INTRODUCTION

Stroke is a major public health problem as the second commonest cause of death and the commonest cause of adult disability. More than one third of stroke survivors have aphasia, which affects a person’s ability to understand spoken language, talk, read and/or write. This often leads to frustration, depression, and limitation in performing role as a member of family or community. So far there is no clearly effective intervention for aphasia and randomized controlled trials (RCT) to test various hypothesized interventions are urgently needed.

This article outlines some of the methodological issues which warrant attention while designing a RCT to test an intervention for aphasia.

Explanatory versus pragmatic trials

Explanatory trials aim to show that an intervention works in a highly selected homogenous and responsive group of patients and if an intervention is delivered in an ideal way and if outcomes are such that they are most likely to show improvement. In other words, explanatory trials attempt to answer the question: can the treatment work under ideal (best) conditions?

Pragmatic trials aim to show that the intervention works if given to usual patients in usual way and assessed using outcomes that are important to patients, even if their assessment is usually associated with some errors. In other words, pragmatic trials attempt to answer the question: does the treatment work under usual (real-world) conditions?

Accordingly, explanatory trials have very narrow eligibility criteria, intervention is supervised and tightly controlled and outcomes are objective and measurable with low error rate.

Pragmatic trials have wide eligibility criteria, intervention is administered in a practical and widely practicable manner, and outcomes are the most feasible to measure and of importance to patients.

Selecting patients

There are several considerations involved in selecting patients in order to maximize responsiveness and homogeneity.

Time since onset of stroke

One third of stroke survivors are affected by aphasia, 60–70% recover in short term. Approximately 30–40% of those with aphasia remain significantly affected in long term.[1] It is important to target those who really need treatment. They are usually the patients with aphasia persisting for three months or more. It can be argued that earlier one intervenes, the more likely it is for the intervention to enhance the natural improvement but then the sample size required to detect the difference due to interventions is likely to be larger than when one intervenes in those with lower probability of improvement with usual care.

In exploratory trials, patient with persistent aphasia for more than some months (e.g., 9–12 months) may be excluded whereas in pragmatic trials, no upper limit of persistence may be set.

Age group

In explanatory trials, age groups may be younger, more likely responsive whereas in pragmatic trials, wide age range may be selected.

Severity of aphasia

Severely aphasic patients are less likely to respond than those with mild or moderate severity. In explanatory trials, it may be desirable to focus on moderately severe group because mild cases may improve irrespective of the intervention and severe cases may not be responsive.

In pragmatic trials, all levels of severity may be included and the response may be examined separately for mild, moderate, and severe cases.

Aphasia characteristics

In explanatory trials, it may be desirable to include only those cases with a “pure” aphasic syndrome of the type most likely to respond to the intervention and be able to comply with the requirements of the intervention. For example, for a computer-based intervention, only patients with ability to use computers may be included. In pragmatic trials, if there is good rationale, then different types of aphasia may be included.

Co-morbidity

Co-morbidities may affect the ability to adhere to the intervention and the grade of response. In explanatory trials,
eligible co-morbidities may be restricted whereas in pragmatic trials it may be permitted to a greater extent.

**Selecting interventions**

Usually, the intervention of interest is some form of speech therapy. In explanatory trials, an intervention may be administered face to face by an expert in a clinical setting to ensure adequate time of delivery. In a study by Breitenstein *et al.* [2] the therapy was delivered in a clinical settings for \( \geq 10 \) hours per week for at least three weeks (minimum dose of 30 hours) in a combined approach (one to one) with speech therapist, group therapy with the speech and language therapist (SLT) and self-managed computer therapy or pencil and paper linguistic exercises presented by the SLT.

As face to face therapy with SLT is unlikely to be available in the long-term, a pragmatic trial would investigate lower cost option with volunteers trained by SLT or self-managed computer-based therapy with training and supervision, which is widely practicable.

**Selecting Outcomes**

The outcome or response variable needs a careful selection depending on the phase of the RCT and mechanism of action of the intervention. The Research Outcome Measurement in Aphasia (ROMA) consensus statement provides evidence based recommendations for the measurement of outcomes for adults with post-stroke aphasia within phase I–IV aphasia treatment studies [3,4].

Investigators would benefit from this statement while selecting outcomes along with consideration of what the intervention is most likely to achieve, or which deficit is most likely to respond to the intervention.

Clinical trials have been categorized into four phases—Phase 1 to 4. The choice of design, primary outcome and secondary outcomes depends on the phase of the clinical trial. Phase 1 is practically always non-randomized, phase 2 may or may not be randomized, but increasingly they are randomized. Phase 3 is almost always randomized. Phase 4 is usually non-randomized. The design which establishes efficacy and short-term safety is a randomized controlled trial. The following is an outline of steps of a randomized controlled trial (details are beyond the scope of this article).

**The process of a randomized controlled trial (RCT)**

An RCT, like any other research, starts with writing a protocol, that defines the objectives, research question, hypothesis, eligibility criteria, recruitment procedure, consent, random allocation, outcomes and their measurement and methods of analysis to be used. The actual conduct of the trial goes through the following steps [Figure 1].

i. **Eligibility assessment:** As soon as a potential participant appears, the investigators assess whether he (the subject) fulfils the eligibility criteria (Inclusion and exclusion) of the trial.

ii. **Consent:** If the patient is eligible, he is given all the relevant information in a consent form with opportunity to seek clarification. An informed consent is then taken for participating in the RCT, though the patient has right to withdraw consent anytime.

iii. **Random allocation:** A patient who is eligible and consenting is then randomized to one of the arms of the RCT. Random allocation has two steps: random sequence generation; and allocation concealment.

iv. **Baseline assessment:** All patients are assessed at baseline (before initiating intervention) according to the protocol. Sometimes, it may already be complete at step 1 (eligibility assessment).

v. **Initiation of interventions:** Patients receive the intervention according to the random allocation; either experimental intervention or control.

vi. **Standard care:** All patients receive the standard care.

vii. **Follow-up:** Patients are followed-up as per the protocol.

viii. **Outcome assessment:** is performed by blinded assessors whenever possible and desirable.

![Figure 1: Steps for conduct of the trial](image-url)
ix. Adjudication: A group of experts judge whether the outcome measurements and classification are correct and acceptable.

x. Analysis: The data is analyzed usually by statisticians.

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