data, clinical notes, laboratory investigations imaging and reports were available for all participants. The cohort was drawn from acute stroke units, outpatient settings, and ED referrals. Recruitment was from August 2018 to July 2019.

4.5.5

Clinical pathway and available information

Participants underwent the routine clinical assessment for TIA and minor stroke that would be usual practice in the participating sites. This included assessment of demographic data, brain and vascular imaging, and cardiac investigations as determined by the treating clinical team. The clinical assessment was at the discretion of the treating clinical team and investigations were performed until the team were satisfied, they had sufficient diagnostic information. While the investigational approach is not mandated, vascular imaging and a period of assessment for atrial fibrillation are recommended and are audited at national level [274] . These assessments all represent standard care, and the results were subsequently obtained from the medical case notes.

4.5.6
Analysis

ROC analysis is a useful tool for evaluating the performance of diagnostic tests that classify subjects into 1 of 2 categories, diseased or non-diseased [275]. A ROC curve is a plot of the true positive rate (Sensitivity) against the false positive rate (Specificity) for different cut-off points of a parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The Area under the ROC curve (AUC) is a measure of how well a parameter can distinguish between two diagnostic groups (diseased/normal). A perfect test would produce a value of 1, while a test no better than random chance would yield 0.50 and values below 0.5 would indicate a test performing worse than that of random chance.

Data were entered on Microsoft Excel spread sheets (Microsoft® Excel® for Microsoft 365 MSO (Version 2207 Build 16.0.15427.20182Version, Microsoft 2023). Where data had not been captured on the original study clinical research form (excel sheet) I then added these data. This required accessing the participants' electronic medical records and admission case-notes to extract the necessary data. This step allowed calculation of the ROSIER, DOT and Dawson score where items from each had not been recorded in the original study. Unlike the other scores which were simple to manually calculate, assuming each feature was known to be present or absent, the DOT score did not have such a formula which could be utilized and so each patient had to have their component parts entered into an online calculator to obtain their respective DOT score (the calculator can be found in the original paper) [26]. The DOT calculator can be found at Appendix I: Diagnosis of TIA score calculator. Where despite best efforts the data required to derive test scores were not available, then these cases were excluded from the final analyse.

The performance of each test against the clinical reference standard was described using sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) as well as areas under the curves (AUCs). Primary analyses used SPSS (version 25, IBM, Chicago USA).

Sensitivity was calculated based on how many people have the disease, this was done using the equation: sensitivity=number of true positives/number of true positives + number of false negatives) [276]. Specificity was calculated based on how many people do not

have the disease. Therefore, the equation: specificity=number of true negatives/(number of true negatives + number of false positives) was used.

Positive Predictive Value (PPV) is the percentage of patients with a positive test who actually have the disease. PPV tells us about how many of a population who test positive are true positives; and if this number is high (as close to 100 as possible), then it suggests that a test is performing as well as the reference standard. PPV is calculated by PPV: = =true positive /true positive + false positive.

Negative Predictive Value (NPV) is the percentage of patients with a negative test who do not have the disease and therefore tells us how many test negatives are true negatives; and if this number is high (approaching 100), this suggests that the test is as good as reference standard with NPV:= true negative /false negative + true negative

Likelihood ratios (LRs) constitute one of the best ways to measure and express diagnostic accuracy. The LR of any clinical finding is the probability of that finding in patients with disease divided by the probability of the same finding in patients without disease: LR=probability of finding in patients with disease/probability of same finding in patients without disease [277].

The accuracy of a test is its ability to differentiate the patient and healthy cases correctly. To estimate the accuracy of a test, we should calculate the proportion of true positive and true negative in all evaluated cases as follows Accuracy= true positive + true negative/ true positive + true negative + false positive + false negative [278]

Resulting values were collated and graphs constructed within SPSS. MedCalc® Statistical Software version 20.109 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022) [279] was also used to allow the direct comparison of ROC/UAC areas as this functionality is not available in either Microsoft or SPSS. The Delong method was used for these comparative analyses. Delong is a nonparametric approach that allows for comparisons between two or more such indices derived from the same test units or subjects, the implicit correlation between these curves being taken into account [280]. This was an appropriate approach as, in our cohort, there is a high index of suspicion for an intra-cerebral vascular accident and thus there is not ‘normal distribution’ and it would be inappropriate to begin with this assumption. Delong allows for the

comparison of the areas under two or more ROC curves by using the theory developed for generalized U-statistics. A covariance matrix can be estimated and from this covariance matrix confidence regions may also be constructed.

I adjusted for multiplicity of the AUC between tests using the Bonferroni correction to control for the family wide error rate, i.e. incorrectly rejecting the true null hypothesis (i.e. a false positive) [281-283]. This was in recognition that a chance discovery by performing these 6 tests rose to 26.5%, and the correction would adjust the risk of this error to a more acceptable 5%.

4.6

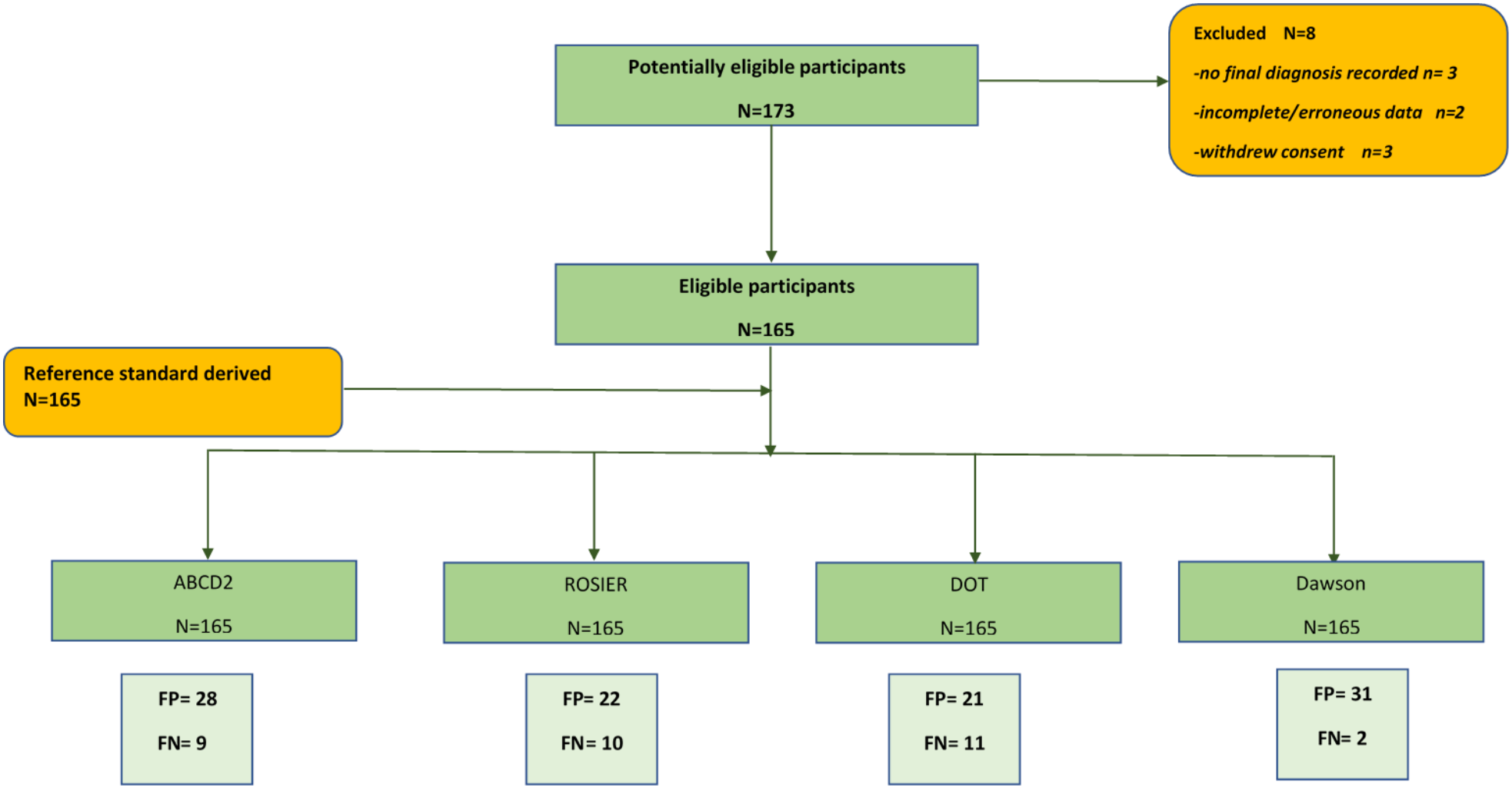
Results

The Queen Elizabeth University Hospital (QUEH) enrolled 119 patients while Glasgow Royal Infirmary (GRI) enrolled 54 patients, giving 173 patients in total.

In our study we had a complete data set for 165 out of 173 participants. There were 86 (52%) females and 79 (48%) males. Median age was 64 years (IQR: 55 to 73, range 24-92). In the cohort 48 (29%) patients had a stroke on reference standard determination, 32 (19%) had a TIA and 85 (52%) had a non-stroke aetiology).

Of the participants with missing data who were not used in the final analysis, the four GRI patients, were all female, aged from 34 to 72 years old. Two had withdrawn consent, and in the remaining two there was discrepancies with them being recorded as both either stroke and or TIA and simultaneously as well as non-mimics which I was unable to resolve and so I removed these indeterminant scores. Therefore, there were eight patients not included in the analysis. From the QUEH those that were not included in the final data set were two males and two females ranging from 36 years old to 80 years old. One male was excluded due to consent withdrawal, while all other excluded participants, at time of my analysis, lacked a final adjudicated stroke type to act as reference standard.

Figure 7: Flow of participants through the study



FP=False positive FN=False negative

Table 7: Demographic data on the Cohort

Risk factors	Yes
Smoker	26.1%
Alcohol excess	4.8%
Hypercholesteremia	13.3%
Prior stroke	20.0%
Hypertensive	44.2%
Diabetes mellitus	20.0%
Atrial fibrillation	7.9%
Peripheral vascular disease	3.6%
Ischaemic heart disease	25.5%
Family history of stroke	21.8%

*N=165

Tables 8: Calculated accuracy values for each clinical scoring system

	Sensitivity	Specificity	Positive Likelihood ratio	Negative Likelihood ratio	Positive predictive value	Negative predictive value	Accuracy
ABCD2	85%	28%	1.2	0.5	64%	55%	62%
ROSIER	83%	42%	1.4	0.4	69%	62%	67%
DOT	81%	46%	1.5	0.4	70%	62%	67%
Dawson	97%	19%	1.2	0.2	65%	78%	66%

4.7

Comparisons between scores

As can be seen from the comparative graph of AUC from the ROCs plotted for each clinical scoring system the Dawson score performs best with an AUC of 0.73, followed by the ROSIER score at 0.68 and the DOT score at 0.63 with the ABCD2 score last at 0.60. No test meets the excellent threshold by this metric and only the Dawson score achieves 'acceptable'. The Dawson score also had statistically significant differences in its AUC as compared to the ABCD2, ROSIER and DOT scores. However, after adjusting for multiplicity only the AUC between the ABCD2 and Dawson remained significant at 0.0012.

On the paired metrics of sensitivity and specificities. The Dawson score sensitivity was also superior to the other scores (97%) but it had the lowest specificity of any score (19%). Comparatively it had a low positive likelihood ratio (the same as the ABCD2 at 1.2) and the lowest negative likelihood ratio (0.2) with its PPV just superior to the ABCD2 (65% and 64% respectively) but inferior to ROSIER and DOT (at 69% and 70% respectively). However, its NPV was highest (78% against the ABCD2 at 55%). In terms of accuracy all tools performed similarly with the ABCD2 being the marginally worst performer at 62% and ROSIER and DOT achieving 67%.

Tables 9: Pairwise comparison of area under curve differences between test curves

Pairwise comparison of ROC curves:	**ABCD2 score v ROSIER score**	**ABCD2 score v DOT score**	**ABCD2 score v Dawson score**	**ROSIER score v DOT score**	**ROSIER score V Dawson Score**	**DOT score v Dawson Score**
Difference between areas	0.08	0.04	0.14	0.04	0.06	0.10
Standard Error	0.04	0.05	0.04	0.03	0.03	0.04
95% Confidence Interval	0.00352 to 0.157	-0.0533 to 0.130	0.0644 to 0.211	-0.0221 to 0.106	0.00933 to 0.105	0.0306 to 0.168
Significance level * Prior to Bonferroni correction**	**0.0404***	0.4110	**0.0002***	0.1993	0.0192	0.0046
Significance level * Post Bonferroni correction	**0.2424**	**2.466**	**0.0012***	**1.1958**	**0.1152**	**0.0276**

(Bonferroni correction alpha factor used in analysis= 0.008 with pre-existing significant defined as P=<0.05 before correction)**

Figure 8: Comparative receiver operating characteristic curve (ROC)

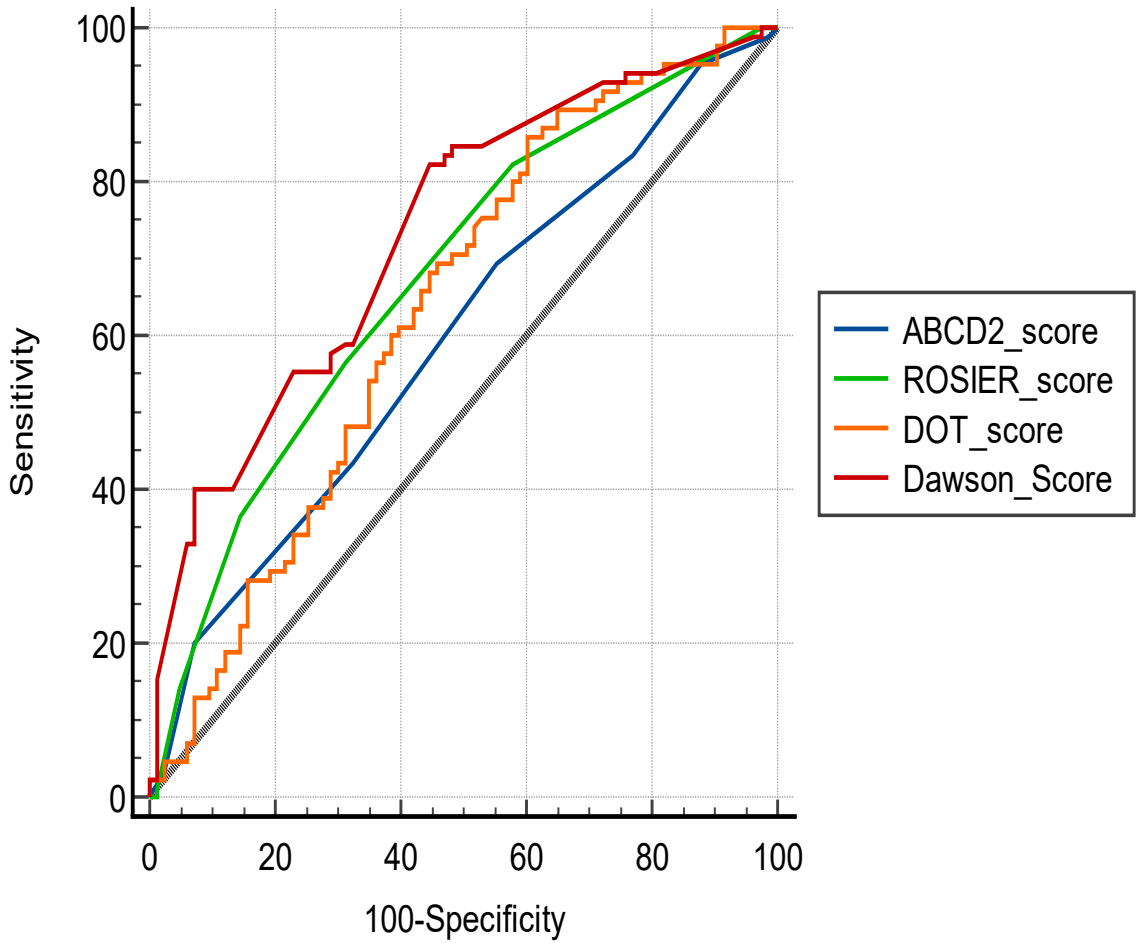


Table 10: Comparative Area Under the Curve values

Tool	AUC	95% CI
ABCD2 score	0.60	0.52-0.67
ROSIER score	0.68	0.60-0.75
DOT score	0.63	0.56-0.71
Dawson score	0.73	0.66-0.81

Table 11: Comparison of each scoring tool in its validation groups V our Cohort

	Sensitivity		Specificity		PPV		NPV		AUC	
	original study	**Our cohort**	**original study**	**Our cohort**	**original study**	**Our cohort**	**original study**	**Our cohort**	**original study**	**Our cohort**
ABCD2 [25,255]	-	**85%**	-	**28%**	-	**64%**	-	**55%**	0·62–0·83	**0.60**
ROSIER [24]	93%	**83%**	83%	**42%**	90%	**69%**	88%	**62%**	-	**0.68**
DOT [26]	89%	**81%**	76%	**46%**	75%	**70%**	89%	**62%**	0.91	**0.63**
Dawson score [27]	93%	**97%**	34%	**18%**	68%	**66%**	76%	**78%**	-	**0.73**

*Where authors have performed or given a value for sensitivity, specificity and PPV, NPV and AUC in their papers

4.8

Discussion

I will frame the discussion by first summarising the main findings from this study and the key messages which result from it. I will then discuss the differences between the tools, what an ideal test would look like and how clinicians should use these results in practice going forward.

4.8.1

Summary

I sought to directly compare the accuracy of commonly used stratification/diagnostic tools i.e., the ABCD2 and the ROSIER scores as well as the DOT and Dawson scores. This demonstrated that by the AUC metric all the tests were imperfect with a range from 0.60 to 0.73, from the ABCD2 up to the Dawson. When looking for significant statistic differences between tests AUC this was only found between the ABCD2 and Dawson score (once adjusted for multiplicity). All scores had sensitivities of 80-100% i.e. a high degree of ability to detect disease and so yield few false negatives. However, specificity was in the range of just 19%-46% i.e. more than half of all results were erroneous false positives. While it is indeed important not to miss a true cerebrovascular diagnosis from this work it is clear there is a need to improve specificity of all tools, and so reduce non-stroke referrals to TIA and stroke services. This would relieve pressure on systems as well as reduce potentially risky treatments in patients for whom no benefit will be conferred. Therefore, future work could be directed at trying to optimize current tools to improve specificity, but without making this so onerous on either clinician or patient (and thus making it unacceptable) that such an improved tool is never clinically utilized.

Comparing respective AUC from the plotted ROCs the Dawson score had the best relative performance and the ABCD2 score had the poorest accuracy. However, with a clinically conventionally accepted minimum of 0.8, The Dawson score still falls short of the usual bar set for diagnostic tests to be considered clinically useful. Nonetheless, this was true of

all the diagnostic tests I calculated accuracy metrics for, including the two that are already widely used.

By its nature, AUC is an aggregate of sensitivity versus specificity, and it is likely that the clinician using the tool will have situation specific requirements for a tool's discrimination ability. Thus, sensitivity and specificities can be considered in more detail for a given situation. The Dawson scores had a sensitivity superior to the others but at a cost of lowest specificity. Thus, for correctly identify those who do not have the disease, i.e. sensitivity, the Dawson score was comparatively best, but was worst at correctly identifying people with the disease (specificity). If we apply the score to a theoretical sample of 200 referrals to a stroke service, with an equal mix of stroke and non-stroke diagnoses, the Dawson score would be expected to accurately identify 97 people who have a TIA/stroke and miss 3%, while identifying only 19 people who had not sustained a TIA/stroke, misidentifying 81 people.

4.8.2
Differences between the scores

It is important to bear in mind the intended purpose and clinical setting in which each tool may be used, the ROSIER is an emergency room tool to recognise a TIA/stroke in an acute environment in those with current symptoms, while the ABCD2s original purpose was to stratify risk of a stroke after a confirmed TIA. This could account for some of the differences between the scores. This is also true of both the DOT and the Dawson scores, with both aimed at non specialist use to aid TIA diagnosis, rather than proceed from the basis that a TIA is confirmed, which again may give rise to some of the differences in accuracy. In our cohort all patients had already been admitted or referred as a high index of suspicion of stroke or TIA, which may also account for observed differences in performance between our data and the original development data for each test.

Considering the sites, and their acuity, and impact upon the data it is likely that as more participants tended to be recruited from clinic at Glasgow Royal Infirmary there might have been more mimics than at the QUEH site which tended to have very acute presentations. The advantage of this mix is it makes the overall sample more representative. Conversely it also means data from one may not represent another, and if one sites recruited participants dominates in terms of numbers it may be less generalizable.

4.8.3
Ideal tool in context

When choosing a test strategy based on accuracy, it is important to consider which should be given greater weighing of sensitivity or specificity. This issue again depends upon the intended purpose of the tool. Within an emergency department setting it may be very useful to stratify the risk of subsequent stroke or indeed imperative to identify if a stroke event has acutely occurred, cognisant of the harm of a missed diagnosis and missed opportunity for acute intervention. In this scenario a high threshold would be desirable in terms of clinically ruling out stroke with a low threshold set to indicate possible stroke and need for further investigation. Necessarily those tools providing best available sensitivity (i.e., to detect true cases) and best available specificity (i.e., to detect true negatives) would be preferred. However, no such perfect clinical scoring test exists and thus it is necessary to consider which tool can best aid in this endeavour, but not replace clinical judgement.

Here a tool's ease of use and acceptability to both clinician and patient plays a part, as easy to score short objective items would be preferable to a long and more complex scoring system which might require specialist stroke training to accurately complete. On these metrics both the ROSIER and ABCD2 are simpler than the DOT and Dawson score. Indeed, however with the relatively similar AUCs for all scores and other accuracy measures, these more complex and difficult to complete scales could be argued to offer few additional benefits. Where time is precious, even if these tools offered a substantially higher accuracy compared to the currently employed ones it is questionable whether they would make it onto the ED or clinic floor. Their applicability to a generalist rather than a stroke specialist is also a key consideration. While cognisant of the fact there is no perfect system, and these tools are designed to aid diagnosis rather than provide definitive answers, for the generalist the Dawson score shows promise with the lowest FN rate of all schemes. This was employing its 2 for 1 misclassification giving a FN rate of just 20%, all of the other tools had higher FP rates. Given the significance of missed strokes in terms of mortality and morbidity, the Dawson scale could be argued to have performed 'best'.

In a primary care setting, which is my usual clinical context, any tool to aid in diagnosis must be easy to use, easy to calculate and not be cumbersome to do within the pressured confines of the typical 10 minute consultation. Therefore, something that can be easily

derived from metrics we commonly already measure and ask for such as BP, age, and simple clinical features would be more likely be accepted. Cumbersome components such as detecting a homonymous hemianopia would likely struggle to gain traction. These more detailed components are more liable to introduce intra-performer differences and are time consuming; a fact which would not escape the notice of most GPs if an acute stroke or TIA was occurring in front of them (or perceived to be), where 'time is (brain) tissue'. Thus, any push to ask for such scores prior to an ambulance being called would likely be against the patient's interests and indefensible. In a different clinical situation, performing these scores whilst awaiting scanning or therapy might be more reasonable in a secondary care setting, as long as it is not impeding care or being used to defer it. Thus, the true valve of these scores might lie in aiding appropriate triage and prioritisation of finite resources and will be dependent on the environment and context.

4.8.4

Test accuracies against original development studies

The original reported accuracy figures for the diagnostic tools were higher in all metrics (except for the Dawson score), indeed our specificity using ROSIER was only half of the original study reported specificity. This may well be reflected in the acuity of presentations i.e., signs, symptoms, and imaging findings in the emergency department, versus fast-track referrals which are not as hyper acute and where these signs and symptoms might change. This can impact upon the subsequent score assigned to the patient, if reliant on history alone versus history and examination. It could also be the case that as clinical signs and symptoms show temporal evolution, differing scores for the same patient may be obtainable at different time points. It is often the case that subsequent validation studies fail to replicate the accuracy seen in the original development papers and this highlights the need for robust, independent validation of all such tools. None met the perfect score of 1, however this is an unrealistic goal. Within a clinical context of test accuracy, 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and more than 0.9 is considered outstanding [284]. In contemporary practice achieving 0.8 to 0.9 would be a success.

4.8.5
Comparisons with other stroke assessment scales

In an analogous presentation, that of aneurysmal subarachnoid haemorrhage, there are two clinical tools for grading the disease, one being the Hunt and Hess grading scheme and the second being the World Federation of Neurosurgeons (WFNS) grading scheme, which incorporates the Glasgow Coma Scale. There is another called the Fisher Scale but this incorporates non contrast computed tomography (NCCT) scans findings and is not purely derived from history and examination. Although these are primarily prognostic rather than diagnostic tools, the clinical setting and component items are similar to the tools I have assessed, and so are worthy of comment. A recent comparison of these clinical scores found that they displayed good performance at predicting poor clinical outcomes and mortality with the HH (AUC 0.806 and 0.782) and the WFNS (AUC 0.785 and 0.740 for predicting unfavourable outcome and mortality) [285]. Interestingly some studies have shown these clinical scores perform better than scores which incorporate radiological elements [286] .Further, another group showed the AUC HH (AUC=0.771) and WFNS (AUC=0.777) for predicting mortality in SAH [287].These AUC figures are not too dissimilar to our own figures for the prognostic scales we evaluated. In a related study looking at comparative analyses of prognostic accuracy of stroke scales the range of was again similar in the region of AUC 0.61- 0.78 [288].

4.8.6
Strengths and weaknesses

Some of the strengths of this study are that rather than compare the tools using indirect comparisons, different reference standards or attempting a network meta-analysis, we have employed the same reference standard in the same patient population for all the tools, making direct comparison possible and accurate. Having access to the full clinical notes, investigations, and radiological notes of each participant, meant I had the most robust and comprehensive data possible. The inclusive recruitment criteria were chosen to reflect real

world practice, this is not always true of test accuracy studies where historical studies have excluded those people with factors that may make scoring difficult and have thus inflated their accuracy estimates.

A weakness in the study, which is common to many clinical test accuracy studies, was my use of expert clinical consensus to arrive at a final reference standard diagnosis. Although the adjudication panel were blinded to the total scores, some of the information used in the scores will have been incorporated into their assessment. This incorporation bias is difficult to avoid in studies with a clinical reference standard. There is also the possibility that subjectivity can lead to inaccurate reference standard diagnosis despite a multidisciplinary, adjudication panel assessment. The lack of a definitive biomarker and inconclusive imaging and/or clinical work-up necessarily means in some participant cases a judgement by those with most expertise requires to be made. This 'imperfect' reference standard is common to many areas of clinical diagnostic test accuracy studies [289]. It could also be argued that as I was involved in all index test scoring, except the ABCD2, and all the consensus clinical diagnosis for the reference standard that this could have influenced the outcome in an unconscious way.

4.9

Future research

Future work could be directed at further refinements of the tools to improve their accuracy. For example, additional diagnostic components could be added to tools without becoming too laborious. Any additional scoring item must have obvious benefit as in busy clinical environment unwieldy tools with many components, particularly items which are geared towards specialist rather than generalists, may jeopardise the credibility and ultimate usage of the tool. The end user of any tool is the ultimate arbiter of that tool's clinical utility. Building on this argument, the user friendliness of tools could be considered in more detail drawing upon design theory.

With the dawn of machine learning (ML) systems to aid in complex computations, it is expected these technologies will have benefits for clinical decision making and could perform at a higher sensitivity and specificity than traditional models [290]. ML systems

constitute a field of artificial intelligence (AI) concerned with the question of how to construct computer programs that automatically improve the accuracy of their output with experience. This has been an ongoing endeavour since the 1970s, with computer-aided technologies developed to assist in medical diagnostics. Here labelled data are utilized by the model to learn a mapping between the input data and the outcome variables. In clinical decision making, ML models produce an inferred function that maps labelled input data to outcome variables. Once trained, the inferred function can be utilized to make predictions of the outcome variables once given new input data.

It has been intriguing that in the SAH tools considered above, incorporation of radiological elements to clinical scoring systems has at best produced an uncertain benefit. This could equally apply to TIA and stroke scales, unless great care is taken. It is a perhaps possible that AI based refinements considering imaging data and the employment of ML could improve the diagnostic accuracy over and above most current approaches. While this is a hope it is likely however that even these augments will never produce a perfect scoring system of 100% accuracy, which is perhaps an unachievable goal in the messy reality of clinical medicine. Again how useable a tool is, and crucially how acceptable such a tool is to the patient is key, as only acceptable tools are likely to make it into a CPG no matter how good at discriminating an unacceptable clinical tool might be.

A potential weakness of the study was that I was not blinded to the reference standard when performing the index cases, having calculated the index tests after categorizing each case to the reference. This being the case as the categorizing had been intended for the original trial, as was the ABCD2 already having been derived.

4.10

Conclusions

It is apparent that there is no current perfect tool to aid in the diagnosis of stroke and TIA. There are, of course, metrics describing accuracy of a tool e.g. AUC and sensitivity and specificity. However, another crucial consideration is around the ‘user friendliness’ and usability, or to use the terminology from the previous chapter the user acceptability. Long, complex and detailed scales may not appeal, nor be used. This is particularly true for

clinicians in time pressed environments. However, the impact that any assessment tool has upon the patient as the single most important end user must also be considered. If there are many components which patients find unacceptable or overly burdensome then even a quantitatively perfect tool whilst technically correct will likely not be employed, nor be recommended by EMB in a CPG, therefore the benefits of increased accuracy versus patient acceptability must be very carefully weighted.

Chapter five

Discussion: Synthesizing the approaches and results

5.1

Introduction

In this final chapter I will summarise each of the original works that have preceded it and then move on to discuss their respective strengths and weakness. I will then set this work in its context of the surrounding current research landscape, as well as the clinical implications that it brings. I will then discuss the future directions for possible research work that flows from it, and then finally conclude and move on to discuss the benefits of mixed methods and looking at the thesis as a whole.

This final chapter, by weaving together the findings from the preceding chapters, will demonstrate that despite focusing upon different elements of stroke, when taken as a whole they provide some novel insights.

In the initial research chapter where I examined CPGs making recommendations around cognitive assessment in stroke, the clinician centric focus of these recommendations (about which assessment tools to use, by who, and when) remain vague. Further despite some CPGs attempts to be more patient centred, given that these are in fact complex health interventions, most CPGs remain likewise unclear in both in how to achieve this, and how to measure it. Being cognisant that an integral part of being patient centred (and its previously discussed benefits) is the provision of acceptable interventions. None of the reviewed guidelines I examined achieving even a modest 20% score for the 'views and preferences' of target population on stakeholders from question 5 of the AGREE-II checklist which I have used as a proxy for considering patient acceptability.

In the second research chapter the view of stroke survivors themselves is considered. Here those factors which make an intervention (i.e. cognitive assessment) acceptable were listened to, analysed and encapsulated and then presented in a way that makes clear to the providers of such interventions what must be considered by them, and attained for such an assessment to be acceptable and appropriately patient centred. Unlike the objective and measured output of the analysis of CPGs, stroke survivor's themselves are given a voice and it is very much a narrative output. I have sought to bring these individual and unique contributions together into a cohesive form from their lived experiential wisdom.

Thus I hope this brings balance to the preceding work by plainly distilling what matters most to patients themselves in these events. Trust, communication and considerations of the burden and harms those assessments can bring are what counts, with our lived experience giving a platform to those who have until recently not had many opportunities to make themselves heard.

In the work around data accuracy of the stroke tools I hope to have demonstrated the utility of the current clinical scoring systems in a modern stroke setting giving clinicians the salient points about each, and what to consider when using them in terms of benefits and pitfalls. I also hope that the potential of modification of these to enhance accuracy has been demonstrated while also ensuring that the voice of stroke survivors themselves in heard here too, these need not be mutually exclusive.

In the final chapter I will give a brief summary of my career and interests.

5.2

Summary of chapter two

To summarise the main findings of chapter two. Having performed a systemic review of the literature it was clear that despite the prevalence of stroke, and stroke related cognitive deficits, there was few guideline recommendations and where recommendations were available, these were based on limited primary research data. Given the lack of primary research, the clinical guidelines that considered post stroke cognition utilized expert opinion as a source of information when making recommendations. This is not a criticism of the guidelines, as expert opinion from distinguished clinicians who are experts in the field is vital in the absence of more empirical evidence, but rather points to the surprising lack of research in exploring the topic of stroke cognitive assessment in a more robust manner.

It is hard to make compelling recommendations without evidence and so the recommendation text was often necessarily vague or cautious, arguably providing limited practical assistance to the clinician’s tasked with assessing cognition after a stroke. For example, guidelines generally refrained from specifically naming a particular tool as most suitable and instead refer to ‘using validated tools’.

An obvious gap for CPGs to fill going forward would be to actually make a recommendation on which tool(s) to use for cognitive assess, who should undertake the assessment, and when to perform this. Given the impetus from government, funding agencies and the third sector, to move towards an even greater person centred care approach; the lack of previous investigation into how acceptable a complex health intervention (in this case assessing a person's cognition) seems rather anomalous. As well as a lack of consensus across guidelines on which specific assessment tool should be used, similarly there was little guidance around the timing(s) of assessment or indeed who should perform these or what training they should possess; again, offering less certainty in statements by using terms such as used by 'trained and competent staff'.

It is important to bear in mind that a clinical guideline, is just that, a tool to guide rather than a mandate. A clinician must recognize when 'deviation' from guidance may be the best option in the context of their patient. Thus completely prescriptive guidance on a specific tool to use and the preferred approach, may not be suitable for a particular patient and so from an acceptability point of view might be a poor fit. Therefore, returning to core concepts of care i.e., practicing patient centredness, will necessarily mean considering language, cultural barriers or practical barriers that may complicate the use of a particular test. Indeed in the context of stroke itself an important consideration is physical disabilities such as impaired vision/hearing, communication issues or, loss of dexterity. While most guidelines did refer to this contextualising and tailored practice, few if any, took account of the patient's perceptions or feeling towards the assessment. I also did not take into consideration the patients' thoughts on the assessment process in this chapter, instead I covered this in the chapter three with the framework analysis work.

Within the context of the current literature it is clear the central prominence that cognitive impairment post stroke occupies, to both patients and clinicians, my findings that CPGs chiefly offering little concrete recommendations with respect to cognitive assessment during stroke care seems out of step. While CPGs were commonly of high quality (as using the AGREE-II tool to quality assess them) they were of little significant clinical usefulness. The core fact that there is a paucity of high-quality study trial in the field was re-affirmed by the 2021 joint European Stroke Organisation (ESO) and European Academy of Neurology (EAN) guidelines on post-stroke cognitive impairment (PSCI) [215]. Thus this represents an ongoing gap in the field.

While both systematic reviews, and meta-analyses of the properties of various cognitive tests in stroke do exist [181], quantitative analysis alone can only ever offer one vista by which to consider interrogation of the user experience. This by itself may not offer the rich and detailed description of the complexities and nuances involved during a multifaceted complex healthcare intervention such as that of cognitive assessment. Indeed here it is likely qualitative methodologies, will at least have a part to play when considering the importance of patient acceptability, and the intricacies of measuring human experience in the pursuit of being patient centred.

A strength of the work on global CPGs was following a GRADE approach, and pre-defining a PICAR criteria (in the same way SIGN advise for CPG development). The search strategy was robust and another methodological asset. Furthermore, by having two clinicians independently assess at all stages including the title reviews, AGREE-II quality rating, data extraction and then producing the final table of condensed recommendations, I ensured that the final materials were the product of a strict quality assurance approach. This safeguarded the fidelity of the master table, ensuring that the final table was a true summation of the included CPGs recommendations.

There are several limitations to consider however one being that by only including English language CPGs this could have resulted in omitting pertinent guidance from other high income health care services in the EU i.e. France, Germany or Switzerland. There is also the possibility of missing important germane guidance from middle and lower income health care systems, although it would be generally expected that there would not be the degree of analogousness of health care systems to allow direct comparisons.

The clinical implications of this mean that to date there remains few concrete and tangible recommendations available to clinicians when assessing cognition and at present this means there is likely to be a wide array of clinical practices and approaches, the outcomes of which are not being studied or reported.

The future research arena will mean that a significant focus of the future CPGs development process will be twofold, on the one hand offering more tangible recommendations about how clinicians concretely assess cognition and identifying which tool to use, this will need to necessarily come from original research to inform these if we want to move away from expert opinion and onto evidence based practice. On the other

hand this envisaged field for future research will need to be rooted in adherence to patient acceptability and considering patient centredness when designing these studies.

5.3

Summary of chapter three

While a focus of chapter two had been to quantitatively examine the reporting and quality of clinical practice guidelines concerning stroke cognitive assessment (primarily from the viewpoint of the clinician). Chapter three, in a complimentary and synergistic manner gives context to those assessments from the patient's perspective. I believed this was important for two reasons. The first is that traditionally this perspective has been overlooked, if not altogether neglected, in the literature around health care interventions such as cognitive assessment following stroke. The second reason was that given the increasing importance attached to patient centred care and/or acceptability of health care, it was vital to consider the patient experience and viewpoint. Care is a partnership and without the requisite information sharing, creating shared goals and allowing patients to become empowered to make their own decisions, then patient centred care, and its benefits, cannot be fully realised. The first step in this process is actively listening to patients.

To achieve this goal of understanding the patient experience of cognitive testing, I undertook a framework analysis of varying patients' views, in a qualitative fashion. This allowed themes and patterns to emerge from the data. Employing a qualitative approach in this way ensured I could add novel data and enhance understanding over and above that which could be captured quantitatively from the preceding CPG systematic review chapter. I wanted to ensure that patients as full partners in their own care were heard. I believe this enriches the findings in the thesis and adds further value to the current body of literature.

The current definition(s) of acceptability are nebulous, and with this in mind I sought to ground the definition I used in Sehkons description of a TFA [110]. What emerged organically here was that patients want tailored information and here there needs to be consideration around the harm of testing and disclosing results. However, most patients were comfortable with the concept of testing and had trust in health professionals., A better

cognitive testing experience may be possible by reducing the burden of participation in the testing process and by taking account of participants differing motive for engagement in the process. It was clear that just as clinicians wish to arrive at an accurate diagnosis through using the most appropriate test, this was also true for patients. However, the parameters that define appropriate or acceptable tests may well differ between clinicians and patients.

This analysis gives some much needed insights, as similar to the cognitive guideline field, I found a paucity of primary research around defining and assessing acceptability for any cognitive testing, and no other papers at all with an exclusive stroke focus.

On considering the other group with a stake in the use of CPGs, not the clinicians, but the patients undergoing assessment, this work is the first to explore the acceptability of cognitive assessment in stroke survivors admitted to hospital in a qualitative manner. The finding of five major themes influencing acceptability from a patients point of view includes participation motives, trust in health professionals, perceived risk of harm, information provision and the burden of that testing. Taken together these outline the essential components of acceptability that stroke survivors name as necessary as being comprised of *a trustworthy professional taking account of their individuality to deliver an assessment, and explanation of the results of that assessment, in a manner they personally find acceptable and which aids in their diagnosis, whilst ensuring the process minimises potential burden and harms as much as possible for the participant.*

Another key finding was that most participants expected to undergo cognitive assessment and engaged with it, when admitted as a suspected stroke, but that individual preferences around the degree of information sharing, when to share it, and any concomitant implications must match individual's explicit preferences and not merely be assumed.

Contextually while here there was no previous literature specifically looking at stroke survivor's experience of cognitive assessment during acute stroke care and so this represents a novel pioneer finding in the field, in one dementia cohort views on post stroke dementia were also likewise explored by qualitative interview participation. The authors too found participants express a wish for a timely diagnosis, anxiety around a dementia diagnosis label, and worry about how a dementia diagnosis might impact on recovery. These all affected the acceptability of screening. These were broadly in line with what I

found in this stroke cohort. Whilst in a pilot study examining the acceptability of four cognitive tests for Australian Aboriginals (unaffected by stroke) the authors found that assessment was generally welcomed as a positive experience i.e. ‘playing a game’ and ‘a good challenge, a view which was echoed by some of participant’s in this cohort too.

A strength within the qualitative analysis work, this is an important account of patients’ experiences of undergoing cognitive assessment, and represents a first interpretation of their views in the field. Given that they are indeed the preeminent partner of the clinician undertaking the assessment it was surprising to me that until now their views had not be explicitly sought and considered before. It is important that we as clinicians hear them, as the important partner in the shared decision making about their own health. This offers important messages for clinicians about the circumstances and behaviours we need to cultivate to ensure such cognitive assessments are acceptable to stroke survivors, and so is a significant strength of this thesis about how to be more patient-centred.

A weakness of this work could be that that that by only having 2 people undertake the analysis that their own interpretations and contexts might have coloured the final analysis, something which is an inherent caveat of qualitative work. On another point would the views of stroke survivors remain the same, it is legitimate to ask, if other forms of qualitative analysis, for example those of grounded theory or discourse theory, had been utilised to analysis the data.

Notwithstanding this clinically the implication is that patients expect a professional that they deem as trustworthy and competent to execute an assessment and then provide personally tailored information about that assessment, which is expected to aid in their diagnosis, whilst limiting prospective burden and harms as far as possible.

Future research efforts could be focused on shedding more light on acceptability and how to measure this, so that funders such as the MRC can be more explicit in how they define acceptability. With a fuller field with newly populated studied upon which to draw this could be clarified and refined further. This could then aid for example CPG stakeholder involvement processes. Another avenue might be seeing if the same factors of acceptability that I found hold true in other complex health interventions during stroke treatment i.e. speech therapies’.

5.4

Summary of chapter four

While both chapters two and three focussed on differing aspects of the cognitive assessment of patients who had sustained a stroke, chapter four provided quantitative analysis of test accuracy for diagnosis of stroke or TIA. Accuracy was a recurring concept in the previous chapters and I used this chapter to explore the statistical analysis and clinical application of test accuracy data. Using comparative test accuracy analyses for the four diagnostic aids, I demonstrated that no clinical tool was perfect at detecting or discriminating stroke and TIA from their mimics. Users of these tests must bear in mind the intended purpose of each tool (and where its intended location of use is) and the context in which it is being employed. For example, the relatively simple and sensitive ROSIER tool performs well for its intended use in busy emergency rooms where time is critical and the stakes around a missed diagnosis of stroke are high. While the Dawson score had greatest overall accuracy and demonstrated best sensitivity, it included features that may be less immediate or require derivation, for example assessing for the presence of diplopia, enquiring about or obtaining previous history of TIA or stroke and then using the patients age multiplied by 0.04. It could be these may limit the clinical utility by increasing the time taken to complete and the perceived burden of calculating the score. It is worth remembering that while all the tools considered were imperfect for detecting stroke or TIA, even the reference or 'gold' standard is not perfect. Indeed in the not insignificant number of times that even when fully investigated, the diagnosis remains elusive, then again expert consensus as a last resort is relied upon. This can bring the potential for subjectivity and may itself be imperfect. Thus in this context, it is perhaps unrealistic and unfair to expect any clinical scoring system to achieve 100% accuracy in clinical practice, and rather look to them as an aid rather than provide the answer of themselves.

Contextualizing these findings in the current literature the results in the cohort I examined show that generally the sensitivities in this thesis where broadly similar to the original studies, (however at times some were up to 10% less so) except in the Dawson which was fractionally more sensitive than in the original. Specificity was however consistently lower at approximately around only a half of those reported in the original studies. Reported PPVs showed some disparity to the original studies, with the largest dissimilarity seen

between this cohort and the ROSIER score at some 21% of variance. NPVs showed a greater discrepancy still, between original studies and this cohort, with the largest difference demonstrated for the DOT at 27%. The Dawson score had the closest calculated PPV & NPV results to the original study valves. While for those original studies providing a reported AUC this cohorts figures appeared to demonstrate that there was an overestimation of the original studies accuracy however.

Examining the tools through the AUC lens metric all systems were imperfect, none met the excellent threshold metric of 0.8 with only the Dawson score achieving 'acceptable' at 0.73. All others tools had an AUC below 0.70 ranging from 0.60-0.68, but despite this there was only a statistically significant difference between the AUC between the ABCD2 and Dawson scores.

When considering the components of each scoring system the simplest systems of ROSIER and ABCD2 each have 7 components, while the most complex consisted of 17 components, was found within the DOT. What the ROSIER demonstrates in contrast to the DOT score is that it is not necessary to merely continually add multiple additional components in an attempt to increase accuracy. This was achieved by the Dawson with a modest increase to 9 components (up from 7), by the addition of history of stroke/TIA, headache, diplopia and then by adjusting for age instead of checking for visual field defects. Thus it built upon the ROSIERs components with minor modification to achieve a higher discrimination. While some parts of the ABCD2 cover these too there is more differences than similarities with it when comparing against the ROSIER or Dawson.

Despite the DOT substantially increasing its components and some of those being relatively difficult to elicit i.e. Homonymous Hemianopia, or Unilateral sensory loss on examination or on history from a dysphasic patient about presence of a headache, amnesia or the presence of tingling and numbness there appears to be little clinical diagnostic gain in terms of discriminating ability. It then has to be reflected on how easily some of these components are for the generalist to accurately elicit, and just as crucial is how acceptable such components might be to comply with during examination for the when they are acutely unwell, and thus acceptability would be vital to reflect on here.

Given the grievous consequences of missed stroke perhaps then it is right that the most important metric to consider is the lowest number of FNs (i.e. where strokes & TIAs are missed by the scoring system), thus in this cohort I analysed the Dawson again performed

best (but did have the highest number of FPs). The DOT had the poorest sensitivity i.e. the largest number of FNs, despite a much more arduous scoring system, but did have the best specificity at only 21 FPs or 46%. All the other scoring systems had lower specificity (of less than 50%) and so it is clear that all systems have big strides to make to improve specificity and reduce FPs, but which will have to be done in a manner which doesn't becoming so unwieldy it cannot be utilised, and which is not so taxing or oppressive for a patient that its unacceptable and fails to meet the aspirations of patient-centred care.

A strength of this study was that the data accuracy study's strength was its direct comparisons head to head using the same reference standards to the same data set in the same patient population for all the tools, making direct comparison possible and accurate which is something which has been lacking in the wider literature and it is an asset of this SWAT adding depth to this thesis.

A weakness of the study could be that it the sample I used was not multi-centred (rather it was drawn from the same city), but this was the case in the original validation studies also. Another potential weakness in the study, which is common to many clinical test accuracy studies, was my use of expert clinical consensus, due to a lack of a definitive biomarker and at times inconclusive imaging and other investigations. Thus the final reference standard could be argued to contain some inherent subjectivity.

The clinical implications of this include that while no tool met the threshold for good predictability and only the Dawson met the acceptable threshold as seen through an AUC lens, given that there is no current perfect reference standard with perfect diagnostic discrimination it is unfair to expect this of a clinical scoring systems,. Nonetheless it was insightful that despite the differences amongst tools there is not a particularly wide spread in AUC discrimination. Some tools like the DOT have a long list of components which do not offer a significantly improved AUC, in fact it was beaten by a scoring system of just 9 components in the Dawson, and it also had the greatest number of FNs, i.e. greatest number of missed strokes but did have the fewest FPs i.e. the fewest number of erroneous strokes labelled strokes. Concluding that despite its much more complex system it critically misidentifies the largest number of true strokes as non-strokes and thus potentially has the greatest deleterious sequalae in that number in whom a true stroke was missed in.

The research implications are clear that ‘more tool’ is not necessarily better, but offers the prospect that the modification of existing tool in a ‘smart tool’ is a feasible way forward. Clearly, the adaptation and augmentation of these existing clinical stroke scoring systems in future could be fruitful avenues of research. However, any work to improve these tools accuracy must be cognisant of the imperative of patient acceptability, and it is conspicuous that the most arduous tool to calculate does not dramatically increase its discrimination ability.

5.5

Integration of chapters & the benefit of mixed methods

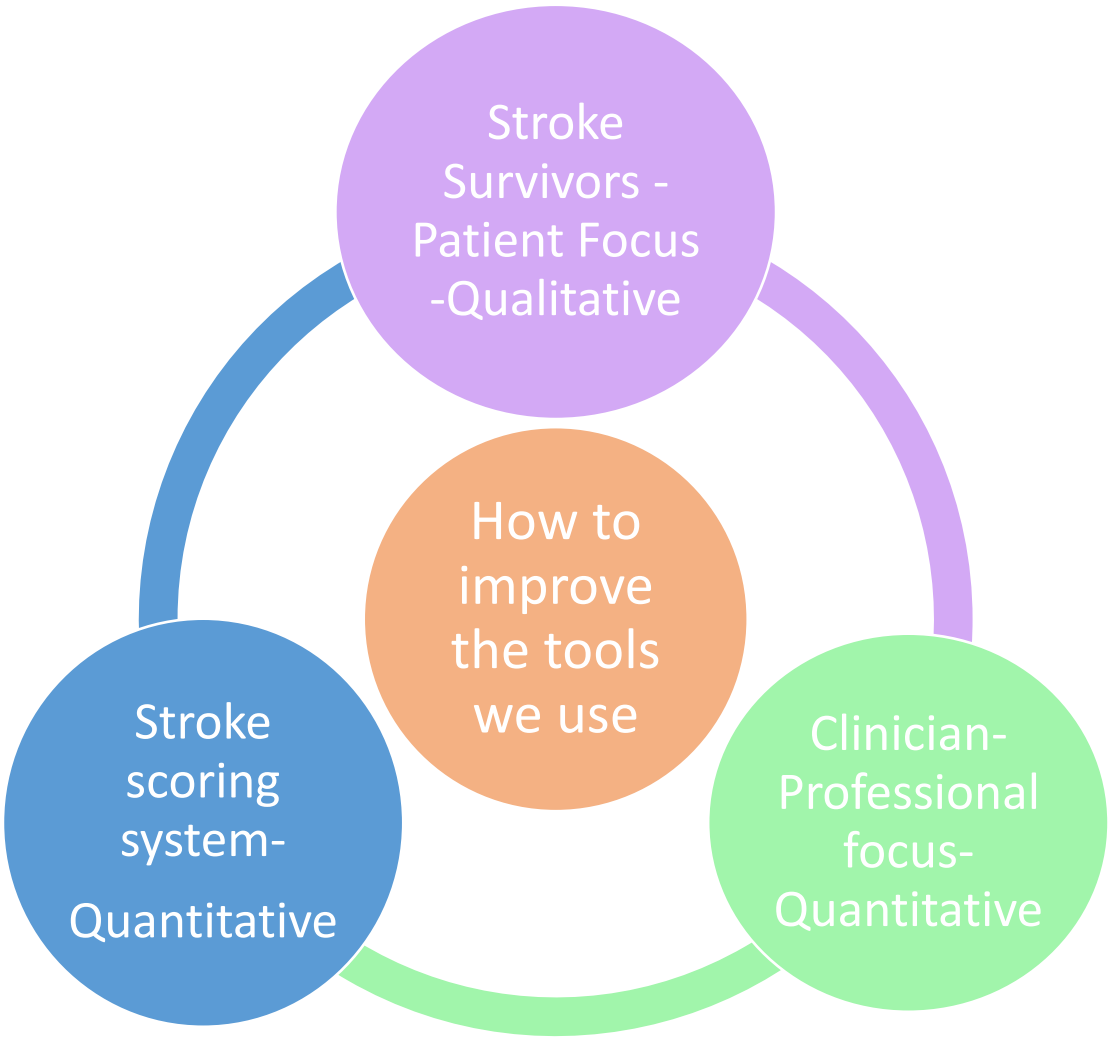
It has been argued by some that the differences between quantitative and qualitative researchers and their respective approaches to gathering and analyzing data (underscoring a broader dogmatic schism for decades) is in contemporary discourse redundant and archaic [231]. Instead, the complexity of today’s research problems demands more inclusive and nuanced efforts, this is especially so when considering the importance attached to acceptability in health care. Thus by recognizing the inherent relatedness of qualitative and quantitative data, i.e. that all quantitative data are based on qualitative judgments and that all qualitative data can be described numerically, the emergence of mixed-methods as a third methodological movement, unencumbered by this past antagonism, has emerged [231,291].

Thus on the one hand quantitative research seeks generalizability through controlled, value-free (or value-neutral) processes that can test and validate theories through a process of falsification. The emphasis on falsification often leads quantitative investigators to focus on sample size and statistics to showcase broad generalizability [231]. On the other hand qualitative investigators focus on the development of theories based on an interpretive or individualized process because there are many possible interpretations of the same data, and hold a belief that researchers must do a better job in telling the stories of individuals. Therefore qualitative investigation seeks to understand or make sense of the world based on how individuals experience and perceives it, framed through social interaction and personal histories and narrative experiences. These types of interactions and personal factors are highly relevant in cognitive assessment processes when someone sustains a stroke and also when undergoing an examination and/or a history in order that a clinical scoring system score can be completed.

I believe employing different methodologies across the different chapters has been a strength of my thesis, providing insights and truths from different stand points. The realisation that truth conveyed via numbers alone cannot be fully realised is understood. I have acknowledged the value of rigorous statistical analysis and demonstrated how robust quantitative data can be used to answer important clinical questions such as accuracy of a test. However, I now also acknowledge that in interactions as complex, nuanced and unique as those seen in clinical inter-personal encounters, qualitative analysis is required, although these data alone would not offer the comprehensive exploration of the topic I wanted. I believe this mixed methods approach provides novel discoveries which would not have emerged from employing a solely mono-methodological strategy. By having evidence synthesis, qualitative and quantitative analyses embedded across the thesis these methods complement, and allowed me to draw conclusions through a more holistic and fuller lens than would be possible with simple binary outcomes based analyses. I hope that my mixed approach makes the thesis findings more relevant to policy makers, clinicians and the public. This can be envisaged in the triangulation model seen in Figure 9.

The intent of the thesis is to expand the knowledge of current clinical guidelines and best practice and for this to be spread and disseminated as widely as possible. Perhaps the most important learning comes from those results that are broadly consistent across all the chapters, namely that consideration needs to be given to the context and purpose of testing in stroke; the patient and clinician expectations and experience of testing is as important as traditional measures such as accuracy and that more original research is required around testing and test strategies in stroke healthcare.

Figure 9: integration benefits this figure demonstrates the triangulation approach that mixed methods offer to inform a fuller appreciation of the results that investigation of complex healthcare interventions offer



5.6

Conclusions

To date, there remain few specific, recommendations in global CPGs with respect to assessing cognitive function following stroke. An ostensibly clear route through which more primary research around cognitive assessment to inform CPGs may contribute to altering this reality. In this context, findings from my CPG meta-analysis and synthesis made clear this is a global phenomenon and not unique to any one country when it comes to answering these fundamental questions.

Somewhat surprisingly my study into what makes (a complex healthcare intervention) in this case a cognitive assessment during the period of inpatient stroke care represents a first contribution in the field. Despite the known benefits of practicing patient centred care, and as an integral part of this, ensuring the acceptability of the interventions to patients this has been little studied. Given the importance of these interventions and the necessary co-operation of the patient, and how this can have significant consequences for the outcome it is perhaps not at all unreasonable to ask why it has taken until now for these matters to be considered more seriously.

My findings serve to illustrate the essential components that stroke survivors themselves speak of as being their defining features of acceptability. Those are that of a professional they deem trustworthy, who taking account of their individuality delivers an assessment, and explanation of the results of that assessment, in a manner they personally find acceptable and which aids in their diagnosis, whilst ensuring the process minimises potential burden and harms as much as possible for the participant.

The TFA which was conceived to offer a framework by which to understand what influences acceptability offers the prospect of having further use to explore and analysis acceptability in other healthcare interventions.

Whilst in chapter 4 when I compared the accuracy of the stroke scoring tools head-to head it was to give a contemporary answer to the utility of these scoring system in a modern population, and importantly this illustrated that simple tools can for a variety of reasons be

superior than more complex tools. An important finding which may aid in the refinement of these in future whilst ensuring continuing patient acceptability and alignment from stroke survivors perspective when participating in such assessments.

5.7

Biography

Below is a short biography of myself to contextualise my background and how I came to research.

5.7.1
Training

In my medical career I have always has a keen interest in evidence-based medicine and in particular evidence as it applies ‘hard to reach’ groups. I recall an electric lecture from Sir Harry Burns on inequalities in medicine and how outcomes varied according to where patients lived [292]. Part of the motivation to pursue an MD was to allow me to further develop my interest in the application of evidence.

Inequalities in health has been an area of ongoing interest. Having undertaken my GP training in an affluent suburb of Glasgow, I was exposed to a predominantly medically well, highly educated population who possessed high levels of employment, high-quality housing and medical literacy, with professional family and friends within their social spheres who augmented their ability to advocate on their own behalf. When I obtained my certificate of completion of training for general practice I then successfully obtained a clinician fellowship post within the ‘Deep end’ pioneer scheme with the aims of providing additional clinical resource to communities traditionally under doctored with high levels of deprivation. These areas were exemplars of the’ inverse care law’[293]. While it would be logical to assume that work within one practice would be much the same as in any other practice, and from a purely medical diagnostician and treatment regime standpoint this is true, the ‘work’ was very different. In general, in these environments, patients where sicker on all most all metrics at an earlier age than their more affluent peers and tended to have poorer outcomes also.

This experience has shaped and enhanced my MD research, and in turn my research has enhanced my clinical work. While the MD did not have an exclusive focus on health inequalities, I was able to explore this aspect of healthcare, for example when describing

the background of participants in my qualitative study. I felt that inequalities and unhelpful power structures also existed for those with chronic disability and cognitive impairment. So, when an opportunity arose to pursue an MD with a focus on cognition and stroke, this seemed ideal. Although not a pre-determined component of the program of work, my interest in empowering patients under pinned the direction that I took the research and subsequent discussions, especially the work around patient centred testing.

5.7.2

Homelessness GP/Complex needs services

After completing my Deep end fellowship, I embarked upon the MD thesis program presented here. Returning to clinical work, I was keen for a new challenge and embarked on my current role working for the health & social care partnership providing primary care specialist input and senior medical officer care to the city of Glasgow's homeless population. Again, I wished to provide care for some of those most at risk, and those with some of the most unmet need.

Whilst the previous Deep end practices had many challenges in comparison to my training practice, an even steeper gradient of need and the associated learning curve accompanies caring for the homeless population. Working for this group presents challenges that are distinctly different to that of mainstream practices. Systems, processes and precedent all make providing care for someone with no home or an unstable housing situation difficult. While I was able to apply the topic learning from my MD, especially a greater understanding of rational testing, this post also benefitted from the generic skills I gained while pursuing an MD during the covid-19 pandemic, namely flexibility, patience and the ability to approach a problem from different angles.

Appendix A: Clinical practice guideline search strategy

Database: Ovid MEDLINE(R) ALL <1946 to February 27, 2019>

Search Strategy [similar terms were used in the other databases searched]:

---

1 cognition/ or comprehension/ (99625)

2 cognition disorders/ or cognitive dysfunction/ (72525)

3 (delirium or (cogniti* adj (disorder* or dysfunction* or declin* or impair* or problem* or issue*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (136095)

4 exp Neuropsychological Tests/ (167474)

5 (cogniti* adj (test* or measur* or assess* or survey* or questionnaire*)).mp. (16279)

6 di.xs. (3325772)

7 (test* or measur* or assess* or survey* or questionnaire*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (8345107)

8 "Surveys and Questionnaires"/ (418917)

9 (1 or 2 or 3) and (6 or 7 or 8) (149041)

10 4 or 5 or 9 (272407)

11 exp Stroke/ (119889)

12 ((cerebrovascular or vascular) adj accident*).mp. (8214)

13 (apoplex* or cva or stroke).mp. (266076)

14 11 or 12 or 13 (291428)

15 10 and 14 (10107)

16 limit 15 to (english language and yr="2012 -Current") (4067)

****

Appendix B: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of	

		automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	

Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix C: AGREE-II Reporting Checklist

AGREE Reporting Checklist

2016

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☐ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☐ Target(s) (e.g., patient population, society)	
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☐ Target population ☐ Intervention(s) or exposure(s) ☐ Comparisons (if appropriate)	

	☐ Outcome(s) ☐ Health care setting or context	
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☐ Target population, sex and age ☐ Clinical condition (if relevant) ☐ Severity/stage of disease (if relevant) ☐ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.*	☐ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☐ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☐ A description of the member's role in the guideline development group	
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☐ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☐ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public	

	information ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☐ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☐ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☐ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☐ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☐ Search terms used (e.g., text words, indexing terms, subheadings) ☐ Full search strategy included (e.g., possibly located in appendix)	
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☐ Target population (patient, public, etc.) characteristics ☐ Study design ☐ Comparisons (if relevant) ☐ Outcomes ☐ Language (if relevant) ☐ Context (if relevant)	
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE	☐ Study design(s) included in body of evidence ☐ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods)	

Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.	☐ Appropriateness/relevance of primary and secondary outcomes considered ☐ Consistency of results across studies ☐ Direction of results across studies ☐ Magnitude of benefit versus magnitude of harm ☐ Applicability to practice context	
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	☐ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☐ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☐ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☐ Supporting data and report of benefits ☐ Supporting data and report of harms/side effects/risks ☐ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☐ Recommendations reflect considerations of both benefits and harms/side effects/risks	
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☐ How the guideline development group linked and used the evidence to inform recommendations ☐ Link between each recommendation and key evidence (text description and/or reference list) ☐ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	

13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☐ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☐ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☐ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☐ Outcomes/information gathered from the external review (e.g., summary of key findings) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☐ A statement that the guideline will be updated ☐ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☐ Methodology for the updating procedure	
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☐ A statement of the recommended action ☐ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☐ Relevant population (e.g., patients, public) ☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply)	

	☐ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☐ Description of management options ☐ Population or clinical situation most appropriate to each option	
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☐ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☐ Specific recommendations grouped together in one section	
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☐ Types of facilitators and barriers that were considered ☐ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☐ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☐ How the information influenced the guideline development process and/or formation of the recommendations	
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☐ Additional materials to support the implementation of the guideline in practice. For example: o Guideline summary documents o Links to check lists, algorithms o Links to how-to manuals	

	○ Solutions linked to barrier analysis (see Item 18) ○ Tools to capitalize on guideline facilitators (see Item 18) ○ Outcome of pilot test and lessons learned	
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☐ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☐ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☐ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☐ Criteria to assess guideline implementation or adherence to recommendations ☐ Criteria for assessing impact of implementing the recommendations ☐ Advice on the frequency and interval of measurement ☐ Operational definitions of how the criteria should be measured	
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☐ The name of the funding body or source of funding (or explicit statement of no funding) ☐ A statement that the funding body did not influence the content of the guideline	
23. COMPETING INTERESTS	☐ Types of competing interests considered	

Provide an explicit statement that all group members have declared whether they have any competing interests.	☐ Methods by which potential competing interests were sought ☐ A description of the competing interests ☐ How the competing interests influenced the guideline process and development of recommendations	

From:

Brouwers MC, Kerkvliet K, Spithoff K, on behalf of the AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016;352:i1152. doi: 10.1136/bmj.i1152.

For more information about the AGREE Reporting Checklist, please visit the AGREE Enterprise website at http://www.agreetrust.org.

Appendix D: All CPGs original verbatim recommendations

Recommendations verbatim		Column 3	Column4			Column6		
High grade evidence	**RCP stroke 2016**	**SIGN stroke 2010**	**SIGN Dysphagia 2010**	**Australian stoke 2017**	**Canadian stroke 2019**	**NICE stroke 2013**	**Moderate grade evidence**	**Irish stroke 2010**
1. People with stroke should be considered to have at least some cognitive impairment in the early phase. Routine screening should be undertaken to identify the person's level of functioning, using standardised measures.	**Evidence quality: consensus; Strength of recommendation: NA**						**All patients at risk should be screened periodically for cognitive impairment, using a simple, standardised screen. (R, C, I)**	**Evidence quality: none; Strength of recommendation: NA**

2.Any person with stroke who is not progressing as expected in rehabilitation should receive a detailed assessment to determine whether cognitive impairments are responsible, with the results explained to the person, their family and the multidisciplinary team	**Evidence quality: consensus; Strength of recommendation: NA**						**All individuals planning to return to cognitively demanding activities, e.g. work or driving, should receive a formal cognitive assessment. (C, I, R)**	**Evidence quality: none; Strength of recommendation: NA**
3. People with communication impairment after stroke should receive a cognitive assessment using valid assessments in conjunction with a speech and language therapist. Specialist advice should be sought if there is uncertainty	**Evidence quality: consensus; Strength of recommenda**							

about the interpretation of cognitive test results	**tion: NA**							
4. People with cognitive problems after stroke should receive appropriate adjustments to their multidisciplinary treatments to enable them to participate, and this should be regularly reviewed	**Evidence quality: consensus; Strength of recommendation: NA**							
5. People with acute cognitive problems after stroke whose care is being transferred from hospital should receive an assessment for any safety risks from persisting cognitive impairments. Risks should be communicated to their primary care team together with any mental	**Evidence quality: consensus; Strength of recommendation: NA**							

capacity issues that might affect their decision-making.								
6.People with stroke returning to cognitively demanding activities such as driving or work should have their cognition fully assessed	**Evidence quality: consensus; Strength of recommendation: NA**							
7. People with continuing cognitive difficulties after stroke should be considered for comprehensive interventions aimed at developing compensatory behaviours and learning adaptive skills	**Evidence quality: consensus; Strength of recommendation: NA**							

8. People with severe or persistent cognitive problems after stroke should receive specialist assessment and treatment from a clinical neuropsychologist/clinical psychologist	**Evidence quality: consensus; Strength of recommendation: NA**							
9.A full understanding of the patient's cognitive strengths and weaknesses should be an integral part of the rehabilitation plan.		**Evidence quality: consensus; Strength of recommendation: NA**						
10. Stroke patients should have a full assessment of their cognitive strengths and weaknesses when undergoing		**Evidence quality: consensus; Strengt**						

rehabilitation or when returning to cognitively demanding activities such as driving or work.		**h of recommendation: NA**						
11. Communication, cognitive function, and the capacity for decision making should be routinely assessed in patients with dysphagia.		**Evidence quality: consensus; Strength of recommendation: NA**	**Evidence quality: moderate; Strength of recommendation: NA**					
12. Information should be provided to patients with communicative or cognitive impairment in an appropriate manner (eg aphasia friendly literature)			**Evidence quality: consensus; Strength of recommendation: NA**					
13. All stroke survivors should be screened for cognitive and perceptual deficits by a trained person (e.g.				**Evidence quality: NA; Strength of recommen**				

neuropsychologist, occupational therapist or speech pathologist) using validated and reliable screening tools, ideally prior to discharge from hospital				**dation: NA**				
14. Stroke survivors identified during screening as having cognitive deficits should be referred for comprehensive clinical neuropsychological investigations.				**Evidence quality: NA; Strength of recommen dation: NA**				
15. All patients with clinically evident stroke or transient ischemic attack should be considered at risk for vascular cognitive impairment					**Evidence quality: moderate; Strength of recommen dation: NA**			
16. Patients with stroke and transient ischemic attack should be considered for screening for vascular cognitive impairment [Evidence					**Evidence quality: consensus ; Strength of recommen**			

Level C]. This may occur prior to discharge from acute care if concerns with cognition are identified; during inpatient rehabilitation, and during post-stroke follow-up in outpatient and community settings [Evidence Level C].					**dation: NA**			
17. People who have experienced a stroke with other significant risk factors for vascular disease and vascular cognitive impairment, such as neuroimaging findings of covert stroke or white matter disease, hypertension, diabetes, atrial fibrillation, or other cardiac disease may be considered for screening for vascular cognitive impairment, particularly those people who have experienced a stroke with cognitive, perceptual or functional					**Evidence quality: moderate; Strength of recommen dation: NA**			

changes that are clinically evident or reported during history taking [Evidence Level B]								
18. Screening for vascular cognitive impairment should be conducted using a validated screening tool, such as the Montreal Cognitive Assessment screen [Evidence Level B].					**Evidence quality: moderate; Strength of recommendation: NA**			
19. The diagnosis of vascular cognitive impairment requires confirmation of cerebrovascular disease. Brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is useful to evaluate cerebrovascular disease [Evidence Level B]					**Evidence quality: moderate; Strength of recommendation: NA**			

20. People who have experienced a stroke and who demonstrate cognitive impairments (either clinically, by history, by report of the individual or family, or detected in the screening process) should be assessed by healthcare professionals with the appropriate expertise in neurocognitive functioning, ideally by a clinical neuropsychologist [Evidence Level C].					**Evidence quality: consensus; Strength of recommendation: NA**			
21. The impact of deficits on function and safety in activities of daily living, instrumental activities of daily living, occupational function and/or academic functioning should be considered as part of a cognitive assessment (e.g.,					**Evidence quality: consensus; Strength of recommendation: NA**			

driving, home safety) [Evidence Level C].								
22. People who have experienced a stroke with suspected cognitive impairment should also be screened for depression, given that depression has been found to contribute to vascular cognitive impairment [Evidence Level B]					**Evidence quality: moderate; Strength of recommendation: NA**			
23. Prior to discharge or transfer from acute care or inpatient rehabilitation, people with acute cognitive problems following stroke should receive an assessment for any safety risks from persisting cognitive impairments and this should be communicated to their					**Evidence quality: consensus; Strength of recommendation: NA**			

primary care team [Evidence Level C].								
24. The results of these assessments should be considered to guide selection and implementation of appropriate remedial, compensatory and/or adaptive intervention strategies according to person-centered needs and goals [Evidence Level C]					**Evidence quality: consensus; Strength of recommendation: NA**			
25. People who have experienced a stroke should have a full assessment of their cognitive strengths and weaknesses when undergoing rehabilitation or prior to returning to cognitively demanding activities such as driving or work [Evidence Level C].					**Evidence quality: consensus; Strength of recommendation: NA**			

26. Screen people after stroke for cognitive deficits. Where a cognitive deficit is identified, carry out a detailed assessment using valid, reliable and responsive tools before designing a treatment programme.						**Evidence quality: moderate; Strength of recommendation: NA**		
Provide education and support for people with stroke and their families and carers to help them understand the extent and impact of cognitive deficits after stroke, recognising that these may vary over time and in different settings.						**Evidence quality: moderate; Strength of recommendation: NA**		

Appendix E: Interview schedule

SCHOOL OF PSYCHOLOGICAL SCIENCES & HEALTH

University of Strathclyde Humanities & Social Sciences

Research project: How do patients experience cognitive assessment on admission for stroke: a qualitative interview study

Interview schedule for study: Qualitative interviews with stroke patients regarding their experience of cognitive assessment

Researchers:

This study is being undertaken by the chief investigator Dr Diane Dixon.

Dr Diane Dixon University of Strathclyde School of Psychological Sciences and Health Graham Hills Building, 40 George Street Glasgow, G1 1QE Diane.dixon@strath.ac.uk 01415482571	Dr Terry Quinn Institute of Cardiovascular and Medical Sciences New Lister Building Glasgow Royal Infirmary Glasgow, G4 0SF Terry.quinn@strath.ac.uk 01412214976

Sponsor

University of Strathclyde
40 George Street
Glasgow, G1 1QE

Insurance and Indemnity

The University of Strathclyde has insurance policies that provide cover for any professional negligence of its staff and/or students.

Interview Schedule

The interview is in two parts. The first part aims to elicit the participant's experience of cognitive and mood assessment on admission to and during their hospital stay. The second part will explore the participant's views and opinions on the measures used to assess cognitive function and mood at the participating hospitals.

The Ci will have introduced herself and will have reiterated the aims of the study and what participation involves. The participant will have been invited to ask any questions or seek clarification on any issues or concerns about the study or their participation in it. Written consent will have been obtained where possible and verbal consent obtained for individuals who due to impairments cannot provide written consent.

Part 1: Patient Experience Of Cognitive And Mood Assessment.

General Opening Question: I would like you to think back to when you first arrived at the hospital because of your stroke. Can you describe what happened in your own words?

If the participant does not mention the assessments (likely) then ask the following (ask about mood and cognition separately): Do you recall being asked questions about your mood/memory when you first arrived at hospital or during your stay in hospital?

Depending upon the response to the above use the following prompts to aid memory:

- Provide an example mood question
- Provide an example cognition question
- Provide a copy of a mood measure
- Provide a copy of a cognition measure

After each of the above, ask: Do you recall being asked a question(s) like this?

If the participant cannot recall the assessment then move on to part 2.

If the participant does recall being assessed then elicit the following information for cognition and mood separately (NB: terminology use (test, questions, assessment) should be guided by how the participant describes their experience):

- Who asked the questions?
- Was the reason(s) for the questions explained / was the purpose of the assessment explained?
- What did you think they were for?
- Where you given a choice about whether to answer the questions/do the test?
- When did you do the tests? Did you do them more than once during your stay?

- How did you find them (potentially probe with: easy, difficult, fine, neutral, tiring, worrying, confusing, distressing, interesting)?
- How did they make you feel at the time? How do you feel about them now?
- Were you asked if you wanted to know the results/outcome?
- Were you told how you had done/your results/outcome?
    - Who told you?
    - When where you told?
    - How did you feel/what did you think?
    - What happened after you were told your results?
- How do you feel about them now?

Invite the participant to add any comments: I have asked all my questions. Is there anything that you want to add about your experience?

Summarise the aims of the study and the content of their interview and again invite them to add any comments: Is there anything that we've missed out? Anything that you would like me to know about your experience of being admitted to hospital or your hospital stay for your stroke.

Part 2: Patient Views On Cognitive And Mood Measures Used In Stroke.

General Linking Question To Part 2: Ok – you've told me about your experience. Now I would like to get your opinions and views on how your mood and your memory are assessed. I have some questions with me that are typically used to assess stroke patients (give measures to participant or read through them for patients with reading difficulties). I'd like to know what you think of them. There are no right or wrong answers. I am just after your own personal views and opinions, so you can be as frank as you like.

General Opening Question: These are questions typically used to assess your mood/memory. We would like to know your views on these questions. Do you remember being asked any of these questions when you were in hospital?

Follow-Up General Question: What do you think about them?

Depending upon the response to the above use the following prompts:

- If you had been asked these questions when you were admitted to hospital what would you think they were for?
    - Do you think you should be given a choice as to whether or not you answer them?
- What do you think completing these questions would be like?
- How do you think they would they make you feel?
- How easy or difficult would they be to answer?
- What do you think about being given your results?

- Do you think you should be able to choose whether or not you are told the results?
- Do you think you'd want your results?
- Who do you think should give you the results?
- When do you think it would be best to be given the results?
- What do you think would be best to happen after you have been given the results?

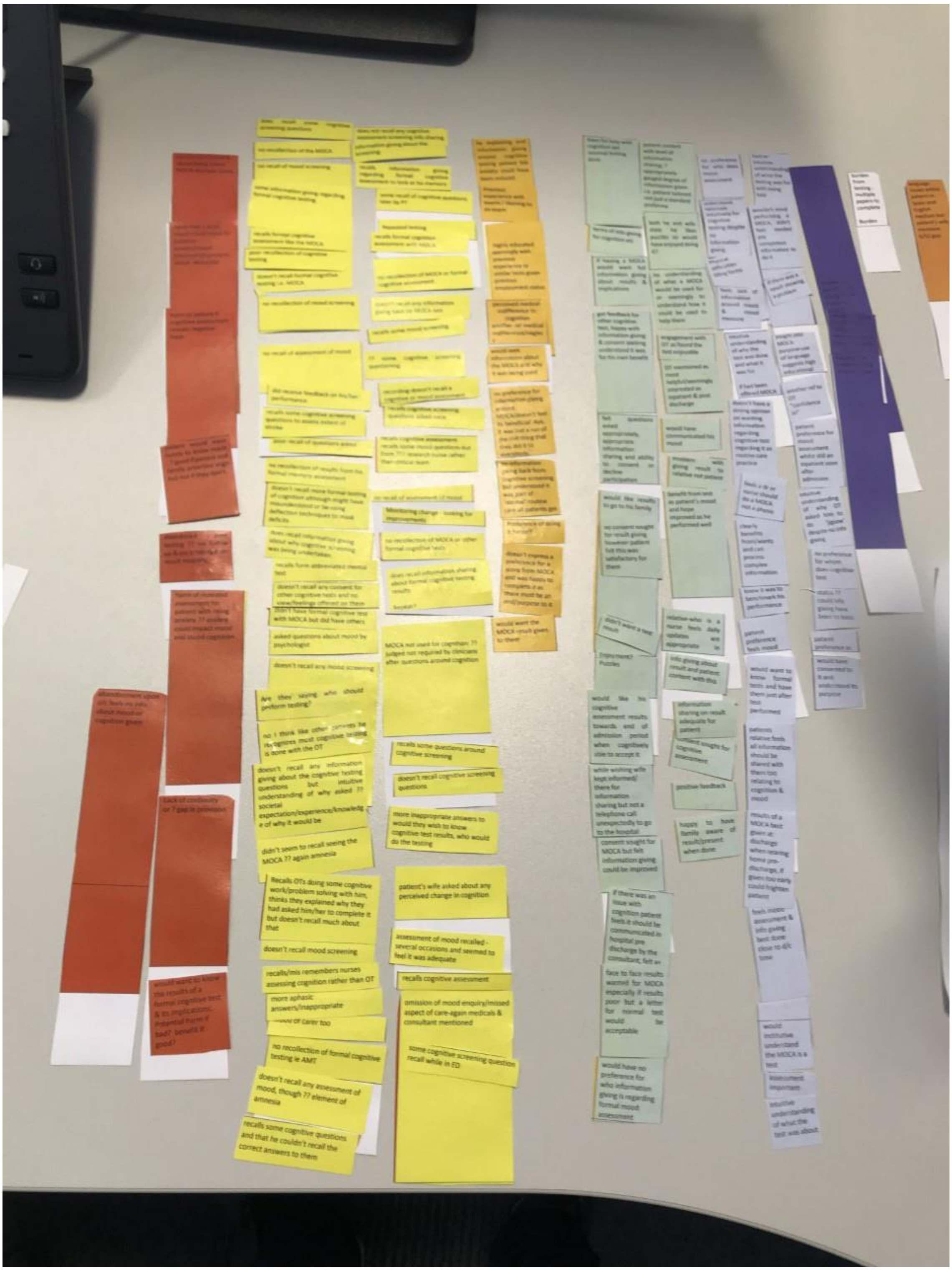
Depending upon the response to the above, i.e. depending upon whether the participant appears to understand what the results might mean - consider providing the following information and re-eliciting beliefs about the communication of results: for example, it might be that the results indicate you are depressed/ have a memory problem – what do you think should happen next?

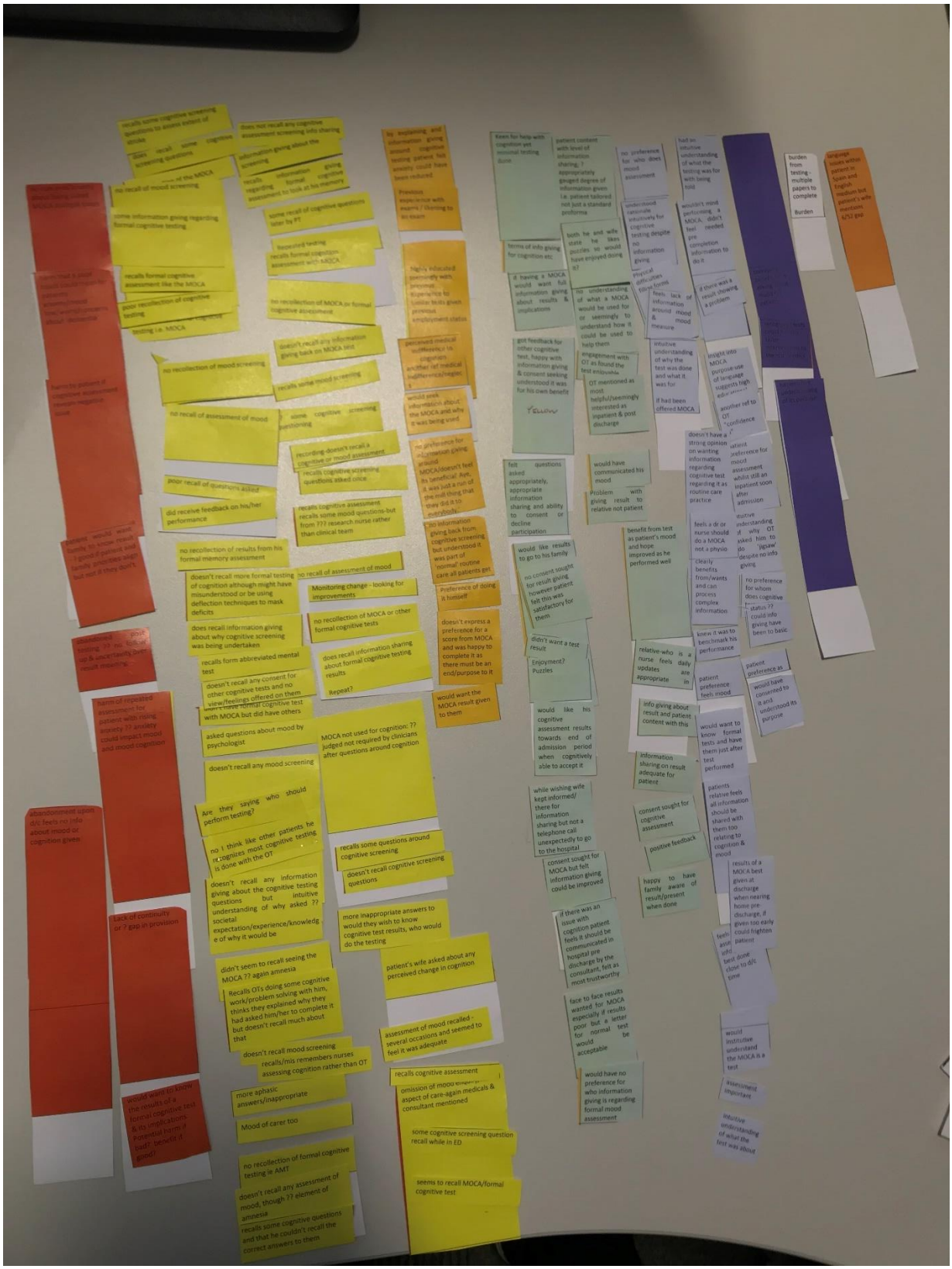
Invite the participant to add any comments: I have asked all my questions. Is there anything that you want to add?

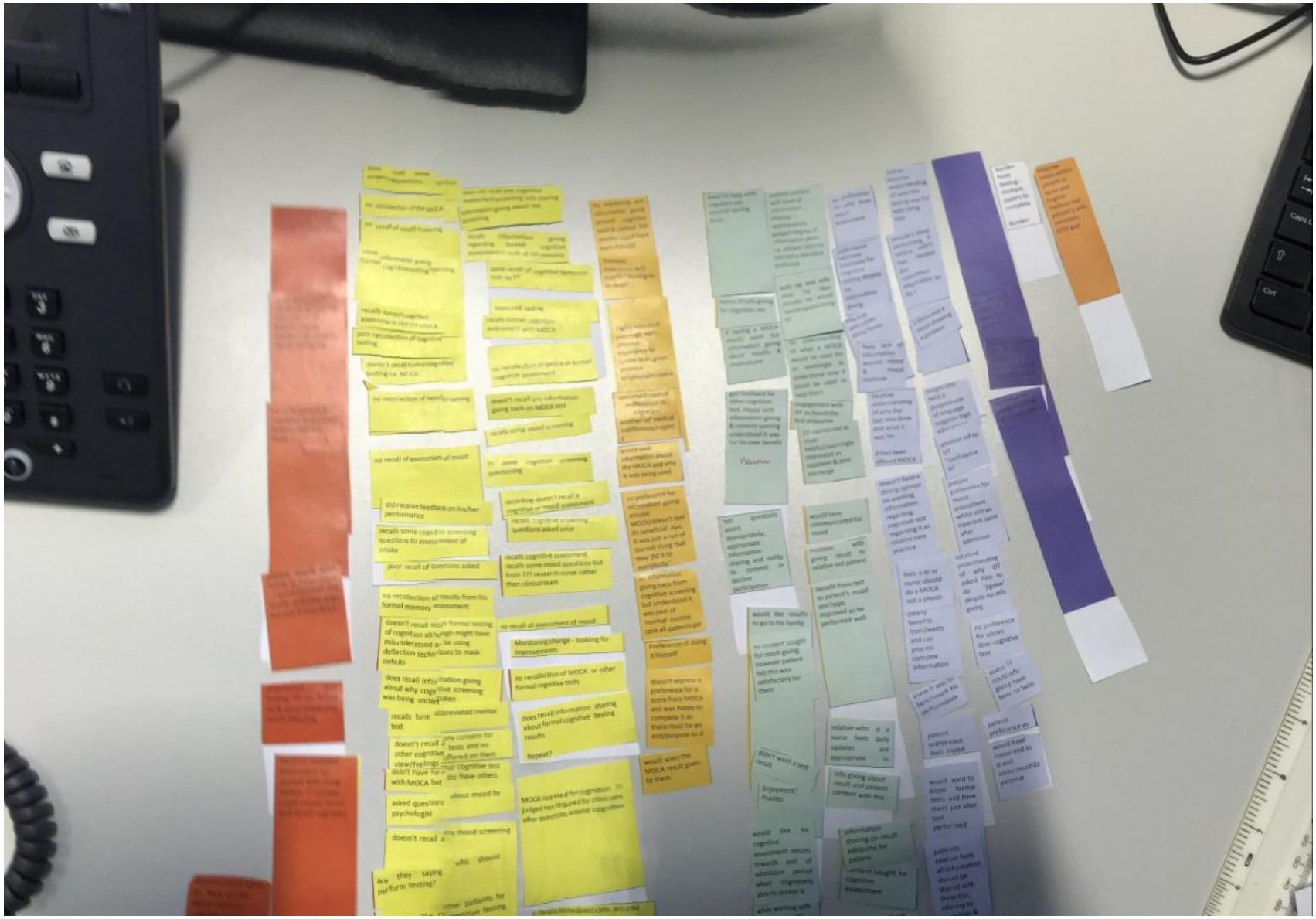
Summarise the aims of the study and their responses and invite them to add any comments: Is there anything that we've missed out? Is there anything else that you would like to say about your experience of being admitted to hospital or your hospital stay for your stroke? Is there anything else you'd like to say about the mood and memory questions?

Provide the participant with the debrief sheet and talk them through it. Highlight the contact details of the research team. Thank the participant for their time and input.

Appendix F: Manual coding process




recalls some cognitive screening questions to assess extent of stroke
does not recall any cognitive assessment screening info sharing
does recall some cognitive screening questions
information giving about the screening
no recall of mood screening
recalls information giving regarding formal cognitive assessment to look at his memory
some information giving regarding formal cognitive testing
some recall of cognitive questions later by PT
Repeated testing
recalls formal cognitive assessment like the MOCA
recalls formal cognitive assessment with MOCA
poor recollection of cognitive testing
no recollection of MOCA or formal cognitive assessment
testing i.e. MOCA
doesn't recall any information giving back on MOCA test
no recollection of mood screening
recalls some mood screening
would seek information about the MOCA and why it was being used
no recall of assessment of mood
some cognitive screening questioning
recalls cognitive screening questions asked once
poor recall of questions asked
did receive feedback on his/her performance
recalls cognitive assessment recalls some mood questions-but from ??? research nurse rather than clinical team
no recollection of results from his formal memory assessment
doesn't recall more formal testing of cognition although might have misunderstood or be using deflection techniques to mask deficits
no recall of assessment of mood
Monitoring change - looking for improvements
does recall information giving about why cognitive screening was being undertaken
no recollection of MOCA or other formal cognitive tests
recalls form abbreviated mental test
doesn't recall any consent for other cognitive tests and no view/feelings offered on them
does recall information sharing about formal cognitive testing results
Repeat?
asked questions about mood by psychologist
MOCA not used for cognition: ?? judged not required by clinicians after questions around cognition
doesn't recall any mood screening
Are they saying who should perform testing?
no I think like other patients he recognizes most cognitive testing is done with the OT
recalls some questions around cognitive screening
doesn't recall any information giving about the cognitive testing questions but intuitive understanding of why asked ?? societal expectation/experience/knowledge of why it would be
doesn't recall cognitive screening questions
more inappropriate answers to would they wish to know cognitive test results, who would do the testing
didn't seem to recall seeing the MOCA ?? again amnesia
Recalls OTs doing some cognitive work/problem solving with him, thinks they explained why they had asked him/her to complete it but doesn't recall much about that
patient's wife asked about any perceived change in cognition
assessment of mood recalled - several occasions and seemed to feel it was adequate
doesn't recall mood screening
recalls/mis remembers nurses assessing cognition rather than OT
recalls cognitive assessment
more aphasic answers/inappropriate
Mood of carer too
omission of mood
aspect of care-again medicals & consultant mentioned
some cognitive screening question recall while in ED
no recollection of formal cognitive testing ie AMT
seems to recall MOCA/formal cognitive test
doesn't recall any assessment of mood, though-?? element of amnesia
recalls some cognitive questions and that he couldn't recall the correct answers to them
Keen for help with cognition yet minimal testing done
patient content with level of information sharing, ? appropriately gauged degree of information given i.e. patient tailored not just a standard proforma
no preference for who does mood assessment
had an intuitive understanding of what the testing was for with being told
understood rationale intuitively for cognitive testing despite no information giving
wouldn't mind performing a MOCA, didn't feel needed pre completion information to do it
both he and wife state he likes puzzles so would have enjoyed doing it?
if having a MOCA would want full information giving about results & implications
physical difficulties filling forms
if there was a result showing a problem
no understanding of what a MOCA would be used for or seemingly to understand how it could be used to help them
feels lack of information around mood & mood measure
got feedback for other cognitive test, happy with information giving & consent seeking understood it was for his own benefit
engagement with OT as found the test enjoyable
intuitive understanding of why the test was done and what it was for
OT mentioned as most helpful/seemingly interested as inpatient & post discharge
if had been offered MOCA
insight into MOCA purpose-use of language suggests high
another ref to OT "confidence"
felt questions asked appropriately, appropriate information sharing and ability to consent or decline participation
would have communicated his mood
Problem with giving result to relative not patient
doesn't have a strong opinion on wanting information regarding cognitive test regarding it as routine care practice
patient preference for mood assessment whilst still an inpatient soon after admission
would like results to go to his family
no consent sought for result giving, however patient felt this was satisfactory for them
benefit from test as patient's mood and hope improved as he performed well
feels a dr or nurse should do a MOCA not a physio
routine understanding if why OT asked him to do "jigsaw" despite no info giving
didn't want a test result
Enjoyment? Puzzles
clearly benefits from/wants and can process complex information
No preference for whom does cognitive status ?? could info giving have been to basic
knew it was to benchmark his performance
relative-who is a nurse feels daily updates are appropriate in
patient preference feels mood
patient preference as
would have consented to it and understood its purpose
would like his cognitive assessment results towards end of admission period when cognitively able to accept it
info giving about result and patient content with this
would want to know formal tests and have them just after test performed
information sharing on result adequate for patient
while wishing wife kept informed/there for information sharing but not a telephone call unexpectedly to go to the hospital
consent sought for cognitive assessment
patients relative feels all information should be shared with them too relating to cognition & mood
positive feedback
consent sought for MOCA but felt information giving could be improved
happy to have family aware of result/present when done
results of a MOCA best given at discharge when nearing home pre-discharge, if given too early could frighten patient
if there was an issue with cognition patient feels it should be communicated in hospital pre discharge by the consultant, felt as most trustworthy
face to face results wanted for MOCA especially if results poor but a letter for normal test would be acceptable
would have no preference for who information giving is regarding formal mood assessment
would institutive understand the MOCA is a test
assessment important
Intuitive understanding of what the test was about
burden from testing - multiple papers to complete
Burden
Language issues within patient is Spain and English medium but patient's wife mentions 6/52 gap
abandonment upon d/c feels no info about mood or cognition given
Lack of continuity or ? gap in provision
would want to know the results of a formal cognitive test & its implications potential harm if bad? benefit if good?


no recollection of the MoCA
no recall of mood screening
recalls formal cognitive assessment like the MoCA
poor recollection of cognitive testing
doesn't recall formal cognitive testing i.e. MoCA
no recollection of mood screening
no recall of assessment of mood
did receive feedback on his/her performance
recalls some cognitive screening questions to assess extent of stroke
poor recall of questions asked
no recollection of results from his formal memory assessment
doesn't recall much formal testing of cognition although might have misunderstood or be using deflection techniques to mask deficits
does recall information giving about why cognitive screening was being undertaken
recalls formal abbreviated mental test
doesn't recall any cognitive tests
didn't have for the with MoCA but did have others
asked questions about mood by psychologist
doesn't recall any mood screening
Are they saying who should perform testing?
recalls some mood screening
recalls cognitive screening questions asked once
recalls cognitive assessment, recalls some mood questions but from FU research nurse rather than clinical team
doesn't recall any information giving back on MoCA test
recalls some mood screening
no recollection of MoCA or other formal cognitive tests
Monitoring change - looking for improvements
no recollection of MoCA or other formal cognitive tests
does recall information sharing about formal cognitive testing results
Repeat?
MoCA not used for cognition. FU judged not required by clinicians after questions around cognition
would want the MoCA result given to them
Preference of doing it himself
doesn't express a preference for a score from MoCA and was happy to complete if as there must be an end/purpose to it
would like results to go to his family
no consent sought for result giving however patient felt this was satisfactory for them
didn't want a test result
Enjoyment/ Puzzles
relative who is a nurse feels daily updates are appropriate in
why giving 4/30 result and patient content with this
would like his cognitive assessment results towards end of admission period when momentarily able to access it
would want to know formal tests and have their just other test performed
patients relative feels all information should be shared with them too relating to
benefit from test as patient's mood and hope improved as he performed well
would have communicated his mood
feels a rle or nurse should do a MoCA not a physio
clearly benefits from/wants and can process complex information
some it was to benchmark his performance
patient preference was most
patient preference as
would have consented to it and understood its purpose
no preference for whom does cognitive test
could info given have been to beds
intuitive understanding of why OT asked him to do 'spoke' despite no info giving
patient preference for most instrument whilst still an imminent soon after admission
doesn't have a strong opinion on wanting information regarding cognitive test regarding it as routine care practice
engagement with OT as found the test enjoyable
OT mentioned as most helpful/seemingly interested as inpatient & post discharge
would seek information about the MoCA and why it was being used
no preference for information given around MoCA/doesn't feel its beneficial/ Aye, it was just a run of the mill thing that they did it to everybody
no information giving back from cognitive screening but understood it was part of 'normal' routine care all patients get
Are they saying who should perform testing?
other patients he
MoCA not used for cognition. FU judged not required by clinicians after questions around cognition

Appendix G: TriMethS' protocol (TriMethSylamine derivative)

TriMethS – A novel urinary biomarker for minor stroke and transient ischaemic attack

Running Title	**TriMethS**
Protocol Version:	**1.1**
Date:	**12th December 2017**
REC Reference Number	**17/WS/0252**
Sponsors Protocol Number:	**1**
Sponsor:	**NHS Greater Glasgow and Clyde**

F

Contacts

Chief Investigator

Professor Jesse Dawson

Room M0.05

Office Block

Queen Elizabeth University Hospital

Glasgow

G51 4TF

Tel: 0141 451 5868

Email: jesse.dawson@glasgow.ac.uk

Co-investigators

Professor Rob M.J. Liskamp

Joseph Black Building

University Avenue

University of Glasgow

Glasgow

G12 8QQ

Tel: 0141 330 5168

Email: robert.liskamp@glasgow.ac.uk

Professor Michael P Barrett

Sir Graeme Davis Building,

University of Glasgow,

Glasgow

G12 8TA

Tel: 0141 330 6906

Email: Michael.barrett@glasgow.ac.uk

Dr Karl Burgess

Metabolomics Facility

Glasgow Polyomics Wolfson Wohl Cancer Research Centre

University of Glasgow

Glasgow

G61 1QH

Tel: 0141 330 8746

Email: karl.burgess@glasgow.ac.uk

Professor Craig J Smith

Clinical Sciences Building,

Manchester Academic Health Science Centre (MAHSC)

Salford Royal NHS Foundation Trust

Salford

M6 8HD

Tel: 0161 206 0623

Email: Craig.Smith-2@manchester.ac.uk

Sponsor:

NHS Greater Glasgow and Clyde is the study sponsor. Contact:

Dr Maureen Travers

R&D Management Office,

Clinical Research & Development

West Glasgow Ambulatory Care Hospital

Dalnair Street

Glasgow G3 8SW

Tel: 0141 232 1813

Email: Maureen.Travers@ggc.scot.nhs.uk

Protocol Approval

The Biomarkers in Stroke Programme

Chief Investigator: **Professor Jesse Dawson**

Room M0.05

Office Block

Queen Elizabeth University Hospital

Glasgow

G51 4TF

Tel: 0141 451 5868

Email: jesse.dawson@glasgow.ac.uk

Signature:

Date:

Sponsor Representative: **Dr Maureen Travers**

R&D Management Office,

Clinical Research & Development

West Glasgow Ambulatory Care Hospital

Dalnair Street

Glasgow G3 8SW

Tel: 0141 232 1813

Email: Maureen.Travers@ggc.scot.nhs.uk

Signature:

Date:

Table of Contents

Figures and Tables

Abbreviations

ASCO	Atherosclerotic, Small vessel, Cardioembolic, Other
CNORIS	Clinical Negligence and Other Risks Indemnity Scheme
CRF	Case report form
CT	Computed tomography
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
HPLC	Hydrophilic liquid chromatography
HSQC	Heteronuclear single quantum coherence spectroscopy
ICH	Intracerebral haemorrhage
LC-MS	Liquid Chromatography Mass Spectrometry
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Score
NHS	National Health Service
NMR	Nuclear magnetic resonance
REC	Research Ethics Committee
RNA	Ribonucleic acid
SAP	Statistical Analysis Plan
SST	Serum-separating tube
STARD	Standards for Reporting Diagnostic Accuracy
TIA	Transient ischaemic attack
TMC	Trial management Committee

Study Summary/Patient Flow Chart

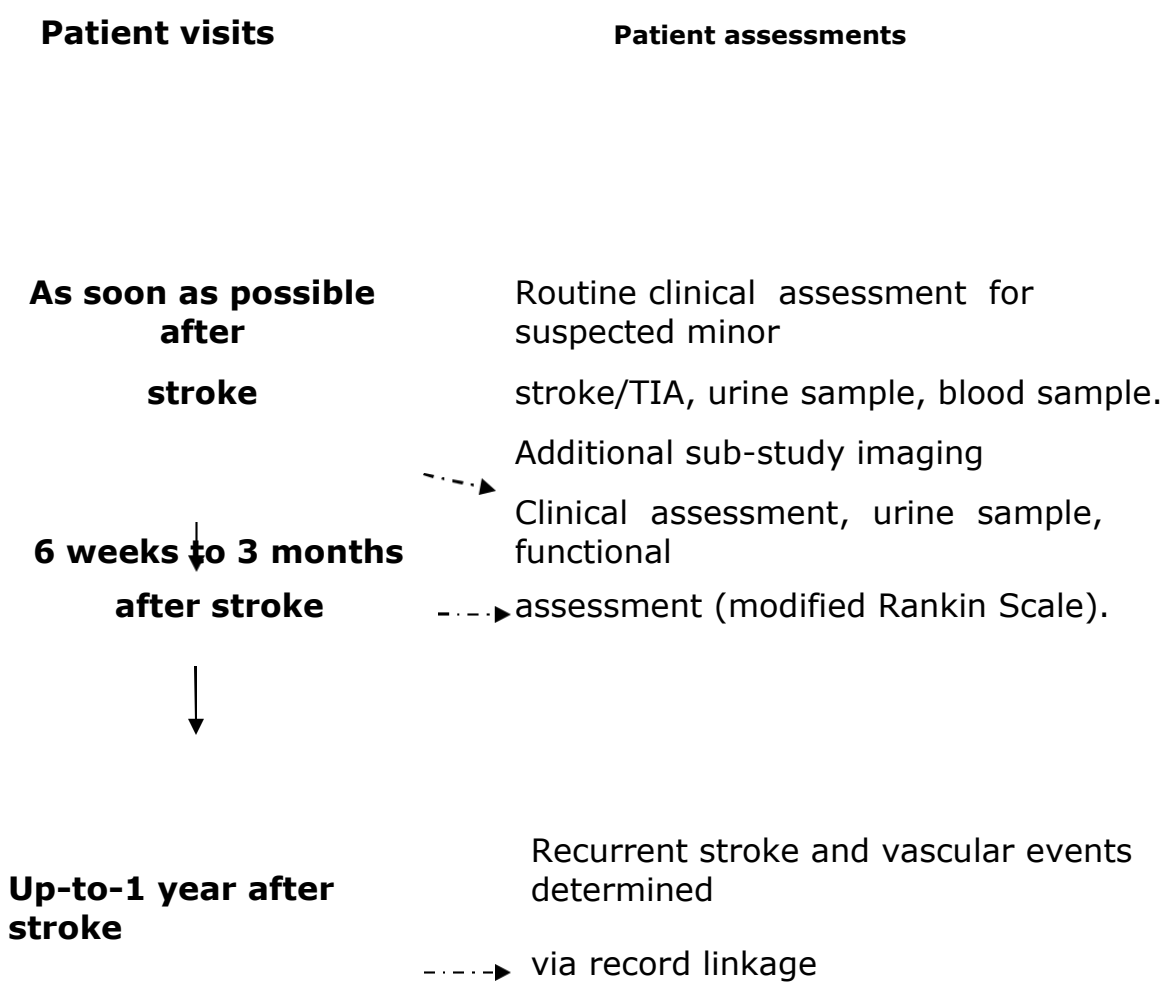


Figure 1 Summary of study visits

TriMethS – A novel urinary biomarker for minor stroke and transient ischaemic attack

1 Introduction

1.1 Rationale

Rapid assessment and treatment of patients with suspected transient ischaemic attack (TIA) and minor stroke reduces stroke risk [1] but up to one half of referrals with suspected TIA have a mimic such as seizure or syncope [2]. Only 30% of patients with TIA have evidence of brain ischaemia on diffusion weighted MRI. MRI cannot be performed in up to a fifth of patients [3] and many centres use CT scanning, which has lower sensitivity. This leaves diagnostic uncertainty, with no objective confirmation, in a substantial number of cases of suspected TIA and minor stroke. This means some patients may undergo investigation and treatment that are not indicated or needed, whilst others may miss appropriate treatment. Further, a diagnosis of TIA or minor stroke mandates a 4-week ban from driving and carries other implications for patients. New diagnostic biomarkers to facilitate diagnosis in suspected TIA are an important clinical need and could 1) improve diagnostic accuracy in primary and emergency care environments reducing referral of mimics to secondary care, 2) provide objective support for diagnosis in secondary care thereby rationalizing investigation and treatment approaches, 3) improve longer term risk stratification and 4) provide information on the biochemical events associated with stroke, offering potential targets for intervention. There are no such biomarkers currently in routine clinical use.

We propose that a recently identified and validated a novel urinary biomarker could meet this need. This is a trimethylamine derivative, currently called ”TriMethS.” Identified via mass spectrometry coupled to hydrophilic liquid chromatography (HPLC) TriMethS has an exact molecular of mass 203.18 Da, equating to a calculated protonated chemical formula of $C_{10}H_{22}N_2O_2$, and chromatographic retention time of 26.6 minutes on a ZIC-HILIC column. Mass spectra of the fragmented compound are consistent with its being derived from trimethylamine. This is of particular interest given the growing appreciation of microbiome-derived trimethylamine derivatives as determinants of cardiovascular disease [4].

TriMethS is a potential biomarker to facilitate diagnosis in cases of suspected TIA or minor stroke and that large scale study is needed because 1) we have validated its presence and higher levels in stroke / TIA patients in an independent prospective study, 2) our studies have included the clinical environment in which the test will be used (using mimics as controls), 3) we have identified the clinical scenario in which biomarker levels differ most between cases and mimic, 4) levels remain elevated for a prolonged window (1 week at least) optimizing the window for testing and 5) urine is a simple sample medium to obtain and test in primary / emergency care. We have followed best practice concerning design of our studies [5]

1.2 Pilot Studies

Initial Case-Control Study in Minor Stroke / TIA - We first performed a case-control study in 40 patients with minor stroke and TIA and 40 high cardiovascular risk controls. Stroke / TIA patients were all admitted within 48 hours of symptoms and gave a sample of their first urine thereafter. We used an untargeted liquid chromatography-mass spectrometry (LC-MS) approach [6]. This demonstrated a novel urinary metabolite that was significantly increased in stroke or TIA patients compared to controls (figure 2). We called this TriMethS. (48-fold higher, peak intensity 61226 vs 1276, p<0001). Levels were not different between cases that were stroke and cases of TIA (p=0.14).

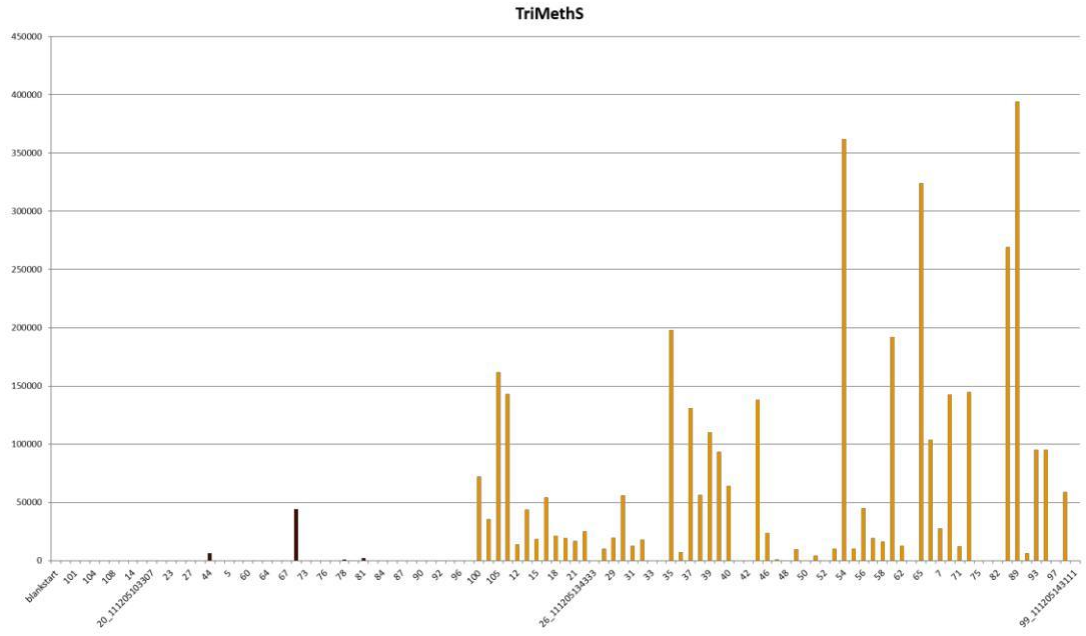


Figure 1. TriMethS levels in urine of cases of minor stroke / TIA (orange) and controls with high cardiovascular risk (black).

Prospective Validation Study - We then performed a prospective validation study in patients referred to hospital with suspected stroke (n=134). Patients all had a urine sample obtained at 48 hours after symptom onset and a diagnosis was assigned in a multi-disciplinary team meeting based on clinical and routine clinical imaging findings. Participants were split into cases of confirmed stroke (where imaging revealed an ischaemic lesion in the relevant territory, n=82), stroke mimic (where a definitive alternative diagnosis was made, n=18) and probable stroke (where imaging (predominantly CT) did not reveal an acute ischaemic lesion but stroke was likely, n=34). TriMethS levels were 9.4 fold higher at the 48-hour time point in confirmed stroke compared to mimics (p=0.035, n=100). They were also higher in most cases of probable stroke (figure 3).

There was no correlation between stroke severity and TriMethS levels in patients with confirmed stroke. Measures of stroke symptom severity correlated with TriMethS levels in patients with mimic (r = 0.729, p=0.001 at 48 hours and r = 0.70, p=0.025 at day 7).

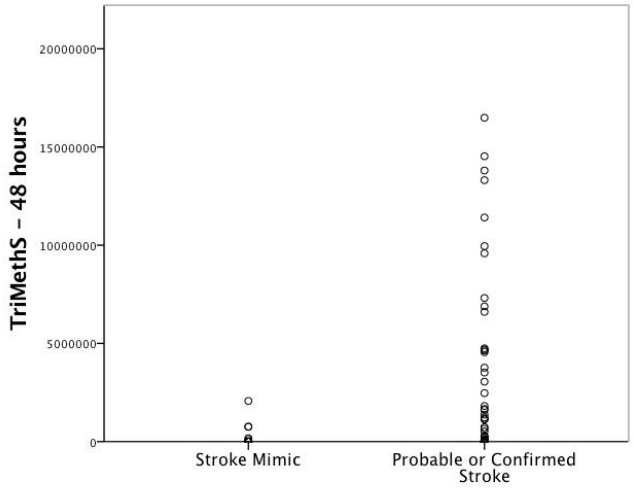


Figure 2. TriMethS Levels in cases of confirmed stroke vs mimic

We conclude from our pilot studies that TriMethS levels identify cases of stroke and TIA but levels are more likely to be low in TIA mimic than in stroke mimic. In summary, our studies have 1) shown TriMethS levels are higher in cases of stroke / TIA vs. cardiovascular risk controls, 2) shown TriMethS levels are higher in cases of stroke / TIA vs. mimics in a validation study, 3) have included the clinical environment in which the test will be used (using mimics as controls), 4) have identified the clinical scenario in which biomarker levels differ most between cases and mimic.

2 Aims

Our aim is to assess the clinical utility of urine TriMethS levels in patients with suspected minor stroke and TIA.

2.1 Research Questions

The specific research questions are;

1. Do levels of TriMethS differ in cases of TIA / minor stroke compared to mimic?
2. Are TriMethS levels sufficiently sensitive for cases of suspected TIA / minor stroke for clinical use?
3. What is the improvement in sensitivity and specificity and net classification improvement when using TriMethS levels in cases of suspected TIA / minor stroke?
4. Do TriMethS levels predict adverse long-term outcomes after TIA / minor stroke?
5. What is the role of TriMethS and what types of assay may be developed to measure it in the future?
6. (Sub-study only). Are appearances on 7T-MRI scanning the same as on 1.5 T or 3T MRI scanning in people with suspected stroke or TIA?

3 Study Design

3.1 Study Population

This will be a prospective diagnostic accuracy study, in line with Standards for Reporting Diagnostic Accuracy (STARD) guidance [7], with record linkage follow-up in patients referred to secondary care with suspected minor stroke/TIA. We will recruit 300 patients who have been referred to stroke services for suspected TIA/minor stroke (in-patient and outpatient referrals). The study will be conducted in stroke services in Glasgow and Manchester and additional sites in the UK and Scottish Stroke Research Networks. Eligibility criteria are shown in the table.

3.2 Main Inclusion / Exclusion Criteria

Inclusion criteria	**Exclusion criteria**
Age > 18 years	Previous diagnosis of a structural brain disease, with exception of TIA or stroke
Referral to a stroke service with suspected TIA or minor stroke	Frailty of other illness likely to lead to death within 3 months
Attendance within 48 hours of onset	
Urine sampling possible at baseline	
Able to provide informed consent	

Table 1 Inclusion and Exclusion Criteria TriMeths study

For the purposes of eligibility, suspected TIA is defined as transient symptoms felt to be possibly, probably or definitely due to TIA by a referring clinician. Minor stroke is defined in out-patients as residual symptoms or symptoms lasting more than 24 hours felt to be possibly, probably or definitely due to stroke by a referring clinician but not referred for in-patient assessment. For the purposes of in-patients, minor stroke is defined as ambulant patients with a NIHSS of ≤ 4.

Note people unable to undergo MRI can be included but will not undergo MRI.

3.3 Identification of Participants And Consent

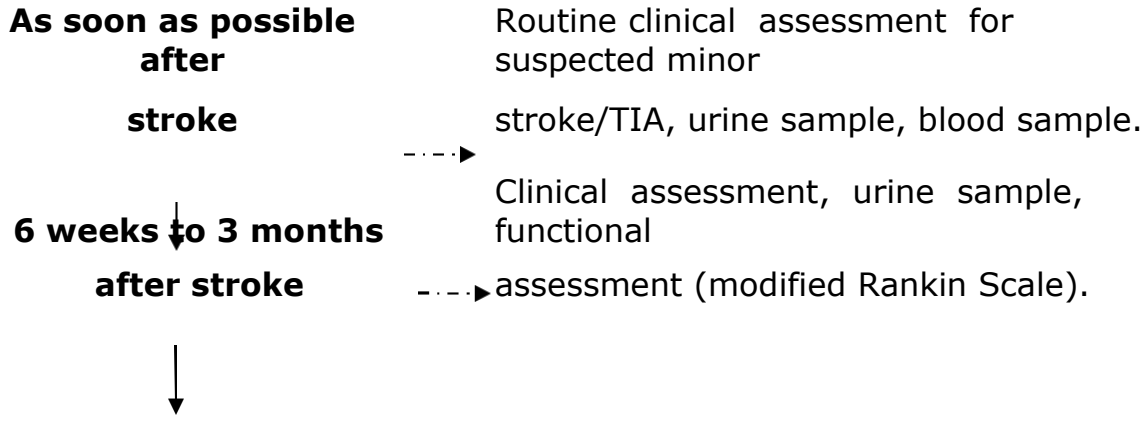
Participants will be identified by the clinical team during attendance at stroke services. They will be asked if they are willing to be approached by a researcher. If so, they will be given a participant information sheet. Informed consent will be obtained. We will allow patients to consent at the initial visit, without 24-hour delay, subsequent to anticipated ethical committee approval. Having a minimum 24-hour delay will inevitably mean potential out-patient participants would need to return and have an additional visit for consent and study assessments. We will not include adults with incapacity. This is because in a minor stroke and TIA population incapacity will typically be caused by a different condition (such as underlying dementia) and we believe we can establish clinical utility of the marker without including such patients.

3.4 Visit Schedule

Participants will undergo the routine clinical assessment for TIA and minor stroke. This will include assessment of demographic data, assessment of ABCD2 score, brain and vascular imaging, drug therapy and cardiac investigations. These tests all represent standard care and results will be obtained from the medical notes. The diagnosis of the G.P and specialist clinician will be recorded. If brain MRI is not a part of standard care, they will undergo a brain MRI scan as soon as possible after presentation. This is regarded as an optimal standard of clinical care rather than a research intervention.

Participants will provide a urine and blood sample during their initial clinical consultation. Where possible the blood samples will be taken with routine clinical samples to minimise discomfort. An EDTA tube for DNA and one SST for serum will also be obtained. Samples will be identified by a unique 1D barcode number. The blood samples are for biobanking to allow us to help others by validating other biomarkers under investigation.

Patients will be followed up once at the same time as their routine clinical follow up. This is typically between at between 6 weeks to 3 months. If no routine clinical follow-up is planned, this will be done at 3 months +/- 2 weeks. This visit is to assess for recurrent stroke and vascular events, to assess functional outcome and to record medications taken. A further urine sample will be obtained at this point. Subsequent up-to 1-year follow up will be remote via record linkage [8].



Up-to-1 year after stroke

Recurrent stroke and vascular events determined

via record linkage

Figure 3 Summary of study visits

3.5 Blood and Urine Samples

Subjects with suspected minor stroke or TIA will provide a urine and blood sample as soon as possible and within 48 hours of event onset. The samples will be taken with routine clinical samples to minimise discomfort to the patient. An EDTA tube for DNA and one SST for serum will also be obtained (total volume approx. 9 mls). Samples will be identified by a unique 1D barcode number. The blood samples are for

biobanking to allow us to help others by validating other biomarkers under investigation.

3.6 Blood and Urine Sample Storage

A standard operating procedure for sample storage and shipping will be finalised before recruitment starts. Urine samples will be aliquoted and immediately stored the local site at -80°C (preferable) or -20°C. Blood samples for serum will be processed, centrifuged and stored at -80°C (preferable) or -20°C at the local site. EDTA tubes will be frozen at -80°C (preferable) or -20°C at the local site. The temperature of storage will be recorded.

Samples will be couriered frozen to the NHS Greater Glasgow and Clyde bio-repository at a time agreed with local sites. A courier will be organised by the trial co-ordinating team. Samples will then be stored in line with NHS Greater Glasgow and Clyde policies for biobanking at -80°C.

3.7 Assessment of Functional Outcome

This will be measured by trained observers using the modified Rankin scale (mRS) at day 90 (+/- 14). The mRS is an ordinal hierarchical scale from 0 to 5 and a good outcome will be defined as mRS < 3 (independence) (table 2). The Stroke Impact Scale short form will also be measured.

3.8 Assessment of Final Diagnosis

All participants will be diagnosed and treated as decided by the clinical team. Data will be recorded during (but will not interfere with) this process. Clinical data from the patient's record will be anonymised by the local team and sent to the trial co-ordinating centre via secure NHS email. All cases will be reviewed by a diagnostic committee, which will include at least two stroke physicians / stroke neurologists. The diagnostic committee will review cases virtually in the first instance, A radiologist with suitable experience will be available if needed. This data will include reports of all imaging and an anonymised copy of electronic

brain imaging. A mimic will be diagnosed when clinical presentation is not felt to be consistent with a vascular event or if an alternative firm diagnosis (such as brain tumour or demyelination) is made. A definite TIA / minor stroke will be diagnosed if the clinical presentation is compatible with stroke / TIA and will be subdivided according to whether brain imaging confirms an ischaemic vascular event in a corresponding anatomical territory. Aetiological subtype will be assessed using the Atherosclerotic, Small vessel, Cardioembolic, Other (ASCO) classification [9]. Each clinician reviewer will submit their diagnosis electronically. If all the opinions agree, this diagnosis will be assigned. If they do not, the case will be reviewed at a formal face to face diagnostic committee meeting. The result of this process will be forwarded to the clinical team.

3.9 Measurement of TriMeths Levels

Urine samples will be batch analysed after recruitment of 100 participants across all sites and then at the end of the study. Relative quantities of TriMethS in patients will be ascertained by determining the area under the curve of the peak representing the metabolite in each patient and this compared to the total useable signal (*i.e.* the total signal minus background and contaminant signals) in the mass chromatogram from urines related to each patient. Normalisation by comparing to creatinine levels

in patient urine is frequently used in clinical chemistry, but our untargeted approach provides us with an unbiased measure of the majority of metabolites in urine and can therefore serve as a better gauge of overall urine concentration, hence the use of total usable signal. Once we have the definitive structure for TriMethS we can use a custom synthesised authentic standard to provide absolute quantification in each patient. Since the metabolomics platform also acquires information on several hundred additional metabolites, and we have previously noted a panel of metabolites that offer good positive predictive value in distinguishing stroke/TIA from stroke mimic, we will also exploit this data set to test other classifier models. This is not a primary aim of the research.

3.10 Incidental findings on MRI

All MRI scans will be performed on clinical NHS scanners, will be reported by NHS radiologists and the results will be passed to the Consultant Stroke Physician in charge of the participants care to deal with any incidental findings. Importantly, the MRI scan is the standard of care for patients with suspected TIA or minor stroke.

3.11 7T MRI sub-study

Subjects may also be approached to participate in the 7T pilot MRI sub-study at the Queen Elizabeth University Hospital (QUEH) in Glasgow. Participants will be asked to undergo an additional MRI scan using the more powerful 7T scanner available at the ICE facility at the QEUH. Patients will be given an additional patient information sheet and consent to participate in this sub-study. All these participants will already have had a diagnostic MRI scan. The purpose of this study is to assess feasibility of 7T imaging in this group and ensure the sequences on the new scanner provide similar information to on CE marked 1.5 and 3T systems.

This is a pilot study so the sample size has been selected only to provide a sufficient number of images to assess feasibility.

Participants for this sub-study will be from the Glasgow sites only. The additional exclusion criteria are;

1. Any metallic implants (including those normally suitable for 1.5 T and 3T MRI).
2. Any tattoo.

4 Statistics and Data Analysis

4.1 Statistical Analysis Plan

Full details of all statistical issues and planned statistical analyses will be specified in a separate statistical analysis plan (SAP) which will be agreed by the trial management committee before the final locking of the study database.

4.2 Statistical Analysis

To determine if levels of TriMeths differ in TIA/minor stroke compared to mimic will be tested using either a t-test or non-parametric equivalent. We will assess sensitivity and specificity of using TriMethS levels for the diagnosis of minor stroke and TIA compared to the final consensus diagnosis. An optimal cut-off value will be identified and used for assessment of sensitivity and specificity. We will calculate the

improvement in diagnostic classification by addition of biomarker data to the G.P diagnosis (using C statistics and net reclassification improvement (NRI)) compared to the consensus diagnosis.

We will also assess the relationship between TriMethS levels, diagnostic category and ASCO classification, imaging findings and ABCD score to assess construct validity. Finally, we assess the relationship between TriMethS levels and recurrent stroke and cardiovascular events.

In general we will apply parametric statistical methods; any variable not suitable for parametric analysis will be analysed using non-parametric methods. Hypothesis testing will be carried out at the 5% significance level. Where appropriate, this will be adjusted to take account of multiple comparisons. There are no planned safety analyses as this is a non-interventional study.

4.3 Sample Size

It is estimated that 30-40% of referrals will be mimic. This will give approximately 100 to 120 patients with mimic and 180 to 200 patients with TIA / minor stroke. We have based our sample size calculation on the number needed to demonstrate acceptable sensitivity for clinical use (deemed to be 95%).

We have used the following formula (10);

$TP+FN = 1.96^2 * (SN(1-SN))/W^2$

$TP+FN = 3.8416 * (0.90(1-0.90))/0.0025$

$TP+FN = 3.8416 * (0.09/0.0025)$

$N = (TP+FN) / P$

$N = 138.297/0.6$

$N=230$

TP = true positives, FN = false negative, SN = acceptable sensitivity, W = confidence / alpha (5%).

We will therefore enrol at least 300 referrals with suspected TIA or minor stroke to ensure 230 with complete data and MRI data to support final diagnosis. This will also give sufficient numbers to identify a 10% increase in specificity of diagnosis using TriMethS levels (11).

4.4 Procedures for Accounting for Missing Data

There will be no imputation of missing data for any of the analyses.

4.5 Procedures for Deviations from the Original Statistical Plan

A detailed statistical analysis plan (SAP) will be agreed before the final locking and unblinding of the study database. Any deviations from this plan will be documented and justified in the final study report.

4.6 Selection of Subjects to be Included in the Analyses

Subjects will be included in analyses provided they have a urine sample from baseline and information of clinical and consensus diagnosis.

5 Trial Closure / Definition of the end of trial

The end of the study will be the completion of record linkage at one-year after recruitment of the last recruited participant (participant 300).

6 Timetable

The trial start date is 1st November 2017 with a 3-year project duration. There will be a 3-month set up period and, a 2-year recruitment window, a further 3-months to complete follow up and then 6 months to complete data entry, analysis and reporting. This recruitment rate is high and requires 12.5 participants per month. However in excess of 30 referrals with suspected TIA and minor stroke per week occur in Glasgow and a further 20 per week in the Manchester site giving a recruitment pool of at least 200 participants per month. Additional sites from the Scottish Stroke Research Network and UK CRN can also be included.

7 Source Data/Documents

All participant data will be identified by the participant study identification (TriMeths

##(where ## = study number)). The source data are outlined in table four. All CRF data will be held in linked anonymous fashion in secure locked cabinets on hospital premises. Data will then be entered into an electronic database and stored on a dedicated area on a secure NHS server.

A copy of the participants NHS number will be kept on a secure NHS server for record linkage.

	Source Data	Entry of Source Data to CRF
Baseline Demographic Variables	NHS clinical records	Direct entry into CRF during visit one
Routine Blood Tests	Stored in NHS Laboratory System	Direct entry of results into CRF
Routine Imaging Tests	Stored in NHS System	Direct entry of results into CRF
Study MRI	Stored in NHS System	Direct entry of results into CRF
Consensus diagnosis meeting	Emails of discussions Entered into meeting form	Direct entry of results into CRF
Urine / Blood Sample Log	Sample log	Details of samples taken entered into CRF

Table 2 Summary of Source Data 7.1 Completion of CRF

The CRF will be developed under guidance of Prof. Dawson. The Investigator, or his/her designee will be responsible for all entries into the CRF and will confirm that the data are accurate and complete, and that they have reviewed all of the data

contained in the CRF. Copies of CRFS will be sent to the trial co-ordination centre by courier or by transfer using a secure NHS server.

7.2 Data Validation

Data will be validated by the Investigator or designee at the point of entry into the CRF. Data will be reviewed centrally following transfer of the CRFs. Any data falling outwith pre-defined ranges defined in the data management plan will be flagged to the investigator and queried.

Any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

7.3 Data Security

CRFs will be kept in a locked cabinet under the care of the research team on NHS premises. Linked anonymised data will then be entered into an electronic database and stored on a dedicated area on a secure NHS server. This will only be accessible to the named investigators.

7.4 Record Retention / Archiving

CRFs will be stored for 10 years after completion of the trial. Samples will be kept for 10 years, as will the electronic case report database.

8 Trial Management

The trial management teams will be in place before the start of the study.

8.2 Routine Management of the Study

The study will be co-ordinated from the Queen Elizabeth University Hospital Stroke Unit, Glasgow by the Trial Management Committee (TMC). The research team meet weekly in person or via teleconference to discuss progress of all studies and to identify issues surrounding recruitment and trial conduct. This meeting included Investigators, trial managers and research nurses.

8.2 Trial Management Committee (TMC)

The TMC will oversee conduct of the study. The committee will include the grant applicants (and co-investigators named in protocol) and trials manager and will be chaired by Prof Dawson. The TMC will meet bi-annually. They will review recruitment figures and develop statistical analysis plans and plan any required amendments. The meeting will be quorate if the chair, the trials manager and one member of laboratory staff are present.

8.3 Trial Writing Committee

The writing committee have responsibility for writing all abstracts and manuscripts for publication and will comprise the co-investigators listed in the protocol. They are responsible for approving content and dissemination, and will be named authors, of all publications, abstracts and presentations arising from the study and for assuring the confidentiality and integrity of the study. It will provide collaborators with approved publicity material and information updates at regular intervals during the course of the study. The definitive publications from the trial will be written with input from the collaborators and will acknowledge all those who have contributed to the study.

No individual will publish data without prior approval of the writing committee.

9 Study Auditing

This study will be audited by designated representatives of the Sponsor. NHS Greater Glasgow and Clyde audit processes will be followed. It is the sponsor's responsibility to inform the investigator(s) of all intended study centre audits involving the study centre. It is the investigator's responsibility to ensure appropriate resources at site and that the auditor(s) have access to all study personnel, documentation and patient medical notes as appropriate.

10 Protocol Amendments

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the Chief Investigator on behalf of the trial management committee and any required amendment forms will be submitted to the ethics committee and sponsor. The Sponsor will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the Chief Investigator and sponsor representative. Before the amended protocol can be implemented (or sent to other participating sites) favourable opinion/approval must be sought from the original reviewing REC and the Research and Development (R & D) office. The Chief Investigator will sign any amended versions of the protocol. All protocol versions and their amendments must be notified to the study team.

11 Ethical Considerations

11.1 Ethical Conduct of Study

Study will be carried on accordance with the World Medical Association Declaration of Helsinki (1964) and it revisions (Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000) and Forteleza (2013)).

Trial patients will only be allowed to enter the study once they have provided written informed consent. The Chief Investigator will update the ethics committee of any new information related to the study.

11.2 Informed Consent

Written informed consent should be obtained from each participant, The research nurse or investigator will explain the exact nature of the study in writing, provision of patient information sheet, and verbally. This will include the risks of participating in the study. Participants will be informed that they are free to withdraw their consent from the study or study treatment at any time.

12 Sponsor, Insurance and Indemnity

The study is sponsored by NHS Greater Glasgow and Clyde. The University of Glasgow will be liable for negligent harm caused by the design of the trial. NHS Indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS). The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical

negligence and other negligent harm to patients under this duty of care. As this is a clinician-led study there are no arrangements for no-fault compensation.

13 Funding

Funding for this study has been granted by the Chief Scientist Office of Scotland, grant ID TCS/17/06.

14 Annual Reports

Annual reports will be submitted to the ethics committee and sponsor with the first submitted one year after the date that all trial related approvals are in place. Additional progress reports will be submitted to funders as required.

15 Public Engagement in Science

The University of Glasgow enjoys vigorous public engagement and public lecture programmes, and strongly supports the highly successful Café Scientifique programme (http://cafescientifique.org). Opportunities also arise for public engagement through International Science Festival (www.sciencefestival.co.uk). Public engagement is a key objective of the Scottish Stroke Research Network, this is achieved through annual events, which are attended by mainstream media, patients and the public, at which stroke research is demystified and a clear message about societal benefits arising from research is transmitted.

16 Dissemination of results

Data will be presented at appropriate international and national scientific meetings and we have a strong track record of presenting and anticipate publication of our findings in a high impact journal, all of which subscribe

to open access publishing policy. Data from this study will also be incorporated into the Virtual International Stroke Trials Archive (www.vista.gla.ac.uk) making it available for academic collaborators.

17 Key References

1. Rothwell PM, Giles MF, Chandratheva A et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study). Lancet 2007;370:1432-1442.

2. Hand PJ, Kwan J, Lindley RI, Dennis MS, Wardlaw JM. Distinguishing between stroke and mimic at the bedside: the brain attack study. Stroke 2006;37:769-75

3. Wardlaw JM, Farrall AJ. Diagnosis of stroke on neuroimaging. BMJ 2004; 328:655-

6

4. Ufnal M, Zadlo A, Ostaszewski R. TMAO: A small molecule of great expectations. Nutrition 2015;31:1317-23.

5. Whiteley W, Chong WL, Sengupta A, Sandercock P. Blood markers for the prognosis of ischemic stroke: a systematic review. Stroke 2009;40:380-389.

6. Creek DJ, Jankevics A, Breitling R, Watson DG, Barrett MP, Burgess KE. Toward global metabolomics analysis with hydrophilic interaction liquid chromatography-mass spectrometry: improved metabolite identification by retention time prediction. Anal Chem. 2011 83, 8703-10.

7. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, Irwig L, Levine D, Reitsma JB, de Vet HCW, Bossuyt PMM. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open 2016;6:e012799

8. Fleming, M., Kirby, B. and Penny, K. I. (2012), Record linkage in Scotland and its applications to health research. Journal of Clinical Nursing, 21: 2711–2721. doi:10.1111/j.1365-2702.2011.04021.x

9. Amarenco P, Bogousslavsky J, Caplan LR et al. New approach to stroke subtyping: the A-S-C-O (phenotypic) classification of stroke. Cerebro Dis 2009;27:502-508.

10. Dolmans LS, Rutten FH, Bartelink ML et al. MIND-TIA study protocol/ BMC Neurology 2015;15:119.

10. Jones SR, Carley S, Harrison M. An introduction to power and sample size estimation. Emerg Med J 2003;20:453-458.

11. Arkin CF, Mitchell S, Wachtel MS. How many patients are necessary to ass

Appendix H: TriMethS' protocol (Trimethylamine derivative) final follow up preform

TRIMETHS FINAL FOLLOW UP

Centre ID: Patient ID:

Follow Up Date (dd/mm/yyyy):

Assessor Name:

FINAL DIAGNOSIS

Minor Stroke	Yes	No
TIA	Yes	No
Non-Minor Stroke / TIA	Yes	No

If Non-Minor Stroke/TIA, please give cause of mimic:

CNS Mimic Non-CNS Mimic

Please give details of cause of mimic:

If Minor Stroke / TIA, imaging confirmed:

d^ >

W^

>^ SVD

WK^ Other

Unclassified

If 'Other', please give details:

Appendix I: Diagnosis of TIA score calculator

DIAGNOSIS OF TIA SCORE CALCULATOR

The DOT score is a diagnostic tool designed to help non-specialists diagnose a transient ischaemic attack (TIA) or minor stroke with greater accuracy.This score is currently for research purposes only and has not yet been externally validated.

Instructions for use

Enter age of patient in years and check each box that applies to your patient. Please take a thorough history and enter each item as accurately as possible. Then click the 'Calculate DOTS' button. Click the 'Reset' button to clear the form.

Data Entry

Item	Input	Explanatory notes
Age		Enter age in years.
History of hypertension		Select if patient has a history of hypertension even if recently diagnosed.
Atrial fibrillation (AF or PAF)		Select if patient has known AF,PAF or atrial flutter or has just been found by you to be in AF.
Dysphasia (disorder of language)		Select ONLY if patient had word finding difficulties, jumbled speech or was unable to speak. Slurring of speech (dysarthria) does NOT count as dysphasia.
Unilateral facial weakness		Select if patient had unilateral upper motor neurone (forehead sparing) facial weakness. If patient has isolated facial weakness at present and it is a lower motor neurone weakness, consider Bells Palsy.
Unilateral weakness of arm, leg or both		This must be GENUINE weakness. Tingling, numbness, heaviness, deadness or pain does NOT count unless there was true weakness. Ask if it was difficult to move the limb or grip.

Unilateral sensory loss		This must be genuine LOSS of sensation. Tingling, numbness or deadness does NOT count unless patient is sure there was loss of pain, temperature or touch sensation.
Visual loss in one eye		Either partial or complete monocular blindness. Check if patient is sure it was one eye - did they close each eye in turn? Transient loss can be due to a TIA affecting the eye. Persistent visual loss can have a broader differential diagnosis and in all cases, an ophthalmology review is required.
Visual loss in both eyes		Applies to complete blindness affecting both eyes.
Diplopia		Double vision.Does NOT apply to non specific blurring of vision.
Homonymous hemianopia		Applies to visual loss in either the right or left visual field. Please do not mistake this for monocular blindness or vice versa.
Visual aura		Applies to scintillations (flashing lights), fortification spectra (zig-zag lines) or spreading scotoma as in a migraine type visual aura.
Ataxia		Applies to inco-ordination of the limbs or gait.

Headache		Applies to any headache before, with or after the episode.
Amnesia		Does the patient remember the episode? Do not select if patient has dementia and is unlikely to remember what happened.
Loss of consciousness or near LOC		This applies to loss of consciousness due to any reason or near LOC.
Tingling and numbness		This applies to tingling, numbness or pins and needles to any part of the body including face.
Evaluate		

Designed by Dr Dipankar Dutta, Gloucestershire Royal Hospital, Gloucester, UK. November 2015.

Reference:Dutta D. Diagnosis of TIA (DOT) score – design and validation of a new clinical diagnostic tool for transient ischaemic attack. BMC Neurology. DOI: 10.1186/s12883-016-0535-1

List of References

1. Hankey GJ. Stroke. The Lancet. 2017 2017/02/11/;389(10069):641-654.
2. Sacco Ralph L, Kasner Scott E, Broderick Joseph P, et al. An Updated Definition of Stroke for the 21st Century. Stroke. 2013 2013/07/01;44(7):2064-2089.
3. Adams HP, Zoppo Gd, Alberts MJ, et al. Guidelines for the Early Management of Adults With Ischemic Stroke. Stroke. 2007;38(5):1655-1711.
4. Tawil SE, Muir KW. Thrombolysis and thrombectomy for acute ischaemic stroke. Clin Med (Lond). 2017;17(2):161-165.
5. Schellinger PD, Fiebach JB, Hacke W. Imaging-Based Decision Making in Thrombolytic Therapy for Ischemic Stroke. Stroke. 2003;34(2):575-583.
6. Everdingen KJv, Grond Jvd, Kappelle LJ, et al. Diffusion-Weighted Magnetic Resonance Imaging in Acute Stroke. Stroke. 1998;29(9):1783-1790.
7. Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014;2014(7):CD000213-CD000213.
8. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. New England Journal of Medicine. 2008 2008/09/25;359(13):1317-1329.
9. Magid-Bernstein J, Girard R, Polster S, et al. Cerebral Hemorrhage: Pathophysiology, Treatment, and Future Directions. Circ Res. 2022 Apr 15;130(8):1204-1229.
10. Ray B, Keyrouz SG. Management of anticoagulant-related intracranial hemorrhage: an evidence-based review. Critical Care. 2014 2014/05/23;18(3):223.
11. Maru DS-R, Schwarz R, Andrews J, et al. Turning a blind eye: the mobilization of radiology services in resource-poor regions. Globalization and Health. 2010 2010/10/14;6(1):18.
12. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. The Lancet. 1991 1991/06/22/;337(8756):1521-1526.
13. Yan LL, Li C, Chen J, et al. Prevention, management, and rehabilitation of stroke in low- and middle-income countries. eNeurologicalSci. 2016 2016/03/01/;2:21-30.
14. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991 Jun 22;337(8756):1521-6.
15. Pittock SJ, Meldrum D, Hardiman O, et al. The Oxfordshire Community Stroke Project classification: correlation with imaging, associated complications, and prediction of outcome in acute ischemic stroke. J Stroke Cerebrovasc Dis. 2003 Jan;12(1):1-7.
16. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993 1993/01/01;24(1):35-41.
17. Amarenco P, Bogousslavsky J, Caplan LR, et al. The ASCOD Phenotyping of Ischemic Stroke (Updated ASCO Phenotyping). Cerebrovascular Diseases. 2013;36(1):1-5.
18. Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke. 2007 Nov;38(11):2979-84.
19. Yaghi S, Bernstein RA, Passman R, et al. Cryptogenic Stroke. Circulation Research. 2017;120(3):527-540.
20. Amarenco. New Approach to Stroke Subtyping: The A-S-C-O (Phenotypic) Classification of Stroke. Cerebrovascular diseases (Basel, Switzerland). 2009;27:502-8.

21. Fonseca AC, Merwick Á, Dennis M, et al. European Stroke Organisation (ESO) guidelines on management of transient ischaemic attack. European Stroke Journal. 2021 2021/06/01;6(2):CLXIII-CLXXXVI.
22. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-e418.
23. Foundation HaS. Canadian stroke best practice recommendations acute stroke management. Canada: Acute Stroke Management Best Practice Writing Group; 2018.
24. Nor AM, Davis J, Sen B, et al. The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. Lancet Neurol. 2005 Nov;4(11):727-34.
25. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007 Jan 27;369(9558):283-92.
26. Dutta D. Diagnosis of TIA (DOT) score – design and validation of a new clinical diagnostic tool for transient ischaemic attack. BMC Neurology. 2016 2016/02/09;16(1):20.
27. Dawson J, Lamb KE, Quinn TJ, et al. A recognition tool for transient ischaemic attack. QJM: An International Journal of Medicine. 2008;102(1):43-49.
28. Nadarajan V, Perry RJ, Johnson J, et al. Transient ischaemic attacks: mimics and chameleons. Practical Neurology. 2014;14(1):23-31.
29. Vilela P. Acute stroke differential diagnosis: Stroke mimics. Eur J Radiol. 2017 Nov;96:133-144.
30. B HB, Akhtar N, Alrohimi A, et al. Stroke mimics: incidence, aetiology, clinical features and treatment. Ann Med. 2021 Dec;53(1):420-436.
31. Angus-Leppan H. Migraine: mimics, borderlands and chameleons. Practical Neurology. 2013;13(5):308-318.
32. Ippen FM, Walter F, Hametner C, et al. Age-Dependent Differences in the Rate and Symptoms of TIA Mimics in Patients Presenting With a Suspected TIA to a Neurological Emergency Room [Original Research]. Frontiers in Neurology. 2021 2021-February-15;12.
33. Prabhakaran S, Silver AJ, Warrior L, et al. Misdiagnosis of transient ischemic attacks in the emergency room. Cerebrovasc Dis. 2008;26(6):630-5.
34. Wilkins SS, Bourke P, Salam A, et al. Functional Stroke Mimics: Incidence and Characteristics at a Primary Stroke Center in the Middle East. Psychosom Med. 2018 Jun;80(5):416-421.
35. Kristoffersen ES, Grande RB, Aaseth K, et al. Management of primary chronic headache in the general population: the Akershus study of chronic headache. The Journal of Headache and Pain. 2012 2012/03/01;13(2):113-120.
36. Ridsdale L, Clark LV, Dowson AJ, et al. How do patients referred to neurologists for headache differ from those managed in primary care? Br J Gen Pract. 2007 May;57(538):388-95.
37. GARBER D. Descartes, René. Routledge Encyclopedia of Philosophy. London: Routledge; 1998, 2003.
38. Jorgensen LM. Seventeenth-Century Theories of Consciousness. In: Zalta EN, editor. The Stanford Encyclopedia of Philosophy. Winter 2014 ed. USA: Metaphysics Research Lab, Stanford University; 2014.
39. Van Gulick R. "Consciousness". In: Zalta EN, editor. The Stanford Encyclopedia of Philosophy. Spring 2018 ed. USA: Metaphysics Research Lab, Stanford University; 2018.
40. Petersen RC, Caracciolo B, Brayne C, et al. Mild cognitive impairment: a concept in evolution. Journal of internal medicine. 2014 Mar;275(3):214-28.

41. Palmer K, Fratiglioni L, Winblad B. What is mild cognitive impairment? Variations in definitions and evolution of nondemented persons with cognitive impairment. Acta Neurologica Scandinavica. 2003 2003/02/01;107(s179):14-20.
42. organization WH. International classification of diseases, eleventh revision (ICD-11) Geneva: World Health organization; 2022 [updated 01/01/2022; cited 2023 28/09/2023]; https://creativecommons.org/licenses/by-nc-nd/3.0/igo/; 11th:[Available from: https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/897917531
43. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. Jama. 2019 Oct 22;322(16):1589-1599.
44. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. The Lancet. 2014 2014/03/08/;383(9920):911-922.
45. Shaw RC, Walker G, Elliott E, et al. Occurrence Rate of Delirium in Acute Stroke Settings: Systematic Review and Meta-Analysis. Stroke. 2019 Nov;50(11):3028-3036.
46. Al-Qazzaz NK, Ali SH, Ahmad SA, et al. Cognitive impairment and memory dysfunction after a stroke diagnosis: a post-stroke memory assessment. Neuropsychiatr Dis Treat. 2014;10:1677-91.
47. Rost NS, Brodtmann A, Pase MP, et al. Post-Stroke Cognitive Impairment and Dementia. Circulation Research. 2022;130(8):1252-1271.
48. Young J, Meagher D, MacLullich A. Cognitive assessment of older people. 2011;343:d5042.
49. Harvey PD. Domains of cognition and their assessment. Dialogues Clin Neurosci. 2019 Sep;21(3):227-237.
50. Lezak MD, Howieson DB, Loring DW, et al. Neuropsychological assessment. Oxford University Press, USA; 2004.
51. Kipps CM, Hodges JR. Cognitive assessment for clinicians. J Neurol Neurosurg Psychiatry. 2005 Mar;76 Suppl 1(Suppl 1):i22-30.
52. Fitzpatrick D, Doyle K, Finn G, et al. The collateral history: an overlooked core clinical skill. Eur Geriatr Med. 2020 Dec;11(6):1003-1007.
53. Parkin AJ. Amnesic syndrome: a lesion-specific disorder? Cortex. 1984 Dec;20(4):479-508.
54. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec 8;25(24).
55. Akhouri S, Kuhn J, Newton EJ. Wernicke-Korsakoff Syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.
56. Arena JE, Rabinstein AA. Transient global amnesia. Mayo Clin Proc. 2015 Feb;90(2):264-72.
57. Fouchard A-A, Mondon K, De Toffol B. Transient epileptic amnesia. Presse Medicale (Paris, France: 1983). 2016;46(1):31-35.
58. Perini G, Cotta Ramusino M, Sinforiani E, et al. Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatr Dis Treat. 2019;15:1249-1258.
59. Leong S, Waits W, Diebold C. Dissociative Amnesia and DSM-IV-TR Cluster C Personality Traits. Psychiatry (Edgmont). 2006 Jan;3(1):51-5.
60. Krause-Utz A. Dissociation, trauma, and borderline personality disorder. Borderline Personality Disorder and Emotion Dysregulation. 2022 2022/04/19;9(1):14.
61. Buchanan TW, Laures-Gore JS, Duff MC. Acute stress reduces speech fluency. Biol Psychol. 2014 Mar;97:60-6.
62. Montembeault M, Stijelja S, Brambati SM. Self-reported word-finding complaints are associated with cerebrospinal fluid amyloid beta and atrophy in cognitively normal older adults. Alzheimers Dement (Amst). 2022;14(1):e12274.
63. Kertesz A, Jesso S, Harciarek M, et al. What Is Semantic Dementia?: A Cohort Study of Diagnostic Features and Clinical Boundaries. Archives of Neurology. 2010;67(4):483-489.
64. Tetsuka S. Depression and Dementia in Older Adults: A Neuropsychological Review. Aging Dis. 2021 Dec;12(8):1920-1934.

65. Schramm E, Klein DN, Elsaesser M, et al. Review of dysthymia and persistent depressive disorder: history, correlates, and clinical implications. Lancet Psychiatry. 2020 Sep;7(9):801-812.
66. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research. 1975;12(3):189-198.
67. Trivedi D. Cochrane Review Summary: Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Primary health care research & development. 2017;18(6):527-528.
68. Sheehan B. Assessment scales in dementia. Ther Adv Neurol Disord. 2012 Nov;5(6):349-58.
69. Gordon HB, Letsou A, Bonkowsky JL. The leukodystrophies. Semin Neurol. 2014 Jul;34(3):312-20.
70. Giagkou N, Höglinger GU, Stamelou M. Progressive supranuclear palsy. Int Rev Neurobiol. 2019;149:49-86.
71. Donders FC. On the speed of mental processes. Acta Psychol (Amst). 1969;30:412-31.
72. Sanford AM. Lewy Body Dementia. Clin Geriatr Med. 2018 Nov;34(4):603-615.
73. Mattison MLP. Delirium. Ann Intern Med. 2020 Oct 6;173(7):Itc49-itc64.
74. Hamedani AG, Pelak VS. The Charles Bonnet Syndrome: a Systematic Review of Diagnostic Criteria. Curr Treat Options Neurol. 2019 Jul 25;21(9):41.
75. Josephs KA. Capgras Syndrome and Its Relationship to Neurodegenerative Disease. Archives of Neurology. 2007;64(12):1762-1766.
76. Adolphs R. The social brain: neural basis of social knowledge. Annu Rev Psychol. 2009;60:693-716.
77. Beaudoin C, Beauchamp MH. Social cognition. Handb Clin Neurol. 2020;173:255-264.
78. Kemp J, Després O, Sellal F, et al. Theory of Mind in normal ageing and neurodegenerative pathologies. Ageing Res Rev. 2012 Apr;11(2):199-219.
79. Byom LJ, Mutlu B. Theory of mind: mechanisms, methods, and new directions. Front Hum Neurosci. 2013;7:413.
80. Baron-Cohen S, Wheelwright S, Hill J, et al. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry. 2001 Feb;42(2):241-51.
81. Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind. J Cogn Neurosci. 1998 Sep;10(5):640-56.
82. Baksh RA, Abrahams S, Auyeung B, et al. The Edinburgh Social Cognition Test (ESCoT): Examining the effects of age on a new measure of theory of mind and social norm understanding. PLoS One. 2018;13(4):e0195818.
83. Tchalla A, Laubarie-Mouret C, Cardinaud N, et al. Risk factors of frailty and functional disability in community-dwelling older adults: a cross-sectional analysis of the FREEDOM-LNA cohort study. BMC Geriatrics. 2022 2022/09/19;22(1):762.
84. Guo H, Sapra A. Instrumental Activity of Daily Living (IADL) - PMID: 31985920. 2019.
85. Briggs R, O'Neill D. The informant history: a neglected aspect of clinical education and practice. Qjm. 2016 May;109(5):301-2.
86. Liu Y, fu Q, Fu X. The interaction between cognition and emotion. Chinese Science Bulletin. 2009 11/01;54:4102-4116.
87. Marvel CL, Paradiso S. Cognitive and neurological impairment in mood disorders. Psychiatr Clin North Am. 2004 Mar;27(1):19-36, vii-viii.
88. Tyng CM, Amin HU, Saad MNM, et al. The Influences of Emotion on Learning and Memory. Front Psychol. 2017;8:1454.

89. Baena-Oquendo S, García Valencia J, Vargas C, et al. Neuropsychological aspects of bipolar disorder [10.1016/j.rcpeng.2022.08.003]. Revista Colombiana de Psiquiatría (English Edition). 2022;51(3):218-226.
90. Zuckerman H, Pan Z, Park C, et al. Recognition and Treatment of Cognitive Dysfunction in Major Depressive Disorder [Review]. Frontiers in Psychiatry. 2018 2018-December-04;9.
91. Rabins PV, Merchant A, Nestadt G. Criteria for diagnosing reversible dementia caused by depression: Validation by 2-year follow-up. The British Journal of Psychiatry. 1984;144(5):488-492.
92. Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. Neurology. 2002 Aug 13;59(3):364-70.
93. Cullen B, Smith DJ, Deary IJ, et al. Understanding cognitive impairment in mood disorders: mediation analyses in the UK Biobank cohort. Br J Psychiatry. 2019 Nov;215(5):683-690.
94. Greenberg SA. How to try this: the Geriatric Depression Scale: Short Form. Am J Nurs. 2007 Oct;107(10):60-9; quiz 69-70.
95. Buccianelli B, Marazziti D, Arone A, et al. Depression and Pseudodementia: Decoding the Intricate Bonds in an Italian Outpatient Setting. Brain Sci. 2023 Aug 13;13(8).
96. Voros V, Martin Gutierrez D, Alvarez F, et al. The impact of depressive mood and cognitive impairment on quality of life of the elderly. Psychogeriatrics. 2020 May;20(3):271-277.
97. Butler C, Zeman AZJ. Neurological syndromes which can be mistaken for psychiatric conditions. Journal of Neurology, Neurosurgery &; Psychiatry. 2005;76(suppl 1):i31.
98. Szymkowicz SM, Gerlach AR, Homiack D, et al. Biological factors influencing depression in later life: role of aging processes and treatment implications. Transl Psychiatry. 2023 May 10;13(1):160.
99. Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. Int J Geriatr Psychiatry. 2011 Nov;26(11):1109-18.
100. Köhler CA, Freitas TH, Maes M, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand. 2017 May;135(5):373-387.
101. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010 Mar 1;67(5):446-57.
102. Sartori AC, Vance DE, Slater LZ, et al. The impact of inflammation on cognitive function in older adults: implications for healthcare practice and research. J Neurosci Nurs. 2012 Aug;44(4):206-17.
103. Mustapha M, Nassir C, Aminuddin N, et al. Cerebral Small Vessel Disease (CSVD) - Lessons From the Animal Models. Front Physiol. 2019;10:1317.
104. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry. 1997 Apr;154(4):497-501.
105. the International Classification of Health Interventions Beta-3 [Internet]. the WHO. 2020 [cited 10/05/2021]. Available from: https://mitel.dimi.uniud.it/ichi/docs/ICHI%20Beta-3%20Reference%20Guide.pdf.
106. Campbell NC, Murray E, Darbyshire J, et al. Designing and evaluating complex interventions to improve health care. Bmj. 2007 Mar 3;334(7591):455-9.
107. Brady MC, Stott DJ, Norrie J, et al. Developing and evaluating the implementation of a complex intervention: using mixed methods to inform the design of a randomised controlled trial of an oral healthcare intervention after stroke. Trials. 2011 2011/07/05;12(1):168.
108. O'Cathain A, Croot L, Duncan E, et al. Guidance on how to develop complex interventions to improve health and healthcare. BMJ Open. 2019;9(8):e029954.
109. Bucyibaruta JB, Peu D, Bamford L, et al. Closing the gaps in defining and conceptualising acceptability of healthcare: a qualitative thematic content analysis. African Health Sciences. 2022;22(3):703-709.

110. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Services Research. 2017 2017/01/26;17(1):88.
111. Balint E. The possibilities of patient-centered medicine. J R Coll Gen Pract. 1969;17(82):269-276.
112. Coulter A, Oldham J. Person-centred care: what is it and how do we get there? Future Hosp J. 2016;3(2):114-116.
113. England NHe. Person-Centred Approaches: Empowering people in their lives and communities to enable an upgrade in prevention, wellbeing, health, care and support. England: NHS; 2020 [cited 2021]. Available from: https://skillsforhealth.org.uk/wp-content/uploads/2021/01/Person-Centred-Approaches-Framework.pdf
114. Government W. Prudent health care and patient activation: An appraisal prepared for the Planned Care Programme Wales: NHS; 2015 [cited 2021]. Available from: https://gov.wales/sites/default/files/publications/2019-04/prudent-health-care-and-patient-activation.pdf
115. EU. Patient enpowerment and centredness EU: Health parliament; 2017 [cited 2021]. Available from: https://www.healthparliament.eu/wp-content/uploads/2017/09/EHP-papers_Patients-empowerment.pdf
116. Government S. Person-centred care Scotland: Scottish government; 2019 [updated 15/09/2019]. Available from: https://www.gov.scot/publications/person-centred-care-non-executive-members/
117. Dyer TA, Owens J, Robinson PG. The acceptability of healthcare: from satisfaction to trust. Community Dent Health. 2016 Dec;33(4):242-251.
118. Corry DAS, Doherty J, Carter G, et al. Acceptability of a nurse-led, person-centred, anticipatory care planning intervention for older people at risk of functional decline: A qualitative study. PLoS One. 2021;16(5):e0251978.
119. Vennedey V, Hower KI, Hillen H, et al. Patients' perspectives of facilitators and barriers to patient-centred care: insights from qualitative patient interviews. BMJ Open. 2020;10(5):e033449.
120. Dwamena F, Holmes-Rovner M, Gaulden CM, et al. Interventions for providers to promote a patient-centred approach in clinical consultations. Cochrane Database Syst Rev. 2012 Dec 12;12:Cd003267.
121. Santana MJ, Manalili K, Jolley RJ, et al. How to practice person-centred care: A conceptual framework [https://doi.org/10.1111/hex.12640]. Health Expectations. 2018 2018/04/01;21(2):429-440.
122. Roumie CL, Greevy R, Wallston KA, et al. Patient centered primary care is associated with patient hypertension medication adherence. J Behav Med. 2011 Aug;34(4):244-53.
123. Thompson L, McCabe R. The effect of clinician-patient alliance and communication on treatment adherence in mental health care: a systematic review. BMC Psychiatry. 2012 Jul 24;12:87.
124. Bertakis KD, Azari R. Patient-centered care is associated with decreased health care utilization. J Am Board Fam Med. 2011 May-Jun;24(3):229-39.
125. Ekman I, Wolf A, Olsson LE, et al. Effects of person-centred care in patients with chronic heart failure: the PCC-HF study. Eur Heart J. 2012 May;33(9):1112-9.
126. Kuipers SJ, Cramm JM, Nieboer AP. The importance of patient-centered care and co-creation of care for satisfaction with care and physical and social well-being of patients with multi-morbidity in the primary care setting. BMC Health Services Research. 2019 2019/01/08;19(1):13.
127. Gallacher K, May CR, Montori VM, et al. Understanding patients' experiences of treatment burden in chronic heart failure using normalization process theory. Ann Fam Med. 2011 May-Jun;9(3):235-43.

128. Sav A, King MA, Whitty JA, et al. Burden of treatment for chronic illness: a concept analysis and review of the literature. Health Expectations. 2015;18(3):312-324.
129. Hounkpatin HO, Roderick P, Harris S, et al. Change in treatment burden among people with multimorbidity: a follow-up survey. Br J Gen Pract. 2022 Nov;72(724):e816-e824.
130. Gallacher KI, May CR, Langhorne P, et al. A conceptual model of treatment burden and patient capacity in stroke. BMC Fam Pract. 2018 Jan 9;19(1):9.
131. May C, Montori VM, Mair FS. We need minimally disruptive medicine. BMJ. 2009;339:b2803.
132. Sheehan OC, Leff B, Ritchie CS, et al. A systematic literature review of the assessment of treatment burden experienced by patients and their caregivers. BMC Geriatr. 2019 Oct 11;19(1):262.
133. Ahmed HM, Alalaf SK, Al-Tawil NG. Screening for postpartum depression using Kurdish version of Edinburgh postnatal depression scale. Arch Gynecol Obstet. 2012 May;285(5):1249-55.
134. Alder EM, Reid M, Sharp LJ, et al. Policy and practice in the management of postnatal depression in Scotland. Archives of women's mental health. 2008;11(3):213-219.
135. Armstrong SJ, Small RE. The paradox of screening: Rural women's views on screening for postnatal depression. BMC Public Health. 2010;10(1):1-9.
136. Austin M-PV, Hadzi-Pavlovic D, Priest SR, et al. Depressive and anxiety disorders in the postpartum period: how prevalent are they and can we improve their detection? Archives of women's mental health. 2010;13(5):395-401.
137. El-Den S, O'Reilly CL, Chen TF. A systematic review on the acceptability of perinatal depression screening. Journal of Affective Disorders. 2015 2015/12/01/;188:284-303.
138. Laferton JA, Kube T, Salzmann S, et al. Patients' Expectations Regarding Medical Treatment: A Critical Review of Concepts and Their Assessment. Front Psychol. 2017;8:233.
139. Laver KE, Adey-Wakeling Z, Crotty M, et al. Telerehabilitation services for stroke. Cochrane Database of Systematic Reviews. 2020 (1).
140. Cruz JE, Fahim G, Moore K. Practice Guideline Development, Grading, and Assessment. P t. 2015 Dec;40(12):854-7.
141. SIGN. A guideline developer's handbook Scotland: SIGN; 2015 [updated 04/06/2020]. Available from: https://www.sign.ac.uk/assets/sign50_2015.pdf
142. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. In: Graham R, Mancher M, Miller Wolman D, et al., editors. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US) Copyright 2011 by the National Academy of Sciences. All rights reserved.; 2011.
143. Brignardello-Petersen R, Carrasco-Labra A, Guyatt GH. How to Interpret and Use a Clinical Practice Guideline or Recommendation: Users' Guides to the Medical Literature. JAMA. 2021;326(15):1516-1523.
144. Johnston A, Kelly SE, Hsieh SC, et al. Systematic reviews of clinical practice guidelines: a methodological guide. J Clin Epidemiol. 2019 Apr;108:64-76.
145. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA Clinical Practice Guideline Methodology Summit Report. Circulation. 2013 2013/01/15;127(2):268-310.
146. Granholm A, Alhazzani W, Møller MH. Use of the GRADE approach in systematic reviews and guidelines. Br J Anaesth. 2019 Nov;123(5):554-559.
147. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926.
148. McGowan J, Akl EA, Coello PA, et al. Update on the JCE GRADE series and other GRADE article types. Journal of Clinical Epidemiology. 2021 2021/12/01/;140:163-164.
149. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. Bmj. 2001 Aug 11;323(7308):334-6.

150. Shea BJ, Bouter LM, Peterson J, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One. 2007 Dec 26;2(12):e1350.
151. Liddle J, Williamson M, Irwig L. Method for evaluating research & guideline evidence. NSW Department of Health; 1996.
152. Whiting P, Rutjes AWS, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology. 2003 2003/11/10;3(1):25.
153. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. Bmj. 1996 Jan 13;312(7023):71-2.
154. Brems JH, Davis AE, Clayton EW. Analysis of conflict of interest policies among organizations producing clinical practice guidelines. PLoS One. 2021;16(4):e0249267.
155. Guerra-Farfan E, Garcia-Sanchez Y, Jornet-Gibert M, et al. Clinical practice guidelines: The good, the bad, and the ugly. Injury. 2022 2022/02/01/.
156. Miguel RTD, Silvestre MAA, Salaveria-Imperial MLA, et al. Disclosures of conflicts of interest in clinical practice guidelines. Clinical Epidemiology and Global Health. 2021 2021/01/01/;9:355-359.
157. Afshari A, De Hert S. Pitfalls of clinical practice guidelines in the era of broken science: Let's raise the standards. European Journal of Anaesthesiology | EJA. 2018;35(12):903-906.
158. Alonso-Coello P, Irfan A, Solà I, et al. The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. Quality and Safety in Health Care. 2010;19(6):e58-e58.
159. Franco JVA, Arancibia M, Meza N, et al. Clinical practice guidelines: concepts, limitations and challenges. Medwave. 2020;20(3):e7887.
160. Langa KM, editor Cognitive aging, dementia, and the future of an aging population. Future Directions for the Demography of Aging: Proceedings of a Workshop; 2018: National Academies Press.
161. Yousufuddin M, Young N. Aging and ischemic stroke. Aging (Albany NY). 2019 May 1;11(9):2542-2544.
162. Douiri A, Rudd AG, Wolfe CDA. Prevalence of Poststroke Cognitive Impairment. Stroke. 2013;44(1):138-145.
163. Mancuso M, Demeyere N, Abbruzzese L, et al. Using the Oxford Cognitive Screen to Detect Cognitive Impairment in Stroke Patients: A Comparison with the Mini-Mental State Examination [Original Research]. Frontiers in Neurology. 2018 2018-February-28;9(101).
164. Melkas S, Laurila JV, Vataja R, et al. Post-stroke delirium in relation to dementia and long-term mortality. Int J Geriatr Psychiatry. 2012 Apr;27(4):401-8.
165. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: epidemiology, mechanisms and management. Ann Transl Med. 2014 Aug;2(8):80.
166. Kalaria RN, Akinyemi R, Ihara M. Stroke injury, cognitive impairment and vascular dementia. Biochim Biophys Acta. 2016 May;1862(5):915-25.
167. Cumming TB, Brodtmann A, Darby D, et al. The importance of cognition to quality of life after stroke. J Psychosom Res. 2014 Nov;77(5):374-9.
168. Pollock A, St George B, Fenton M, et al. Top ten research priorities relating to life after stroke. The Lancet Neurology. 2012;11(3):209.
169. Alliance TJ. Stroke survivor, carer and health professional research priorities relating to life after stroke. Scotland: Glasgow caledonian university; 2012.
170. Rudberg A-S, Berge E, Laska A-C, et al. Stroke survivors' priorities for research related to life after stroke. Topics in Stroke Rehabilitation. 2020 07/05;28:1-6.
171. Siqueira GSA, Hagemann PDMS, Coelho DDS, et al. Can MoCA and MMSE Be Interchangeable Cognitive Screening Tools? A Systematic Review. The Gerontologist. 2019;59(6):e743-e763.

172. Pinto TCC, Machado L, Bulgacov TM, et al. Is the Montreal Cognitive Assessment (MoCA) screening superior to the Mini-Mental State Examination (MMSE) in the detection of mild cognitive impairment (MCI) and Alzheimer's Disease (AD) in the elderly? International Psychogeriatrics. 2019;31(04):491-504.
173. Chua SIL, Tan NC, Wong WT, et al. Virtual Reality for Screening of Cognitive Function in Older Persons: Comparative Study. Journal of Medical Internet Research. 2019;21(8):e14821.
174. Nasreddine ZS, Phillips NA, Bã©Dirian VR, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. Journal of the American Geriatrics Society. 2005;53(4):695-699.
175. Toornstra A, Hurks P, Van der Elst W, et al. Measuring Visual, Spatial, and Visual Spatial Short-Term Memory in Schoolchildren: Studying the Influence of Demographic Factors and Regression-Based Normative Data. Journal of Pediatric Neuropsychology. 2019 09/01;5:1-13.
176. Quinn TJ, Elliott E, Langhorne P. Cognitive and Mood Assessment Tools for Use in Stroke. Stroke. 2018 Feb;49(2):483-490.
177. Burton L, Tyson S. Screening for cognitive impairment after stroke: A systematic review of psychometric properties and clinical utility. Journal of Rehabilitation Medicine. 2015;47(3):193-203.
178. McGovern A, Pendlebury ST, Mishra NK, et al. Test Accuracy of Informant-Based Cognitive Screening Tests for Diagnosis of Dementia and Multidomain Cognitive Impairment in Stroke. Stroke. 2016 Feb;47(2):329-35.
179. Chapman JE, Cadilhac DA, Gardner B, et al. Comparing face-to-face and videoconference completion of the Montreal Cognitive Assessment (MoCA) in community-based survivors of stroke. Journal of Telemedicine and Telecare.0(0):1357633X19890788.
180. Elliott E, Green C, Llewellyn DJ, et al. Accuracy of Telephone-Based Cognitive Screening Tests: Systematic Review and Meta-Analysis. Curr Alzheimer Res. 2020;17(5):460-471.
181. Lees R, Selvarajah J, Fenton C, et al. Test accuracy of cognitive screening tests for diagnosis of dementia and multidomain cognitive impairment in stroke. Stroke. 2014 Oct;45(10):3008-18.
182. Shaneyfelt TM, Mayo-Smith MF, Rothwangl J. Are Guidelines Following Guidelines? JAMA. 1999;281(20):1900.
183. Ward JE, Grieco V. Why we need guidelines for guidelines: a study of the quality of clinical practice guidelines in Australia. Medical Journal of Australia. 1996;165(10):574-576.
184. Navarro Puerto MA, Ibarluzea IG, Ruiz OG, et al. Analysis of the quality of clinical practice guidelines on established ischemic stroke. International Journal of Technology Assessment in Health Care. 2008;24(03):333-341.
185. McMahon D. McMahon, D. (2020, September 19). Systematic review of clinical practice guidelines detailing cognitive assessment in stroke. 2020.
186. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. AMIA Annu Symp Proc. 2006;2006:359-363.
187. Foundation S. Clinical Guidelines for Stroke Management Australia & New Zealand2023. Available from: https://informme.org.au/guidelines/living-clinical-guidelines-for-stroke-management.
188. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Medicine. 2009;6(7):e1000100.
189. Koo T, K., Li, M, Y. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. Journal of Chiropractic Medicine. 2016;15(2):155-163.

190. Hatakeyama Y, Seto K, Amin R, et al. The structure of the quality of clinical practice guidelines with the items and overall assessment in AGREE II: a regression analysis. BMC Health Services Research. 2019;19(1).
191. Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ. 2016:i1152.
192. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Canadian Medical Association Journal. 2010;182(18):E839-E842.
193. Johnston A, Hsieh SC, Carrier M, et al. A systematic review of clinical practice guidelines on the use of low molecular weight heparin and fondaparinux for the treatment and prevention of venous thromboembolism: Implications for research and policy decision-making. PLoS One. 2018;13(11):e0207410.
194. Liljequist D, Elfving B, Skavberg Roaldsen K. Intraclass correlation – A discussion and demonstration of basic features. PLOS ONE. 2019;14(7):e0219854.
195. Clarke V, Braun V. Teaching thematic analysis: Overcoming challenges and developing strategies for effective learning. The psychologist. 2013;26(2).
196. Royal College of Physicians of London, editor Acute care toolkit 3: acute medical care for frail older people2012: Royal College of Physicians.
197. (SIGN) SIGN. 118: Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning A national clinical guideline Scotland: Scottish Intercollegiate Guidelines Network; 2010. Available from: https://www.sign.ac.uk/media/1056/sign118.pdf
198. (SIGN) SIGN. Management of patients with stroke: identification and management of dysphagia. 2010. (SIGN publication 119. 2010 [cited 2019]. Available from: https://www.sign.ac.uk/our-guidelines/
199. Foundation IH. National Clinical Guidelines and Recommendations for the Care of People with Stroke and Transient Ischaemic Attack Ireland: Council for Stroke; 2010 [cited 2019]; Revised Version March 2010:[Available from: https://www.hse.ie/eng/about/who/cspd/ncps/stroke/resources/irish-heart-foundation-2010-guidelines.pdf
200. Winstein CJ, Stein J, Arena R, et al. Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016 Jun;47(6):e98-e169.
201. Chung CSY, Pollock A, Campbell T, et al. Cognitive rehabilitation for executive dysfunction in adults with stroke or other adult non-progressive acquired brain damage. Cochrane Database Syst Rev. 2013;2013(4):CD008391-CD008391.
202. Delavaran H, Jönsson AC, Lövkvist H, et al. Cognitive function in stroke survivors: A 10-year follow-up study. Acta Neurol Scand. 2017 Sep;136(3):187-194.
203. Pendlebury ST, Mariz J, Bull L, et al. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and stroke. Stroke. 2012 Feb;43(2):464-9.
204. Ayerbe L, Ayis S, Wolfe CDA, et al. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. British Journal of Psychiatry. 2013;202(1):14-21.
205. London KC. Acute organisational report Sentinel stroke national audit program (SSNAP) England, Wales, N Ireland2019 [cited 2022 23/10/2022]. Available from: https://www.strokeaudit.org/Documents/National/AcuteOrg/2019/2019-AOANationalReport.aspx
206. Brady MC, Kelly H, Godwin J, et al. Speech and language therapy for aphasia following stroke. Cochrane Database of Systematic Reviews. 2016 (6).

207. Soiza RL, Myint PK. The Scottish Intercollegiate guidelines network (sign) 157: guidelines on risk reduction and management of delirium. Medicina. 2019;55(8):491.
208. NICE. Delirium overview https://pathways.nice.org.uk/pathways/delirium#content=view-node%3Anodes-assess-for-delirium: NICE Pathways; 2010 [updated MARCH 2019; cited 2019 01/04/2019]. Available from: https://pathways.nice.org.uk/pathways/delirium#content=view-node%3Anodes-assess-for-delirium
209. Physicians Rco. Acute care toolkit 3 - acute medical care for frail older people https://www.rcplondon.ac.uk/guidelines-policy/acute-care-toolkit-3-acute-medical-care-frail-older-people: Royal College physicians; 2012.
210. Harrison JK, Fearon P, Noel-Storr AH, et al. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within a secondary care setting. Cochrane Database of Systematic Reviews. 2015 (3).
211. Beishon LC, Batterham AP, Quinn TJ, et al. Addenbrooke's Cognitive Examination III (ACE-III) and mini-ACE for the detection of dementia and mild cognitive impairment. Cochrane Database of Systematic Reviews. 2019 (12).
212. Zwolsman S, te Pas E, Hooft L, et al. Barriers to GPs' use of evidence-based medicine: a systematic review. British Journal of General Practice. 2012;62(600):e511-e521.
213. Hong B, O'Sullivan ED, Henein C, et al. Motivators and barriers to engagement with evidence-based practice among medical and dental trainees from the UK and Republic of Ireland: a national survey. BMJ Open. 2019;9(10):e031809.
214. Takwoingi Y, Quinn TJ. Review of Diagnostic Test Accuracy (DTA) studies in older people. Age and Ageing. 2018;47(3):349-355.
215. Quinn TJ, Richard E, Teuschl Y, et al. European Stroke Organisation and European Academy of Neurology joint guidelines on post-stroke cognitive impairment [https://doi.org/10.1111/ene.15068]. European Journal of Neurology. 2021 2021/12/01;28(12):3883-3920.
216. Harrison JK, Noel-Storr AH, Demeyere N, et al. Outcomes measures in a decade of dementia and mild cognitive impairment trials [journal article]. Alzheimer's Research & Therapy. 2016 November 21;8(1):48.
217. recommendations Csbp. Mood, cognition and fatigue following stroke. 6th ed. Canada: Canadian stroke best practice recommendations; 2019.
218. (JLA) JLA. Stroke Priority Setting Partnership UK: Stroke Priority Setting Partnership; 2021 [cited 2021 29/20/2021]; Stroke Priority Setting Partnership]. Available from: https://www.jla.nihr.ac.uk/priority-setting-partnerships/Stroke/downloads/JLA%20Stroke%20PSP%20final%20sheet%20of%20data.pdf
219. NICE. Stroke rehabilitation in adults UK: National Institute for Health and Care Excellence; 2013. Available from: https://www.nice.org.uk/guidance/cg162/resources/stroke-rehabilitation-in-adults-pdf-35109688408261
220. Merriman NA, Bruen C, Gorman A, et al. "I'm just not a Sudoku person": analysis of stroke survivor, carer, and healthcare professional perspectives for the design of a cognitive rehabilitation intervention. Disability and rehabilitation. 2020 Nov;42(23):3359-3369.
221. Leitch S, Logan M, Beishon L, et al. International research priority setting exercises in stroke: A systematic review. Int J Stroke. 2023 Feb;18(2):133-143.
222. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021;374:n2061.
223. Rosengren K, Brannefors P, Carlstrom E. Adoption of the concept of person-centred care into discourse in Europe: a systematic literature review. J Health Organ Manag. 2021 Sep 13;35(9):265-280.

224. Dawda P, Janamian T, Wells L. Creating person-centred health care value together [https://doi.org/10.5694/mja2.51531]. Medical Journal of Australia. 2022 2022/06/06;216(S10):S3-S4.
225. Sinaiko AD, Szumigalski K, Eastman D, et al. Delivery of patient centered care in the US Health Care System: What is standing in its way. Academy Health Retrieved October. 2019;30:2019.
226. Sekhon M, Cartwright M, Francis JJ. Acceptability of health care interventions: A theoretical framework and proposed research agenda. British Journal of Health Psychology. 2018;23(3):519-531.
227. Donabedian A. An introduction to quality assurance in health care. Oxford University Press; 2002.
228. Bartlett YK, Kenning C, Crosland J, et al. Understanding acceptability in the context of text messages to encourage medication adherence in people with type 2 diabetes. BMC health services research. 2021;21(1):608-608.
229. Herron D, Chew-Graham CA, Hider S, et al. Acceptability of nurse-led reviews for inflammatory rheumatological conditions: A qualitative study. J Comorb. 2021 Jan-Dec;11:26335652110024402.
230. Sofaer S. Qualitative methods: what are they and why use them? Health Serv Res. 1999;34(5 Pt 2):1101-1118.
231. Wheeldon J, Ahlberg M. Mapping mixed-methods research: Theories, models, and measures. Vis Soc Sci Res. 2012;4:113-48.
232. Proudfoot K. Inductive/Deductive Hybrid Thematic Analysis in Mixed Methods Research. Journal of Mixed Methods Research.0(0):15586898221126816.
233. Ritchie J, Lewis J. Qualitative Research Practice—A Guide for Social Science Students and Researchers. London: sage; 2003.
234. Gale NK, Heath G, Cameron E, et al. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Medical Research Methodology. 2013 2013/09/18;13(1):117.
235. Executive S. Scottish index of multiple deprivation 2006 technical report. Office of the Chief Statistician, Scottish Executive. 2006;10.
236. Government S. Scottish Index of Multiple Deprivation 2020 Edinburgh: Scottish Government; 2020 [cited 2021 10/12/2021]. Available from: https://simd.scot/#/simd2020/BTTTFTT/12.666666666666666/-4.1747/55.8904/
237. Scotland Ph. Data and intelligence Scotland: Public Health Scotland; 2020 [cited 2021 13/12/2021]; GPD Support Deprivation]. Available from: https://www.isdscotland.org/products-and-services/gpd-support/deprivation/simd/
238. Hobden G, Tang E, Demeyere N. Cognitive assessment after stroke: A qualitative study of patients' experiences. BMJ Open. 2023 Jun 29;13(6):e072501.
239. Tang E, Exley C, Price C, et al. The views of public and clinician stakeholders on risk assessment tools for post-stroke dementia: A qualitative study. BMJ Open. 2019 03/01;9:e025586.
240. Renovanz M, Reitzug L, Messing L, et al. Patient reported feasibility and acceptance of Montreal Cognitive Assessment (MoCA) screening pre- and postoperatively in brain tumour patients. J Clin Neurosci. 2018 Jul;53:79-84.
241. Olson RA, Chhanabhai T, McKenzie M. Feasibility study of the Montreal Cognitive Assessment (MoCA) in patients with brain metastases. Support Care Cancer. 2008 Nov;16(11):1273-8.
242. Dingwall KM, Gray AO, McCarthy AR, et al. Exploring the reliability and acceptability of cognitive tests for Indigenous Australians: a pilot study. BMC Psychology. 2017 2017/08/02;5(1):26.
243. Holsinger T, Boustani M, Abbot D, et al. Acceptability of dementia screening in primary care patients. International Journal of Geriatric Psychiatry. 2011;26(4):373-379.

244. Mortensen GL, Theódórsdóttir Á, Sejbæk T, et al. Patient Attitudes to Routine Cognitive Testing in Multiple Sclerosis. Patient Prefer Adherence. 2020;14:693-704.
245. Tyrrell M, Hedman R, Fossum B, et al. Feeling valued versus abandoned: Voices of persons who have completed a cognitive assessment. Int J Older People Nurs. 2021 Nov;16(6):e12403.
246. Makin SD, Doubal FN, Dennis MS, et al. Clinically Confirmed Stroke With Negative Diffusion-Weighted Imaging Magnetic Resonance Imaging: Longitudinal Study of Clinical Outcomes, Stroke Recurrence, and Systematic Review. Stroke. 2015 Nov;46(11):3142-8.
247. Tarnutzer AA, Lee S-H, Robinson KA, et al. ED misdiagnosis of cerebrovascular events in the era of modern neuroimaging. Neurology. 2017;88(15):1468.
248. Kothari RU, Pancioli A, Liu T, et al. Cincinnati Prehospital Stroke Scale: reproducibility and validity. Ann Emerg Med. 1999 Apr;33(4):373-8.
249. Kidwell CS, Starkman S, Eckstein M, et al. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). Stroke. 2000 Jan;31(1):71-6.
250. Bray JE, Martin J, Cooper G, et al. Paramedic identification of stroke: community validation of the melbourne ambulance stroke screen. Cerebrovasc Dis. 2005;20(1):28-33.
251. Chenkin J, Gladstone DJ, Verbeek PR, et al. Predictive value of the Ontario prehospital stroke screening tool for the identification of patients with acute stroke. Prehosp Emerg Care. 2009 Apr-Jun;13(2):153-9.
252. Studnek JR, Asimos A, Dodds J, et al. Assessing the validity of the Cincinnati prehospital stroke scale and the medic prehospital assessment for code stroke in an urban emergency medical services agency. Prehosp Emerg Care. 2013 Jul-Sep;17(3):348-53.
253. Andsberg G, Esbjörnsson M, Olofsson A, et al. PreHospital Ambulance Stroke Test - pilot study of a novel stroke test. Scand J Trauma Resusc Emerg Med. 2017 Apr 11;25(1):37.
254. Harbison J, Hossain O, Jenkinson D, et al. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test. Stroke. 2003 Jan;34(1):71-6.
255. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet. 2005 Jul 2-8;366(9479):29-36.
256. Giles MF, Rothwell PM. Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD2 transient ischemic attack risk scores. Stroke. 2010 Apr;41(4):667-73.
257. Terzoni S, Destrebecq A, Modaffari F, et al. Validation of the Italian version of the ROSIER scale for stroke patients at triage. Australasian Emergency Care. 2021 2021/11/19/.
258. Han F, Zuo C, Zheng G. A systematic review and meta-analysis to evaluate the diagnostic accuracy of recognition of stroke in the emergency department (ROSIER) scale. BMC Neurology. 2020 2020/08/18;20(1):304.
259. Gibson NS, Sohne M, Kruip MJ, et al. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. Thromb Haemost. 2008 Jan;99(1):229-34.
260. Modi S, Deisler R, Gozel K, et al. Wells criteria for DVT is a reliable clinical tool to assess the risk of deep venous thrombosis in trauma patients. World J Emerg Surg. 2016;11:24.
261. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606-13.
262. Arroll B, Goodyear-Smith F, Crengle S, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. Ann Fam Med. 2010 Jul-Aug;8(4):348-53.
263. Bhatt A, Jani V. The ABCD and ABCD2 Scores and the Risk of Stroke following a TIA: A Narrative Review. ISRN Neurol. 2011;2011:518621-518621.
264. Johnston SC, Gress DR, Browner WS, et al. Short-term prognosis after emergency department diagnosis of TIA. Jama. 2000 Dec 13;284(22):2901-6.

265. Quinn TJ, Cameron AC, Dawson J, et al. ABCD2 scores and prediction of noncerebrovascular diagnoses in an outpatient population: a case-control study. Stroke. 2009 Mar;40(3):749-53.
266. Sheehan OC, Merwick A, Kelly LA, et al. Diagnostic Usefulness of the ABCD2 Score to Distinguish Transient Ischemic Attack and Minor Ischemic Stroke From Noncerebrovascular Events. Stroke. 2009 2009/11/01;40(11):3449-3454.
267. Wu Z. Validation of the use of the ROSIER stroke recognition instrument in an Irish emergency department: Comment. Irish Journal of Medical Science. 2009 2009/12/01;178(4):515-516.
268. Yuan J, Jia Z, Song Y, et al. External Validation of the Diagnosis of TIA (DOT) Score for Identification of TIA in a Chinese Population [Original Research]. Frontiers in Neurology. 2019 2019-August-13;10.
269. Hankey GJ, Blacker DJ. Is it a stroke? BMJ : British Medical Journal. 2015;350:h56.
270. Nor AM, McAllister C, Louw SJ, et al. Agreement between ambulance paramedic- and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. Stroke. 2004 Jun;35(6):1355-9.
271. Yang B, Mallett S, Takwoingi Y, et al. QUADAS-C: A Tool for Assessing Risk of Bias in Comparative Diagnostic Accuracy Studies. Annals of Internal Medicine. 2021 2021/11/16;174(11):1592-1599.
272. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. Bmj. 2015 Oct 28;351:h5527.
273. Brott T, Adams HP, Olinger CP, et al. Measurements of acute cerebral infarction: A clinical examination scale [Article]. Stroke. 1989;20(7):864-870.
274. Scotland Ph. Scottish Stroke Improvement Programme 2022: national report Scotland: Scottish government; 2022; 79]. Available from: https://www.publichealthscotland.scot/media/13795/2022-scottish-stroke-imrprovment-national-report.pdf
275. Zou KH, O'Malley AJ, Mauri L. Receiver-Operating Characteristic Analysis for Evaluating Diagnostic Tests and Predictive Models. Circulation. 2007 2007/02/06;115(5):654-657.
276. Parikh R, Mathai A, Parikh S, et al. Understanding and using sensitivity, specificity and predictive values. Indian J Ophthalmol. 2008 Jan-Feb;56(1):45-50.
277. McGee S. Simplifying likelihood ratios. J Gen Intern Med. 2002 Aug;17(8):646-9.
278. Baratloo A, Hosseini M, Negida A, et al. Part 1: Simple Definition and Calculation of Accuracy, Sensitivity and Specificity. Emerg (Tehran). 2015 Spring;3(2):48-9.
279. 19.2.6 MSSv. Ostend, Belgium: MedCalc Software bv; 2020. Available from: https://www.medcalc.org
280. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988 Sep;44(3):837-45.
281. Lehmann EL. Introduction to Neyman and Pearson (1933) On the Problem of the Most Efficient Tests of Statistical Hypotheses. In: Kotz S, Johnson NL, editors. Breakthroughs in Statistics: Foundations and Basic Theory. New York, NY: Springer New York; 1992. p. 67-72.
282. Armstrong RA. When to use the Bonferroni correction. Ophthalmic Physiol Opt. 2014 Sep;34(5):502-8.
283. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol. 2017 Apr 1;46(2):746-755.
284. Mandrekar JN. Receiver Operating Characteristic Curve in Diagnostic Test Assessment. Journal of Thoracic Oncology. 2010 2010/09/01/;5(9):1315-1316.
285. Maragkos GA, Enriquez-Marulanda A, Salem MM, et al. Proposal of a Grading System for Predicting Discharge Mortality and Functional Outcome in Patients with Aneurysmal Subarachnoid Hemorrhage. World Neurosurgery. 2019 2019/01/01/;121:e500-e510.

286. Fang Y, Lu J, Zheng J, et al. Comparison of aneurysmal subarachnoid hemorrhage grading scores in patients with aneurysm clipping and coiling. Scientific Reports. 2020 2020/06/08;10(1):9199.
287. Naval NS, Kowalski RG, Chang TR, et al. The SAH Score: A Comprehensive Communication Tool. Journal of Stroke and Cerebrovascular Diseases. 2014 2014/05/01/;23(5):902-909.
288. Quinn TJ, Singh S, Lees KR, et al. Validating and comparing stroke prognosis scales. Neurology. 2017 Sep 5;89(10):997-1002.
289. Cerullo E, Jones HE, Carter O, et al. Meta-analysis of dichotomous and ordinal tests with an imperfect gold standard. Res Synth Methods. 2022 Apr 30.
290. Adlung L, Cohen Y, Mor U, et al. Machine learning in clinical decision making. Med. 2021 2021/06/11/;2(6):642-665.
291. Creswell JW, Clark VLP. Designing and conducting mixed methods research. Sage publications; 2017.
292. Burns H. Health inequalities - why so little progress? Public Health. 2015 Jul;129(7):849-53.
293. Hart JT. The inverse care law. Lancet. 1971 Feb 27;1(7696):405-12.