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Research protocol – Assessing Post-Stroke Psychology Longitudinal Evaluation (APPLE) study: A prospective cohort study in stroke

Terence J Quinn [a,*], Martin Taylor-Rowan [a], Emma Elliott [a], Bogna Drozdowska [a], David McMahon [a], Niall M Broomfield [b], Mark Barber [c], Mary Joan MacLeod [d], Vera Cvoro [e], Anthony Byrne [f], Sarah Ross [g], Jennifer Crow [h], Peter Slade [i], Jesse Dawson [a], Peter Langhorne [a]

[a] Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom
[b] Department Clinical Psychology and Psychological Therapies, University of East Anglia, United Kingdom
[c] Stroke Unit, University Hospital Monklands, United Kingdom
[d] Department of Medicine and Therapeutics, University of Aberdeen, United Kingdom
[e] Stroke Unit, Victoria Hospital, Kirkcaldy, United Kingdom
[f] Department of Ageing & Health, Forth Valley Royal Hospital, Larbert, United Kingdom
[g] Stroke Unit, Perth Royal Infirmary, Perth, United Kingdom
[h] Imperial College Healthcare NHS Trust, United Kingdom
[i] Morriston Hospital, Swansea, United Kingdom

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ABSTRACT

Background: Cognitive and mood problems have been highlighted as priorities in stroke research and guidelines recommend early screening. However, there is limited detail on the preferred approach.
We aimed to (1) determine the optimal methods for evaluating psychological problems that pre-date stroke; (2) assess the test accuracy, feasibility and acceptability of brief cognitive and mood tests used at various time-points following stroke; (3) describe temporal changes in cognition and mood following stroke and explore predictors of change.
Methods: We established a multi-centre, prospective, observational cohort with acute stroke as the inception point – Assessing Post-stroke Psychology Longitudinal Evaluation (APPLE). We approached patients admitted with stroke or transient ischaemic attack (TIA) from 11 different hospital sites across the United Kingdom. Baseline demographics, clinical, functional, cognitive, and mood data were collected. Consenting stroke survivors were followed up with more extensive evaluations of cognition and mood at 1, 6, 12 and 18 months.
Results: Continuous recruitment was from February 2017 to February 2019. With 357 consented to full follow-up. Eighteen-month assessments were completed in September 2020 with permissions in-place for longer term in-person or electronic follow-up. A qualitative study has been completed, and a participant sample biobank and individual participant database are both available.
Discussion: The APPLE study will provide guidance on optimal tool selection for cognitive and mood assessment both before and after stroke, as well as information on prognosis and natural history of neuropsychological problems in stroke. The study data, neuroimaging and tissue biobank are all available as a resource for future research.

1. Introduction

Neuropsychological problems are common both before and after a stroke event [1] and those affected by stroke have consistently emphasised their importance [2]. Despite this, problems with memory, thinking and mood have received comparatively less attention in stroke research than other topics.

Recent reviews have highlighted a number of important gaps in our understanding of psychology in stroke [3,4]. The landscape around neuropsychological research following stroke is evolving. While large cohorts, data registers and trials [5–7] are all improving our understanding and management of post-stroke psychology, there still remains

* Corresponding author.
E-mail address: terry.quinn@glasgow.ac.uk (T.J. Quinn).

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much to learn, especially around the practicalities of cognitive and mood assessment in the acute stroke setting.

A particular area of interest for clinicians is around the use of short screening tools for the assessment of stroke related neuropsychological issues. Although very brief (less than five minutes administration time) and brief (less than twenty minutes) cognitive and mood assessments are commonly used in stroke care [8] and these tools are recommended in international guidelines [9], we have relatively little empirical data on their properties. To date, studies have tended to focus on the accuracy of a screening test in isolation. To inform our use of these tools in the acute stroke setting, we need information on the comparative accuracy of the available tools, and also descriptions of their feasibility and acceptability.

The neuropsychological consequences of stroke are dynamic. Following a stroke event, various trajectories are possible, and we have limited understanding of their nature or the factors that may predict a particular outcome. At the other end of the stroke journey, pre-stroke cognitive and mood factors are likely to be important in determining the post-stroke state, but the optimal approach to assessment for these issues and the implications of pre-stroke cognitive and mood disorder have not been fully described.

In response to all of this we created a prospective, acute stroke, cohort study with embedded work packages designed to answer questions around accuracy, feasibility and prognostic utility of brief cognitive tests - the *APPLE* study (Assessing Psychological Problems in stroke: a Longitudinal Evaluation).

2. Materials and methods

2.1. Objectives

The main objectives of the APPLE study are delivered as a series of work-packages (WP):

WP1. To validate and compare the diagnostic test accuracy of informant tools for assessment of pre-stroke cognition and mood.

WP2. To determine the optimal method and timing of neuropsychological assessment in the acute stroke setting. (In this WP we focus on accuracy but also consider feasibility and acceptability, including a qualitative study).

WP3. To describe the trajectories of post-stroke cognition and mood disorders and explore potential predictors of improvement and decline.

An important secondary objective of the APPLE cohort was to create a resource that can be used for future research. To this end we have permissions to create an anonymised research database containing demographic, clinical and neuroimaging data along with cognitive, mood, disability, and frailty assessment results; an anonymised individual participant level data resource from all participants who consented to prospective in-person or electronic follow-up; contact details of participants who have agreed to participate in future relevant stroke research and a biobank containing participant samples. Full details of these resources are given below along with the process for investigators to apply to access the materials.

2.2. Ethical and regulatory approvals

This study was performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended). All investigators and key study personnel undergo biennial GCP training.

A protocol for the study was submitted to the Research Registry online repository prior to first participant recruitment (ID:1018).

The main APPLE study was approved by the Scotland A Research Ethics committee and local R&D approval was obtained for all participant sites (REC number 16/SS/0105). Three amendments to the original protocol have been approved: to allow recruitment from sites across the UK; to ensure anonymised data can be made available and to allow for continued follow-up of consenting participants.

The APPLE study was adopted onto the NHS Research Scotland Stroke portfolio in November 2016 and the NHS England and Wales portfolios in October 2018.

2.3. Patients and setting

Inclusion and exclusion criteria: The APPLE study was designed to be inclusive, recognising that many previous stroke cohorts offered potentially biased results through overly restrictive entry criteria [10]. (Table 1) Patients admitted with stroke or transient ischaemic attack (TIA) to the stroke units of participating hospitals were approached to take part. Diagnosis of stroke or TIA was clinical and made by the parent team using their usual approach. Recruiting sites were UK hospitals offering hyper-acute stroke services, which admit all patients referred with suspected stroke.

The APPLE study operated minimal exclusions and in particular there were no restrictions based on prior stroke, stroke related impairments or comorbidity. The primary criterion for inclusion was that the parent stroke team felt that some form of cognitive or mood assessment would be clinically appropriate. Patients unable to consent to participation at baseline (e.g. due to severe aphasia or cognitive impairment) could still be included if a suitable proxy was willing to provide assent. As a major theme of the study was around feasibility, we actively encouraged recruitment of participants with stroke related, or other impairments, that may complicate assessment. Recruiting these patients formed a major part of the site training.

Participation in another stroke study was not a barrier to recruitment. Co-enrolment in other observational studies or clinical trials was encouraged, provided the studies would not confound respective results or overburden participants.

The focus of the APPLE study was the acute stroke setting and research teams were encouraged to recruit and assess as close to the index stroke as possible. However, no absolute restriction was placed on timing of assessment. Where a person was deemed too unwell to participate, they could be approached later when their clinical condition improved.

We recognise the importance of selection bias in studies with a focus on cognitive and emotional consequences of stroke [10]. We did not ask study teams to keep a recruitment log. As the study operates minimal exclusion criteria, almost all inpatients with stroke would be potentially eligible. Rather we will compare clinical and demographic features of included participants to national stroke audit data. This will allow us to comment on generalisability of results. Once recruited, we recorded numbers of participants who did not complete single tests or complete assessments and recorded the reasons given, if any.

2.4. Consent

Consent was taken by site investigators or suitably trained researchers. Consent was staged to ensure that participation in the study was always voluntary and fully informed. At all points, the study team stressed that taking part in the study was voluntary and if participants wished to terminate the cognitive testing early, we would respect this

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion Criteria
• Clinical diagnosis of stroke or TIA at time of assessment. • Age greater than 18 years. • Clinical team comfortable that patient is suitable for some form of psychological testing.	• No spoken English prior to stroke. • Non-stroke diagnosis at time of assessment. • Unable to consent and no suitable proxy available.

wish which would not impact on the clinical care that they received.

We offered additional complementary studies looking at informant assessment; biobanking; prospective follow-up; data storage and linkage. Participants were given the option to consent to all aspects of the study or to limit their participation to certain aspects only.

We involved the nearest relative/guardian/welfare attorney in the study, regardless of participant ability to consent as some of our measures required to be completed by an informant that knows the participant well. There was an option for informants to provide data with no corresponding assessment of the stroke survivor. We developed a participant information leaflet for recruiting informants with separate materials where the informant may be giving proxy consent.

For patients unable to provide informed consent, we had the option to seek consent from a legal proxy or family, carer, friend. Capacity to consent was re-assessed at one month follow-up. If a patient had been included using proxy consent but it was felt the patient had regained capacity, consent was rechecked. In this scenario, if the participant did not give consent to continue, the participant was withdrawn from the study. No further data or tissue would be collected, or any other research procedures carried out on or in relation to the participant. However, we asked if those identifiable data or tissue already collected with consent could be retained and used in the study. If the participant did not agree to this, the data and biobank samples were removed from the study registers.

If the patient was felt to no longer have capacity to consent, the assessor followed procedures outlined for including a patient that lacks capacity. In this scenario, if a relevant proxy did not give consent, the participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected, or any other research procedures carried out on or in relation to the participant.

2.5. Participant baseline assessments

These were completed as soon as possible following stroke and ideally within five days of admission to the stroke service. Clinical and demographic details were extracted from case-notes. The extracted information included comorbidities, risk factors for stroke and cognitive decline, physiological measures, medications and laboratory results. Neuroimaging was assessed for evidence of old infarcts, atrophy (global and hippocampal) and white matter lesions using ordinal scales [11]. Clinical assessments comprised National Institute of Health Stroke Scale (NIHSS) score, modified Rankin Scale (mRS); Barthel Index (BI) of activities of daily living, the five-question phenotypic assessment for frailty (Fried) and a version of the Lawton Instrumental (Extended) Activities of Daily Living scale (E-ADL). A delirium assessment using the Confusion Assessment Method (CAM-ICU) and 4 A Test (4AT) was also included. (Fig. 1)

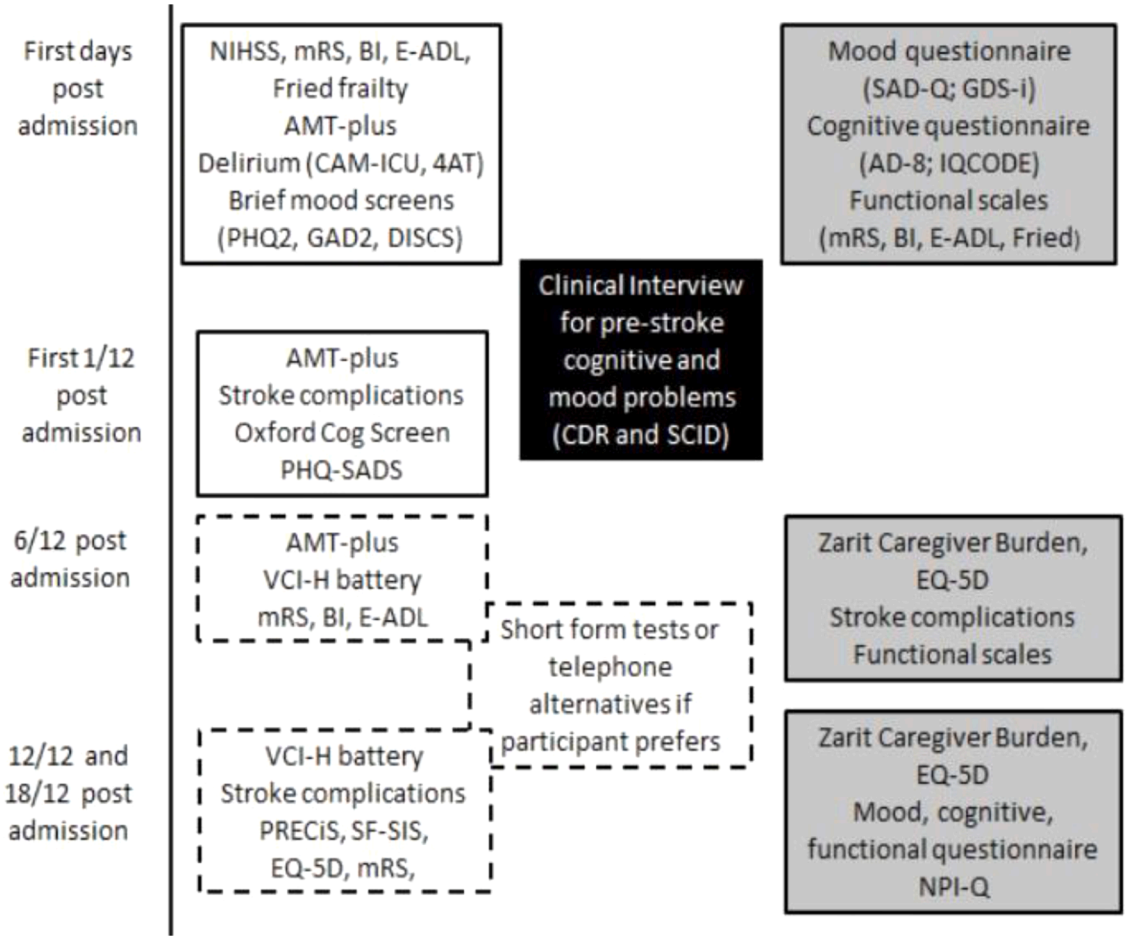

Fig. 1. *Participant Assessments*. Solid outline:screening tests; broken outline: detailed tests; greyfill: informant tests NIHSS:National Institutes of Health Stroke Scale; mRS:modifed Rankin Scale; BI:Barthel Index; E-ADL:Extended Activities of Daily Living; AMT:Abbreviated Mental Test; CAM-ICU:Confusion Assessment Method for Intensive Care Units; 4AT:4 A's Test; PHQ:Patient Health Questionnaire; GAD:Generalised Anxiety Disorder; DISCS:Depression Intensity Scaled Circles; SADS:Somatic Anxiety and Depression Symptoms; VCI-H:Vascular Cognitive Impairment Harmonization Standards; PRECiS:Patient Reported Evaluation of Cognitive Status; SF-SIS: Short Form Stroke Impact Scale; EQ-5D:EuroQol 5 Dimensions; CDR:Clinical Dementia Rating; SCID:Structured Clinical Interview for Depression: GDS-i:Geriatric Depression Scale (informant); AD-8:Alzheimers Dementia 8 questions; IQCODE:Informant Questionnaire for Cognitve Decline in the Elderly; NPI-Q: Neuropsychiatric Inventory (questionnaire).

2.6. Participant cognitive assessments

All participants underwent assessments of cognition and mood at baseline (conducted as close to the date of admission as possible), then again at 1-, 6-, 12- and 18-months following admission. (Fig. 1, Table 2) We did not modify assessments for those with communication problems, as describing feasibility of tests across a range of stroke related impairment was an important outcome of our work.

Baseline cognitive assessment involved a bespoke instrument that combines elements from a variety of popular very brief (less than 5 minutes administration) tests into a single assessment. As a short-hand, we refer to this combination of tests as the 'AMT-Plus'. The intention was not to create a new single test with bespoke scoring criteria etc. Rather this approach of amalgamating various tests that have common items creates a resource that allows derivation of the various component cognitive test scores whilst minimising test burden.(Fig. 2) Baseline mood testing comprised a depression and anxiety questionnaire (Patient Health Questionnaire – 2 questions (PHQ2); Generalized Anxiety Disorder – 2 questions (GAD2)) and pictorial assessment (Depression Intensity Scale Circles (DISCS)).

At *one month*, assessments comprised a repeat of the short patient cognitive battery performed at baseline (AMT-Plus). A longer, stroke specific cognitive assessment was performed using the Oxford Cognitive Screen (OCS). For mood assessment the Patient Health Questionnaire for Somatic Anxiety and Depression Symptoms (PHQ-SADS) was used. We collected information on stroke complications (cardiac, seizure, infection, falls, fatigue [using brief fatigue inventory]) and any change in medication.

Longer term follow-up was at *6, 12 and 18* months. Permissions are in place for longer term follow-up, either in-person or electronic. These time-points were chosen to reflect common clinical and study assessment times.

We made no assumptions around the pathology underlying post-stroke cognitive change and so for the longer-term follow-up, we devised a battery of assessments that is primarily designed for vascular cognitive impairment but is suitable for the assessment of other pathologies including Alzheimer's disease dementia.

At the six-month assessment the assessor used the 30-minute version of a neuropsychological battery (the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards – VCI-H [12]). If the patient struggled with this assessment, did not wish such a lengthy assessment or the assessment was not possible for any other reason, a shorter assessment based on the VCI-H five-minute battery [12] could be used as an alternative. Assessments could be face-to-face or use the telephone according to participant preference.

For twelve- and eighteen-month assessments, the full VCI-H [12] (around 45 minutes) or shorter assessments were available. Choice of assessment was at the discretion of the researcher in discussion with participant and informant. In addition, at the twelve- and eighteen-month visits the patient completed generic and stroke specific quality of life measures: Euro-Qol 5 domains (EQ-5D); Short Form of the Stroke Impact Scale (SIS) and Patient Reported Evaluation of Cognitive Status (PRECiS). Function was assessed with mRS, BI and E-ADL. Brief questionnaires around physical activity and social support were administered. The patient was asked about specific stroke complications of interest and the list of medications was updated.

Participants were assessed for *pre-stroke* cognition and mood issues using a multicomponent, hierarchical assessment.(Fig. 3). Medical records were searched for any prior diagnosis of dementia or use of cholinesterase inhibitor drugs. Then, for consenting participants, the Clinical interview for Dementia Rating (CDR) and Structured Clinical Interview for Depression version 5 (SCID-5) was conducted by a trained and experienced researcher. The interview was completed within one month of admission. This information was triangulated with any ancillary reports related to the patient's baseline post-stroke cognitive performance or other investigations and neuroimaging to reach a final diagnostic formulation based on discussion and consensus between the interviewing researcher and a stroke physician. For those cases that were difficult to assess, further assessment by a clinician with expertise in stroke neuropsychology was available. The final categorisation was clinical and based on DSM-5 criteria. Results were operationalised as pre-stroke dementia or depression using categories of: probable; possible (includes MCI); unlikely; unable to assess. To maximise specificity, where there was doubt over the categorisation, the final label preferred the less impaired state.

As a primary purpose of the study was to assess the diagnostic accuracy of screening tools for the pre-stroke state, the data from these informant questionnaires were not part of the diagnostic formulation process.

For the *end of primary study assessments* the data from all previous assessments are collated and assessed along with clinical, laboratory and imaging data. Domain specific tests are assessed using VCI-H recommended normative data where available [12]. The cognitive data are considered as a complete 'package' and include pre-stroke assessments, informant data and change in cognitive test scores over time. While informed by cut-offs and scoring rules, the final diagnostic formulation is clinical and seeks evidence of impairment in multiple domains, not accounted for by another process and then assesses the functional impact of the impairments ie DSM-5 criteria for major and minor neurocognitive impairment.

Using a similar process to the categorisation of pre-stroke cognition, all the information is triangulated to reach a final diagnostic formulation based on discussion and consensus between the research team, other experts and the Principal Investigator. Operationalisation of the cognitive state is designed to mirror the pre-stroke cognitive categorisation. DSM-5 criteria are used to inform the diagnostic labels with options of dementia: probable; possible (includes MCI); unlikely; unable to assess. To maximise specificity, where there is any doubt over the categorisation, the final label will prefer the less impaired state. For example, if the consensus is between probable and possible dementia, a label of 'possible' will be assigned. We will not attempt to further categorise by subtype of dementia but will collect these data if available from clinical records.

The final categorisation will be used as a reference for assessments of accuracy of short screening tools. There is a risk of incorporation bias, as the screening tools of interest form part of the complete 'package' of

Table 2.
Participant schedule of assessments.

	ASU	Follow up			
	Week 1	1 month	6 months	12 months	18 months
Review Eligibility	x				
Consent	x				
Blood / Urine for Biobanking*	x	x			
Patient baseline assessment	x				
Short screening tests (AMT-Plus)	x	x	x	x	x
Informant baseline assessment	x				
Structured clinical interview study*	x				
Consent re-assessed		x			
Patient psychological screen		x			
Patient neuropsychological battery			x	x	x
Informant questionnaires			x	x	x
Consensus assessment	x				x

* Optional study

Question	10-AMT	4-AMT	GP-Cog	Minicog (adapted)	6-CIT	VCI-H	Short form MoCA	4Atest
1.Age	■	■						■
2.Time	■				■			
3. Date	■	■	■		■	■		■
4.Place	■	■				■		■
5.Date of Birth	■	■	■					■
6.World War 1	■							
7.Prime Minister	■							
8.Count 20-1	■				■			
9.Recall (5-item)	■		■	3-word recall	■	■	■	
10.Clock draw			■	■			■	
11.News item			■					
12.Months backwards					■			■
13.One letter fluency						■		

Fig. 2. Cognitive test matrix (AMT-plus) *The combination of screening tests (AMT-plus) is not designed as a new test, rather it is a method to allow application of a variety of short screens with common items that minimises test burden.*

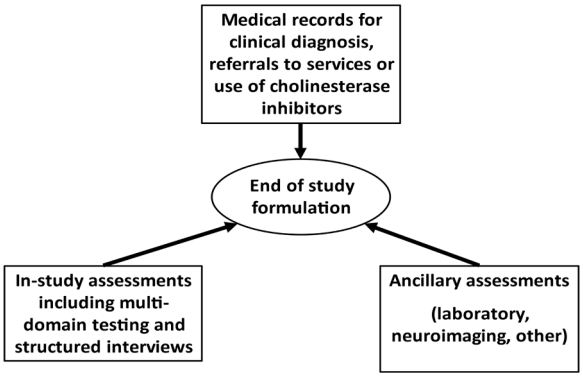

Fig. 3. End of study assessment process.

tests that will inform the diagnostic categorisation. We have tried to minimise the bias by including all the screening tools into a single assessment (AMT-Plus) that requires post-hoc derivation of the results for each individual test. We also recognise that the short screening tools are only part of the multi-domain assessment data available. It is difficult to completely negate the effect of incorporation bias in studies of cognitive test accuracy as the reference standard of clinical dementia invariably includes cognitive testing of some description.

2.7. Informant assessments

Participants with a suitable and consenting informant were asked to complete a battery of questionnaire assessments. Choice of informant was based on discussion between patient and research team, we recommended that the informant should have known the patient for at least 10 years and see them at least two times per week. The informant questionnaires included assessments of cognition, mood, function and frailty they comprised: A short-form version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-SF;16 item), the 8-item interview to Ascertain Dementia (AD8), the hospital version of the Stroke Aphasic Depression Questionnaire (SADQ-H10), and the short-form informant version of the Geriatric Depression Scale (GDS-SF). At 6-, 12- and 18-month follow-up, informant versions of the mRS, BI, E-ADL and Fried frailty phenotype questionnaire were offered. Questionnaire assessments were conducted by stroke research nurses or researchers. The sequence of tests differed in respective study case report forms, allowing for pseudo-randomisation of the order of questionnaire administration. At baseline, informants were asked to answer the questions in each questionnaire in relation to how the participant was before their presenting stroke. These questionnaires were completed as close to date of admission to the acute stroke unit as possible and time from stroke to completion was recorded.

At 6-, 12- 18-month assessment, the informant completed a caregiver burden scale (Zarit Caregiver Burden) and the generic health related quality of life measure - EQ-5D, completed in relation to their perception of the stroke survivor's quality of life. At 12 and 18 months the informant also completed the cognitive and mood questionnaires employed at baseline and the neuropsychiatric inventory questionnaire (NPI-Q).

2.8. Data capture and management

Primary data collection used paper-based case report forms (CRF). Inpatient assessment scores were shared with the hospital team on request. Screening test summary results were not routinely shared with the participant's General Practitioner (GP), recognising that the screening tests employed in the study are not diagnostic. If assessment suggested a serious cognitive or mood disorder that required urgent treatment, results were shared with the appropriate clinical team.

To ensure confidentiality, all study-related information is stored securely at the study site and all participant information is stored in locked file cabinets in areas with limited access. CRF data is securely transferred to the Robertson Centre for Biostatistics (RCB) for electronic entry. All databases are secured with password-protected access systems. Data and participant identifiers are stored separately.

All participant data is identified by a participant study identification number. Data are validated at the point of entry into the study and at regular intervals during the study. Data discrepancies are flagged to the study site by the statistician and resolved by the Principal Investigator with input from the site teams as necessary. Any data changes are recorded in order to maintain a complete audit trail (reason for change,

date change made, who made change).

2.9. Biobanking

Consenting participants had blood taken for biobanking (optional and only available in Glasgow centres). Urine and blood samples were obtained and stored in an approved biorepository. After venesection and centrifuge, aliquots of 0.5 to 1.0 ml of serum and plasma were transferred to small storage vials and frozen immediately at -80 °C.

To create a data biobank, participants were asked for consent to hold their anonymised clinical, laboratory and imaging data in a secure database (optional), for consent to access de-identified data from electronic health records (optional) and for consent to re-contact them for future research.

2.10. Efforts to minimise bias

We employed a series of measures to ensure that our study was conducted to the highest quality, with minimal risk of bias. Our methodology was based on best practice in conduct and reporting guidance for dementia test accuracy studies (STARDdem) [13]. Our prognosis work was modelled around the "fundamental" prognosis research paradigm as described by MRC PROGRESS prognosis research group [14].

We worked with topic experts and our lay panel to choose the assessments included in the APPLE programme. This includes commonly used tests and assessments that may have particular utility in stroke but as yet lack external validation (OCS, PRECiS) [15,16].

All sites completed a standard set up procedure, ensuring appropriate capabilities and resources were in place. Study assessors were trained in administration of cognitive tests, as well as measures of mood and functioning using in-person and video [17] materials. Sites receive training in APPLE recruitment, completing the CRF, methods to encourage retention of participants, completeness of data, blood and imaging acquisition, and processing and transfer for central storage and analysis.

2.11. Sample size estimates

Data to allow sample size calculations for future studies is an intended output of this work. Recognising the uncertainty, we do not offer definitive "power" calculation per se, but our recruitment estimates suggest we will have sufficient patients to achieve our research aims.

Given the inclusive nature of the cohort, attrition is expected, and descriptions of attrition will be an output of this work. There will be no imputation of missing data for the primary or secondary endpoints in the first instance. As part of the analyses, we will explore the effects of various approaches to handling missing data.

2.12. Statistical analysis

The APPLE study is designed as a resource for future research. We anticipate that the included data will inform many future analyses, either restricted to APPLE data or in combination with other relevant datasets. We outline here the proposed analyses for the three main WPs, but these serve as exemplars of how the data could be employed.

2.12.1. WP 1. Assessing pre-stroke psychological problems

We will use a classical test accuracy study design to describe the properties of informant tools in acute stroke. Accuracy of screening tools will be described in terms of sensitivity; specificity; predictive value; receiver operating space analyses. Index test questionnaires will be compared against each other and against the reference standard of 'consensus diagnosis'. The primary analysis will be the description of test accuracy for each screening test against clinical diagnosis.

To describe feasibility, we will collate numbers completing each test fully and partially. To incorporate feasibility into analyses, we will employ an "intention to diagnose" approach, including those unable to complete tests [18].

2.12.2. WP 2. Test accuracy and feasibility of brief screening tools

The potential index tests will be the very brief screening tools performed at each study visit. These can be compared with each other contemporaneously; can be compared against more detailed test performed at the same visit; or analyses can assess the utility of an assessment for predicting a future cognitive outcome. The various tests will also be compared against the end of study assessment formulation. Accuracy will be described in terms of the test accuracy metrics described for WP1. From the acute assessments, we will describe the accuracy of brief screening tests used in isolation and combined with Boolean operators of "OR"/"AND". The primary analysis will be the description of test accuracy for each screening test against clinical diagnosis. To describe feasibility, we will collate numbers completing each test fully and partially; time and assistance required for completion. We will employ various sensitivity analyses to explore the effect of missing data [19].

2.12.3. WP 3. Describing and predicting neuropsychological prognosis

For prospective follow up, outcomes of interest are change in scores on cognitive and mood screening tools and incident clinical mood disorder or multi-domain cognitive impairment. Multi-domain tools will be analysed as ordinal data and dichotomised at varying thresholds.

We will explore repeated measures analyses adjusting for baseline covariates and describe temporal change in test scores. Cognitive test scores will be standardised to allow an assessment of temporal change.

We will create prognostic models and, if these data allow, predictive risk scores for the various cognitive and mood outcomes, describing calibration and discrimination. We will describe univariable and adjusted independent predictors of our "outcomes" of interest. The primary analysis will be the description of prognostic utility of baseline measures for end of study diagnostic formulation.

2.13. Patient and care-giver involvement

A lay panel of stroke survivors and their care-givers was formed at the study design stage and continues to inform the study conduct and interpretation. The panel composition varied across the timeline of the study as some members were no longer able to contribute. The group meet in person for study updates complemented by email communication on an ad hoc basis for matters concerning study design, acceptability or to comment on potential research proposals.

2.14. Data access

After study completion, data will be cleaned and locked via data handling specialists at the Robertson Centre. The intention is that the APPLE data will be available as a resource for other researchers. In the first instance, we will securely deposit the data in the Virtual International Stroke Trials Archive (VISTA) [20]. Access to these data will be through the standard VISTA application process. Access to biobanking samples is through email contact with the Principal Investigator in the first instance.

Relevant data obtained via APPLE will be shared with the ongoing Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD) study [21] and the OX-Chronic study [22] to enhance study numbers and precision of analyses.

2.15. Sub-studies

A qualitative study was planned as part of the original application. The views of patients and care-givers around acute assessment of mood

and cognition were explored through semi-structured interviews that were transcribed in full and then assessed. Patient recruitment for this study included 40 patients with consent to contact and 16 completed interviews. We have reached data saturation and no further interviews are planned.

We would hope that the APPLE resource could be used for other studies and already have formulated plans and acquired funding with external teams to use the neuroimaging data and frailty data. Requests to work with any of the tissues or data comprising the APPLE resource should be directed to the Principal Investigator in the first instance.

2.16. COVID-19 contingencies

Due to COVID-19, we had to move all follow-up activity to remote assessment (telephone, postal questionnaire). For participant safety and in-line with social distancing restrictions, we also had to cancel the in-person advisory group meetings planned and limit the in-person bio-banking. By making all our in-study assessments remote, we were able to complete last patient follow-up according to protocol. As we had planned our study with options for assessments to be either partially or completely delivered remotely, we did not require any modifications to our main protocol. However, as a result of the pandemic, more participants were assessed with the shorter telephone battery, rather than the full, in-person, multi-domain assessment.

Local lock-down and other disruption delayed aspects of data entry, quality control and archiving, and our study end date and database lock was modified accordingly. As we had flexibility in our assessment schedule, with options for remote assessment, our study was less disrupted by the viral pandemic than many other research programs [23].

2.17. Study funding

APPLE is funded by the Stroke Association and Chief Scientist Office of Scotland through a priority program grant (funding reference: PPA 2015/01_CSO)

Further support towards WP1 (pre-stroke assessment) was through the funder Chest, Heart and Stroke Scotland. Further support towards WP2 (Qualitative study) was from the David Cargill Trust.

These funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

3. Results to date

Continuous recruitment for APPLE began on February 2017 and ended on 1st February 2020. Total recruitment numbers are 354 participants (with a further 151 informants). Initial sites were limited to Glasgow, with subsequent approvals to open sites in other Scottish health boards and then NHS England and Wales.

Participating sites are: Glasgow Royal Infirmary, Queen Elizabeth University Hospital Glasgow, Royal Alexandra Hospital Paisley, University Hospital Monklands, Forth Valley Royal Hospital, Victoria Hospital Fife, Perth Royal Infirmary, Aberdeen Royal Infirmary, Morriston Hospital Swansea; Charing Cross Hospital London.

Data cleaning, quality control and query resolution are ongoing and full database lock is anticapted in early 2022. Ongoing follow-up, either in-person or through electronic case records has ethical approval and will continue.

Based on initial data, the mean age of recruited stroke participants was 69.1 years (SD:12.8); 157 (44.4%) were female. Thirty-two (9.0%) had a total anterior circulation stroke and 47(13.3%) had a TIA. Median NIHSS score was 2 (25th-75thIQR = 1–4); mean pre-stroke mRS was 1 (SD:1.18). Forty-eight (13.5%) patients had mild to moderate aphasia and a further 7 (2.0%) severe aphasia. Patient comorbidities included 57 (16.1%) atrial fibrillation, 27 (7.6%) heart failure and 44/354 (12.4%) COPD.

4. Discussion

The first step to management of neuropsychological problems following stroke is recognition and diagnosis. Previous surveys and analyses have suggested substantial inconsistency in neuropsychological assessment strategies both in stroke clinical practice and in stroke research [24,25]. This lack of standardisation is perhaps unsurprising as International clinical practice guidelines recommend cognitive and mood screening, but offer only vague guidance on how to perform these assessments [26]. The APPLE study was designed to provide practical guidance to clinical teams around method and timing of neuropsychological assessment and also around the natural history of post-stroke cognitive and mood problems.

The data from APPLE contribute to a growing pool of prospective stroke cohorts with a focus on mood and cognition. To maximise the power of these resources, key outcomes measures in APPLE are harmonised with other studies [21,22].

Although there are many ongoing stroke cohort studies, the APPLE study offers data that are suitably different to these other studies to be an important resource in its own right. Research describing cognitive and mood problems following stroke often assumes that the person had no problems prior to the stroke event. This overly reductionist approach fails to appreciate the complex relationship between psychological symptoms and cerebrovascular disease [27]. Our focus on the pre-stroke state offers richness of pre-stroke assessment not seen in other cohorts. Historically, assessments of stroke and neuropsychology used detailed assessment batteries that are not practical in the acute setting [28]. Our inclusive approach to recruitment and use of short screening tools should improve our understanding of how to employ these tests in a busy stroke service [29] and offer data that has immediacy to the practicing clinician. In formulating our outcomes assessment, we make use of all information available, including routine clinical details [30]. Finally, we recognise the dynamic nature of mood and cognition following stroke and our serial assessments are designed to allow a detailed description of temporal change and the predictors of such changes. Outcome assessment at various times allows for a more sophisticated modelling of neuropsychological trajectory than traditional approaches that have described assessments at fixed time-points.

An indirect aim of the programme is to create an open access resource that can be used to support other research activity, thus building capacity in the field of post-stroke cognitive and mood disorder. The APPLE study has already supported three PhDs to completion, creating new research capacity in the field of stroke psychology research, and will continue to be a resource for future research.

5. Conclusions

We have created a cohort study that will facilitate a programme of research designed to improve our understanding of neuropsychological effects of stroke. We focus on themes of assessment, prognosis and natural history. Outputs will have immediate relevance and impact, providing an evidence base to policy and practice around early cognitive and mood screening and informing the design and conduct of future studies. The prospective cohort and biobank/big data resources created through this work will act as foundation for an ongoing portfolio, creating cross institutional research synergy; encouraging new researchers and providing the substrate for ongoing interdisciplinary work in the field.

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CRediT authorship contribution statement

Terence J Quinn: Visualization, Writing – original draft, Supervision, Writing – review & editing. **Martin Taylor-Rowan:** Writing – original draft, Writing – review & editing. **Emma Elliott:** Writing – original draft, Writing – review & editing. **Bogna Drozdowska:** Writing – original draft, Writing – review & editing. **David McMahon:** Writing – original draft, Writing – review & editing. **Niall M Broomfield:** Writing – original draft, Writing – review & editing. **Mark Barber:** Writing – original draft, Writing – review & editing. **Mary Joan MacLeod:** Writing – original draft, Writing – review & editing. **Vera Cvoro:** Writing – original draft, Writing – review & editing. **Anthony Byrne:** Writing – original draft, Writing – review & editing. **Sarah Ross:** Writing – original draft, Writing – review & editing. **Jennifer Crow:** Writing – original draft, Writing – review & editing. **Peter Slade:** Writing – original draft, Writing – review & editing. **Jesse Dawson:** Supervision, Writing – original draft, Writing – review & editing. **Peter Langhorne:** Supervision, Writing – original draft, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2022.100042.

References

[1] L.E. Craig, Z.L. Hoo, T.Z. Yan, J.M. Wardlaw, T.J. Quinn, Prevalence of dementia in ischaemic or mixed stroke populations: systematic review and meta-analysis, J. Neurol. Neurosurg. Psychiatry (2021), https://doi.org/10.1136/jnnp-2020-325796. Published Online First: 15 November 2021.
[2] A. Pollock, B. St George, M. Fenton, L. Firkins, Top ten research priorities relating to life after stroke, Lancet Neurol. 11 (2012) 209.
[3] M. Brainin, J. Tuomilehto, W.D. Heiss, N.M. Bornstein, P.M.W. Bath, Y. Teuschl, E. Richard, A. Guekht, T.J. Quinn, and the Post Stroke Cognition Study Group, Post-stroke cognitive decline: an update and perspectives for clinical research, Euro. J. Neurol. (2015), https://doi.org/10.1111/ene.12626.
[4] M.D. Mijajlović, A. Pavlović, M. Brainin, et al., Post-stroke dementia – a comprehensive review, BMC Med. 15 (2017) 11, https://doi.org/10.1186/s12916-017-0779-7.
[5] Metacohorts Consortium, M. Dichgans, J. Wardlaw, E. Smith, et al., METACOHORTS for the study of vascular disease and its contribution to cognitive decline and neurodegeneration, Alzheimers Dement. 12 (2017) 1235–1249.
[6] P. Thingstad, T. Askim, M.K. Beyer, et al., The norwegian cognitive impairment after stroke study (Nor-COAST): study protocol of a multicentre, prospective cohort study, BMC Neurol. 18 (2018) 193, https://doi.org/10.1186/s12883-018-1198-x.
[7] P.S. Sachdev, J.W. Lo, J.D. Crawford, et al., STROKOG (stroke and cognition consortium): an international consortium to examine the epidemiology, diagnosis, and treatment of neurocognitive disorders in relation to cerebrovascular disease, Alzheimers Dement. 7 (2016) 11–23. Amst.
[8] T.J. Quinn, E. Elliott, P. Langhorne, Cognitive and mood assessment tools for use in stroke, Stroke 49 (2019) 483–490.
[9] T.J. Quinn, E. Richard, Y. Teuschl, et al., European stroke organisation (ESO) and European Academy Neurology (EAN) joint guidelines on post stroke cognitive impairment, Eur. J. Neurol. (2021), https://doi.org/10.1111/ene.15068. Sep 3Epub ahead of print.
[10] S.T. Pendlebury, P.J. Chen, L. Bull, et al., Methodological factors in determining rates of dementia in transient ischemic attack and stroke: (I) impact of baseline selection bias, Stroke 46 (2015) 641–646.
[11] J.P. Appleton, L.J. Woodhouse, A. Adami, et al., Imaging markers of small vessel disease and 'brain frailty' and outcomes in acute stroke, Neurology 94 (2020) 1–14.
[12] V. Hachinski, C. Iadecola, R.C. Petersen, et al., National institute neurological disorders and Canadian stroke network vascular cognitive impairment harmonization standards, Stroke 37 (2006) 2220–2241.
[13] A.H. Noel-Storr, J.M. McCleery, E. Richard, et al., Reporting standards for studies of diagnostic test accuracy in dementia: the STARDdem initiative, Neurology 83 (2014) 364–373.
[14] H. Hemingway, P. Croft, P. Perel, et al., Prognosis research strategy (PROGRESS) 1: framework for researching clinical outcomes, BMJ 346 (2013) e5595.
[15] N. Demeyere, M.J. Riddoch, E.D. Slavkova, W.L. Bickerton, G.W. Humphreys, The oxford cognitive screen (OCS): validation of a stroke-specific short cognitive screening tool, Psychol. Assess. 27 (2015) 883–894.
[16] E. Patchick, A. Vail, A. Wood, A. Bowen, PRECiS (Patient Reported Evaluation of Cognitive State): psychometric evaluation of a new patient reported outcome measure of the impact of stroke, Clin. Rehabil. 30 (2016) 1229–1241.
[17] T.J. Quinn, K.R. Lees, H.G. Hardemark, J. Dawson, M.R. Walters, Initial experience of a digital training resource for modified Rankin scale assessment in clinical trials, Stroke 38 (2007) 2257–2261.
[18] M. Schuetz Georg, P. Schlattmann, M. Dewey, Use of 3×2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: meta-analytical evaluation of coronary CT angiography studies, BMJ 345 (2012) e6717.
[19] R.A. Lees, K. Hendry Ba, N. Broomfield, D. Stott, A.J. Larner, T.J. Quinn, Cognitive assessment in stroke: feasibility and test properties using differing approaches to scoring of incomplete items, Int. J. Geriatr. Psychiatry 32 (2017) 1072–1078.
[20] M. Ali, P. Bath, M. Brady, et al., VISTA Steering Committees, Development, expansion, and use of a stroke clinical trials resource for novel exploratory analyses, Int. J. Stroke 7 (2012) 133–138.
[21] N. Demeyere, O.A. Williams, E. Milosevich, et al., Long term psychological consequences of stroke (ox-chronic): a longitudinal study of cognition in relation to mood and fatigue after stroke: protocol, Eur. Stroke J. 6 (2021) 428–437.
[22] J.M. Wardlaw, F. Doubal, R. Brown, et al., Rates, risks and routes to reduce vascular dementia (R4vad), a UK-wide multicentre prospective observational cohort study of cognition after stroke: protocol, Eur. Stroke J. 6 (2020) 89–101.
[23] S.J. Richardson, C.B. Carroll, J. Close, et al., Research with older people in a world with COVID-19: identification of current and future priorities, challenges and opportunities, Age Ageing 49 (2020) 901–906.
[24] R.A. Lees, N.M. Broomfield, T.J. Quinn, Questionnaire assessment of usual practice in mood and cognitive assessment in Scottish stroke units, Disabil. Rehabil. 36 (2014) 339–343.
[25] P. Lees RA Fearon, J.K. Harrison, N.M. Broomfield, T.J. Quinn, Cognitive and mood research in stroke research: focussed review of contemporary studies, Stroke 43 (2012) 1678–1680.
[26] D. McMahon, C. Micaleffe, T.J. Quinn, Review of clinical practice guidelines specifying cognitive assessment in stroke, Disabil. Rehabil. (2021), https://doi.org/10.1080/09638288.2021.1980122.
[27] A. McGovern, S.T. Pendlebury, N.K. Mishra, Y. Fan, T.J. Quinn, Test accuracy of informant-based cognitive screening tests for diagnosis of dementia and multidomain cognitive impairment in stroke, Stroke 47 (2016) 329–335.
[28] S.T. Pendlebury, S.P. Klaus, R.J. Thomson, Z. Mehta, R.M. Wharton, P.M. Rothwell, Oxford Vascular Study, Methodological factors in determining risk of dementia after transient ischemic attack and stroke: (III) applicability of cognitive tests, Stroke 46 (2015) 3067–3073.
[29] R. Lees, J. Selvarajah, C. Fenton, et al., Test accuracy of cognitive screening tests for diagnosis of dementia and multidomain cognitive impairment in stroke, Stroke 45 (2014) 3008–3018.
[30] T. Wilkinson, A. Ly, C. Schnier, et al., Identifying dementia cases with routinely collected health data: a systematic review, Alzheimers Dement. 14 (2018) 1038–1051.