Statistical analysis plan for the Aphasia Action Success (ASK) trial: A 2-arm randomised controlled trial to evaluate the effectiveness of a brief early preventative mental health and wellbeing intervention compared to an attentional control in post-stroke aphasia.

#  Introduction, study design, and key trial objectives

The ASK study was a multi-site pragmatic two level (cluster and individual) single blind cluster randomised controlled trial. Clusters, which are represented by Australian Health Service Districts, were randomized to the experimental intervention (Aphasia ASK) or an attention control (SSPIP). Both arms of the study received usual care in addition to either the experimental or the attention control intervention at the discretion of the governing health site and their treatment protocols.

Clusters for the study were Health Service Districts that offer speech pathology rehabilitation services as a single operational unit across multiple site locations within a defined service area in Australia. Health Service Districts were chosen as clusters (instead of individual hospital/health service sites) to reduce the risk of treatment contamination issues that may arise from conducting both arms of the study within the same service area. Health Service Districts were also chosen so that the study interventions could be provided alongside the usual continuum of care for the study duration (that is, across multiple health facilities within the first-year post stroke). The recruitment of clusters was programmatic if they met the criteria upon response to an Expression of Interest.

The study aim was to determine whether an early intervention (Aphasia Action Success Knowledge Program; Aphasia ASK) for people with aphasia after stroke and their family members lead to better mood and quality of life outcomes for people with aphasia, less caregiver burden, and better mental health for family members compared to an attention-control intervention (Secondary Stroke Prevention Information Program; SSPIP) at 12 months post stroke.

## Hypotheses

## Primary hypothesis

It was hypothesised that people with aphasia who received the Aphasia ASK intervention would have significantly better outcomes in mood and quality of life at 12 months post stroke compared to those who received the attention control intervention (SSPIP).

## Primary Outcome measures

The two primary outcomes for people with aphasia were mood as measured by the Stroke Aphasic Depression Questionnaire- 21 item (SADQ-21) and quality of life as measured by the Assessment for Living with Aphasia (ALA).

The rationale for the selection of the two primary outcome measures was: 1) participants with aphasia are the main target for the improved outcomes (although caregiver outcomes are important); 2) the acknowledged difficulty of measuring depression in aphasia is overcome by choosing both a self-report measure (personal subscale in the ALA) and an observational measure (SADQ-21) 46; 3) both quality of life and depression improved in the pilot study of the APHASIA ASK program; 4) both measures have good demonstrated psychometric properties for people with aphasia including responsiveness to intervention; 5) the relationship between depression and quality of life can be explored within the subscales of the ALA; and 6) participants with very severe aphasia had difficulty completing the HADS self-report measure used in the pilot study so the SADQ-21 was chosen because it is an observational tool completed by the carer.

## Secondary hypothesis

It was hypothesised that family members of people with aphasia who received the Aphasia ASK intervention would have significantly better outcomes on measures of impact of caregiving and mental health at 12 months post stroke than family members who received the attention control intervention (SSPIP).

In addition, people with aphasia who completed the attention control intervention (SSPIP) were hypothesized to have a significantly better score on a stroke risk-related behaviour measure compared to those who received the Aphasia ASK intervention.

## Secondary Outcome measures

## The secondary outcome for people with aphasia included a 10-item measure of self-reported stroke risk-related behaviours.

## Secondary outcomes for family members of people with aphasia were the impact of caregiving measured by the Bakas Caregiving Outcomes Scale Revised (BCOS) and mental health as measured by the General Health Questionnaire-28 item (GHQ).

## Summary of data collection

Participants with aphasia and family members were assessed pre intervention (Ax1) and at follow-up (Ax2) by a blinded assessor.

Outcomes targeting the person with aphasia were measured with the following:

Assessment for Living with Aphasia (ALA)

The ALA is a self-rated aphasia-friendly assessment of the impact of aphasia on a person’s life including mood and quality of life. It is based on the Living with Aphasia: Framework for Outcome Measurement (A-FROM) framework (Kagan et al., 2008), an adaptation of the World Health Organization's International Classification of Functioning, Disability, and Health for people with aphasia. The ALA is psychometrically sound, with analysis of 101 participants indicating good inter-rater reliability and internal consistency (ICC 0.86; Cronbach alpha 0.85). The ALA has significant correlations with the Stroke & Aphasia Quality of Life - 39 (r = 0.721, p<0.001), Visual Analogue Self-Esteem Scale (r=0.617 p<0.032) and Burden of Stroke Scale - Communication-Associated (r= 0.689, p<0.008)( Simmons-Mackie et al., 2014).

Stroke Aphasic Depression Questionnaire (SADQ-21)

The SADQ-21 is completed by a patients’ carer, based on his/her observations of behaviour. Items such as “Does he/she avoid eye contact when you talk to him/her?” are rated across 4 levels from ‘Often’ (rated 3) to ‘Never’ (rated 0). Scores range from 0 to 63. Bennet et al 2006 concluded that the SADQ 21 is a valid and reliable observational screening measure of depressive symptoms for stroke patients. At a recommended a cut off of 18 or more for the presence of depression (sensitivity = 1.0 and specificity = 0.81 Bennet et al., 2006).

Self-reported stroke risk-related behaviours

The secondary outcome for people with aphasia included a 10-item measure of self-reported stroke risk-related behaviours. Both ideal (e.g., taking medication as prescribed) and non-ideal behaviours (e.g., smoking cigarettes) were measured with higher scores out of 10 obtained indicating performance of more ideal behaviours (Eames et al., 2014).

Outcome Assessments for family members

Outcomes targeting the family members of the person with aphasia were measured with the following measures:

Bakas Caregiver Outcomes Scale - Revised.

The Bakas Caregiver Outcomes Scale (BCOS) is a 15-item scale measuring life changes as a result of caregiving, including emotional well-being, ability to cope with stress, physical health and self-esteem. Internal consistency (alpha = 0.90) and test-retest reliability (ICC = 0.66; 95% CI = 0.42-0.81) was satisfactory. Criterion-related validity was supported by correlations with the SF-36 (r = 0.32, p < .001) and a criterion variable measuring how caregivers' lives had changed (r = 0.67, p < .001) (Bakas et al., 2006).

General Health Questionnaire (GHQ-28)

The General Health Questionnaire (GHQ) is a measure of current mental health. The scale asks whether the respondent has experienced a particular symptom or behaviour recently. The GHQ screens for non-psychotic psychiatric disorders. This self-administered questionnaire focuses on two major areas: 1) the inability to carry out normal functions and 2) the appearance of new and distressing phenomena. GHQ-28 has 28 items to assess somatic symptoms, anxiety and insomnia, social dysfunction and severe depression (Goldberg, 1979).

## In summary, this table outlines the participant group and the primary and secondary outcomes

|  |  |  |
| --- | --- | --- |
| Participant group | Primary outcome | Secondary outcome  |
| People with aphasia | Stroke Aphasic Depression Questionnaire- 21 item (SADQ-21) and Assessment for Living with Aphasia (ALA).  | Self-reported stroke risk-related behaviours  |
| Family members | N/A  | Bakas Caregiving Outcomes Scale Revised (BCOS)General Health Questionnaire-28 item (GHQ) . |

## Sample size

Sample size calculations were calculated for both primary outcome measures (ALA and SADQ-21). Power calculations on the ALA were calculated from an intensive aphasia treatment study [Rodriguez et al., 2013] and an Australian longitudinal aphasia study [[Worrall](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4802646/#CR27) et al., 2016]. Power calculations on the SADQ21 were calculated from the Cost analysis of the Communication and Low Mood (CALM) study [Thomas et al., 2013]. The ALA required a larger sample size compared to the SADQ-21, and therefore, the larger sample size required by the ALA was determined necessary to adequately power the study. To achieve a power of 80 % with a 5 % level of significance in comparing the two arms of the study (Aphasia ASK versus attention control - SSPIP), we needed 186 patients (93 per arm) with an effect size of 0.367, computed using ALA data (26, 27). The extent to which power was diminished by clustering was considered in relation to the design effect (DE) = 1 + (m -1) r10, where m = the average size of a cluster and r is the intra-class correlation coefficient. Typically, intraclass correlation coefficients are small (<0.02); thus a conservatively estimated intra-class correlation of 0.02 was used. A cluster size of 20 was chosen based on the feasibility of running the intervention, as well as the availability of patients with aphasia within clusters. Thus DE = 1+ (20-1)\*0.02 = 1.38, and the total sample size required was calculated as 186 \* 1.38 ≈ 258. To account for an attrition rate of 25 % to the 12-month follow-up period, 344 patients would be needed (172 per arm).

## Participants

Participants were people with aphasia who were within the first 6 months following a stroke and their family member(s). The diagnosis of aphasia was based on a qualified speech-language pathologist’s clinical judgement and their administration of the Western Aphasia Battery-Revised [23]. Potential participants with aphasia and their family members were included if they were older than 18 years of age, had sufficient English language to participate without a translator, and had adequate hearing and vision levels to participate as judged by the treating speech pathologist. People with aphasia and their family member(s) were excluded if they have concomitant progressive neurological conditions (for example, dementia) or a concurrent medical condition impacting on their mental health (for example, cancer) as confirmed by self-report. There were no other inclusion or exclusion criteria for family member participants. People with aphasia must have presented with their first incidence of post stroke aphasia and were excluded for the following reasons: 1) aphasia as an etiology other than stroke, 2) a history of recurrent depression (that is, three or more previous diagnosed episodes defined as needing to see a health practitioner for treatment - either psychotherapy or medication prescribed, confirmed by self-report), 3) a current psychiatric diagnosis (for example, depressive disorder or anxiety disorder confirmed by medical record), 4) current depressive symptoms upon screening with the Stroke Aphasic Depression Questionnaire Hospital Version-10 [17] (score of 9 or more) or The Depression Intensity Scale Circles [24] (score of 3 or more), 5) receiving treatment in a psychiatric setting, or 6) enrolled in other aphasia or depression treatment studies.

To increase the low rate of recruitment early in the study, the above-mentioned criteria changed during the trial. The following changes were made:

* If the screening date was on or after the 14.11.2016 the selection criteria about existing aphasia no longer applied
* If the screening date was on or after the 13.02.2017 the selection criteria about previous depression history no longer applied
* If the screening date was on or after the 13.02.2017 there was an increase to the cut-off score for entry into the study on our depression screening tool SADQH-10 from 9 to 12. In other words, people who score 11 or less on the SADQ-H were eligible to enter the study

## Study settings

The inclusion criterion for clusters was that they must have provided aphasia rehabilitation services, with the capacity to provide services over the period of intervention. Clusters were excluded if participants were enrolled in other clinical trials at the time of randomization, which limited the recruitment capacity and/or conflict with the intervention requirements of the current trial. Each Health Service District provided either the experimental or the attention control intervention to a maximum of 20 people with aphasia plus their family members.

## Randomisation

A factor that had the potential to affect the outcome of this study was the level of psychological services provided to patients in each cluster. A National Stroke Foundation Rehabilitation Services Report (2012) indicated that lower levels of psychological care might be provided to patients with stroke in non-urban areas in Australia. Hence, clusters were selected in a way such that they represented either urban (capital city) or non-urban (regional/rural) areas. Considering a cluster size of 20, the required sample size of N = 344 (see sample size estimates for details) was predicted to be achieved from 18 clusters (nine per arm, with five in urban and four in non-urban clusters). However, 20 clusters were recruited to account for the potential of cluster attrition during the study. See Table [1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4802646/table/Tab1/) for how the 20 clusters were stratified. Randomization occurred using a computer-generated random number scheme.

### Table 1

Stratification of clusters

|  | **Experimental intervention** | **Attention control intervention** |
| --- | --- | --- |
| Urban clusters (n = 10) | five clusters | five clusters |
| Non-urban clusters (n = 10) | five clusters | five clusters |

Sequential numbers were assigned to each cluster within each stratum, and only the cluster numbers were sent to the trial statistician to ensure allocation concealment.

Interested health districts were considered as clusters for the trial. Randomisation of clusters into intervention and control groups was conducted by using computer generated random numbers. Of the 20 participating health districts, 10 were randomly allocated to study arm and 10 were allocated to study arm 2.

## Blinding

People with aphasia, their family members, and outcome assessors were blinded to the study design and treatment allocation (that is, they were not informed that there were two arms to the study). The speech-language pathologists who completed the outcome assessments were different from the treating therapists. Unblinding of the outcome assessors did not result in the discontinuation of a participant’s involvement in the study. Attempts were made to replace the outcome assessor if unblinding occurred and re-administration of any unblinded assessments occurred. The statistician who completed the data analyses was also blinded to group allocation until the analysis was completed.

## Statistical methods

Baseline characteristics of participating patients of the two groups were presented and compared for any clinically meaningful differences at baseline and any variables considered to be significantly different were further evaluated for their influence (e.g., included as covariates in statistical analyses) on outcomes as potential confounding effects. Outcomes of interest were analysed on an intention to treat basis. In the event of a non-normally distributed continuous outcome, a suitable transformation (e.g., log) was implemented to make the outcome variable normal. A multilevel mixed-effects model, that took into account patients being nested within hospital clusters, was able to examine whether changes in the outcomes of interest varied over time as well as across the two groups (ASK and attention control program), after adjusting for the effects of any potential confounders (if any). The model included fixed effects for treatment group, time-point and the treatment-by-time-point interaction. Covariates included in the modelling include age, gender, educational level, change in living situation during the intervention, discontinuation of usual care speech pathology services during the intervention period, walking status at the start of the intervention, baseline severity of aphasia during the intervention. These covariates were chosen based on literature indicating the major predictors of depression after stroke include gender, severity of stroke (Laures-Gore et al 2020), physical disability (Kutlabaev & Hackett 2014) and more severe impairment at 12 months post-stroke (Kauhanen et al 2000) and discontinuation of rehabilitation services (Almhdawi et al., 2020). Collinearity of the covariates was assessed before including them in the multivariable modelling. In addition, attrition pattern across the two groups was examined to determine randomness of missing data and, if required, multiple imputation was implemented. In the assessment of the hypotheses, missing data were assumed as missing at random (MAR), which was assessed with a missing data sensitivity analysis. The residuals of the fitted models were examined to ensure that all required assumptions were met. An alpha level of 0.05 was accepted as significant. The results of the statistical models are presented in the form of odds ratios and their 95% confidence intervals. All statistical analyses were performed using Stata 14.0.

A per protocol analysis may occur considering individual participants’ completeness of primary outcome data as well as the dose and fidelity of the intervention received.

## Missing data handling

To describe the missing data, the frequency and percentage of people with aphasia with missing data at baseline and 12 months were summarised for the ALA, SADQ-21 and self-reported stroke risk-related behaviours. In addition, baseline and demographic characteristics were summarized for those with and without missing data for the ALA and SADQ-21 (at baseline and 12 months) to explore the missing data assumption and identify any variables not included in the target analyses that were potentially associated with missingness (known as auxiliary variables). A multiple imputation approach was used to handle missing data. This approach relies on the underlying assumption that the probability of missing outcome data is not related to the missing data but to some of the observed measured data in the model (Missing At Random [MAR]). This assumption was assessed with a reference-based sensitivity analysis approach. Logistic regression of the missing-data indicator for each imputed variable on other explanatory variables was used to test for associations.

## Approval

The final version of this statistical analysis plan was approved by the CI on 30th April, 2021.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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Table 1 – Characteristics of participants in the intervention and control group.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Control group (SSPIP) | Intervention group (ASK)  | All |
| Type of health district (n= ; % metropolitan) | 5, 25% | 5, 25% | 10 , 50% |
| Participants with aphasia (n= ) |  |  |  |
| Family member participants (n= ) |  |  |  |
| Severity of aphasia (WAB AQ. Mean SD Range)* Mild AQ >76
* Moderate AQ 51-75
* Severe AQ 26-50
* Very severe AQ <25
 |  |  |  |
| Sex (n= ; % female) |  |  |  |
| Age (mean, SD, Range) |  |  |  |
| Educational level (n= ; % completed Grade 12 or equivalent)  |  |  |  |
| Speaks language other than English (n= , % speaks a language other than English) |  |  |  |
| Employment status (n= ; % employed) |  |  |  |
| Living situation (n= ; % community) |  |  |  |
| Marital status* Married/de facto
* Widowed/divorced/separated
* Never married
 |  |  |  |
| Walking status (n= ; % independent)  |  |  |  |
| Time post stroke at start of intervention (Mean, SD, Range) |  |  |  |
| Stroke Aphasic Depression Questionnaire- 21 item (SADQ-21) Score range 0-63; higher scores = higher levels of depression.* Mean, SD, Range;
* (n= ;% not depressed SADQ<18)
 |  |  |  |
| Assessment for Living with Aphasia (ALA) Mean, SD, Range. Score range 0- 148. Higher scores = higher quality of life |  |  |  |
| Family members’ Bakas Caregiving Outcomes Scale Revised (BCOS) (Mean, SD, Range). Score range = 15-105. Higher scores = more positive caregiver outcomes. |  |  |  |
| Family members’ General Health Questionnaire-28 item (GHQ). (Mean, SD, Range) Score range 0-36 Higher scores = less desirable health outcomes |  |  |  |
| Self-reported stroke risk-related behaviours (Mean, SD, Range). Score range 0-10. Higher scores = better performance of ideal behaviours. |  |  |  |

Table 2 – Additional aphasia and psychosocial interventions (usual care)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Control group (SSPIP)** | **Intervention group (ASK)**  | **All** |
| Minutes of aphasia management (Mean, SD, Range) during intervention |  |  |  |
| Minutes of formal counselling by health professional (Mean, SD, Range) during intervention |  |  |  |
| Minutes of peer support group attendance (Mean, SD, Range) during intervention |  |  |  |
| Participation in specific manualised stroke or aphasia programs (n= , % yes)  |  |  |  |

Table 3 Primary and secondary outcome measures pre- and post intervention group comparison

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Primary outcome measures** | Control group (SSPIP) Pre-intervention | Control group (SSPIP) Post-intervention | Experimental group (ASK) Pre-intervention | Experimental group (ASK) Post intervention |
| Stroke Aphasic Depression Questionnaire- 21 item (SADQ-21) Score range 0-63; higher scores = higher levels of depression.* Mean, SD, Range;
* (n= ;% not depressed SADQ<18)
 |  |  |  |  |
| Assessment for Living with Aphasia (ALA) Mean, SD, Range. Score range 0- 148. Higher scores = higher quality of life |  |  |  |  |
| **Secondary outcome measures** |  |  |  |  |
| Self-reported stroke risk-related behaviours Score range 0-10. Higher scores = better performance of ideal behaviours. |  |  |  |  |
| Family members’ General Health Questionnaire-28 item (GHQ). Score range 0-36 Higher scores = less desirable health outcomes |  |  |  |  |
| Family members’Bakas Caregiving Outcomes Scale Revised (BCOS) Score range = 15-105. Higher scores = more positive caregiver outcomes. |  |  |  |  |

Table 4. Intervention characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | Aphasia ASK |  | SSPIP |
| Face to Face modules  |
| Your story n (%) |  | Stroke- what is it? n (%) |  |
| Living the learning n (%) |  | Stroke- What are the risk factors? n (%) |  |
| Finding the positive n (%) |  | Understanding medications for stroke prevention n (%) |  |
| Not just words n (%) |  | Lifestyle changes to prevent stroke n (%) |  |
| Stay connected n (%) |  | Develop an action plan to prevent stroke n (%) |  |
| Total number of modules completed (mean, SD, range) |  |  |  |
| Total face to face minutes (mean, SD, range) |  |  |  |
| Total phone call minutes (mean, SD, range) |  |  |  |
| Adhered to phone call f/u schedule (yes, %) |  |  |  |
| Met intervention fidelity (yes, %) |  |  |  |
| Met intervention dose (yes, %) |  |  |  |

Table 5. Adverse events and serious adverse events

|  |  |  |
| --- | --- | --- |
|  | SSPIP | Aphasia ASK |
| Adverse events |  |  |
| Serious adverse events |  |  |
|  0 |  |  |
|  1 |  |  |
|  2 |  |  |
|  >2 |  |  |
| Deaths |  |  |

Table 6 Results of multilevel regression modelling examining the effect of the experimental (ASK) versus attention control (SSPIP) interventions on outcomes.

|  |  |  |
| --- | --- | --- |
|  | Intention-To-Treat analysisβ (95% CI) p value | Per protocol analysis β (95% CI) p value |
| Type of intervention-ASK (Experimental group) -SSPIP (Attention Control group)  |  |  |
| Time point* Pre-intervention
* Post-intervention
 |  |  |
| Age  |  |  |
| Gender |  |  |
| Educational level |  |  |
| Change in living situation during the intervention |  |  |
| Discontinuation of usual care speech pathology services during the intervention period |  |  |
| Walking status at the start of the intervention |  |  |
| Baseline severity of aphasia during the intervention. |  |  |
| Individual level Primary outcomes measures-Assessment for Living with Aphasia (ALA)-Stroke and Aphasia Depression Questionnaire – 21 item (SADQ-21) |  |  |
| Secondary outcome measures-self reported stroke risk-related behaviours-Bakas Caregiver Outcome Scale (Revised) -General Health Questionnaire – 28 items (GHQ-28)  |  |  |
| Cluster level* Health Region
 |  |  |

β:regression coefficient; CI: Confidence interval

**CONSORT Flow Diagram**

Analysed (n= number of clusters) (x= number of participants)
 Excluded from analysis (n= number of clusters) (x= number of participants)

Analysed (n= number of clusters) (x= number of participants)
 Excluded from analysis (n= number of clusters) (x= number of participants)

Assessed for eligibility.

 (n=number of clusters)

(x=number of participants)

## Analysis

## Follow-Up

Allocated to ASK intervention (n= number of clusters) (x= number of participants)

 Received allocated intervention (n= number of clusters) (x= number of participants)

 Did not receive allocated intervention (n= number of clusters) (x= number of participants)

Allocated to SSPIP intervention (n= number of clusters) (x= number of participants)

 Received allocated intervention (n= number of clusters) (x= number of participants)

 Did not receive allocated intervention ((n= number of clusters) (x= number of participants)

## Enrollment

## Allocation

Excluded (n= number of clusters) (x= number of participants)

  Not meeting inclusion criteria (n= number of clusters) (x= number of participants)

  Declined to participate (n= number of clusters) (x= number of participants)

  Other reasons (x= number of participants)

Randomized (n= number of clusters) (n= number of participants)

Lost to follow-up (n= number of clusters) (x= number of participants)

Discontinued intervention (n= number of clusters) (x= number of participants)

* Withdrew consent (x= number of participants)
* Died (x= number of participants)

Lost to follow-up (n= number of clusters) (x= number of participants)

Discontinued intervention (n= number of clusters) (x= number of participants)

* Withdrew consent (x= number of participants)
* Died (x= number of participants)