Title: Constraint-induced **o**r **M**ulti-modal **p**ersonalised **a**phasia **re**habilitation (COMPARE): A randomised controlled trial for stroke related chronic aphasia

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Word count: 1965

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Abstract

Rationale: The comparative efficacy and cost-effectiveness of constraint-induced and multi-modality aphasia therapy in chronic stroke are unknown.

Aims and hypotheses: In the COMPARE trial we aim to determine whether Multi-Modal Aphasia Treatment (M-MAT) and Constraint-Induced Aphasia Therapy Plus (CIAT-Plus) are superior to usual care (UC) for chronic post-stroke aphasia. Primary hypothesis: CIAT-Plus and M-MAT will reduce aphasia severity (Western Aphasia Battery-Revised Aphasia Quotient [WAB-R-AQ]) compared with UC: CIAT-Plus superior for moderate aphasia; M-MAT superior for mild and severe aphasia.

Sample size estimates: 216 participants (72 per arm) will provide 90% power to detect a 5-point difference on the WAB-R-AQ between CIAT-Plus or M-MAT and UC at $\alpha = 0.05$.

Methods and design: Prospective, randomized, parallel group, open-label, assessor blinded trial. Participants: Stroke >6 months; aphasia severity categorised using WAB-AQ. Computer-generated blocked and stratified randomization by aphasia severity (mild, moderate, severe), to 3 arms: CIAT-Plus, M-MAT (both 30 hours therapy over 2 weeks); UC (self-reported usual community care).

Study outcomes: WAB-R-AQ immediately post intervention. Secondary outcomes: WAB-R-AQ at 12-week follow-up; naming scores, discourse measures, Communicative Effectiveness Index, Scenario Test, and Stroke and Aphasia Quality of Life Scale-39g immediately and at 12 weeks post intervention; incremental cost-effectiveness ratios compared with UC at 12 weeks.

Discussion: This trial will determine whether CIAT-Plus and M-MAT are superior and more cost-effective than UC in chronic aphasia. Participant subgroups with the greatest response to CIAT-Plus and M-MAT will be described.

Key words
Aphasia therapy, stroke, multimodal, constraint, intensity, rehabilitation, randomised controlled trial

Introduction and rationale:

Aphasia, an acquired language disability, impacts understanding speech, reading, writing, and speaking. Aphasia affects one third of stroke survivors[1,] with significant negative impacts on mental health[2] and quality of life[3]. People with stroke-aphasia vary widely in aphasia type and severity, and co-morbid cognitive impairments. This variability has underpinned the development of a range of aphasia treatments. In the recent Cochrane review, analysis of 57 aphasia therapy trials revealed statistically significant treatment effects for functional communication, reading, writing, and expressive language[4]. Significant benefits were found for high intensity, high dose, or long duration interventions, although these schedules had a larger drop-out rate[4]. Benefits were not maintained at 3-6 month follow-up[4]. The review results are limited by small numbers of randomized participants and inferior study quality. Recently, Breitenstein et al. compared intensive language therapy (30 hours over 3 weeks) to usual care in 156 people with chronic (>6 months) post-stroke aphasia and found significantly improved verbal communication (*d-0.58)* immediately post-intervention and at 6-month follow-up[5].

Constraint-Induced Aphasia Therapy (CIAT) is an intensive, high-dose intervention aimed at improving verbal output in a group setting of 2-3 patients[6]. CIAT assumes that people with aphasia experience a worsening of symptoms through non-use of language and a reliance on nonverbal communication (e.g., gesture, drawing). Therefore, CIAT focuses on speaking activities and nonverbal communication is discouraged. CIAT-Plus is an enhanced protocol including written cues and home practice[6].

Multi-Modality Aphasia Therapy (M-MAT) also aims to improve verbal output but specifically utilises nonverbal strategies[7] that may be useful if speaking fails after treatment. Evidence from a pilot study[7] and a systematic review[8] suggest CIAT-Plus and M-MAT may be equally efficacious. However, high quality comparative-effectiveness evidence is required to refine treatment prescription and describe potential cost-effectiveness.

Methods:

The aims of the COMPARE trial are to determine whether CIAT-Plus and M-MAT are superior to usual care (UC) for people with chronic aphasia and determine if CIAT-Plus or M-MAT are superior for particular subgroups. The primary hypothesis is that compared to UC, both CIAT-Plus and M-MAT will result in reduced aphasia severity (≥5-point improvement on the Western Aphasia Battery-Revised Aphasia Quotient (WAB-R-AQ))[9] immediately post intervention. CIAT-Plus is predicted to be superior for moderate aphasia and M-MAT superior for both mild and severe aphasia[7]. The potential cost-effectiveness of these interventions over UC is assessed.

Design:

COMPARE is a three-armed prospective, single-blinded multicenter, randomized controlled trial with primary outcome immediately following treatment and follow-up 12 weeks after treatment (see Figure 1) with an intention-to-treat analysis. The protocol is aligned with the CONSORT extension for non-pharmacologic interventions[10], is registered with the Australian and New Zealand Clinical Trials

Registry (12615000618550), and has ethics approval from La Trobe University, Gold Coast University Hospital (Queensland, Australia), and each participating hospital site's ethics committee.

Figure 1 about here

Patient population - inclusion and exclusion criteria:
Stroke >6 months; aphasia severity categorised using WAB-R-AQ. See Table 1 for full details.

Table 1 about here

Randomisation:
Each participant is assessed for baseline aphasia severity, (WAB-R-AQ mild= 93.7-62.6; Moderate= 62.5-31.3; Severe< 31.2) and allocated to a group of 2-3 participants with the same severity level. Each group is randomized to one of three arms. The randomization schedule was created by an independent statistician, using a computer-generated permuted blocked procedure and allocation ratio of 1:1:1.

Intervention:
CIAT-Plus and M-MAT interventions are provided by qualified, study-trained speech pathologists for 3 hours per weekday for 2 weeks (30 hours) with 15-minute daily home practice tasks monitored via written log/carer report. All assessment staff are blinded to group allocation.

Arm 1: UC
The UC control group undergo aphasia therapy at the type and frequency available in the community at the time of recruitment and randomisation (estimated at <2 hours/week). Participants keep a study-specific diary of therapy activity.

Arm 2: CIAT-Plus
In CIAT-Plus, participants produce functional words, phrases and sentences in response to pictured object and action cards in communication games. Visual barriers between participants discourage non-verbal communication. Therapists cue and shape verbal responses, providing verbal models to repeat and written words for participants to read aloud. As performance improves, participant responses are progressively shaped from single words (e.g., "Coffee?") to elaborated sentences (e.g., "John, do you want a large, black coffee?").

Arm 3: M-MAT
M-MAT also involves communication game activities, in a group setting, but there are no visual barriers, and participants have access to pen and paper. Therapists cue and shape verbal *and* multimodal responses from participants involving gestures, written words, simple drawings, and verbal repetitions of the targets.

Therapists complete daily therapy logs (REDCap[11] Case Report Form) for each participant, including content and duration of therapy sessions, nature of home exercise, and self-reported fatigue or distress. CIAT-Plus and M-MAT sessions are video recorded and monitored. Protocol deviations are addressed with the therapist

and documented in REDCap.

Primary outcome:
Required study assessments with timelines are outlined in Figure 1. The primary outcome is the WAB-R-AQ score assessed by a blinded assessor immediately post-intervention. The WAB-R-AQ is a reliable measure of language impairment, is sensitive to change, and forms a recommended core outcome for aphasia intervention trials[9,12].

Secondary outcomes:
Secondary outcomes include: aphasia severity (WAB-R-AQ[9] score at 12-week follow-up); health related quality of life (SAQoL-39[13], EQ-5D-3L[14]), multimodal communication (Scenario Test[15]) and functional communication (Communication Effectiveness Index[16]) immediately and at 12 weeks post-intervention. A resource use and cost questionnaire is collected at 12 week follow-up.

Data monitoring body:
Participants are monitored for adverse events (AEs) throughout this trial. AEs relating to a new diagnosis or worsening of clinical symptoms are reported up to the follow-up assessment. An independent Data Safety Monitoring Committee reviews safety data annually (or earlier if necessary).

Sample size estimates:
After adjusting for the clustering effect of group therapy, 216 participants will provide 90% power to detect a 5-point difference on the WAB-AQ at $\alpha = 0.05$.

Statistical analyses:
Separate Linear Mixed Models (LMMs) will be used to analyse differences between M-MAT and UC, and CIAT-Plus and UC on each outcome measure immediately and at 12 weeks post-intervention. The LMM for WAB-R-AQ will assess the differences in efficacy between M-MAT and CIAT-Plus. All analyses will control for baseline aphasia severity (fixed effect) and for the clustering effect of treatment groups (random effect). Details will be published in a formal statistical analysis plan, prior to trial completion.

Economic evaluation
Resource utilisation is captured using a standardized approach from a societal perspective with the main focus on the health sector and costs to individuals. Costs involved in the organisation and delivery of the intervention are included. Incremental cost-effectiveness ratios will be reported as the net cost per unit improvement in the primary and secondary outcomes. Sensitivity and uncertainty analyses will be undertaken.

Study organization and funding:
The COMPARE trial is managed by the management committee comprising all chief investigators and trial managers and supported by a National Health and Medical Research Council Project grant (#1083010).

Summary and conclusion:
COMPARE is the first trial to assess the comparative efficacy of constraint induced

and multi-modal aphasia therapies for chronic post-stroke aphasia. Results will enable more effective treatment prescription. Cost-effectiveness information will provide support for business cases in adapting current management practice and policy for chronic aphasia. Since trial commencement, 135 participants have been randomized.

Authors' contributions:
MR, DC, LN, LT, EG and MM secured funding for the trial and with DAC, JK, AF, MC, and MH conceived and developed the study. MR and MH drafted the main protocol with input from all. MR, MH and MC coordinate the ongoing study. TR wrote the statistical protocol, and DAC and JK the economic protocol. MR, DC, LN, LT, MM, EG, AF, MH and MC developed and drafted the COMPARE intervention protocol.

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

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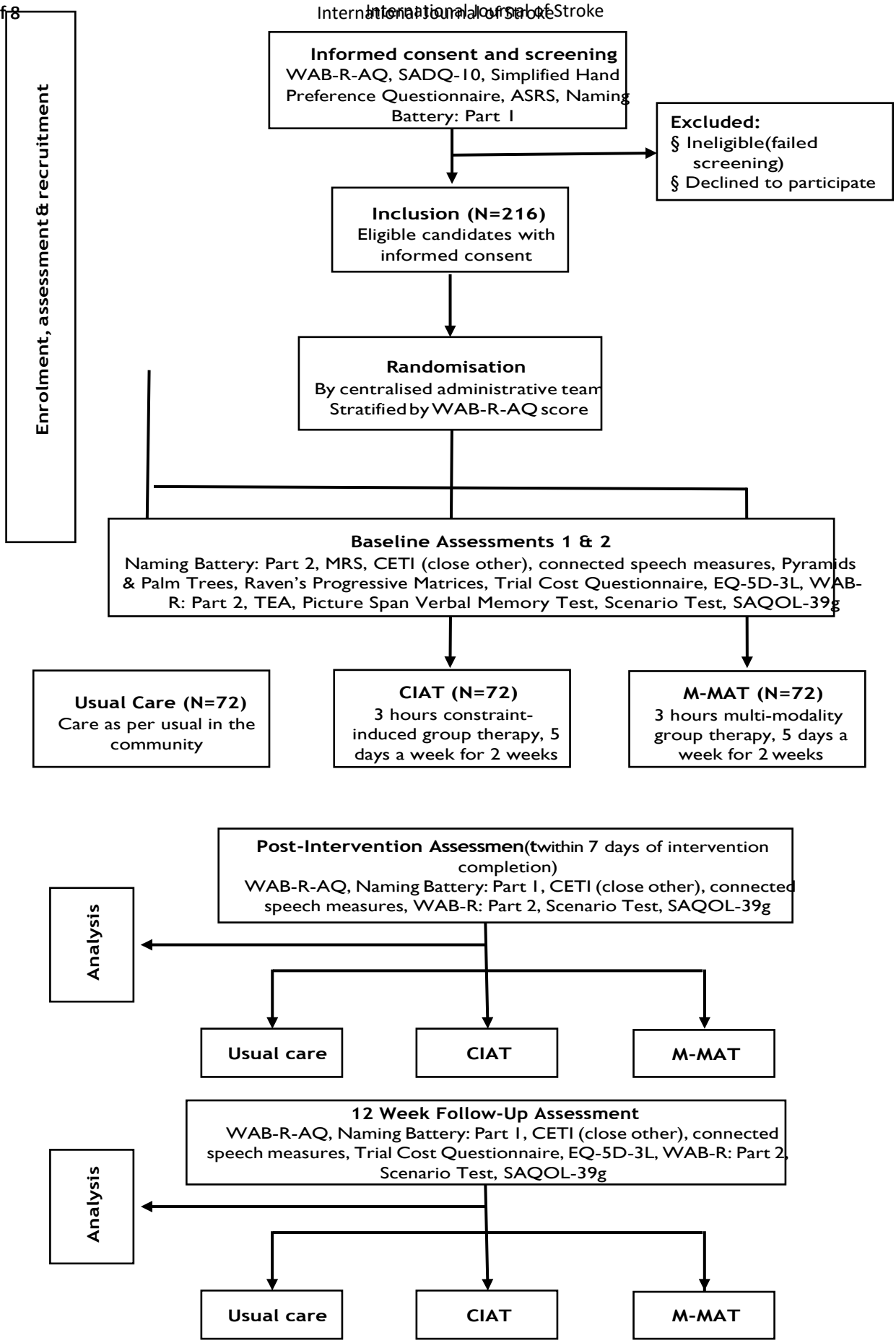
Table 1. Eligibility criteria

Inclusion criteria
Over the age of 18 with documented stroke and resultant aphasia of any type
A WAB-AQ score <93.8
Medically stable at recruitment
Fluent in English prior to stroke
Independent toileting
Carer/significant other able to participate in assessments
Exclusion criteria
Previous history of non-stroke neurological event
Severe apraxia of speech or dysarthria on the Apraxia of Speech Rating Scale
Current diagnosis of major clinical depression or other mental health condition that may affect adherence to the study protocol
Uncorrected sensory loss preventing participation in communication assessments and treatments
Serious medical condition prior to their stroke (including malignancies, psychiatric, behavioural or drug-dependency problems) likely to influence participation or prevent adherence to protocol


Enrolment, assessment & recruitment
Informed consent and screening
WAB-R-AQ, SADQ-10, Simplified Hand Preference Questionnaire, ASRS, Naming Battery: Part 1
Excluded:
§ Ineligible(failed screening)
§ Declined to participate
Inclusion (N=216)
Eligible candidates with informed consent
Randomisation
By centralised administrative team
Stratified by WAB-R-AQ score
Baseline Assessments 1 & 2
Naming Battery: Part 2, MRS, CETI (close other), connected speech measures, Pyramids & Palm Trees, Raven's Progressive Matrices, Trial Cost Questionnaire, EQ-5D-3L, WAB-R: Part 2, TEA, Picture Span Verbal Memory Test, Scenario Test, SAQOL-39g
Usual Care (N=72)
Care as per usual in the community
CIAT (N=72)
3 hours constraint-induced group therapy, 5 days a week for 2 weeks
M-MAT (N=72)
3 hours multi-modality group therapy, 5 days a week for 2 weeks
Post-Intervention Assessmen(twithin 7 days of intervention completion)
WAB-R-AQ, Naming Battery: Part 1, CETI (close other), connected speech measures, WAB-R: Part 2, Scenario Test, SAQOL-39g
Analysis
Usual care
CIAT
M-MAT
12 Week Follow-Up Assessment
WAB-R-AQ, Naming Battery: Part 1, CETI (close other), connected speech measures, Trial Cost Questionnaire, EQ-5D-3L, WAB-R: Part 2, Scenario Test, SAQOL-39g
Analysis
Usual care
CIAT
M-MAT