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A randomized controlled trial of very early rehabilitation in speech after stroke

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Abstract

Rationale: The efficacy of rehabilitation therapy for aphasia caused by stroke is uncertain.

Aims and hypothesis: The Very Early Rehabilitation of Speech (VERSE) trial aims to determine if intensive prescribed aphasia therapy (VERSE) is more *effective* and *cost saving* than non-prescribed, intensive (usual care-plus) and non-intensive usual care (UC) therapy when started within 15 days of stroke onset and continued daily over four weeks. We hypothesize that aphasia therapy when started very early after stroke and delivered daily could enhance recovery of communication compared with UC.

Sample size estimates: A total of 246 participants (82 per arm) will provide 80% power to detect a 4.4% improvement on aphasia quotient between VERSE and UC plus at a significance level of $\alpha = 0.05$.

Setting: Acute-care hospitals and accompanying rehabilitation services throughout Australia, 2014–2017.

Design: Three-arm, prospective, randomized, parallel group, open-label, blinded endpoint assessment (PROBE) trial.

Participants: Acute stroke in previous 14 days and aphasia diagnosed by aphasia quotient (AQ) of the Western Aphasia Battery (WAB).

Randomization: Computer-generated blocked randomization procedure stratified by aphasia severity according to Western Aphasia Battery, to one of three arms.

Intervention: All participants receive UC—usual ward-based aphasia therapy. *Arm 1:* UC—no additional therapy; *Arm 2*: UC-plus usual ward-based therapy; *Arm 3:* VERSE therapy—a prescribed and structured aphasia therapy program. Arms 2 and 3 receive a total of 20 additional sessions (45–60 min, provided daily) of aphasia therapy. The additional intervention must be provided before day 50 post stroke.

Study outcome measures: The aphasia quotient of Western Aphasia Battery at 12 weeks post stroke. Secondary outcomes include discourse measures, the Stroke and Aphasia Quality of Life Scale-39 and the Aphasia Depression Rating Scale at 12 and 26 weeks.

Economic evaluation: Incremental cost-effectiveness ratios at 26 weeks will be reported.

Discussion: This trial is designed to test whether the intensive and prescribed VERSE intervention is effective in promoting maximum recovery and preventing costly health complications in a vulnerable population of survivors of stroke. It will also provide novel, prospective, aphasia specific cost-effectiveness data to guide future policy development for this population.

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Introduction and rationale

Aphasia affects approximately a third of the 440,000 individuals living with stroke in Australia.[1] Recovery from aphasia is highly variable with multiple factors believed to contribute to the overall extent of communication recovery achieved by each individual.[2] There are currently few available specific medical treatments designed to reduce the impacts of aphasia occurring as a consequence of stroke; therefore, aphasia rehabilitation is the mainstay of recovery for people with aphasia.

Early aphasia rehabilitation is thought to enhance the natural processes of spontaneous recovery by strengthening neural networks through the use of highly repetitious, task-specific behaviors that require coinciding neuronal firing of a group of connected neurons.[3] These behaviors are believed to minimize independent neuronal activation that may produce maladaptive behaviours.[3]

The 2012 Cochrane Review examined 39 trials of aphasia therapy following stroke and found no Level 1 evidence[4] for the efficacy of aphasia treatments in the long term. There was *some* evidence that speech and language therapy (SLT) was more effective than no SLT; however, caution is required when interpreting the Cochrane Review[4] results as many studies were comparative in nature, lacked adherence to the CONSORT statement[5] and demonstrated inferior design quality.[4] Additionally, little is known about the costs of available treatment options.

Aims and hypotheses

VERSE aims to determine if intensive aphasia therapy provides greater efficacy and is at least cost-effective when compared to usual ward-based rehabilitation (usual care (UC)) at 12 weeks post stroke, when therapy is commenced within the first 15 days post stroke. Aphasia therapy in this trial refers to direct impairment-based aphasia treatment in contrast to other communication therapy, case-management, patient/family counselling and education.

Our primary hypothesis is that compared to UC, early intensive aphasia therapy will result in improved communication ability, determined by at least a 20% greater score on the aphasia quotient (AQ) of the Western Aphasia Battery (WAB)[6] at 12 weeks post stroke.

Secondary hypotheses

1. VERSE aphasia therapy will result in a 4.4% greater score on the AQ when compared to UC-*plus* aphasia therapy at 12 and 26 weeks post stroke.
2. Very early intensive aphasia therapy will result in better quality of life using SAQol—39 at 12 and 26 weeks post stroke than UC control.
3. Very early intensive aphasia therapy will be more cost-effective than UC at 26 weeks post stroke.

VERSE is a three-armed prospective, single-blinded multicenter, randomized controlled trial with primary outcome 12 weeks and follow-up at 26 weeks post stroke (see Figure 1) and intention to treat analysis.

Patient population

Approximately 16 acute care hospitals and related rehabilitation services in Australia and New Zealand will be involved. Participants include acute stroke patients (>18 years) with aphasia (AQ score < 93.7) who are otherwise medically stable, who provide consent, and are assessed and randomized by the baseline assessor within 14 days of stroke. See Table 1 for inclusion and exclusion criteria.

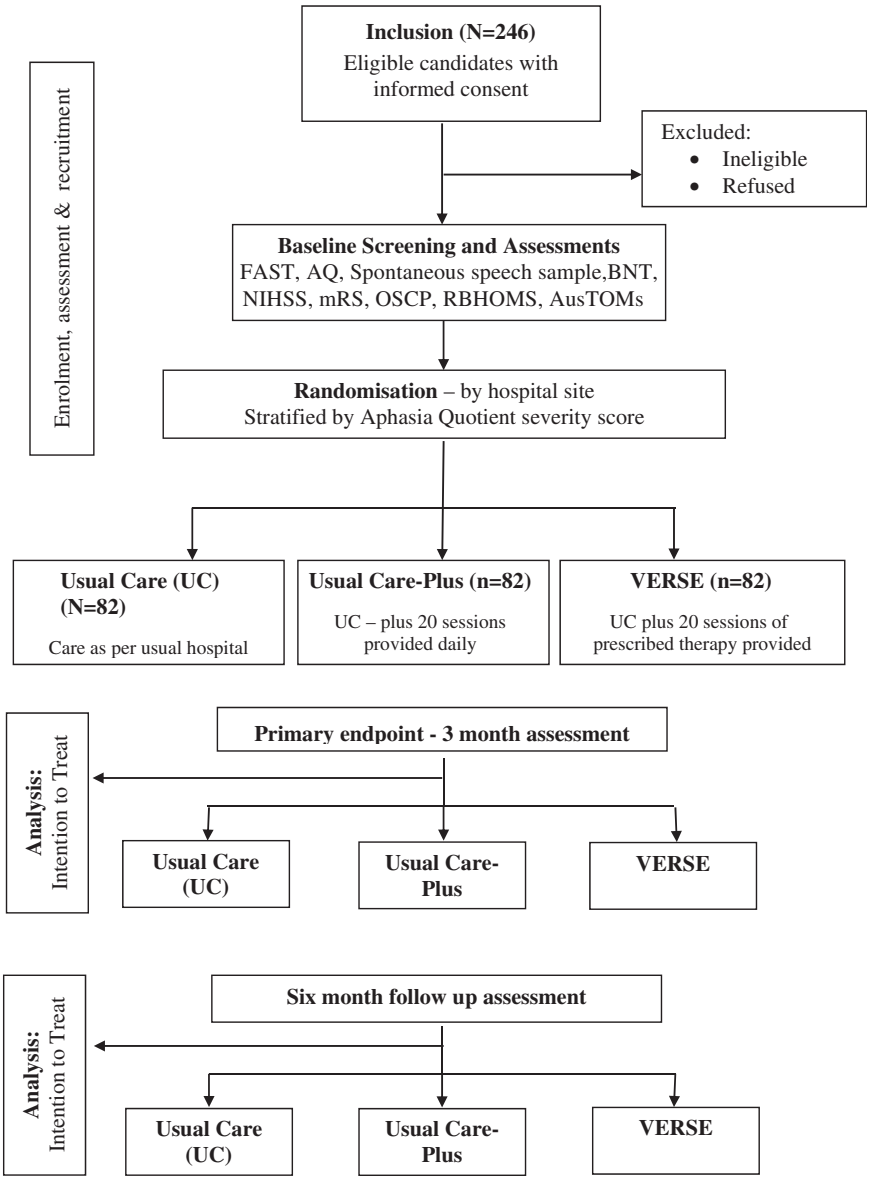
Methods

The intervention is provided by qualified and trained speech pathologists for a maximum of 25 working days, commencing the day after baseline assessment and randomization. Intervention and assessments are outlined in the Schedule of Assessments. (see Table 2). Participants and families in addition to staff not involved in providing the intervention to participants are blinded to group allocation.

Randomization

Participants are stratified by baseline aphasia severity, (AQ scores mild: 62.6–93.7, Moderate: 31.3–62.5 and severe: 0–31.2) and then randomized to one of three groups. The randomization schedule was created by an independent statistician, using a computer-generated permuted blocked procedure and allocation ratio of 1:1:1. Participants are randomized via a web-based electronic data collection system (REDCap™).[7]

Figure 1. CONSORT Flow diagram of the VERSE trial.



Intervention

ARM 1: UC

Participants will receive UC alone. UC speech pathologists will be responsible for all speech pathology services including case management, education, counselling and any co-occurring dysphagia management for all trial participants. We have anticipated the intensity of UC direct aphasia therapy to be *less than 6 hours in total* based on our previous work.[6,8]

ARM 2: Usual care-plus

In addition to usual care, the usual care-plus (UC-plus) group will receive aphasia therapy that is determined by the treating therapist; at the prescribed regimen:

a. between 45 and 60 min of 1:1 therapy 5 days per week for 20 sessions (15–20 h) (within a maximum of 25 working days).
b. a minimum of 3 and a maximum of 5 sessions per week.

Table 1. Eligibility criteria

Inclusion criteria
Patients over the age of 18 with acute stroke and resultant acute aphasia of any type (ICD-10 codes 161–164, i.e. no TIA, SAH or SDH)
A score of less than 93.7 of the Aphasia quotient.
Patients who are deemed medically stable at recruitment.
Patients with the ability to maintain a wakeful alert state for 30 consecutive minutes within 14 days of stroke onset.
Patients with normal or corrected hearing and vision.
Patients with informed consent obtained by participant or person responsible.
Exclusion criteria
Patients will be excluded from the study if they have any of the following:
Pre-existing aphasia at the time of enrollment.
Patients who have suffered a head injury, have had or require neurosurgery (clot retrieval.
surgery is not an exclusion if patient is stable post operatively and meets the above criteria).
Pre-existing clinical diagnosis of dementia.
Clinical diagnosis or treatment of major depression at time of enrollment.
Concurrent progressive neurological disorders.
Patients unable to participate in English-based therapy due to English being a second language.
Participation in other intervention trials without prior approval from VERSE trial manager.

ARM 3: VERSE therapy

The VERSE aphasia therapy intensity and timing of commencement of intervention will match the UC-plus group; however, the VERSE treatment is prescribed by an Intervention Protocol provided only to the trained VERSE therapists and is designed for all aphasia types and severity levels.

Therapists complete a daily therapy log in an electronic Case Report Form (eCRF) REDCap[7] for each participant including content, duration and frequency of all therapy sessions. UC-plus and VERSE sessions will be video recorded, monitored and cross-referenced with information provided in the eCRF. Deviations from the VERSE protocol will be addressed with the clinician.

Required study assessments and the assessment timeline are outlined in Table 2.

All outcome assessments will be carried out by qualified and study-trained speech pathologists who are independent blinded assessors. Information relating to resource utilization will be obtained from the participant.

Participants will be assessed for adverse events (AEs) throughout this trial. All AEs reported during the intervention period (between consent and 50 days post stroke), will be reported. AEs that relate to the new diagnosis or worsening of clinical depression will be reported up to week 26.

AEs that meet the criteria for serious adverse events will be reported for the duration of the project. Trial therapists and blinded assessors staff will identify and report events and reviewed by a medical monitor and independent Data Safety Monitoring Committee.

Primary outcome

The primary outcome is the AQ score of the WAB assessed by a blinded assessor at 12 weeks post stroke. The WAB is considered a reliable measure of severity of language impairment and is sensitive to change.[6]

Secondary outcomes

These are assessed by a blinded assessor and include; AQ score, cost-related health questionnaire, health related Quality of life as determined by SAQoL-39[9] at 12 and 26 weeks.

Resource Utilization

Participant provided services will be collected at 12 and 26 weeks by the blinded assessor. A standard protocol is

Table 2. Schedule of assessment

Assessment	Baseline	Treatment	Follow-up post stroke	
	Between day 2 and day 14 post stroke	Day after baseline (4-5 weeks)	Week 12 12 weeks (±7 days)	Week 26 26 weeks (±7 days)
Screening/eligibility	X[1]			
Frenchay aphasia screening test (FAST)[12]	X[1]			
Consent	X[1]			
Western aphasia battery (AQ)[6]	X[2]		X[5]	X[5b]
Randomization	X[1]			
Demographics	X[1]			
Medical history	X[1]			
NIHSS[8]	X[1]			
mRS[10]	X[1]			
RBHOMB[13]	X[1]			
Oxfordshire classification (OCSP)[14]	X[1]			
Clock drawing/Cog test	X[1]			
Boston naming test (BNT)[15]	X[2]		X[5b]	X[5b]
Discourse collection[16]	X[2]		X[5b]	X[5b]
Intervention and recording of therapy		X[3 or 4]		
Stroke and Aphasia Quality of life Scale (SAQoL-39)[9]			X[5b]	X[5b]
Aphasia depression rating scale[17]			X[5b]	X[5b]
Resource utilization			X[5]	X[5]
Patient diary provided		X[3 or 4a]	X[5]	
Adverse events		X[3]	X[5]	X[5]
Serious adverse events		X[3]	X[5]	X[5]

X[1]: person screening and enrolling the subject. May be X[2]; X[2]: Trained speech pathologist; X[3]: Usual care speech pathologist (UC and UC plus); X[4]: VERSE therapist; X[5]: Blinded assessor.
[a]Diary provided on last day of therapy with treating speech pathologist. This may be on discharge from the acute ward or as late as day 50.
[b]Secondary outcome measure.

used to collect these data for all participants. Information will be used to estimate the cost effectiveness of VERSE therapy compared to UC and UC-plus. Amount and type of inpatient and outpatient rehabilitation, length of acute hospital stay, discharge destination, hospital readmissions, general practitioner visits, community and health care service use, medication use, respite and informal care services and any speech and communication aids/devices changes in employment status and services utilized as a result of the stroke will be collected.

Sample size

A sample of 246 participants will provide 80% power to detect this difference at a (two-tailed) significance level of $\alpha = 0.05$, after adjusting for 5% non-adherence and a loss to analysis of 12% (due to death and dropout).

Statistical analysis

An intention-to-treat analysis will be used. A secondary per protocol analysis will explore dose-related differences in the primary outcome.

Primary analysis

This will be a between-group comparison of recovery on AQ at 12 weeks. A generalized estimating equations model will be developed to analyze difference in recovery between groups. Differences in baseline AQ scores and baseline National Institute of Health Stroke Scale (NIHSS)[8] will be included as covariates in the model. The intervention effect will be represented as the difference in percent of maximal potential recovery achieved.

Secondary analyses

The generalized estimating equations model developed for the primary analysis will also examine differences in recovery on AQ between the three groups (VERSE, UC-plus and UC) and to assess whether these differences are sustained at 26 weeks.

A generalized estimating equations model will be developed to analyze differences between the three groups (VERSE, UC-plus and UC) in recovery of connected speech (discourse measures) at 12 weeks and 26 weeks. Baseline AQ scores and baseline modified Rankin Score,[10] will be controlled for by including these as covariates in the model. The intervention effect will be represented as the difference in amount of connected speech.

A generalized estimating equations model will be used to determine the effect of intervention group on Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39)[9] scores at 12 and 26 weeks post stroke, adjusting for known confounding variables (e.g. age, gender, NIHSS,[8] mRS[10]).

Resource utilization will be captured using a standardized approach from a societal perspective with the main focus on the health sector. This will include out-of-pocket costs to patients and family members and workforce impacts. Incremental cost-effectiveness ratios will be reported as costs per unit improvement in AQ-score and per occurrence of depression (medically diagnosed and treated and/or an ADRS score of 9 and above) avoided at 26 weeks post stroke. Societal perspective costs will include government as third party payer, costs to patients and carers/family members and limited costs to other sectors. Probabilistic multivariable analysis will be conducted to account for variability around the point estimates and results will be reported as medians (95% uncertainty intervals) using @RISK software (Palisade Corporation).[11]

Discussion

This trial is designed to test whether the intensive and prescribed VERSE intervention is effective in promoting maximum recovery and preventing costly health complications in a vulnerable population of survivors of stroke. It will also provide novel, prospective, aphasia specific cost-effectiveness data which may be used to improve resource allocation and policy development in acute and subacute hospital settings for very early aphasia intervention. Since the trial commenced recruitment, 109 patients have been enrolled from 14 hospitals.

Authors' contributions

EG, EA, TR, SM, NC, MR, AW, AH, GH, DC and JB secured funding for the trial. EG, EA, JB, TR, SM, AH conceived and developed the study. EG and FE drafted the main protocol with input from all. EG and FE coordinate the ongoing study. TR and DC developed the statistical and economic evaluation protocols for the study, respectively. EG, EA, NC, AH, MR, AW and FE developed and drafted the VERSE intervention protocol. GH provided medical input to the protocol development, ongoing medical advice and oversees the AEs adjudication.

Declaration of conflicting interests

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Registration

Australasian Clinical Trials Register (number: 12613000776707).

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