Statistical Analysis Plan

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1 SAP Signatures

I give my approval for the attached SAP for the trial entitled Improving Primary Care After Stroke, version number 1.0, dated 23rd April 2020.

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Signature: 

Date: 24/04/2020

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Name: Dr Mark Pilling

Signature: 

Date: 24/04/2020

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3 Abbreviations and Definitions

Abbreviation	Definition
AE	Adverse Event
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DMC	Data Monitoring Committee
EQ-5D-5L	The 5-level version of EQ-5D, a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life
GP	General practitioner
HEAP	Health Economic Analysis Plan
HLQ	Health Literacy Questionnaire
ICECAP-A	ICEpop CAPability measure for Adults
IPCAS	Improving Primary Care After Stroke
IRAS	Integrated Research Application System
MLAS	My Life After Stroke
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIS	Stroke Impact Scale
SIS-SF	Stroke Impact Scale Short Form
SSSMQ	Southampton Stroke Self-management questionnaire
TSC	Trial Steering Committee

4 Introduction

4.1 Preface

No formal Primary Care based model of care exists to support stroke survivors living in the community. A large variation in the range, quality and access to health services offered to stroke survivors between and within local primary care trusts suggests that many of the stroke survivors' needs are not being met systematically. Therefore, to address the longer-term needs we have developed a multi-factorial Primary Care model that seeks to enable greater engagement with stroke care and community services, to link effectively to specialist services, and to improve the lives of stroke survivors.

4.2 Purpose of the analyses

These analyses will assess the efficacy and safety of a novel model of primary care for stroke survivors living in the community compared to standard care. A health economic analysis plan (HEAP) will be documented separately.

5 Study Objectives and Endpoints

5.1 Study Objectives

The main aim of the IPCAS trial is to evaluate the clinical and cost effectiveness of a novel model of primary care for stroke survivors living in the community.

The primary objective is:

- To assess the clinical effectiveness of the new model of primary care for stroke survivors compared with standard care. The two co-primary endpoints for the trial will be two sub-scales (emotion and handicap) of the Stroke Impact Scale (SIS v3.0) at 12 months.

The secondary objective is

- To assess the long-term cost effectiveness of the new model of primary care for stroke survivors compared with standard care.

5.2 Endpoints

The primary endpoint for the trial will be two sub-scales (emotion and handicap) of the Stroke Impact Scale (SIS v3.0) as co-primary outcomes at 12 months.

Secondary endpoints include data collected via a series of questionnaires at baseline, 6 months and 12 months, comprising:

- SIS short form
- EuroQol EQ-5D-5L
- ICEpop CAPability measure for Adults (ICECAP-A)
- Southampton Stroke Self-management questionnaire (SSSMQ)*
- Health Literacy Questionnaire (HLQ)*

** Only collected at 12 months follow-up.*

Secondary endpoints to examine cost-effectiveness will be collected, and details of these and any planned health economic analyses will be detailed by the health economist (they are beyond the scope of this SAP).

6 Study Methods

6.1 General Study Design and Plan

The IPCAS trial is an open-label, two-level cluster randomised trial of patients clustered within general practices, with randomisation occurring at the level of the general practice.

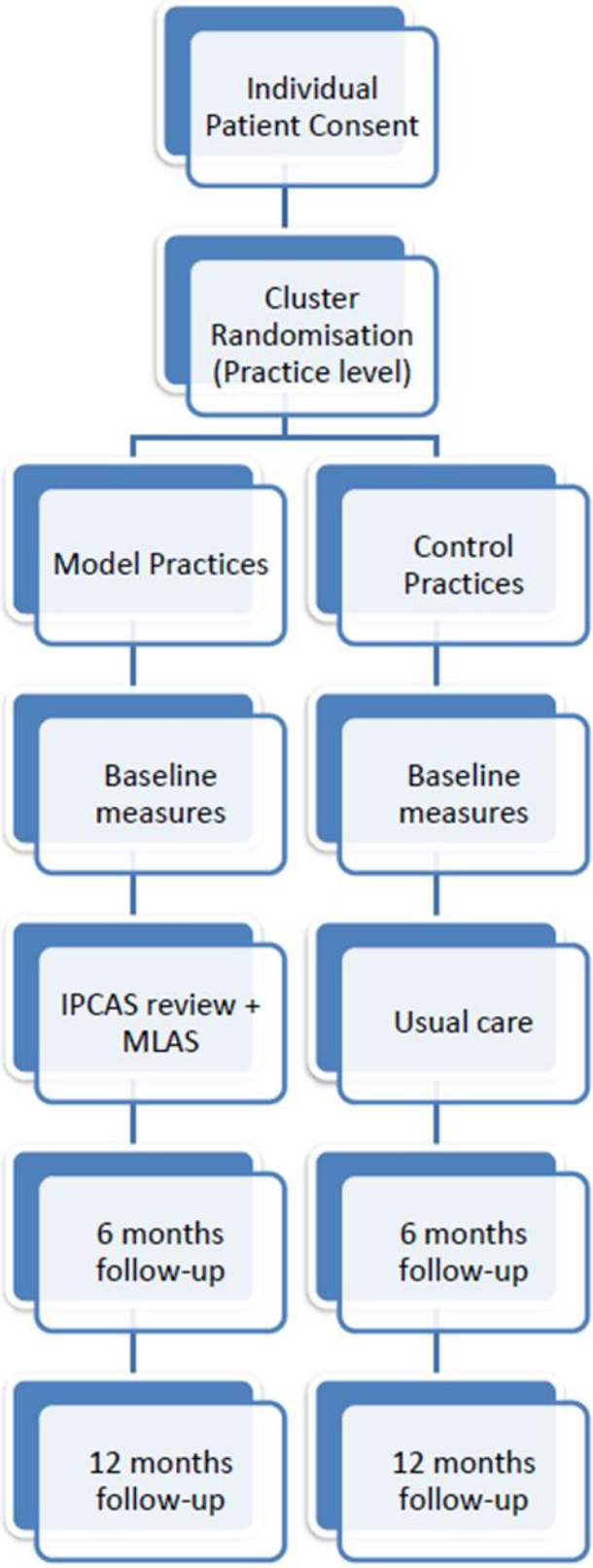
General practices are randomised in a ratio of 1:1 to the control or experimental group. General practices in the control arm offer standard care to their patients. General practices in the experimental arm offer a novel model of care to their patients. Once all invitation letters and reminders are sent out to patients in a general practice, the general practice can be randomised.

Randomisations are performed using a stratified, random permuted block design. The stratification factor is general practice list size, split into two levels based on the approximate median general practice list size for the geographic areas likely to be included in the trial. The two strata levels are:

i) Strata 1: General practice list size less than 10,500 patients;
ii) Strata 2: General practice list size equal to or greater than 10,500 patients.

Random permuted blocks are used in order to maintain close balance in the allocation of the two treatment groups within each strata, and to minimise opportunities for selection bias. The exact block sizes used to produce the randomisation lists is documented separately by the statistician in order to help maintain blinding.

The sequence of key study points is summarised in the following flow chart.


Individual Patient Consent
Cluster Randomisation (Practice level)
Model Practices
Control Practices
Baseline measures
Baseline measures
IPCAS review + MLAS
Usual care
6 months follow-up
6 months follow-up
12 months follow-up
12 months follow-up

6.2 Inclusion-Exclusion Criteria and General Study Population

As this is a two-level cluster trial, there are two levels at which the inclusion and exclusion criteria apply: the general practice level and the individual patient level.

General practices from the East of England and the East Midlands were eligible to take part in the IPCAS trial. Practices representing a range of urban/rural and different socio-economic status were identified, with a particular focus on practices with a stroke register comprising a minimum of 100 patients (to ensure that we maintain a target cluster size of 16-24 patients where possible).

For individual patients, the following inclusion/exclusion criteria apply:

Inclusion criteria

- On practice register with a history of stroke
- Able to provide written informed consent (with or without the help of a carer)
- Age 18 years or older

Exclusion criteria

- Patients on the palliative care register
- Living in a nursing home

The inclusion criteria were designed with the aim of achieving the broadest reach to maximise inclusivity. For example, we included survivors regardless of the severity of their stroke. However, due to the nature of research and the service offered, it was recognised that certain groups of patients would most likely be excluded. For example, patients living in nursing care homes may not be able to benefit from the components offered (e.g. referrals to other services). These groups were therefore excluded from taking part in the IPCAS trial.

6.3 Blinding

The IPCAS trial is open-label due to the nature of the intervention under investigation. As this trial is open-label, there is the potential for bias related to knowledge of the treatment arm assigned to each cluster (general practice) by patients, carers, clinicians and the study team, particularly so because some of the endpoints, including the two co-primary endpoints, are subjective. In addition, blinded treatment outcome assessment for individual patients is not feasible due to the cluster-randomised nature of the trial, and because the co-primary endpoint scores are chosen by the patients themselves or their carer (so an independent assessor cannot be used). This is a limitation of the trial and will need due consideration when interpreting the results upon conclusion of the trial.

Blinding with respect to randomisation is discussed in section 6.4.

6.4 Randomisation

The IPCAS trial is an open-label, two-level cluster randomised trial of patients clustered within general practices, with randomisation occurring at the level of the general practice. General practices will be randomised in a ratio of 1:1 to the control or experimental group.

Randomisation will be performed using a stratified, random permuted block design. The stratification factor will be general practice list size, split into two levels based on the approximate median general practice list size for the geographic areas likely to be included in the trial. The two strata levels are:

iii) Strata 1: General practice list size less than 10,500 patients;
iv) Strata 2: General practice list size equal to or greater than 10,500 patients.

Random permuted blocks will be used in order to maintain close balance in the allocation of the two treatment groups within each strata, and to minimise opportunities for selection bias. The exact block sizes used to produce the randomisation lists will be documented separately by the statistician and access to this document will be restricted.

Randomisation will be set up and administered by the MRC Biostatistics Unit. An individual randomisation list will be produced programmatically for each strata level using random permuted blocks. A random number seed will be used in the production of the randomisation lists and, for reproducibility purposes, this will be recorded at the time the randomisation lists are generated.

The statistician will maintain the randomisation lists and access to the randomisation lists will be restricted to the statistician plus other appropriately trained and delegated members of staff. A back-up randomiser will be nominated to cover periods when the trial statistician is on leave. Members of the operational trial team will not have access to the randomisation lists, but only the outcome of randomisation as each general practice is randomised.

To randomise a cluster, a designated person from the trial team will contact the statistician. They will provide the name of the cluster and the cluster size. The statistician will then refer to the relevant randomisation list for the stratum concerned, choosing the next unallocated treatment arm on the list. This treatment arm will then be assigned to the cluster. The statistician will communicate the allocated treatment arm to the designated person from the trial team in writing, and a record of this will be maintained by the statistician.

As the trial is open-label, procedures for emergency unblinding are not needed.

An audit trail of all randomisation requested and performed will be maintained by the statistician or other appropriately trained and delegated members of staff.

Access to restricted randomisation documents, including the block sizes, random number seeds and randomisation lists, will be made available at the end of the study.

6.5 Study Variables

The frequency and timing of the main variable assessments is outlined in the Table 1. The primary outcome data will be collected via postal questionnaire at the time of invite to the study prior to Practice randomisation. Secondary outcome data (SIS Short Form, EuroQol EQ-5D-5L, and ICEpop CAPability measure for Adults (ICECAP-A)) will also be collected by postal questionnaire after randomisation. Non-responders to the secondary outcome questionnaire will be followed-up by telephone.

Follow-up via postal questionnaire will take place at six months after entry into the trial. These will include all of the baseline instruments. Non-responders will be followed up by telephone.

Follow-up at twelve months will comprise a combination of postal and telephone administered questionnaires including all of the baseline instruments plus the Southampton Stroke Self-

management questionnaire (SSSMQ) and the Health Literacy Questionnaire (HLQ). Non-responders to the postal questionnaires will be followed up by telephone.

Table 1: Frequency and timing of main variables and questionnaires.

Study assessment	Throughout	Baseline	6 months	12 months
Demographics (age, gender, etc)		x		
SIS short-form questionnaire		x	x	x
SIS full-form (emotional and handicap domains only) questionnaire		x	x	x
EQ-5D-5L questionnaire		x	x	x
ICECAP-A questionnaire		x	x	x
Health Literacy Questionnaire (HLQ)				x
Southampton Stroke Self-Management Questionnaire (SSSMQ)				x
SAE monitoring	x			
Review of general practice data (number and nature of primary care visits, secondary care inpatient and outpatient visits, investigations, medications and use of social services, etc)				x

7 Sample Size

With 23 clusters per arm and an average of 20 patients per cluster, assuming an intra-class correlation of 0.03, a typical coefficient of variation of the cluster size of 0.65 (Campbell, 2014), and 2.5% significance (adjusted to 2.5% because of the use of two co-primary outcomes), we would be able to detect an effect size of 0.33 with at least 90% power on the co-primary outcomes (emotion and handicap sub-scales of the Stroke Impact Scale (SIS v3.0)). The sample size calculation has been inflated to allow for a rate of 20% loss to follow-up for patients within clusters. Loss to follow-up of entire clusters is not anticipated.

The conservative estimate of 20 patients per practice is drawn from the trials pilot data (unpublished) and the research groups experiences of running previous trials in this population (Fletcher K, 2010; Fletcher K, 2010; O'Brien C, 2013). A typical practice with a list size of between 7,000 to 10,000 will have approximately 100 - 150 patients on the stroke register (Progress in improving stroke care, 2010). We anticipate that the electronic search applying the exclusion criteria will eliminate around 40% of these (based on the pilot study) leaving 60 – 90 eligible patients per practice, of which about 30% will agree to take part (18 – 27 per practice). This will yield between 16 – 24 participants per practice.

The IPCAS trial was powered based upon the two co-primary outcomes (SIS emotional and handicap domains). It is important to be aware that the trial was not powered based on any secondary or exploratory end-points, and this should be considered in particular when interpreting any resulting p-values.

8 General Considerations

8.1 Timing of Analyses

The final statistical analysis will be performed after all patients have completed their 12 month follow-up or have dropped out of the trial. The final statistical analysis will be performed on data that has been cleaned and hard locked. The final statistical analysis should only be performed after the finalisation and approval of this SAP document.

8.2 Analysis Populations

Patients may be included or excluded from particular analysis populations on the basis of certain characteristics or criteria. These are detailed below.

8.2.1 Full Analysis Population

The full analysis population, also often referred to as the "intention-to-treat" population, comprises all randomised general practices and consented patients within them, regardless of eligibility error, post-randomisation withdrawal, and whether the assigned treatment was received, with sufficient or insufficient compliance. Any analyses will be based on the treatment arm assigned at randomisation, regardless of what treatment was actually received.

A subset of the full analysis population will be used to analyse the two co-primary efficacy end-points, including only the patients with the necessary data available at baseline and twelve months.

The full analysis population will also be used to analyse several secondary and exploratory end-points as outlined elsewhere in this SAP, some of which, like the primary efficacy analyses, may require data to be complete at particular time points and therefore will only include a subset of the full analysis population with the necessary data available.

8.2.2 Per Protocol Population

A per protocol analysis population typically includes only the subjects (in this case including both general practices and patients) who adhered to the study protocol, including full compliance with the assigned treatment regime and scheduled follow-up. Given the difficulty in measuring compliance to intervention arm treatment, as it is a package of care with several optional components, a per protocol population will not be defined. Instead, intervention fidelity will be assessed to examine how well the intervention was implemented as planned (see Section 9.4 and 14).

8.2.3 Safety Population

The safety population comprises all consented patients, regardless of whether they received any study intervention, including control, and regardless of length of time in the study. The safety population will be used to provide summary statistics on adverse events.

8.3 Covariates and Subgroups

As the randomisation for the IPCAS trial is stratified by general practice list size (Strata 1: General practice list size less than 10,500 patients; Strata 2: General practice list size equal to or greater than 10,500 patients). There is an *a priori* hypothesis that smaller practices can deliver the intervention more successfully due to more personal care, therefore general practice list size will be adjusted for in the secondary analyses using the same category levels as used in the randomisation. This will be included as a cluster-level fixed effect in the mixed effect models for the analyses of the two co-primary end-points.

Various subject-level covariates are considered as important baseline covariates or clinically significant in this study. These subject-level and cluster-level covariates will be included as subject-level or cluster-level fixed effects in the mixed effects model for the analyses of the two co-primary end-points, and in the mixed effect models of secondary end-points where deemed appropriate:

- Baseline categorical variable gender (male/female).
- Age at baseline in the following categories: 20-64, 65-74, 75-84, 85+ years.
- Time since last stoke at baseline in the following categories: 0-6months, 6 months-1year, 1-2 years, 2-5 years, 5-10years, 10 years +.
- Deprivation score (subject and practice).

8.4 Interim Analyses and Data Monitoring

8.4.1 Interim Analyses

No formal interim analyses are planned.

8.4.2 Data Monitoring

Oversight of the trial will fall to an independent committee fulfilling the combined roles of trial steering committee (TSC) and Data Monitoring Committee (DMC). They will provide overall supervision of the conduct of the trial. The committee will consider relevant factors in interim decision-making such as recruitment rate and completion schedule, baseline comparability across treatment arms, data completeness and follow-up, safety profile and ethical issues. Initially, the TSC/DMC will meet after the first 100 participants are recruited, then 6-monthly. This frequency may increase or decrease according to need. The statistician will be involved in producing data monitoring reports.

A snapshot of the data used for each analysis, including that for data monitoring reports, should be preserved by the data manager. The statistician will also maintain a separate copy of the data files provided for each analysis, including that for data monitoring reports, and will also maintain a copy of all programming code and analysis reports provided by the statistician to the data monitoring committee and/or trial team.

Analyses performed for data monitoring purposes will not include efficacy analyses. In order to minimise bias, only the final analyses will include efficacy analyses. This is particularly important given that the IPCAS trial is open-label.

8.5 Multi-centre Studies

IPCAS is a multi-centre trial, comprising multiple GP practices. The trial uses a two-level cluster randomised design, with GP practices representing the clusters, and patients nested within GP practice. GP practice is the unit of randomisation. The data will be analysed to reflect the hierarchical nature of the study design using mixed effect models.

8.6 Multiple Testing

This study has two co-primary outcomes: (emotion and handicap subscales of the SIS). The Holm-Bonferroni procedure (Holm, 1979) will be used to handle the co-primary endpoints and issue of multiplicity. 97.5% CIs for the two primary outcomes will be reported as a conservative measure.

Confidence intervals for secondary and exploratory outcomes will be reported at the 95% level.

9 Summary of Study Data

Summary data will be provided for a variety of study data via tables and/or graphs as outlined in *IPCAS SAP V1.0_23April2020 figures and tables listing.xlsx*.

Where results are presented as summary statistics, continuous variables will be summarised using the following descriptive statistics:

- n (the non-missing sample size)
- mean
- standard deviation
- median
- 25th percentile
- 75th percentile
- maximum
- minimum.

Where results are presented as summary statistics, categorical variables will be summarised using frequency and percentages (based on the non-missing sample size) of all observed levels. Non-observed levels should also be included if they form part of an expected set of category levels (e.g. from a categorical questionnaire question with a finite set of response options).

In general, summary statistics will be presented in tables by treatment and by gender, with a column for each treatment group or gender. If appropriate, a table may also be split by questionnaire number (baseline, 3 months, 6 months, etc). For study data that is summarised in a more raw form and without the need for summary statistics (e.g. recruitment, withdrawals, SAEs, etc), data will be presented in a table or graph as appropriate. The quantity of missing data will also be summarised for relevant outcomes, by treatment group, at 6months at also 12 months.

Descriptive statistics for Intervention fidelity will be presented as detailed in Section 6 (*IPCAS V1.0_23April2020 figures and tables.docx*.)

9.1 Subject and Cluster Disposition

Summary data for subject disposition and an overview of the time-dependent rates of recruitment will be presented:

- Summary of cluster randomisation to treatment sequence (Table 1.1)
- Summary of time dependent rates of GP practice recruitment (Table 1.1 and Figure 1.1)
- Summary of time dependent rates of patient recruitment (Figure 1.2 and 1.3)
- Summary of patient flow (Table 2.1)
- Subject disposition CONSORT diagram (Figure 2.3)

Questionnaire date for each patient will be recorded at baseline, 6 and 12 months and return rates tabulated:

- Return rates for questionnaires at baseline, 6 and 12 months (Table 2.5).
- Data completeness for SIS emotional domain and SIS handicap domain at 12 months (the co-primary end-points) [where complete data is considered a binary variable for each subject at a given domain] (Table 2.6).

At each stage of the trial, the following variables will be recorded and define whether a patient reached that stage of the trial:

- Questionnaire date (dd-mmm-yyyy)

Patients without the above information will have missed a visit, been lost to follow-up or withdrawn due to one of the following:

- Death
- Health deterioration
- Taking part is too burdensome
- 2nd questionnaire not relevant
- 6m questionnaire not relevant
- Left the practice
- No reason given
- Intervention is not relevant
- Will not complete 12m questionnaire
- Not a stroke.

Summary tables of withdrawal will be presented (Tables 4.3 - 4.6).

Intervention progress will be summarised in the following figures and diagrams:

- Breakdown of stroke review progress per recruited intervention GP practice up to [date] (Table 2.2)
- Breakdown of MLAS interest per recruited intervention GP practice up to [date] (Table 2.3)
- Breakdown of the number of stroke survivors attending MLAS by area up to [date] (Table 2.4)
- Progress of enhanced stroke review completion at each intervention GP practice from May 2018 to end of study. GP practice in order of randomisation (Figure 2.1)
- Breakdown of MLAS progress by intervention site over the period May 2018 to [date] (Figure 2.2)

Data concerning the intervention care model will be collected under the following:

1) Training
2) Enhanced Stroke Review
3) MLAS

Process data, fidelity of delivery and receipt will be discussed in Section 10.2.1.

Data concerning usual care will be collected from control GP practices either face-to-face, over the phone, or email correspondence with n (%) being reported for the following categories:

1) Frequency of reviews (annually, as needed, not reported)
2) Mode of review (face to face, combination)
3) Healthcare professional(s) involved in review (GP-led, nurse-led, HCA-led, combination)
4) Type of review (stroke-specific, multi-morbidity, other)
5) Review content (Quality and Outcomes Framework-related, other)

Descriptive statistics for the Intervention and usual care models will be presented as detailed in Section 6 (IPCAS V0.7_28JAN2020 figures and tables.docx.)

9.2 Derived variables

There are several derived variables in the IPCAS trial, primarily relating to the questionnaire data. The derived variables and how they are calculated are detailed below.

9.2.1 SIS domain total scores

The SIS questionnaire has 8 domains, and each domain contains a series of questions which are each scored on a scale of 1-5. A total score for each domain can be calculated and then transformed onto a standardised scale of 0-100 for each individual.

Three questions within the SIS emotional domain (domain 3) are reverse scored (3f, 3h and 3i). For the three reverse scored questions, these are back-transformed using the following equation:

$$(x + 1) – y$$

Where x=maximum possible score and y=raw score.

For example, for an SIS 3h score of 4, this would be back-transformed to:

$$(5 + 1) - 4 = 2.$$

For each domain, the total raw score is calculated as the sum of the raw scores, using the back-transformed scores in place of the "raw" reverse scores in the case of 3f, 3h and 3i. For example, for the emotional domain the total raw score for each individual is the sum of SIS 3a, 3b, 3c, 3d, 3e and 3g, and the back-transformed scores for 3f, 3h and 3i.

The domain total score can then be calculated on a standardised scale of 0-100 for each individual:

Standardised domain total score = [(total raw score for domain-lowest possible raw score for domain)/possible raw score range for domain]*100

For example, for the emotional domain (domain 3), the lowest possible raw score is 9 (a score of 1 for all 9 questions in domain 3), and the possible raw score range is 45-9=36 (maximum possible score is 9x5=45, minimum possible score is 9x1=9).

9.2.2 SIS-SF total score

The SIS-SF is made up of 8 questions, one from each domain of the full SIS questionnaire. It includes the following 8 questions only: 1c, 2f, 3d, 4b, 5h, 6f, 7e, 8b. Each question is scored on a scale of 1-5. A total score for SIS-SF can be calculated and then transformed onto a standardised scale of 0-100 for each individual. There are no reverse scored questions within the SIS-SF.

For SIS-SF total, the total raw score is calculated as the sum of the raw scores for the eight questions. The domain total score can then be calculated on a standardised scale of 0-100 for each individual:

Standardised SIS-SF total score = [(total raw score-lowest possible raw score)/possible raw score range]*100

The lowest possible raw score is 8 (a score of 1 for all 8 questions in SIS-SF), and the possible raw score range is 40-8=32 (maximum possible score is 8x5=40, minimum possible score is 8x1=8).

Q9 is a visual analogue scale (VAS) score of perceived overall health which asks participants to indicate their overall health post-stroke ranging from 0 (No recovery) to 100 (Full recovery).

9.2.3 EQ-5D-5L total score

The EQ-5D-5L questionnaire is made up of five questions, on:

i) mobility
ii) self-care
iii) usual activities
iv) pain & discomfort
v) anxiety & depression

Each of the five questions is scored on a scale of 1-5, where:

- 1 indicates no problem
- 2 indicates slight problems
- 3 indicates moderate problems
- 4 indicates severe problems
- 5 indicates extreme problems

A "health state" score is given for each individual by writing the score for each of the five questions as a 5-digit number (in order of questions i-v). For example, if an individual scored 1 on mobility, 2 on self-care, 3 on usual activities, 4 on pain & discomfort, and 5 on anxiety & depression, their "health state" score would be written as 12345.

There are a total of 3125 possible different "health states", each represented by a 5 digit number. A health state of 11111 indicates no problems in any of the five dimensions measured, whereas a health state of 55555 indicates extreme problems in all of the five dimensions measured. These "health states" can be converted into a single index value for each individual using country-specific crosswalk value sets available along-side the EQ-5D-5L instrument.

For IPCAS, the UK crosswalk value set (see EQ-5D-5L_Crosswalk_Index_Value_Calculator.xls) will be used in the EQ-5D-5L total score calculations. The profile/health state is converted into a Country specific index value ranging from -0.594 (extreme problems across all health states) to 1 (no problems across all health states). The VAS score ranges from 0 (Worst health) to 100 (Best health imaginable).

The VAS score ranges from 0 (Worst health) to 100 (Best health imaginable).

9.2.4 ICECAP-A total score

The ICECAP-A questionnaire is made up of five "questions", with each question assigned a score between 1 and 4. A score of 1 is given to a response reflecting the lowest quality of life, and a score of 4 is given to a response reflecting the maximum quality of life. For example, for question one, "Feeling settled and secure", the following scores would be assigned:

- I am unable to feel settled and secure in any areas of my life: score=1
- I am able to feel settled and secure in a few areas of my life: score=2
- I am able to feel settled and secure in all areas of my life: score=3
- I am able to feel settled and secure in all areas of my life: score=4

The scores assigned to the five questions within a patient are then written as five consecutives numbers to give an overall 5-digit score for each patient. An overall score of '44444' for a patient represents the maximum quality of life measured by the questionnaire, and a score of '11111' measures the minimum quality of life measured by the questionnaire. All five questions must be answered to assign an overall score.

These overall 5-digit scores are then translated into an overall "tariff" for each patient using a look-up table to assign a value according to the score the patient has given to each question.

Table 2: The ICECAP-A look-up table (Flynn, 2013)

1. Feeling settled and secure	
Level 4	0.222
Level 3	0.191
Level 2	0.101
Level 1	-0.001
2. Love, friendship and support	
Level 4	0.228
Level 3	0.189
Level 2	0.096
Level 1	-0.024
3. Being independent	
Level 4	0.188
Level 3	0.156
Level 2	0.084
Level 1	0.006
4. Achievement and progress	
Level 4	0.181
Level 3	0.159
Level 2	0.091
Level 1	0.021
5. Enjoyment and pleasure	
Level 4	0.181
Level 3	0.154
Level 2	0.069
Level 1	-0.003

To calculate the overall tariff for a patient, the values next to their five scores in the look-up table are simply summed. For example, the tariff for a patient scoring 43211 would be calculated as follows:

$$0.222 + 0.189 + 0.084 + 0.021 – 0.003 = 0.513$$

ICECAP-A tariffs can range from zero to one (*note there is a small degree of rounding error in the look-up values provided, which may result in small deviations to this range*).

Either the overall tariff or the raw categories may be used in the statistical analyses, depending on the intended purpose of each individual analysis.

9.2.5 HLQ scores

The Health Literacy Questionnaire comprises 9 scales. Unlike the other questionnaires in this study, the HLQ does not provide a single overall score. Instead, it provides means and standard deviations for each of the nine HLQ scales that indicate a person's strengths and needs in relation to their health literacy.

The Excel file (Q:\IPCAS\Documents\CRF\Information for Statistician\HLQ\HLQ Data Entry and Scoring\HLQ Scoring Using Excel.xlsx) contains information about the scales, instructions for scoring and how to handle missing data.

9.2.6 SSMQ total score

The scale consists of 28 items that measure an individuals' self-management competency following stroke. Higher summed scores from the scale equate to someone with better self-management competency following stroke (Boger *et al*, 2015).

Each item is rated on a six-point response scale anchored by the responses 'Always True' and 'Always False'. Responses are allocated scores as follows:
Always true = 6
Mostly true = 5
Somewhat true = 4
Somewhat false = 3
Mostly false = 2
Always false = 1

Table 3: 15 items that are reverse scored (where 1=6, 2=5, 3=4, 4=3, 5=2, 6=1, shaded)

1	The effects of stroke mean that I cannot manage my recovery and health
2	When things do not go well with my stroke, it is hard to stay positive
3	It is not up to me to decide the best ways to manage my stroke
4	The physical effects of stroke mean that I cannot manage my health
5	It is hard to be motivated to seek out solutions to problems relating to stroke
6	I am not sure what signs or symptoms mean my health is changing
7	My problems with communication mean that I cannot manage my health
8	My condition would improve if I received more professional help
9	Whatever I do, I will not improve my condition
10	The effects I take to manage my health have a positive effect
11	I find it difficult to tell health professionals what I want or need
12	I work out ways of managing my health together with health care professionals
13	I am confident that health care professionals can answer my questions
14	I feel confident at discussing any advice I don't understand with Doctors
15	I feel confident at getting the information I need from health care professionals
16	I know how to get help if I am concerned about my condition
17	I plan my day so I can get things done without being tired
18	I feel confident asking family members to help me do things important to my health
19	I manage things related to stroke as well as other people with stroke
20	I try different ways of doing things until I find out what works for me
21	Ideas and things that work for other people with stroke are helpful to my recovery
22	I have useful information or advice to give to others regarding managing after stroke
23	I feel comfortable asking friends to help me do things important to my health
24	I am concerned that the things I do to manage stroke may cause harm if not guided by my health care professionals
25	I cannot alter what my health care professionals decide to do about my stroke
26	Following advice from health care professionals is the only way I will manage stroke
27	I always follow professional advice about my health, to the letter
28	Constant professional advice would help me to manage stoke

9.3 Demographic and Baseline Variables

The demographic variables include age at baseline, gender, ethnicity and time since last stroke:

- Baseline demographics for the ITT population by trial arm up to [date] (N=) (Table 3.1)
- Baseline demographics for the ITT population by gender up to [date] (N=) (Table 3.2)

Questionnaire data will also be collected at baseline for SIS (short-form and full-form), EQ-5D-5L and ICECAP-A. A breakdown of the frequency of responses per level for each item of SIS domains 3 (emotion) and 8 (handicap) will be reported, as well as summary statistics for SIS domain 3 (emotion) and 8 (handicap), SIS-SF derived total score, EQ-5D-5L derived total score, and ICECAP-A derived total score. These summary statistics will be reported by treatment arm and gender (Tables 5.1-5.10).

9.4 Treatment Compliance

Treatment compliance is difficult to assess in the IPCAS trial as not all components of the intervention package are mandatory. Data on the delivery and uptake of the intervention components will be collected by the trial team with the intention of being able to demonstrate intervention fidelity (see Section 10.2.1 for details).

10 Efficacy and Fidelity Analyses

All efficacy variables will be summarised overall and by trial arm and gender at baseline and follow-up. N, mean, median, standard deviation, IQR will be used to summarise continuous efficacy variables, whereas number and percent will summarise categorical efficacy variables, as described in Section 9. Variables will not be summarised by cluster.

10.1 Primary Efficacy Analyses

The standardised domain total scores will be calculated (as described in section 9.2.1) for each of the two co-primary outcomes (SIS emotional domain and SIS handicap domain). The analyses will focus on the evidence for a difference in SIS score (handicap or emotion) between the intervention and control group.

Each domain will be modelled separately and the following model fitted:

$$Y_i = \beta_0 X_{0i} + \beta_1 X_{1i} + \epsilon_i$$

For each co-primary outcome there is the potential for clustering and therefore a mixed effect model will be fitted with a random effect for general practice and fixed effects for the treatment group to assess the effect of clustering:

$$Y_{ij} = \beta_0 X_{0ij} + \beta_1 X_{1ij} + u_j + \epsilon_{ij}$$

Where,

Y_{ij} = continuous outcome SIS score (emotion/ handicap domain)
i = individual patient
j = cluster/ practice
X_1 = dummy variable for the intervention treatment group.
X_0 = baseline covariates (baseline score, gender, cluster size, time since last stroke at consent)
β_0 = intercept which represents the population average SIS score
β_1 = difference in score between intervention and control groups at 12 months
$u_j \sim N_1(0, \sigma_b^2)$ is the cluster-level random practice effect
$\epsilon_{ij} \sim N_1(0, \sigma_e^2)$ is the residual error

There is an a priori hypothesis that the following covariates may be associated with the co-primary outcomes: gender, age at baseline (categorical), time since last stroke (categorical), general practice list size (the stratifying variable used in the randomisation, split into two categories; <10,500 and ≥10,500 patients) and deprivation score (continuous, both at the patient and practice level). Once the primary analysis model is decided, these covariates will be added to assess and changes in treatment effect on the co-primary outcomes.

Each data point will be assumed to have an error term that is identically and independently normally distributed with constant variance. These assumptions will be checked using histograms and box plots to look at the distributional form of the primary outcome SIS scores. All assumptions for the linear mixed effects models will be assessed by viewing plots of the residual values and QQ plots. If any of the assumptions of the linear mixed model are violated then the dependent variable, SIS score, may be transformed to normality or if this fails to correct the distributional assumptions, non-Gaussian or semi/non-parametric methods for analysis will be used.

The analysis population for the primary outcome will be all patients with 12-month outcome measure as the mixed effects model assumes missing at random (MAR).

For missing data analysis the following model will be fitted if there is a cluster effect:

$$Y_{ijk} = \beta_0 X_{0ij} + \beta_1 X_{1ij6} + \beta_2 X_{1ij12} + u_j + \varepsilon_{ijk}$$

Where,

Y_{ijk} = continuous outcome SIS score (emotion/ handicap domain)
i = individual patient
j = cluster/ practice
k = 6 month and 12 follow-up scores
X_1 = dummy variable for the intervention treatment group.
X_0 = baseline covariates (baseline score, gender, cluster size, time since last stroke at consent)
β_0 = intercept which represents the average baseline SIS score for person *i*
β_1 = difference in score between intervention and control groups at 6 months
β_2 = difference in score between intervention and control groups at 12 months (primary)
$u_j \sim N_1(0, \sigma_b^2)$ is the cluster-level random practice effect

$$\begin{pmatrix} Y_{ij0} \\ Y_{ij6} \\ Y_{ij12} \end{pmatrix} \sim MuN \begin{pmatrix} \beta_0 \\ \beta_0 + \beta_1 + X_{ij6}\,, \\ \beta_0 + \beta_2 + X_{ij12} \end{pmatrix} \quad \Sigma$$

$\varepsilon_{ijk} \sim MuN \begin{pmatrix} 0 \\ 0, \Sigma_0 \\ 0 \end{pmatrix}$ is the residual error, and Σ_0 initially has an AR1 structure.

Once the model assumptions have been checked the primary outcome will be presented as a p-value from all model coefficients. Each of the coefficients from the mixed models will be reported with standard error (SE) and 97.5% CIs. The mean treatment differences in each ethnic group will be reported with SEs and 97.5% CIs (Tables 7.1 and 7.2). 6-month and 12-month follow-up questionnaire data will be summarised as in Tables 5.11-14 and Tables 5.21-24). The primary outcome from the linear mixed effects models will be summarised as in Tables 7.1 and 7.2.

10.2 Secondary Analyses

Summary scores will calculated for each questionnaire as outlined in Section 9.2. Summary statistics for the SIS-SF, EQ-5D-5L, ICECAP-A, SSSQ and HLQ scores will be produced in Tables 5.15-5.34. Analysis from these questionnaires and scores will be included in the HEAP.

It should be noted that these secondary analyses are exploratory and that the sample size is enough to power the primary analyses only.

10.2.1 Intervention Sub-group and Fidelity Analysis

The intervention cohort will be considered as a separate sub-group analysis with an *a priori* hypothesis that the 'dose' level of intervention is associated with outcome SIS emotion/ handicap score. Exposure to the intervention is difficult to summarise succinctly as some aspects of the intervention are optional, and patients in the intervention arm can therefore decide, to some extent, which aspects of the package of care available to them they wish to receive.

Consideration will be given to participants in the intervention as a separate sub-group analysis in three areas: 1) Structured stroke review, 2) MLAS and 3) Fidelity.

1) Structured Stroke Review

There is an *a priori* hypothesis that stroke review attendance and the level of action taken at a stroke review is associated with SIS handicap and emotion 12 month score. A linear mixed effect model will be fitted in line with the primary analysis with fixed effects for the stroke review attendance (y/n), and categorical variable for action taken (no review, review with no action plan, review with action plan).

2) MLAS

Participants in the intervention group can only attend MLAS if they have attended a structured stroke review. A linear mixed effect model will be fitted in line with the primary analysis with fixed effects for gender, baseline score and categorical variable MLAS compliance (yes, partial, no), where

- Complete - an individual attended both individual appointments and at least 3 of the 4 group sessions (including group session 1).
- Incomplete - an individual has attended at least 1 session (either an individual appointment or group session).
- No - an individual has not attended any MLAS sessions.

3) Intervention fidelity

The trial team will collect data on intervention fidelity (Table 4) to monitor exposure and quality of various aspects of the intervention as follows:

- Fidelity of training – Audio-recorded training sessions (IPCAS) will be scored against a pre-specified checklist containing planned curriculum content and materials (n= 16 items). Three response options are used: done (2 points), partially done (1 point) and not done (0 points). Video-recorded training sessions (MLAS) will be scored against a pre-specified checklist containing planned curriculum content and materials (n= 205 items). Three response options are used: present (2 points), attempted (1 point) and absent (0 points).

- Fidelity of delivery – Audio-recorded structured reviews will be scored against a pre-specified checklist (n= 9 items). Three response options are used: done (2 points), partially done (1 point) and not done (0 points). Self-reported structured reviews will be scored against a pre-specified checklist (n= 9 items). Three response options are used: done (2 points), partially done (1 point) and not done (0 points). Checklist data will be summarised using descriptive statistics (i.e. proportions, means). Data relating to the 15-item checklist of needs will be summarised using descriptive statistics (i.e. proportions, frequencies, means), and outliers may be excluded as a sensitivity summary. Action plans (i.e. referrals/advice/further appointments) made during the structured review will be summarised using descriptive statistics (i.e. proportions, frequencies, means).

- Fidelity of receipt – Self-reported experience of structured reviews will be scored against a pre-specified checklist (n= 9 items). Three response options are used: done (2 points), partially done (1 point) and not done (0 points). Self-reported experience of MLAS will be scored using a set of questionnaires (6 questionnaires in total; 74 items). Four response options are used: agree, disagree, don't know, does not apply. Checklist data will be summarised using descriptive statistics (i.e. proportions, means).

Inter-rater reliability of fidelity of training and delivery data, specifically observations and audio-recordings will be assessed using percent agreement and Cohen's Kappa (95% CI):

$$\kappa_w = \frac{\sum v_{ij}\, p_{oij}}{\sum v_{ij} p_{eij}}$$

Where,

κ_w= agreement value (-1 to +1 ,where +1 represents perfect agreement between raters)
v_{ij}= disagreement weight (quadratic weights)
p_{oij}= is the proportion of the joint judgements
p_{eij}= is the proportion of judgements expected by chance

Intervention fidelity scores between 80-100% are classed as 'high', 51-79% 'moderate' and <50% as 'low'.

Table 4: Intervention fidelity components collected from participants and practices.

Intervention components	**HCP**	**Participant**
Structured review	✓ Duration/frequency: One-off, up to 30min Mode: Face-to-face	✓
15-item checklist of needs	✓	✓ Sent before structured review
My Life After Stroke (MLAS)		✓ Duration/frequency: 6-week self-management course (2x individual appointments up to 45min each; 4x weekly group sessions up to 2.5hrs each)

		Mode: Face-to-face
Direct point of contact service	✓	✓ Duration/frequency: As and when required Mode: Telephone
Service mapping tool	✓ Duration/frequency: As and when required	✓
Optimised communication	✓ Duration/frequency: As and when required	
Healthcare professional training	✓ Duration: Up to 2hrs Mode: Face-to-face	

11 Missing Data

The primary analysis will be the ITT participants who are in the primary analysis population. Linear mixed effects models will be used to analyse the co-primary end-points that are repeated measured. One key benefit of mixed effect models is that this type of model can include data from incomplete cases, so missing data does not necessarily preclude a subject's data from the analysis. In this instance, missing data will be dealt with using a missing at random (MAR) assumption on the analysis population. The outcome variable will include baseline, 6months and 12months outcomes. The mixed effect model will have participant id as a random effect (i.e. random baseline) and the fixed factors will be time, included as a factor variable, and treatment indicator. To help the MAR assumption the residuals of the model will be assumed to have autocorrelation (if the data allow an unstructured correlation structure stratified by treatment indicator). Additional baseline covariates will be included in the model that are potential confounders.

If there is a large amount of missing outcome data from the questionnaires, we will do a sensitivity analysis missing outcome data for the primary analysis as described in White et al. (2011) and Sullivan *et al* (2018). For each questionnaire, where guidelines exist for missing data, they will be followed (see Section 11.1).

11.1 HLQ – Missing Data Guidelines

Guidelines for missing responses in the HLQ questionnaire include:

Overall rule

- if >50% data is missing, then do not add it up or include it in further analysis.
- If exactly or less than 50% is missing then average the available responses for that scale and include in analysis.

Scales with 4 items/questions (i.e. scales 1 and 2)

- If missing data in 3 or more items, this scale should be excluded for this participant (i.e. leave cells blank for all items in that scale)
- If missing data in 1 or 2 items, scale can be included.

Scales with 5 items (scales 3, 4, 5, 6, 8, 9)

- If missing data in 3 or more items, this scale should be excluded for this participant (i.e. leave cells blank for all items in that scale).
- If missing data in 1 or 2 items, scale can be included.

Scales with 6 items (scale 7 only)

- If missing 4 or more answers should also be excluded as above.
- If missing 3 or less items, scale can be included.

12 Sensitivity Analyses

To account for COVID-19 effects of the UK lockdown (on Monday 23rd March 202) during part of the study, a patient-level binary factor for this will be created by using the date of the 12-month assessment relative to this. As both co-primary endpoints of "emotion" and "handicap" (i.e. participation) may be affected by this event, a sensitivity analysis will be conducted by repeating the primary analyses but now including this new variable.

As a sensitivity analysis, the co-primary end-points will also be analysed under the assumption that missing data is either "missing completely at random" or "missing at random". In this instance, multiple imputation will be used to impute missing outcome data and the various potential predictors of missingness will be included in the imputation model.

Multiple imputation for cluster randomised trials should be based on a multilevel imputation model (Karla Diaz-Ordaz, 2014). For example, missing data will be imputed under different assumptions such as X=4 or X=5 and the primary analysis repeated to check the impact of this. Altering X to be different values: 5,6,7,8. Will eventually mean a "significant" result disappears and that might happen at say 7, which is the tipping point.

13 Safety Analyses

Patient-level safety data collected during the trial will be included in the reporting of safety events, from the point of patient consent to participate in the trial until the end of the follow-up period or loss to follow-up.

Coding of safety events (e.g. MedDRA) is not being utilised in the IPCAS trial.

13.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject who has been administered any research procedure. The trial team will not formally record or report non-serious AEs. No statistical analysis will be performed on non-serious AEs.

13.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse event or effect that results in death; is life threatening; requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is an otherwise medically important event. The trial team will formally record and report all SAEs.

The statistical analysis of SAE data will include a simple summary table of SAEs with one row per SAE. The number of SAEs in the trial is expected to be low given the nature of the intervention, and given that no formal coding system is being used for safety events the data will not be further categorised to provide a summary based on frequency of SAE types.

14 Health Economic Analyses

A health economic analysis plan (HEAP) will be prepared separately by the trial health economist. The HEAP will document the planned health economic analyses.

15 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The majority of summary statistics will be reported to one decimal place greater than the original data. Exceptions include minimum and maximum which will use the same number of decimal places as the original data. Exceptions may be made where appropriate. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

16 Technical Details

At the time of writing, the statistical documents for the IPCAS trial are stored on the "Projects" network drive at the MRC Biostatistics Unit, within a main folder named "IPCAS". Study documents, including the SAP and protocol, are stored within the sub-folder: \IPCAS\Documents.

Current and previous statistical analyses for IPCAS (including data, statistical code, and output) are stored within the sub-folder: \IPCAS\Analysis.

At the time of writing, it is anticipated that the statistical analyses will be performed in R Studio or Stata. The results will be assembled into an XML report, where each page of output should also contain a title and figure/table number, as well as a page number, author, date and time, and the file path and name of the code file that produced the output.

17 Summary of Changes to the Protocol

This statistical analysis plan does not proposes any changes to the statistical approach described in the protocol (*Trial Protocol v1.1_28-02-2018.pdf*). Supplemental analysis of fidelity not outlined in the protocol is described in Section 10.2.1 above.

18 References

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19 Listing of Tables and Figures

Listing of tables and figures are in file:

- *IPCAS SAP V1.0_23April2020 figures and tables listing.xlsx*.

Skeleton figures and tables are in file:

- *IPCAS SAP V1.0_23April2020_figures and tables.docx*.

Figures and tables are listed under the following sections:

1. Trial recruitment
2. Trial Progression
3. Baseline demographics
4. Withdrawals
5. Descriptive statistics – Scores
6. Descriptive statistics - Fidelity
7. Analysis – Primary outcome
8. Analysis – Secondary outcomes
9. Analysis – Intervention subgroup and Fidelity
10. Analysis – Safety and SAEs