Article:
Palmer, R. (2020) Design considerations for clinical trials in aphasia. Annals of Indian Academy of Neurology, 23 (8). S52-S56. ISSN: 0972-2327

https://doi.org/10.4103/aian.AIAN_453_20

ISSN 0972-2327

www.annalsofian.org

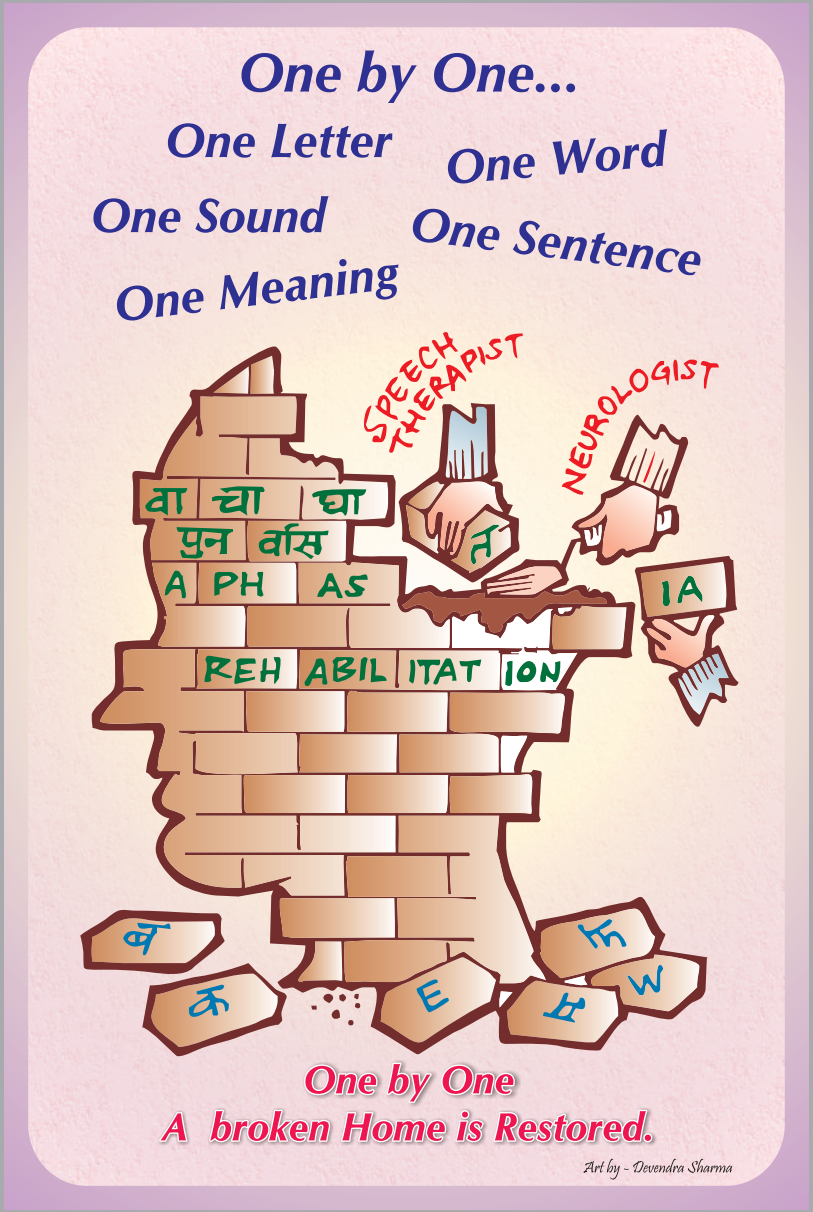
AIAN

Annals of Indian Academy of Neurology

Official Publication of Indian Academy of Neurology

Volume 23 • Supplement 2 • 2020

APHASIA
Guest Editor: Apoorva Pauranik



Wolters Kluwer Medknow

Indexed with EMBASE and Science Citation Index (E)

Annals of Indian Academy of Neurology impact factor 0.905

PubMed

Design Considerations for Clinical Trials in Aphasia

Rebecca Palmer
School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom

Abstract

The use of the randomised controlled trial (RCT) design to evaluate the effectiveness of new interventions in aphasia has increased in recent years in response to calls for high quality evidence of the effectiveness of interventions for this population. This view-point article highlights some of the important considerations when designing a trial for an aphasia intervention, illustrated with decisions made when designing the Big CACTUS RCT for self-managed computer-based word finding therapy in aphasia. Considerations outlined include whether an RCT is needed, readiness for conducting an RCT, choice of comparators, randomisation options, blinding/masking, selection of outcome measures, pragmatic versus explanatory approaches, and fidelity measurement.

Keywords: Aphasia, randomised controlled trials, trial design

Guest editor's notes: Despite all the genuine difficulties in designing and executing Randomised Controlled Trials of therapy interventions in aphasia, there is no escape from them. It will not be a day too soon when clinicians in India embark on this path. This viewpoint article by Rebecca Palmer and an editorial commentary by Kameshwar Prasad are being proudly published with the hope that they will spur some interest and motivation and offer guidance to potential trialists. Both authors compare 'exploratory' versus 'pragmatic' trials but have different approaches to convey salient messages. Rebecca rests her exposition on the great example of 'Big CACTUS study', an RCT for self-managed computer-based word finding therapy in aphasia.

Introduction

Randomised controlled trials are prospective studies that measure the effectiveness of a new intervention or treatment. The act of randomisation balances observed and unobserved characteristics between intervention and control groups allowing any differences in outcome to be attributed to the intervention.[1] The number of participants required to detect effectiveness (sample size) is calculated. Minimising bias is a key concept in the randomised controlled trial design, achieved through concealment of the random assignment to each intervention group, and blinding or masking of participants, professionals or outcome assessors to the intervention being received.[1] There has been an increase in the number of randomised controlled trials in aphasia, from 30 trials included in a Cochrane review of speech and language therapy in stroke in 2010, to 57 in 2016.[2,3] Many RCTs in the field use small numbers without a priori sample size calculations to ensure they are adequately powered to detect an effect. However, there have been a growing number of adequately powered multicentre RCTs conducted in aphasia more recently.[4-9] Consequently there is increasing insight into what needs to be considered before embarking on a large trial of a complex intervention for people with aphasia. One such trial was the multicentre Big CACTUS RCT of computerised aphasia therapy in 21 speech and language therapy departments in the UK, [ISRCTN68798818].[6] As amounts of speech and language therapy offered in the longer term post-stroke can be limited,[10] and people with aphasia often want more therapy than is available face to face,[11] the Big CACTUS study evaluated the effectiveness and cost-effectiveness of offering self-managed word finding practice using specialist aphasia computer software (StepbyStep),[12] tailored by a speech and language therapist (SLT) and supported by a speech therapy assistant or volunteer.[6,13] This article outlines some of the considerations in designing an RCT for aphasia illustrated with decisions made in the design of Big CACTUS.

Do we need a trial?

Firstly, it is important to consider whether an RCT is needed and if it is the best design to answer the research question. This is particularly important given the associated time and costs of completing an RCT, which can be particularly high for trials in

Address for correspondence: Dr. Rebecca Palmer, Innovation Centre, 217 Portobello, Sheffield S1 4DP, United Kingdom.
E-mail: r.l.palmer@sheffield.ac.uk

Submitted: 14-May-2020 **Accepted:** 14-May-2020
Published: 25-Sep-2020

DOI: 10.4103/aian.AIAN_453_20

aphasia due to the face to face and specialist communication support requirements of providing informed consent and completing outcome measures. An RCT design is appropriate to answer questions about the effectiveness of an intervention where there is uncertainty amongst the profession about whether a particular aphasia intervention is effective, requiring evidence to support its implementation or its decommissioning. The Big CACTUS RCT was conducted as use of computers to deliver increased amounts of SLT is a growth area in the SLT profession, yet the small scale of existing studies leaves uncertainty as to the effectiveness and cost effectiveness of this option.[14] RCTs are also often used to assess safety of new interventions. The extent of safety considerations is likely to vary considerably between different aphasia interventions. We considered safety in Big CACTUS due to the use of electrical equipment and regular screen use.[13]

Are we ready for a trial?

The Medical Research Council (MRC) framework for the evaluation of complex interventions identifies four phases: development, feasibility, evaluation and implementation.[15] An RCT can be used at the evaluation stage to investigate effectiveness of an aphasia intervention.

Prior to evaluation, it is important to develop the intervention based on existing evidence in the literature, and co-design with SLTs and people with aphasia, keeping in mind feasibility of implementing the intervention in practice. We need to identify the intended outcomes and mechanisms by which the intervention is expected to achieve these outcomes.[16] Before the Big CACTUS trial of self-managed aphasia therapy for word finding using a computer, the StepbyStep word finding software underwent iterative development and testing with case series studies investigating the potential benefits for individuals.[12,17] The key components of the intervention and how they were expected to lead to improved word finding were identified through key stakeholder discussions.[18]

The Stroke Recovery and Rehabilitation Round table have recently published a trial development framework to guide decision making (Go, No-go criteria) in the development of trials for stroke recovery.[19] This framework will be useful to guide the planning of future trials in aphasia and identifies important 'knowledge units' for which to understand the pre-clinical and clinical evidence when developing an intervention. These knowledge units include: 'How much treatment?', 'What are the active ingredients of the treatment?', 'Who should be treated?' and 'When is treatment best delivered?'. If such knowledge units cannot be informed by existing literature, the framework suggest that the intervention is not yet ready to be trialled in an RCT and additional preliminary research is indicated.

The feasibility stage of the MRC framework is important to become ready for an adequately powered RCT. At this stage preparatory work can be conducted to investigate whether the intervention is acceptable and whether it can be delivered in a clinical context. Our CACTUS pilot study interviewed people with aphasia, carers and volunteers supporting the self-managed intervention to gauge acceptability of the intervention.[20] In addition to feasibility of delivering an intervention, it is also important to test the feasibility of running a trial before planning a multicentre RCT. It is necessary to collect data on whether it is possible to recruit the population needed for the trial, indications of recruitment and attrition rates, whether randomisation works and is acceptable, and whether outcome measures are useful and acceptable. A pilot trial (CACTUS) was conducted to inform our RCT (Big CACTUS).[21] This pilot helped further develop the intervention protocol in terms of how much computer practice was realistic to expect people with aphasia to complete independently at home and it informed adaptions required to ensure the intervention was feasible to deliver in practice. The pilot also identified that people with very severe word finding did not appear to derive any benefit from this intervention which shaped the patient inclusion criteria for the following RCT. We identified a clinically meaningful effect size for change in word finding ability with which to calculate the sample size for the RCT, and this was inflated by the attrition rate seen in the pilot study (15%). We also found we were able to recruit at a rate of one participant per month per site. This information together enabled planning for sufficient recruitment sites – 20 sites were required to recruit the sample size of 285 participants with aphasia over 15 months each.[13]

What shall we compare the intervention to?

Comparison is a core element of the RCT design. One option is to compare to participants not having any intervention. This is difficult in speech and language therapy given that people live in a world where communication is all around them and they are likely to be receiving language stimulation to some extent either in family interactions or attendance at support groups. Therefore, in the CACTUS pilot study, we compared computerised aphasia therapy to usual stimulation, acknowledging that we cannot (and would not want to) limit exposure to communication in daily life.[21] If we want to know whether the intervention is superior to what people with aphasia usually receive, it can be compared to usual care. If it is envisaged that the new intervention would be given instead of usual care, it can be compared on its own to usual care. In the Big CACTUS trial, we were aiming to evaluate the effectiveness of providing self-managed word finding therapy on a computer to increase the amount of therapy people had access to. Consequently, we viewed this intervention as something that would be provided in addition to usual care and not instead of it. Therefore, we made the decision to compare the computer therapy plus usual care to usual care alone using an 'adjunct' trial design.

It is not uncommon to also compare new rehabilitation interventions to an 'attention control' condition. The purpose of this is to differentiate the effect of the specific therapy from the effect of attention from a professional. In speech and language therapy interventions for aphasia the idea of an attention control needs considerable thought. If using conversation with a professional or volunteer as an attention

control, there is likely to be some overlap between the language stimulation of conversation and the stimulation of the language therapy components.[22] In Big CACTUS, an attention control group was used to differentiate the effect of the language therapy components from the additional support received from volunteers during the intervention. It was also recognised that attention is limited during a self-managed intervention and consequently we also controlled for the self-managed activity carried out in the Big CACTUS intervention. Attention/activity control participants were provided with puzzle books such as Sudoku, spot the difference, colouring activities and asked to complete one activity a day to control for the daily activity being conducted on the computer in the intervention group. Books were tailored to participant's interests and updated each month in terms of difficulty in keeping with the tailoring of language exercises that happened in the computer intervention. The intervention group had volunteers or SLT assistants to provide support for them once a month. To control for this support, the attention/activity control group received monthly phone calls from a researcher to provide general support.[6]

Can we randomise?

Recruitment to a trial is partly contingent upon the acceptability of randomisation to the participants. People with aphasia often do not receive as much speech and language therapy as they would like and are keen to try new treatment approaches in research studies. We understood that one driver for participation in the Big CACTUS trial was likely to be the desire to try self-managed word finding therapy on a computer. Indeed, during the pilot CACTUS study we experienced drop out of 3 participants because they did not get randomised to the computer group. It is therefore important to consider ways of mitigating the effects of randomisation on recruitment and differential attrition between groups. In Big CACTUS, we addressed this issue by explaining the randomisation process in participant information sheets, along with an offer to provide software for participants to have a go with after the trial, if they were randomised to usual care or attention control. Other aphasia trials have addressed the implications of randomisation in different ways, e.g., SUPERB used a modified Zelen design in which participants consented first to being involved in a study monitoring adjustment to life post stroke, but not told what the specific intervention under investigation was. They were randomised and then the participants randomised to the intervention group were asked to consent to having the trial intervention.[23]

An alternative to individual randomisation is cluster randomisation where the trial site is randomised to the intervention or comparator. Cluster randomisation can be considered where there is concern that the treatment given to the control participants might become 'contaminated' by the intervention under evaluation. This may happen in individually randomised RCTs if SLTs are trained to deliver the intervention under evaluation and start to apply some of this new knowledge to control participants they are also treating.[15] We considered likelihood of contamination in the Big CACTUS trial to be low and easy to identify as the intervention required tailoring of a specific computer programme, thus individual randomisation was used.

How can blinding work in an aphasia trial?

Blinding is one of the key concepts in an RCT to minimise the likelihood of a biased outcome. In a trial of a new medicine, it is possible to double blind – i.e., neither the medic providing the medication, nor the patient taking the medication know whether they have been given the medicine being trialled or a placebo. With aphasia interventions, the SLT and the person with aphasia usually both take an active role in intervention delivery and receipt, and therefore cannot be blind to the intervention. However, an alternative way to reduce bias is to blind outcome assessors to the intervention that has been received. The approach we took in Big CACTUS was to train SLTs, who were independent from those who provided the computer word finding therapy, to carry out outcome measures. As there is scope for an outcome assessor to become unblind due to a colleague SLT and the participant and family members knowing the intervention group, it was important to report instances of unblinding so the success of the blinding procedures could be evaluated and reported.[6]

How do you choose outcome measures?

Selecting outcome measures is one of the most important considerations when designing a trial. We need to consider what outcome we expect from the intervention/what people with aphasia are hoping to overcome, and whether there are any validated outcome measures available to measure this outcome. It is important to note that Wallace *et al.* (2017) found that PWA want outcomes from therapy that span the ICF domains of impairment, activity and participation.[23] Coster *et al*. (2013) proposed a description for the relationship of projected outcomes to the intervention activities, suggesting that outcomes can be more proximal to, or more distal from the intervention activities.[24] In the Big CACTUS trial, word finding was the focus of the intervention with the computerised activities promoting practice of naming exercises in single words and sentences. We therefore selected an impairment-based outcome of change in word finding, measured using a personalised naming test. This impairment-based measure was considered proximal to the intervention activities. As the purpose of increasing word finding ability is to improve functional communication in everyday contexts, we also used the activity scale of the validated Therapy Outcome Measure for aphasia (TOM) to assess videoed conversations about topics of interest to the participants.[25] This outcome was more distal from the specific intervention activities. As the intervention directly acts on the proximal outcome of word finding in Big CACTUS, with the hypothesis that improvements in the proximal outcome (impairment) will lead to improvements in the more distal, but functional outcome of conversation (activity), both of these outcomes were considered equally important to measure and were therefore co-primary outcomes. A range of secondary outcome measures were also used to measure effects on participation and wellbeing.[6,13]

In order to conduct meta-analyses of intervention outcomes, it is important that we include measures to enable comparison with other studies or aggregation of data from more than one study. Wallace *et al*. (2018) therefore published a consensus on a core outcome set to use within aphasia trials.[26]

Considering the pragmatic-explanatory continuum for a trial of an aphasia intervention

RCTs can take explanatory or pragmatic approaches. Explanatory trials seek to answer whether an intervention CAN work under ideal conditions. Pragmatic trials focus on whether an intervention DOES work under usual conditions in the setting the intervention is designed for. Given the intervention trialled in Big CACTUS was designed to enable speech and language therapy services to provide more therapy to people with aphasia, it was appropriate to take a pragmatic approach to see whether this was effective when delivered in routine clinical practice. The Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2) has nine domains to help researchers consider consequences of design decisions on the applicability of results to usual settings.[27] The application of these domains to Big CACTUS is described in the supplementary material to the results paper in the Lancet Neurology.[13]

Fidelity measurement considerations

It is important to measure fidelity to the intervention under study in a trial so that we know whether it was delivered and received as intended. To do this the key components of the intervention need to be well articulated, often in a therapy manual. This can form the standard to measure actual delivery and receipt against. A manual was written for the intervention trialled in Big CACTUS (https://www.sheffield.ac.uk/polopoly_fs/1.525339!/file/TherapyManual_Nov15.pdf). The template for intervention description in research (TIDieR) can also be used to assist with communicating the intervention in a transparent way and was used in the Big CACTUS results paper.[6,28] Observation is often used during fidelity measurement. In Big CACTUS, as the intervention was self-managed in participants own homes, adherence to computer practice was measured through practice data recorded within the software used for aphasia therapy. Data collection forms were also used to record when the participants received the software, therapist decisions in tailoring the software, support and contact between therapists and volunteers and SLT assistants, and support time and activities conducted with participants. The approach taken to fidelity within a trial may relate to whether the trial is explanatory or pragmatic. A feedback loop is often used whereby processes can be put in place to maintain fidelity as much as possible during a trial. This is appropriate in explanatory trials, to answer the question 'CAN this work?'. In Big CACTUS, the pragmatic approach we took, asking the question 'DOES this work in usual settings?' required that we understood the fidelity with which the intervention gets delivered in practice. We observed the fidelity with which the intervention was delivered in practice, however we did not attempt to control fidelity in any way that would not be possible to replicate in practice outside of a trial.[19]

Conclusion

This view-point article outlines some of the key decisions that were considered during the Big CACTUS trial of computerised word finding therapy in aphasia. This article is limited to the discussion of design. However, additional considerations relate to trial delivery and reporting. Further perspectives on considerations and solutions will be informed by other recently completed and ongoing multicentre aphasia trials.

Declaration of patient consent

The author certifies that no patient data is reported in this view-point article.

Financial support and sponsorship

The Big CACTUS project was funded by the NIHR Health Technology Assessment Programme (12/21/01). Additional funding support was provided by the Tavistock Trust for Aphasia. The views and opinions expressed are those of the author and do not necessarily reflect those of the Health Technology Assessment Programme, the NIHR, the National Health Service, the Department of Health and Social Care or the Tavistock Trust for Aphasia.

Conflicts of interest

I have provided a conflicts of interest statement and statement of author contribution below:

Competing interests

This manuscript is based on original work and had not been published in whole or part, in any print or electronic media or is under consideration of publication in any print or electronic media other than as abstract of conference proceedings.

References

1. Hariton E, Locascio JJ. Randomised controlled trials-the gold standard for effectiveness research: Study design: Randomised controlled trials. BJOG 2018;125:1716.
2. Kelly H, Brady MC, Enderby P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev 2010:CD000425. doi: 10.1002/14651858.CD000425.pub2.
3. Brady MC, Kelly H , Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev 2016;CD000425. doi: 10.1002/14651858.CD000425.pub4.
4. Audrey B, Anne H, Emma P, Alys Y, Linda D, Andy V, *et al*. Effectiveness of enhanced communication therapy in the first four months after stroke for aphasia and dysarthria: A randomised controlled trial. BMJ 2012;345:e4407.
5. Breitenstein C, Grewe T, Flöel A, Ziegler W, Springer L, Martus P, *et al*. Intensive speech and language therapy in patients with chronic aphasia after stroke: A randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. Lancet 2017;389:1528-38.
6. Palmer R, Dimairo M, Cooper C, Enderby P, Brady M, Bowen A, *et al*. Self-managed, computerised speech and language therapy for patients with chronic aphasia post-stroke compared with usual care or attention control (Big CACTUS): A multicentre, single-blinded, randomised controlled trial. Lancet Neurol 2019;18;9:821-33.
7. Godecke E, Armstrong EA, Rai T, Middleton S, Ciccone N, Whitworth A, *et al*. A randomized controlled trial of very early rehabilitation in speech after stroke. Int J Stroke 2016;11:586-92.
8. Rose ML, Copland D, Nickels L, Togher L, Meinzer M, Rai T, *et al*. Constraint-induced or multi-modal personalized aphasia rehabilitation (COMPARE): A randomized controlled trial for

stroke-related chronic aphasia. Int J Stroke 2019;14:972-6.
9. Worrall L, Ryan B, Hudson K, Kneebone I, Simmons-Mackie N, Khan A, *et al*. Reducing the psychosocial impact of aphasia on mood and quality of life in people with aphasia and the impact of caregiving in family members through the Aphasia Action Success Knowledge (Aphasia ASK) program: Study protocol for a randomized controlled trial. Trials 2016;22;17:153.
10. Palmer R, Witts H, Chater T. What speech and language therapy do community dwelling stroke survivors with aphasia receive in the UK? PLoS One 2018;13:e0200096.
11. Kennedy N. Results of NI RCSLT survey of communication needs after stroke. Available from: https://www.rcslt.org/-/media/Project/RCSLT/ni-rcslt-survey-comm-2018.pdf?la=en&hash=8A66A789407C3CC1BE2A104DD06063E61DEEFF6D. 2018. [Last accessed on 2020 Apr 07].
12. Steps Consulting Ltd. StepByStep Aphasia Therapy 2018. Available from: https://aphasia-software.com/.
13. Palmer R, Cooper C, Enderby P, Brady M, Julious S, Bowen A, *et al*. Clinical and cost effectiveness of computer treatment for aphasia post stroke (Big CACTUS): Study protocol for a randomised controlled trial. Trials 2015;16:18.
14. Zheng C, Lynch L, Taylor N. Effect of computer therapy in aphasia: A systematic review. Aphasiology 2016;30:211-44.
15. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: The new Medical Research Council guidance. BMJ 2008;337:a1655.
16. O'Cathain A, Croot L, Duncan E, Rousseau N, Sworn K, Turner KM, *et al*. Guidance on how to develop complex interventions to improve health and healthcare. BMJ Open 2019;9:e029954.
17. Mortley J, Wade J, Enderby P. Superhighway to promoting a client-therapist partnership: Using the internet to deliver word-retrieval computer therapy monitored remotely with minimal speech and language therapy input. Aphasiology 2004;18:193-211.
18. Harrison M (2020) Measurement of fidelity to the Big CACTUS trial. PhD thesis unpublished.
19. Bernhardt J, Hayward K, Dancause N, Lannin N, Ward N, Nudo R, *et al*. A stroke recovery trial development framework: Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable. Int J Stroke 20019;14:792-802.
20. Palmer R, Enderby P, Paterson G. Using computers to enable self-management of aphasia therapy exercises for word finding: The patient and carer perspective. Int J Lang Commun Disord 2013;48:508-21.
21. Palmer R, Enderby P, Cooper C, Latimer N, Julious S, Paterson G, *et al*. Computer therapy compared with usual care for people with long-standing aphasia poststroke. Stroke 2012;43:1904-11.
22. Brady MC, Godwin J, Kelly H, Enderby P, Elders A, Campbell P. Attention control comparisons with SLT for people with aphasia following stroke: Methodological concerns raised following a systematic review. Clin Rehabil 2018;32:1383-95.
23. Wallace S, Worrall L, Rose T, Le Dorze G, Cruice M, Isaksen J,. Which outcomes are most important to people with aphasia and their families? An international nominal group technique study framed within the ICF. Disability Rehabil 2017;39:1364-79.
24. Coster WJ. Making the best match: Selecting outcome measures for clinical trials and outcome studies. Am J Occup Ther 2013;67:162-70.
25. Enderby P, John A, Petheram B. Therapy Outcome Measures for Rehabilitation Professionals: Speech and Language Therapy, Physiotherapy, Occupational Therapy. 2nd ed.. Chichester: John Wiley & Sons; 2013.
26. Wallace S, Worrall L, Rose T. A core outcome set for aphasia treatment research: The ROMA consensus statement. Int J Stroke 2018;14:180-5.
27. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: Designing trials that are fit for purpose. BMJ 2015;350:h2147.
28. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, *et al*. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687.