Aphasiology

ISSN: 0268-7038 (Print) 1464-5041 (Online) Journal homepage: www.tandfonline.com/journals/paph20

Aphasia treatment research: a decision-making tool to guide the design of phased trials from the Collaboration of Aphasia Trialists (CATs) trials for aphasia panel

Erin Godecke, Emily Brogan, Rebecca Palmer, Marian C. Brady, Frank Becker, Caterina Breitenstein, Sonia Brownsett, Julius Fridriksson, Katerina Hilari, Argye E. Hillis, Paola Marangolo, Miranda L. Rose, Shirley Thomas, Donna C. Tippett, Julie Bernhardt & Kathryn S. Hayward

To cite this article: Erin Godecke, Emily Brogan, Rebecca Palmer, Marian C. Brady, Frank Becker, Caterina Breitenstein, Sonia Brownsett, Julius Fridriksson, Katerina Hilari, Argye E. Hillis, Paola Marangolo, Miranda L. Rose, Shirley Thomas, Donna C. Tippett, Julie Bernhardt & Kathryn S. Hayward (11 Aug 2026): Aphasia treatment research: a decision-making tool to guide the design of phased trials from the Collaboration of Aphasia Trialists (CATs) trials for aphasia panel, Aphasiology, DOI: 10.1080/02687038.2026.2693093

To link to this article: https://doi.org/10.1080/02687038.2026.2693093

Published online: 11 Aug 2026.

APHASIOLOGY
https://doi.org/10.1080/02687038.2026.2693093

Aphasia treatment research: a decision-making tool to guide the design of phased trials from the Collaboration of Aphasia Trialists (CATs) trials for aphasia panel

Erin Godecke [a,b,c], Emily Brogan [c,d], Rebecca Palmer [e], Marian C. Brady [f**], Frank Becker [g,h], Caterina Breitenstein [i], Sonia Brownsett [c,j], Julius Fridriksson [k], Katerina Hilari [l], Argye E. Hillis [m], Paola Marangolo [n], Miranda L. Rose [c], Shirley Thomas [o], Donna C. Tippett [m], Julie Bernhardt [p] and Kathryn S. Hayward [p,q]

[a]Stroke Research Centre, Perron Institute for Neurological and Translational Science, Perth, Australia; [b]Department of Speech Pathology, Edith Cowan University & Sir Charles Gairdner Hospital, Perth, Australia; [c]Centre of Research Excellence in Aphasia Recovery and Rehabilitation, La Trobe University, Melbourne, Australia; [d]Speech Pathology, School of Allied Health, Curtin University & Fiona Stanley and Fremantle Health Service Group, Fremantle, Australia; [e]Sheffield Centre for Health and Related Research, School of Medicine and Population Health, The University of Sheffield, Sheffield, UK; [f]Department of Nursing and Community Health, Glasgow Caledonian University, Glasgow, UK; [g]Sunnaas Rehabilitation Hospital, Nesodden, Norway; [h]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [i]Department of Neurology, University of Muenster, Muenster, Germany; [j]Queensland Aphasia Research Centre, Faculty of Health and Behavioural Research Sciences, The University of Queensland, Brisbane, Australia; [k]Department of Communication Sciences & Disorders, University of South Carolina, South Carolina, USA; [l]Centre for Language and Communication Science Research, School of Health and Medical Sciences, City St George's, University of London, London, UK; [m]Departments of Physical Medicine and Rehabilitation, Neurology, and Otolaryngology—Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [n]Department of Humanities, University Federico II, Naples, Italy; [o]Centre for Rehabilitation and Ageing Research, School of Medicine, University of Nottingham, Nottingham, UK; [p]Stroke Theme, the Florey, University of Melbourne, Melbourne, Australia; [q]Departments of Physiotherapy, Medicine & the Florey, University of Melbourne, Melbourne, Australia

ABSTRACT

Background: Systematic reviews of randomised controlled trials with meta-analyses indicate that speech and language therapy for aphasia after stroke is effective in improving communication. However, high-quality evidence to identify an intervention's target population (who), regimen (what), timing (when), and dose (how much) is lacking. The predominance of underpowered aphasia trials and comparative studies with design limitations may be attributed to: 1) the perceived complexity of designing trials of interventions for a complex behaviour such as human communication, 2) the lack of funded research in the field and 3) a lack of training and understanding in the field of aphasiology regarding the importance of formalised clinical trials and the role they play in advancing clinical practice. Clinical trial phasing is

ARTICLE HISTORY
Received 14 July 2025
Accepted 16 June 2026

KEYWORDS
Aphasia; stroke; controlled clinical trial; research frameworks; stroke rehabilitation

CONTACT Erin Godecke erin.godecke@perron.uwa.edu.au Perron Institute for Neurological and Translational Science, Level 1, 8 Verdun St, Nedlands, Western Australia 6009, Australia

**Faculty of Health and Behavioural Research Sciences, University of Queensland, Australia

Some elements discussed in this article are included in the accompanying editorial. Please refer to the editorial here: http://dx.doi.org/10.1080/02687038.2026.2712740

designed to make sure an intervention is safe and shows proof of concept, with well-defined key components before evaluating for efficacy (and subsequently effectiveness) at scale. The field of aphasiology needs a systematic approach to trial phasing for people in different stages of their recovery.
Scope and Aim: To examine the utility of an adapted decision-making tool to guide the design of aphasia intervention trials. The tool will assist researchers to evaluate key components within existing evidence and address evidence gaps in aphasia treatment research.
Procedures: The expert interdisciplinary group in aphasia treatment research methodology adapted the Stroke Recovery and Rehabilitation Roundtable Trial Development Framework (SRRR-TDF) for use in aphasia research. The Stroke Recovery and Rehabilitation Roundtable-Trials Development Framework-Aphasia (SRRR-TDF-A) was applied to two key treatment components ("how much" and "what" type). Detailed working examples and the processes of applying the framework to the evidence are provided. The SRRR-TDF-A was completed to support each example, with the essential elements addressing: i) developing the research question, ii) designing the study, iii) conducting the research, and iv) evaluating and interpreting the research.
Outcomes: The expert interdisciplinary group adapted the SRRR-TDF, into the Stroke Recovery and Rehabilitation Roundtable Development Framework-Aphasia (SRRR-TDF-A), a decision-making tool appropriate for aphasia trials. The expert group reported that using the SRRR-TDF-A tool enabled a "step-by-step" process to distill and synthesise the evidence. This led to an easy-to-follow process to identify the "next steps" required to address the research question. The expert group provided aphasia researchers with a tangible guide to developing clinical trials using the existing evidence base.
Conclusions/Recommendations: We recommend aphasia researchers apply SRRR-TDF-A decision making tool to guide development of the next trial phase for a targeted aphasia intervention.

This paper is part of a special series of papers in *Aphasiology* on Methodological Issues in Aphasia Trials. The series comprises tutorial-type papers with core recommendations for aphasia intervention studies and randomised controlled trials. The series is guest edited by Professor Katerina Hilari, Dr Caterina Breitenstein, Professor Erin Godecke, Dr Helen Kelly and Professor Miranda Rose on behalf of the Trials for Aphasia Panel of the Collaboration of Aphasia Trialists https://www.aphasiatrials.org/

Introduction

Considerable scientific evidence, including systematic reviews with meta-analyses, demonstrate the immediate benefits of post stroke aphasia intervention treatment efficacy and effectiveness (Brady et al., 2016). Yet, treatment effect sizes to date have been small to moderate; the quality of evidence could have been greater and many evidence gaps exist. These evidence gaps create uncertainty about the translation of interventions to deliver clinical best-practice in post stroke aphasia rehabilitation (Brady et al., 2022). To achieve better long-

term communication and language outcomes for people with aphasia, we need to identify key intervention components to target in future clinical trials. That is, the careful targeting of *who* is treated, *when* the treatment is initiated post-stroke and *how much* of *what* treatment regimen (Bernhardt et al., 2019; RELEASE Collaborators, 2021) is required. Systematically addressing each of these components may help future researchers to design clinical trials that inform existing evidence gaps in these areas.

International synergistic action is needed to address critical knowledge gaps (RELEASE Collaborators, 2020). Recognising that aphasia therapies are complex means the CATs TAP members acknowledge that defining and distilling intervention targets for specific patient groups is challenging (Brogan et al., 2020; Lang et al., 2015; Rose et al., 2022). A phased, systematic process can help disentangle such intervention complexity (Palmer, 2020). We have considered several approaches to assist in this endeavour.

Scope of this paper

This paper integrates the Framework for Developing and Evaluating Complex Interventions to Improve Health (Campbell et al., 2000), the New Framework for Developing and Evaluating Complex Interventions (Skivington et al., 2021) and the SRRR-TDF (Bernhardt et al., 2019) to operationalise them for aphasia intervention research. The paper provides guidance for designing "the most appropriate trial given the current knowledge" (Bernhardt et al., 2019, p. 793). The goal was to create a theoretically based, decision-making guide to designing aphasia specific treatment studies (from exploratory single case experimental designs to confirmatory randomised controlled trials) that considers all components of existing evidence to address aphasia treatment evidence gaps.

Frameworks used in this paper

The Framework for Design and Evaluation of Complex Interventions to Improve Health (Campbell et al., 2000) provides guidance around the goals and considerations of each trial phase. The updated framework for Developing and Evaluating Complex Interventions (Skivington et al., 2021) discusses systematic research approaches addressing clinical trial phases but concludes that these phases may not need to be sequential; rather, all phases should consider six core elements (Skivington et al., 2021).

The SRRR-TDF supports structured decision-making in the selection of key components ("knowledge units") for clinical trial design. Phased trial development that includes essential intervention components should be sufficiently developed for progression through the efficacy pipeline (Campbell et al., 2000). The suggested phasing of clinical trials (Campbell et al., 2000) however, contrasts with the everyday reality of clinical trial development, where researchers from all disciplines and domains often skip trial phases for a range of reasons (Dalton et al., 2023). This practice may have contributed to research waste and inconclusive evidence (Chalmers & Glasziou, 2009) in our field. As we move towards the goal of improving the likelihood of progressing the development and evaluation of promising interventions through to larger trials, several components need to be systematically addressed. Below we outline the original and new Frameworks for Design and Evaluation of Complex Interventions to Improve Health (Campbell et al., 2000; Skivington et al., 2021) and SRRR-TD Frameworks

which provide a foundation for researchers to carefully review the state of evidence and "Knowledge Units" (pg. 793 Bernhardt et al., 2019) being used to make critical decisions in trial design. Using this framework (Appendix A) will support researchers to make decisions based on a thorough, systematic evaluation of the current evidence underpinning that choice.

Discovery research pipeline and phased clinical trials

Traditionally phased clinical trial development requires a series of sequential studies (phased trials) that examine the active ingredients in an intervention to determine if the intervention is safe and efficacious for use under the conditions in which it was tested (Campbell et al., 2000). These phases progress from pre-clinical research through to post-marketing evaluation (Skivington et al., 2021). These phases are frequently referred to as the "Discovery Research Pipeline" (Figure 1) and this important information is covered in detail by Campbell et al. (2000); Kleinman and Mold (2009) and National Institutes of Health (2025). The phases cover: a) Evaluation of the theoretical hypothesis behind the intervention (preclinical phase or "proof of concept", which is frequently done in vitro or in vivo with animals); b) Modelling of the components of the intervention (Phase II, e.g., probing various doses of the intervention in small samples of participants (n = 20–80) for safety reasons); c) Identifying and describing the components of the intervention in larger groups (n = 100–130) while outlining the feasibility of the intervention and first evidence of its efficacy compared to an alternative (Phase II); d) Comparing the fully defined intervention (using the protocol developed in the first three phases) to an appropriate alternative (Phase III) to determine its general efficacy in a sufficiently powered (n = 1000,3000) and confirmatory trial; and finally, e) Determining if an efficacious intervention can be implemented into real world, everyday practice and its outcomes maintained in the long-term via an effectiveness or a pragmatic trial (i.e., evaluating implementation and outcomes of the intervention as a best practice standard, Phase IV).

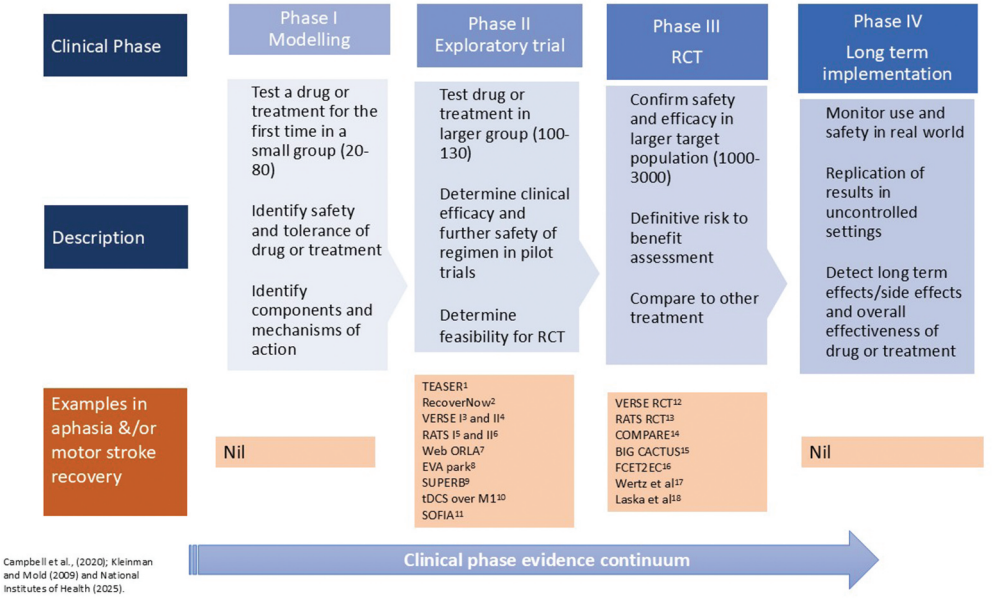


Figure 1. Discovery research pipeline.

Due to the lack of agreement regarding the application of animal models in human language recovery and on the constituent elements of "pre-clinical studies in human language recovery", our expert group chose to exclude this phase from the examples. We believe the remaining phases of the research pipeline are directly applicable to the aphasia research context. As such, we have removed the "pre-clinical" terminology from the remainder of this paper and in the adapted aphasia specific SRRR-TDF-A (Appendix B).

Limited early phase aphasia treatment studies and treatment outcome measures

The traditional phased approach (Phases I to IV in Figure 1) to clinical trials is recommended to achieve high confidence about an intervention's efficacy and effectiveness. Most aphasia research to date reflects Phase II (feasibility and safety) studies and Phase III (efficacy) studies (Figure 1). Phase I trials (dose and safety investigations) are significantly underrepresented. We note that most of the early phase aphasia research has been done in systematic single experimental designs (SCED) rather than group trials and that this is primarily due to the significant heterogeneity of the aphasia population (Thompson, 2014). It is likely in some, if not many, instances in aphasia treatment research that the intervention is not sufficiently detailed enough (RELEASE, 2020) to apply it in later research pipeline phases (Phases II and III). More robustly developed, earlier phase intervention trials regarding dose may help improve the chance of results being confirmed in subsequent Phase III trials (e.g., Bowen et al., 2012; Godecke et al., 2020; Nouwens et al., 2017). It is unlikely that a single study can resolve all elements of an effective aphasia intervention; hence, we recognise the need to carefully manipulate each component in the intervention while attempting to control others. When these gaps are noted in research and clinical practice, the "knowledge unit/s" of the intervention that lack clear evidence must be targeted in robust earlier phase trial designs. Addressing this fundamental gap in aphasia research is of utmost importance for future clinical trials and funding high-quality research and is therefore the primary focus of this paper.

One way to address the significant lag-time in the research discovery pipeline is to use study designs that are faster, more financially efficient, and clinically relevant to address one or more intervention components within the same study (Pallmann et al., 2018). These innovative Adaptive clinical trials study designs (Academy of Medical Sciences, 2019) are not new and have been used in cancer research and other fields to develop medical treatments for largely heterogenous populations (Bhatt & Mehta, 2016; Pallmann et al., 2018). Adaptive clinical trials use interim results to shape the final course of the trial and are based on *a priori* defined principles focusing on subsamples e.g., people with mild or severe aphasia as separate groups which are most likely to benefit from the target intervention. Adaptive trial designs may address some of the methodological difficulties facing aphasia research such as small participant numbers (compared to some other rehabilitation and most drug trials), highly varied participant characteristics, and the need to explore varied treatment doses to identify optimal intervention regimens (Hayward et al., 2024). Before initiating adaptive trials in aphasia rehabilitation, consensus in the field is required regarding the pre-planned adaptation criteria, that is, the decision rules for stopping or continuing a treatment arm after interim analysis.

Careful consideration and selection of research outcome measures in clinical trials are paramount. The varied use of outcome measures in aphasia research (Brady et al., 2016) complicates trial design and makes it challenging to interpret

the results. Therefore, there is a push for a standardized approach to measuring therapy outcomes (Wallace et al., 2014, 2019). The Research Outcome Measurement in Aphasia (ROMA) consensus statement provides a proposed minimum set of outcome measures for research to enhance data collection consistency across post-stroke aphasia intervention trials (Wallace et al., 2019, 2023).

SRRR-TDF framework

The SRRR-TDF (Bernhardt et al., 2019) was selected as the primary structure within this paper due to its ability to guide research decision-making with respect to readiness for a Phase III/IV trial (Appendix A). The authors introduce the "*GO, NO-GO*" concept that indicates if a research topic is ready to progress to a Phase III clinical trial (Bernhardt et al., 2019). The SRRR-TDF was designed specifically for the development of stroke rehabilitation research and addresses the complex nature of aphasia interventions well. In this paper, we demonstrate how it can be applied to designing aphasia clinical trials.

The SRRR-TDF (Bernhardt et al., 2019) has been used in post-stroke cognitive, communication, and motor recovery trial development. The four key knowledge units (*who* is treated, *when* the treatment is initiated post-stroke and with *how much* of *what*) focus on behavioural intervention development with a fifth knowledge unit, "ADJUVANTS" added to acknowledge the increasing use of multi-modal interventions, for example, drugs or non-invasive brain stimulation *paired with behavioural interventions* in trials.

Importantly, three fundamental principles underlie the use of the SRRR-TDF: 1) knowledge units are thought to interact (e.g., the *how much* may differ for different levels of *when*); 2) decision-making is dynamic in that key knowledge units will shift depending on the available evidence and this will affect the rating of the knowledge unit; and 3) the nature of the interaction or relationship between the key knowledge units is rarely known.

Finally, the SRRR-TDF (Bernhardt et al., 2019) provides a way of determining the level of confidence in existing knowledge about a given topic. A '*GO*" decision indicates a 'Very Confident" rating with *most* knowledge units pertaining to the research question to be addressed, while a "*NO-GO*" decision indicates "Not Confident to Somewhat Confident" decision on *some to most* knowledge units in the research question.

If a "*NO-GO*" decision about the knowledge unit(s) is reached, researchers are encouraged to address the evidence gap before proceeding to the next phase in the research pipeline. If a "*GO*" decision is reached, the understanding is that there is sufficient evidence for the treatment to be tested in a Phase III (to determine its general efficacy) or Phase IV trial (to determine if an efficacious intervention can be implemented into everyday practice and its outcomes maintained in the long-term via an effectiveness/pragmatic trial).

Methods

To demonstrate the application of the SRRR-TDF (Bernhardt et al., 2019) to aphasia research we produced examples of how it might be applied to two hypothetical aphasia intervention research questions. To complete the examples, the multidisciplinary expert group ($N = 16$) from Australia, Germany, Italy, UK and USA met regularly (eight teleconferences) between January to April 2021 and engaged in email discussions to facilitate decision-making. The first two meetings were used to:

– Provide education on the development and use of the tool in upper limb recovery following stroke (delivered by author KSH), as used in the SRRR-TDF (Appendix A) paper (Bernhardt et al., 2019)
– Discuss how this framework might be applied to aphasia clinical trial development
– Prioritise knowledge units that would result in differing levels of confidence on the Confidence Rating tool
– Adapt the SRRR-TDF (Bernhardt et al., 2019) form for use with aphasia research i.e., reference to preclinical research was removed and the rating of "somewhat" was added to the "Prioritised Evaluation Criteria" box and labelled "SRRR-TDF-APHASIA" (Appendix B).
– Outline a process for how the SRRR-TDF (Bernhardt et al., 2019) would be applied to the chosen knowledge units in aphasia research.

Specific discussion regarding the use of the term "pre-clinical" research and addition of the "somewhat" term in the confidence rating section resulted in graduated adaptations of the SRRR-TDF (Bernhardt et al., 2019). Between meetings, the expert group members trialled the use of the adapted versions of the SRRR-TDF (Bernhardt et al., 2019) to ensure they were satisfied that changes to the decision-making tool and definitions were fit-for-purpose in aphasia research. Final consensus was reached, and the SRRR-TDF-A (Appendix B) decision-making tool was adopted for use.

The "*what*" and "*how much*" knowledge units were chosen as the target topics by the expert group as these knowledge units were considered two of the most pressing knowledge gaps facing aphasia researchers (Brady et al., 2016; RELEASE, 2021).

The expert group then worked in two self-selected groups (Appendix C -"*How much*" group $n = 9$, "*What*" group two $n = 7$) based on geographical time zones that facilitated virtual meetings to deliver the worked examples. A flow diagram of the process undertaken in this paper is outlined in Figure 2.

Each working group used a consensus-based approach to form the example research questions. The research questions were intentionally broad to allow for the existing evidence to be evaluated. A summary of the studies used in each example is provided in Appendices D and E. The criteria for "*who*" (Table 1) was kept constant for the purposes of the examples. Table 2 shows the definitions of dose used in these examples. The "*when*" knowledge unit was tailored within each example to demonstrate the use of the SRRR-TDF-A (Figures 3 and 4) from the available research (Brady et al., 2016; RELEASE, 2021; Robey, 1998).

A formal systematic review of the evidence was not undertaken for the purposes of this exercise; rather, we obtained expert consensus on existing high-level evidence to include in the examples (Brady et al., 2016; RELEASE, 2021; Robey, 1998). The SRRR-TDF (Bernhardt et al., 2019) working group used a binary scale (Confident/Not confident) to rate the importance and confidence of evidence. For this paper and the resulting process, the expert group amended the binary scale to a three-point scale: "Not confident", "Somewhat confident" and "Very confident" to assist in the evaluation of the evidence used herein (Table 3). No changes were made to the definitions of confidence regarding the existing evidence.

After deciding on the evidence to be rated (stipulating reasons for inclusion and exclusion of the evidence) members of each working group individually rated the evidence using the SRRR-TDF-A confidence rating tool (Appendix B). The ratings were collated and circulated to

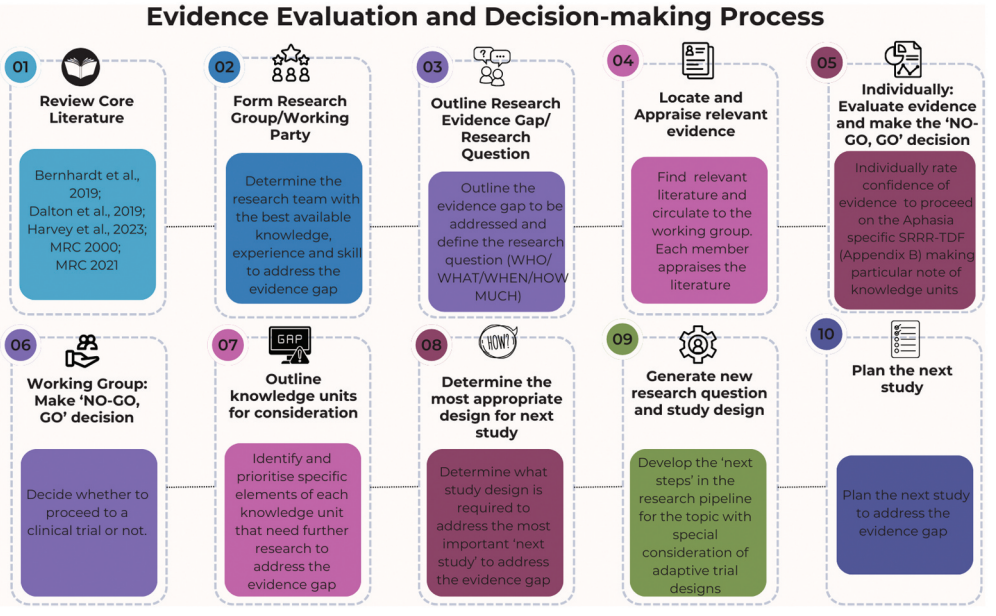


Figure 2. SRRR-TDF-A suggested workflow procedure.

Table 1. Participant selection criteria ("WHO") kept constant across examples.

Inclusion	Exclusion
• Aged 18 years or older • Aphasia resulting from a stroke • Confirmed aphasia by a score of <93.8 on the Western Aphasia Battery-Revised Aphasia Quotient (WAB-R-AQ) or equivalent for tools in languages other than English • Have corrected hearing and vision • Sufficient comprehension to provide their own written informed consent	• Neurological condition other than stroke • Severe apraxia of speech or dysarthria

Table 2. Dose related terminology.

Term	Definition
Duration*	Length of the intervention as measured in days, weeks or months
Session*	An occasion of service in which the intervention is undertaken
Session length*	Total session time
Treatment frequency^	Number of days with sessions per week
Treatment intensity^	Number of session hours per week

Dose Dimensions: *Hayward et al. (2021); ^RELEASE (2021).

the group before a consensus meeting. At the consensus meeting, each point in the "Prioritised Evaluation Criteria" box of the framework was discussed in relation to the strength of the evidence for the research question, together with the individual ratings of the evidence presented in the "Clinical Evidence" box. The expert groups were encouraged to highlight the evidence gaps in each knowledge unit as part of this process. A consensus confidence rating was reached, and the collective decision to "GO, NO-GO" was made. Each expert group then generated recommendations for the next hypothetical study to be completed, taking into

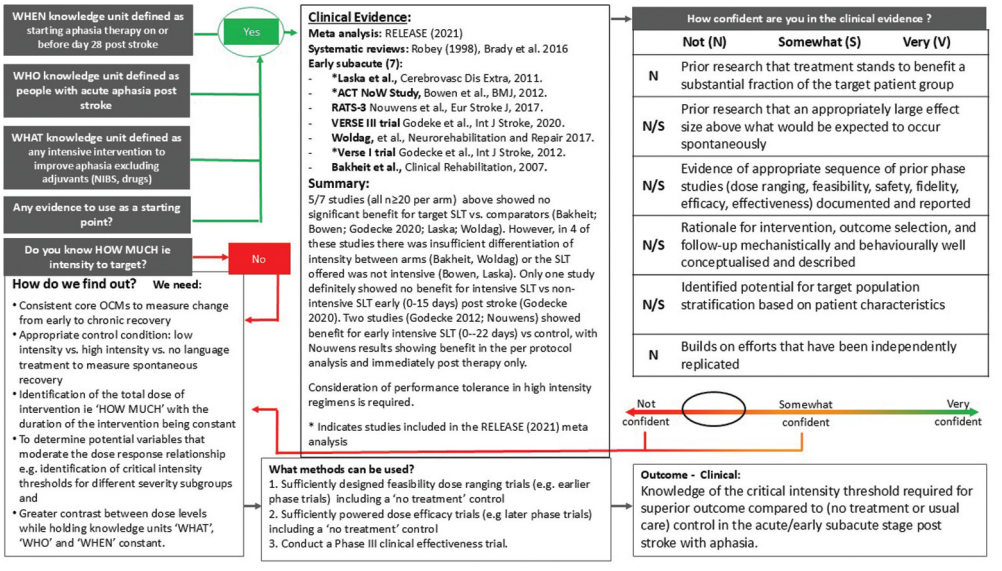


Figure 3. 'How Much' SRRR-TDF-A completed example.

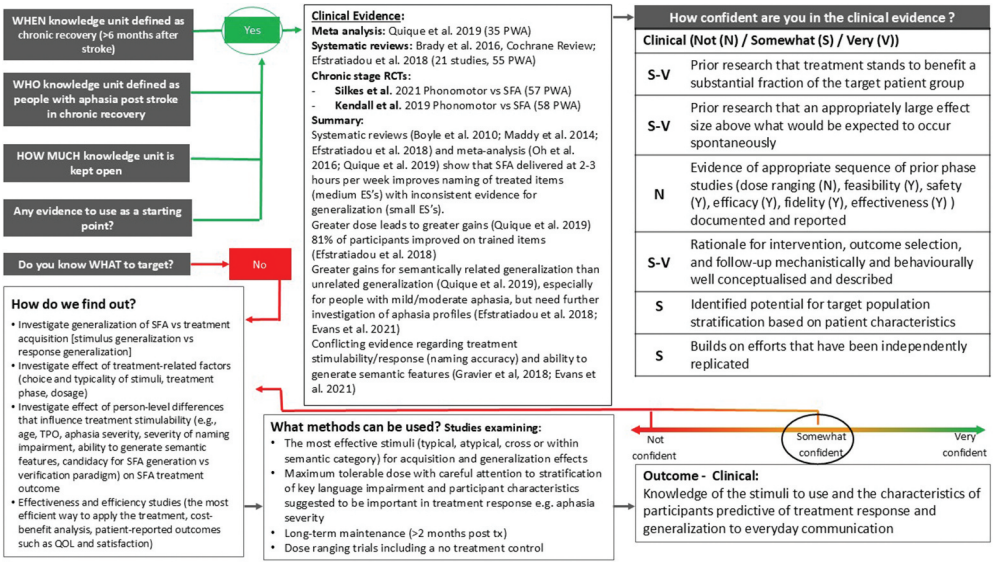


Figure 4. 'What' SRRR-TDF-A completed example.

account that there were several evidence gaps to be addressed in each example. The evidence gaps were prioritised by consensus in relation to the most important "next piece" of information required to progress the topic along the research pipeline. Finally, the "How do we find out?" and "What methods can be used?" boxes were completed incorporating the Medical Research Council's suggested frameworks (Campbell et al., 2000; Skivington et al., 2021) framework for clinical trial phases (Appendix B). A flow-chart of this process is outlined in Figure 2. Using the "How do we find out?" and "What methods can be used?" boxes provided

Table 3. Modified aphasia confidence rating tool taken from the SRRR-TDF evaluation criteria (Bernhardt et al., 2019).

How confident are you in the clinical evidence?	
N S V	Prior research shows that intervention stands to benefit a substantial fraction of the target patient group
N S V	Prior research shows an appropriately large effect size above what would be expected to occur spontaneously
N S V	Evidence of appropriate sequence of prior phase studies (dose ranging, feasibility, safety, efficacy, fidelity, effectiveness) documented and reported
N S V	Rationale for intervention, outcome selection, and follow-up mechanistically and behaviourally well conceptualised and described
N S V	Prior research identified potential for target population stratification based on patient characteristics
N S V	Builds on efforts that have been independently replicated

N = Not, S = Somewhat, V = Very.

clear "next steps" in the process of determining how to address the evidence gaps identified in the decision-making exercise. The "Clinical Outcome" box should produce a consensus derived approach to address the evidence gap in the investigated field.

Results

"HOW MUCH" example

Research question

The "*how much*" research question was, "Does higher compared to lower dose/no aphasia intervention in early recovery (starting before day 28 post-stroke) produce better communication outcomes at 12 weeks post stroke?" The completed example is shown in Figure 3. Limiting the "*when*" knowledge unit to the early phase (12 weeks) post-stroke, facilitated more focused attention on a specific epoch post-stroke, narrowing the available evidence to address this important issue. Additionally, in this example the "*what*" knowledge unit was defined broadly as any intervention to improve communication function following post-stroke aphasia, excluding adjuvants (e.g., non-invasive brain stimulation or drugs). Higher dose intervention was defined as at least five hours of intervention (on-task) per week for four to twelve weeks (Bhogal et al., 2003; Brady et al., 2016; RELEASE, 2021; Robey, 1998).

Ranking of confidence for clinical evidence

The expert group's rankings (Figure 3) showed an overall confidence rating between "Not confident" and "Somewhat confident" for "*how much*" based on the clinical evidence that included an individual participant network meta-analysis (RELEASE, 2021), two meta-analyses (Brady et al., 2016; Robey, 1998) and seven randomised clinical trials (RCT), all of which included data from participants on or before day 28 post stroke. All RCTs ($n = 7$) had more than 20 participants per arm. With the exception of VERSE I (Godecke et al., 2012) which was an earlier phase trial to VERSE III (Godecke et al., 2012), the trials (Bakheit et al., 2007; Bowen et al., 2012; Godecke et al., 2020; Laska et al., 2011; Woldag et al., 2017) showed no significant benefit of higher intensity aphasia treatment over the lower intensity/no treatment comparator intervention at the completion of the intervention period or at follow-up time points. The positive outcome in the VERSE I study (Godecke et al., 2012) could possibly be attributed to the fact that the participants in the "usual care

arm" of this study received limited or no intervention in the first 21 days post stroke, compared to the "daily therapy arm" who received an average of seven hours of face-to-face therapy. The difference in amount and intensity of treatment in this period was statistically significant (Godecke et al., 2012). The lack of difference of dose between intervention arms was noted in 4/5 RCTs with insufficient reported differentiation of intensity between groups (Bakheit et al., 2007; Woldag et al., 2017) or the experiment intervention offered was not intensive (Bowen et al., 2012; Laska et al., 2011). One study (Godecke et al., 2020) showed no benefit of higher over lower dose while one study (Nouwens et al., 2017) showed a higher intensity treatment benefit in the per protocol analysis only (that is in those participants who received the prescribed treatment dose of seven hours, weekly).

Based on the confidence rating of the evidence selected for review, the expert group agreed that a "NO-GO" decision had been reached and further data regarding a critical threshold of dose are required before future Phase III clinical trials can establish the superiority of higher intensity treatment over no treatment /low intensity usual care in early aphasia recovery.

Evidence gaps

To achieve this, the expert group identified five areas that require further research to inform the critical dose threshold in this example. These factors included the need for: i) use of consistent research outcome measures with the ability to sensitively measure communicative change in early recovery; ii) an appropriate control condition with a sufficiently different dose from the intervention group; iii) identification of the target "threshold dose" for testing with the duration of intervention kept constant i.e., "*how much*"; iv) determining potential variables that moderate the dose response relationship for example, identification of critical intensity thresholds for different severity subgroups and v) testing of tolerable maximum dose levels while holding knowledge units "*what*", "*who*" and "*when*" constant.

Recommendations

The methods required to inform the above "evidence gaps" were to: i) develop appropriate feasibility, dose ranging, screening and dose finding studies (phase I and II trials) that included a "no treatment", a wait-list control or very low intensity usual care control (see Cassarly et al., 2021 as an example); and once positive evidence is established, ii) develop sufficiently powered dose efficacy trials (phase III trials) including a wait-list control/"no treatment" for the equivalent duration of the trial intervention to prove that chosen interventions are ready for progression to phase III and IV clinical trials. Specifically, the control interventions in early recovery should aim to account for natural recovery in the study design (e.g., a wait-list control group to account for no therapy) and include interval assessments to monitor change over time.

"What" example

Research question

The "WHAT" example is shown in Figure 4. The research question was "Does Semantic Feature Analysis (SFA) improve communication outcomes to a greater degree than other

interventions in chronic aphasia recovery (after six months post stroke)?" Keeping the "*when*" knowledge unit constant to chronic recovery facilitated more focused attention on a specific epoch post stroke, which in turn narrowed the available evidence to address this important issue. The "*how much"* knowledge unit was not defined, acknowledging that this would differ depending on the study and intervention type. Not keeping the "*how much"* knowledge unit constant within the research question allowed us to demonstrate the importance of the "unknown interaction between knowledge units" and the potential this has to affect the outcome of the confidence rating.

Individual expert group rankings were collated (Figure 4) revealing an overall confidence rating of "Somewhat confident" based on the evaluated evidence (Appendix E). This evidence included a meta-analysis (Quique et al., 2019) that incorporated data from earlier systematic reviews (Boyle, 2010; Maddy et al., 2014) and one more recent systematic review and meta-analysis (Brady et al., 2016) and a systematic review (Efstratiadou et al., 2018). Additionally, two RCTs with higher participant numbers ($N > 20$ PWA per group) were included (Kendall et al., 2019; Silkes et al., 2021). The evidence revealed medium effects sizes for SFA delivered for two to three hours per week to improve treated items and inconsistent evidence for generalization. A greater therapy dose appeared to lead to greater gains (Efstratiadou et al., 2018; Quique et al., 2019). The individual profiles (e.g., type and severity of aphasia, time post stroke onset, cognition, comprehension ability) of responders in these studies indicated that SFA may be more effective for people with fluent and mild/moderate aphasia.

Despite the higher confidence rating in the "*what*" example compared to the "*how much*" example, a "NO-GO" decision was also reached by the expert group for the "WHAT" evidence review. The expert group agreed that several knowledge units required smaller, earlier phase trial designs before results could be scaled up to Phase III efficacy studies. The following research priorities were identified: i) the optimal defined dose (intensity and duration) of SFA (*how much*), ii) generalizability of SFA treatment acquisition outcomes to connected speech (*what*), iii) the effect of individual treatment related components (*what/who*) and iv) person level differences that influence response to treatment (*who*).

Recommendations

The methods required to inform the "what" evidence gaps to be addressed were: i) identify the maximum tolerable dose with dose ranging studies specific to SFA with careful attention to stratification of key language impairment and participant characteristics, ii) establishing long term maintenance effects (>2 months post treatment) on language and overall quality of life outcomes iii) to determine stimuli specific effects for acquisition and generalization. Additionally, the expert group identified all future early-phase trials should include longitudinal / maintenance outcome measures (*when*), Patient Reported Outcome Measures (PROMS) and Quality of Life (QoL) measures (*what*) and data to evaluate treatment cost benefits.

Figure 2 outlines the process we used to complete the examples presented here. The Aphasia specific SRRR-TDF-A (Appendix B) is also provided as a word document in the supplement for use.

Discussion

Our group has developed one of many possible routes to understanding the aphasia evidence base to progress an appropriately phased clinical trial. The expert group adapted the SRRR-TDF (Bernhardt et al., 2019) to fit the lack of preclinical studies in aphasia research (Appendix B). The decision to remove preclinical research from the "Evidence" summary box was made following in-depth discussion within our expert group. The final decision was made following agreement that the definition of "pre-clinical" in the trials design literature was centred around the meaning "before testing in humans or 'in-vitro' (laboratory-based studies) and 'in-vivo' (animal studies)" (Kleinman & Mold, 2009). The lack of cellular and animal model research in the field of aphasiology was clear. In keeping with the overall scientific definitions in clinical trials, the term "pre-clinical" was removed.

Further discussion was undertaken regarding the possibility that single-case experimental designs (SCEDs) could be substituted in for "pre-clinical" research the application of the SRRR-TDF-A. The use of SCEDs may provide clearer links to the theories underpinning aphasia treatment approaches and could equally be argued for (Yang et al., 2023) and be included in the application of the SRRR-TDF-A in future. The issue of terminology around what constitutes a Phase I clinical trial is starting to be addressed in newer frameworks (National Institutes of Health, 2025) ie the use of the word "Modelling" to describe Phase I research allows for broader application of research from all fields and may allow for inclusion of SCED research in the SRRR-TDF-A. This may assist with addressing issues related to developing more personalised / individualised aphasia therapy approaches in a known heterogeneous population.

The Expert group used the aphasia specific SRRR-TDF to identify the existing critical gaps in two clinically relevant examples of aphasia recovery research and to organize our decision making about our confidence in the evidence. A "GO, NO-GO" decision was made and using the remaining prompts "How do we find out?" Priority areas for future research were generated to address the evidence gaps outlined in the "GO, NO-GO" decision. Finally, the expert group drew on the (Campbell et al., 2000; Skivington et al., 2021) frameworks to guide decisions regarding the type of clinical trial required to address the evidence gaps and considered the most time and cost-efficient trial design to answer the research question (presented in the "Clinical Outcomes" box). Overall, the process helped to synthesise vast amounts of information in a systematic and analytical way. The use of this process resulted in the development of a clear and manageable research question and pipeline for each example that can be used systematically to advance aphasia recovery research.

However, the expert group is aware that funding and funder priorities may not allow or provide for several studies to answer each question as suggested by this systematic approach. The expert group argues that the systematic approach provides a guide and justification for increasing the early trial phase exploration of aphasia intervention trials to address possible ethical considerations and to reduce subsequent research waste. The expert group found the process outlined in this paper useful and informative to provide a thorough, systematic evaluation of the current evidence base and to support prioritisation of intervention components for investigation in future research. The expert group

remains pragmatic and is not arguing for a purist approach for the evaluation of the existing evidence.

The expert group also acknowledge that use of the SRRR-TDF (Bernhardt et al. 2019) and SRRR-TDF-A decision-making tools has limitations including insufficient evidence for definitive decision making for each knowledge unit and difficulty incorporating nuanced data from multi-component behavioural interventions. In real-world research contexts, single therapeutic factors can rarely be separated from one another and from the context in which they are measured. Simplifying such complex human behaviours into segmented elements, runs a risk that important and meaningful treatment interactions may be over-looked or masked.

This acknowledgement highlights the value in targeted consideration and investigation of key components in earlier phase designs prior to moving to more definitive trial designs to reduce research waste and knowledge gaps. The expert group agrees with the convincing arguments of our motor training colleagues' (Bernhard et al., 2019) that an honest appraisal of the research evidence may ultimately lead to fewer, but better trials progressing to Phase III.

People with aphasia, their families and healthcare providers find it difficult to decide which treatment options will yield optimal rehabilitation results at an individually tailored intervention level. A concern is that our already financially and resource strained healthcare systems invest in suboptimal therapy regimens (Palmer, 2020), because no evidence exists to the contrary. This in turn adds to the economic burden of post stroke care (Brogan et al., 2023; Kim et al., 2023; Olesen et al., 2012). The expert group urges aphasia researchers to earnestly evaluate the evidence base and consider appropriate trial phasing to drive cutting-edge aphasia treatment research. Strategic international collaboration is needed to prioritise research and address the evidence gaps. This research needs to be done in everyday rehabilitation hospitals, healthcare settings, homes, and communities around the globe so that we can achieve the next "breakthrough" intervention that will improve the lives of people with aphasia in the shortest time possible.

Conclusion and recommendations

The expert group acknowledges the many models and frameworks available to support the synthesis of vast amounts of research. The expert group chose frameworks that were believed to be best suited to the rich body of aphasia treatment research. Having tailored the SRRR-TDF (Bernhardt et al., 2019) to better suit aphasia research (SRRR-TDF-APHASIA), the frameworks were applied in two examples (Figures 3 and 4). The expert group proposed recommendations for using this process (Figure 2) to drive the next generation of aphasia clinical trials. Additionally, the expert group recommend that all aphasia research is co-constructed with people with lived experience, their family members and clinicians to ensure the research questions and outcomes are relevant to the community (Anemaat et al., 2021).

- Review process related background literature including phasing of clinical trials (Campbell et al., 2000; Skivington et al., 2021), SRRR-TDF process for motor stroke (Bernhardt et al., 2019), dose articulation in clinical stroke recovery (Dalton et al., 2019) and examining dose related framework in aphasia rehabilitation (Harvey et al., 2023).
- Form a research working/project group

- Outline the evidence gap to be addressed and define the research question
- Search for all relevant literature and distribute key research papers in the field to working group members
- Honestly evaluate the group's confidence in the evidence base and "NO-GO, GO" decision, taking particular note of key "knowledge units" (*who/ what/ when/ how much* therapy)
- Complete Aphasia specific SRRR-TDF individually and as a consensus process in the group
- Highlight the evidence gaps and potential methods to address these
- Generate a research question or justify your current research question based on identified gaps
- Plan the next study using the framework and process outlined here
- Consider reference to this framework when applying for funding/publishing justification for research.

Before commencing any aphasia intervention evaluation, we strongly encourage aphasia researchers to familiarise themselves with the resources available on the CATs website (https://www.aphasiatrials.org/tap-rct-resources/) concerning trial phasing and design. A user guide and training video for the application of the framework will be on available for researchers to embed the tool into routine research development. The TAP subgroup will support researchers to use this resource through targeted peer support via the CATs website.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Erin Godecke http://orcid.org/0000-0002-7210-1295
Emily Brogan http://orcid.org/0000-0001-9604-4558
Rebecca Palmer http://orcid.org/0000-0002-2335-7104
Marian C. Brady http://orcid.org/0000-0002-4589-7021
Frank Becker http://orcid.org/0000-0002-0857-0628
Caterina Breitenstein http://orcid.org/0000-0002-6408-873X
Sonia Brownsett http://orcid.org/0000-0003-1569-2014
Katerina Hilari http://orcid.org/0000-0003-2091-4849
Argye E. Hillis http://orcid.org/0000-0002-5192-1171
Paola Marangolo http://orcid.org/0000-0002-1516-9832
Miranda L. Rose http://orcid.org/0000-0002-8892-0965
Donna C. Tippett http://orcid.org/0000-0001-9485-9745
Julie Bernhardt http://orcid.org/0000-0002-2787-8484
Kathryn S. Hayward http://orcid.org/0000-0001-5240-3264

References

Academy of Medical Sciences. (2019). *Adaptive trials: Acceptability, versatility and utility*. Academy of Medical Sciences forum.

Anemaat, L., Palmer, V., Copland, D., Mainstone, K., Druery, K., Druery, J., Aisthorpe, B., Binge, G., Mainstone, P., & Wallace, S. (2021). Using experience-based codesign to coproduce aphasia rehabilitation services: Study protocol. *BMJ Open*, *11*(11), e047398. https://doi.org/10.1136/bmjopen-2020-047398

Bakheit, M., Shaw, S., Barrett, L., Wood, J., Carrington, S., Griffiths, S., Searle, K., & Koutsi, F. (2007). A prospective, randomised, parallel group, controlled study of the effect of intensity of speech and language therapy on early recovery from poststroke aphasia. *Clinical Rehabilitation*, *21*(10), 885–894. https://doi.org/10.1177/0269215507078486

Behn, N., Moss, B., McVicker, S., Roper, A., Northcott, S., Marshall, J., Thomas, S., Simpson, A., Flood, C., James, K., Goldsmith, K., & Hilari, K. (2021). Supporting wellbeing through peer-befriending (SUPERB) feasibility trial: Fidelity of peer-befriending for people with aphasia. *BMJ Open*, *11*(8), e047994. https://doi.org/10.1136/bmjopen-2020-047994

Bernhardt, J., Hayward, K. S., Dancause, N., Lannin, N. A., Ward, N. S., Nudo, R. J., Farrin, A., Churilov, L., Boyd, L. A., Jones, T. A., Carmichael, S. T., Corbett, D., & Cramer, S. C. (2019). A stroke recovery trial development framework: Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable. *International Journal of Stroke*, *14*(8), 792–802. https://doi.org/10.1177/1747493019879657

Bhatt, D. L., & Mehta, C. (2016). Adaptive designs for clinical trials. *The New England Journal of Medicine*, *375*(1), 65–74. https://doi.org/10.1056/NEJMra1510061

Bhogal, S. K., Teasell, R. W., Foley, N. C., & Speechley, M. R. (2003). Rehabilitation of aphasia: More is better. *Topics in Stroke Rehabilitation*, *10*(2), 66–76. https://doi.org/10.1310/RCM8-5TUL-NC5D-BX58 PMID: 13680518.

Bowen, A., Hesketh, A., Patchick, E., Young, A., Davies, L., Vail, A., Long, A. F., Watkins, C., Wilkinson, M., Pearl, G., Ralph, M. A., & Tyrrell, P. (2012). Effectiveness of enhanced communication therapy in the first four months after stroke for aphasia and dysarthria: A randomised controlled trial. *BMJ (Clinical Research (Ed))*, *345*(jul13 1), e4407. https://doi.org/10.1136/bmj.e4407

Boyle, M. (2010). Semantic feature analysis treatment for aphasic word retrieval impairments: What's in a name? *Topics in Stroke Rehabilitation*, *17*(6), 411–422. https://doi.org/10.1310/tsr1706-411

Brady, M. C., Brady, M.C, Ali, M., VandenBerg, K., Williams, L.J., Williams, L.R., Abo, M., et al. (2022). Complex speech-language therapy interventions for stroke-related aphasia: The RELEASE study incorporating a systematic review and individual participant data network meta-analysis. *Health and Social Care Delivery Research*, *10*(28), 1–272. https://doi.org/10.3310/RTLH7522

Brady, M. C., Kelly, H., Godwin, J., Enderby, P., & Campbell, P. (2016). Speech and language therapy for aphasia following stroke. *Cochrane Database of Systematic Reviews(6)*, Article CD000425. *2016* (6). https://doi.org/10.1002/14651858.CD000425.pub4

Breitenstein, C., Grewe, T., Flöel, A., Ziegler, W., Springer, L., Martus, P., Huber, W., Willmes, K., Ringelstein, E. B., Haeusler, K. G., Abel, S., Glindemann, R., Domahs, F., Regenbrecht, F., Schlenck, K.-J., Thomas, M., Obrig, H., de Langen, E., Rocker, R. … Bamborschke, S. (2017). 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*, *389*(10078), 1528–1538. https://doi.org/10.1016/S0140-6736(17)30067-3

Brogan, E., Ciccone, N., & Godecke, E. (2020). An exploration of aphasia therapy dosage in the first six months of stroke recovery. *Neuropsychological Rehabilitation*, 1–35. https://doi.org/10.1080/09602011.2020.1776135

Brogan, E., Kim, J., Grimley, R. S., Wallace, S. J., Baker, C., Thayabaranathan, T., Andrew, N. E., Kilkenny, M. F., Godecke, E., Rose, M. L., & Cadilhac, D. A. (2023, 8; S0003-9993(23)00093-4 The excess costs of hospitalization for acute stroke in people with communication impairment: A Stroke123 data linkage sub-study. *Archives of Physical Medicine & Rehabilitation*, *104*(6), 942–949. https://doi.org/10.1016/j.apmr.2023.01.015

Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A. L., Sandercock, P., Spiegelhalter, D., & Tyrer, P. (2000, September 16). Framework for design and evaluation of complex interventions to improve health. *BMJ*, *321*(7262), 694–696. https://doi.org/10.1136/bmj.321.7262.694 PMID: 10987780; PMCID: PMC1118564.

Cassarly, C., Doyle, A., Trinh, L., Horn, J., Aitchison, M., Elm, J., Fridriksson, J., & Bonilha, L. (2021, November 24). Speech entertainment for aphasia recovery (SpArc) phase II trial design. *Contemporary Clinical Trials Communications*, *24*, 100876. https://doi.org/10.1016/j.conctc.2021.100876

Chalmers, I., & Glasziou, P. (2009). Avoidable waste in the production and dissemination of research. *Lancet*, *374*(9683), 86–89. https://doi.org/10.1016/S0140-6736(09)60329-9

Dalton, E. J., Churilov, L., Lannin, N. A., Corbett, D., & Hayward, K. S. (2019). Dose articulation in preclinical and clinical stroke recovery: Refining a discovery research pipeline and presenting a scoping review protocol [study protocol]. *Frontiers in Neurology*, *10*(1148). https://doi.org/10.3389/fneur.2019.01148

Dalton, E. J., Lannin, N. A., Campbell, B. C., Churilov, L., & Hayward, K. S. (2023). Enhancing generalizability of stroke clinical trial results: Illustrations from upper-limb motor recovery trials. *International Journal of Stroke*, *18*(5), 532–542. https://doi.org/10.1177/17474930221135730

Efstratiadou, E. A., Papathanasiou, I., Holland, R., Archonti, A., & Hilari, K. (2018). A systematic review of semantic feature analysis therapy studies for aphasia. *Journal of Speech, Language, & Hearing Research*, *61*(5), 1261–1278. https://doi.org/10.1044/2018_jslhr-l-16-0330

Evans, W. S., Cavanaugh, R., Gravier, M. L., Autenreith, A. M., Doyle, P. J., Hula, W. D., & Dickey, M. W. (2021, February). Effects of semantic feature type, diversity, and quantity on semantic feature analysis treatment outcomes in aphasia. *American Journal of Speech-Language Pathology*, *30*(1S, 344–358. https://doi.org/10.1044/2020_AJSLP-19-00112

Godecke, E., Armstrong, E., Rai, T., Ciccone, N., Rose, M. L., Middleton, S., Whitworth, A., Holland, A., Ellery, F., Hankey, G. J., Cadilhac, D. A., & Bernhardt, J. (2020). A randomised control trial of intensive aphasia therapy after acute stroke: The Very Early Rehabilitation for Speech (VERSE) study. *International Journal of Stroke*, 1747493020961926. https://doi.org/10.1177/1747493020961926

Godecke, E., Hird, K., Lalor, E. E., Rai, T., & Phillips, M. R. (2012, Dec). Very early poststroke aphasia therapy: A pilot randomized controlled efficacy trial. *Int J Stroke*, *7*(8), 635–644. https://doi.org/10.1111/j.1747-4949.2011.00631.x

Harvey, S., Rose, M. L., Brogan, E., Pierce, J. E., Godecke, E., Brownsett, S. L. E., Churilov, L., Copland, D., Dickey, M. W., Dignam, J., Lannin, N. A., Nickels, L., Bernhardt, J., & Hayward, K. S. (2023, May). Examining dose frameworks to improve aphasia rehabilitation research. *Archives of Physical Medicine & Rehabilitation*, *104*(5), 830–838. https://doi.org/10.1016/j.apmr.2022.12.002 Epub 2022 Dec 24. PMID: 36572201.

Hayward, K. S., Churilov, L., Dalton, E. J., Brodtmann, A., Campbell, B. C. V., Copland, D., Dancause, N., Godecke, E., Hoffmann, T. C., Lannin, N. A., McDonald, M. W., Corbett, D., & Bernhardt, J. (2021). Advancing stroke recovery through improved articulation of nonpharmacological intervention dose. *Stroke*, *52*(2), 761–769. https://doi.org/10.1161/STROKEAHA.120.032496

Hayward, K. S., Dalton, E. J., Campbell, B. C. V., Khatri, P., Dukelow, S. P., Johns, H., Walter, S., Yogendrakumar, V., Pandian, J. D., Sacco, S., Bernhardt, J., Parsons, M., Saver, J. L., & Churilov, L. (2024). Adaptive trials in stroke. Current use and future directions. *Neurology*, *103*(8), e209876. https://doi.org/10.1212/WNL.0000000000209876

Hilari, K., Behn, N., James, K., Northcott, S., Marshall, J., Thomas, S., Simpson, A., Moss, B., Flood, C., McVicker, S., & Goldsmith, K. (2021). Supporting wellbeing through peer-befriending (SUPERB) for people with aphasia: A feasibility randomised controlled trial. *Clinical Rehabilitation*, *35*(8), 1151–1163. https://doi.org/10.1177/0269215521995671

Kendall, D. L., Moldestad, M. O., Allen, W., Torrence, J., & Nadeau, S. E. (2019). Phonomotor versus semantic feature analysis treatment for anomia in 58 persons with aphasia: A randomized controlled trial. *Journal of Speech, Language, & Hearing Research*, *62*(12), 4464–4482. https://doi.org/10.1044/2019_jslhr-l-18-0257

Kim, J., Sookram, G., Godecke, E., Brogan, E., Armstrong, E., Ellery, F., Rai, T., Rose, M., Ciccone, N., Middleton, S., Holland, A., Hankey, G. J., Bernhardt, J., & Cadilhac, D. A. (2023). Economic evaluation of the very early rehabilitation in speech (VERSE) intervention. *Topics in Stroke Rehabilitation*. https://doi.org/10.1080/10749357.2023.2229039

Kleinman, M. S., & Mold, J. W. (2009). Defining the components of the research pipeline. *Clinical and Translational Science*, *2*(4), 312–314. https://doi.org/10.1111/j.1752-8062.2009.00119.x

Lang, C. E., Lohse, K. R., & Birkenmeier, R. L. (2015). Dose and timing in neurorehabilitation: Prescribing motor therapy after stroke. *Current Opinion in Neurology*, *28*(6), 549–555. https://doi.org/10.1097/WCO.0000000000000256

Laska, A. C., Kahan, T., Hellblom, A., Murray, V., & von Arbin, M. (2011). A randomised controlled trial on very early speech and language therapy in acute stroke patients with aphasia. *Cerebrovascular Diseases Extra*, *1*(1), 66–74. https://doi.org/10.1159/000329835

Maddy, K. M., Capilouto, G. J., & McComas, K. L. (2014). The effectiveness of semantic feature analysis: An evidence-based systematic review. *Annals of Physical and Rehabilitation Medicine*, *57*(4), 254–267. https://doi.org/10.1016/j.rehab.2014.03.002

Mallet, K. H., Shamloul, R. M., Corbett, D., Finestone, H. M., Hatcher, S., Lumsden, J., Momoli, F., Shamy, M. C., Stotts, G., Swartz, R. H., Yang, C., & Dowlatshahi, D. (2016, December 21). RecoverNow: Feasibility of a mobile tablet-based rehabilitation intervention to treat post-stroke communication deficits in the acute care setting. *PLOS ONE*, *11*(12), e0167950. https://doi.org/10.1371/journal.pone.0167950 PMID: 28002479; PMCID: PMC5176170.

Marshall, J., Devane, N., Talbot, R., Caute, A., Cruice, M., Hilari, K., MacKenzie, G., Maguire, K., Patel, A., Roper, A., & Wilson, S. (2020). A randomised trial of social support group intervention for people with aphasia: A novel application of virtual reality. *PLOS ONE*, *15*(9), e0239715.

National Institutes of Health. (2025, April). *Nih clinical trials*. U.S. Department of Health and Human Services, National Institutes of Health. https://www.nih.gov/health-information/nih.clinical-research-trials-you/basics

Northcott, S., Simpson, A., Thomas, S. A., Hirani, S. P., Flood, C., & Hilari, K. (2019). Solution focused brief therapy in post-stroke aphasia (SOFIA trial): Protocol for a feasibility randomised controlled trial. *AMRC Open Research*, *1*, 11. https://doi.org/10.12688/amrcopenres.12873.2

Nouwens, F., de Lau, L. M. L., Visch-Brink, E. G., van de Sandt-Koenderman, W. M. E., Lingsma, H. F., Goosen, S., Blom, D. M. J., Koudstaal, P. J., & Dippel, D. W. J. (2017). Efficacy of early cognitive-linguistic treatment for aphasia due to stroke: A randomised controlled trial (Rotterdam Aphasia Therapy Study-3). *European Stroke Journal*, *2*(2), 126–136. https://doi.org/10.1177/2396987317698327

Oh, S. J., Eom, B., Park, C., & Sung, J. E. (2016). Treatment efficacy of semantic feature analyses for persons with aphasia: Evidence from meta-analyses. *Communication Sciences & Disorders*, *21*(2), 310–323. https://doi.org/10.12963/csd.16312

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H. U., Jönsson, B., & CDBE2010 study group; European Brain Council. (2012). The economic cost of brain disorders in Europe. *European Journal of Neurology*, *19*(1), 155–162. https://doi.org/10.1111/j.1468-1331.2011.03590.x PMID: 22175760.

Pallmann, P., Bedding, A. W., Choodari-Oskooei, B., Dimairo, M., Flight, L., Hampson, L. V., Holmes, J., Mander, A. P., Odondi, L. O., Sydes, M. R., Villar, S. S., Wason, J. M. S., Weir, C. J., Wheeler, G. M., Yap, C., & Jaki, T. (2018). Adaptive designs in clinical trials: Why use them, and how to run and report them. *BMC Medicine*, *16*(1), 29. https://doi.org/10.1186/s12916-018-1017-7

Palmer, R. (2020). Design considerations for clinical trials in aphasia. *Annals of Indian Academy of Neurology*, *23*(Suppl 2), S52–s56. https://doi.org/10.4103/aian.AIAN_453_20

Quique, Y. M., Evans, W. S., & Dickey, M. W. (2019). Acquisition and generalization responses in aphasia naming treatment: A meta-analysis of semantic feature analysis outcomes. *American Journal of Speech-Language Pathology*, *28*(1s), 230–246. https://doi.org/10.1044/2018_ajslp-17-0155

RELEASE Collaborators. (2020). Communicating simply, but not too simply: Reporting of participants and speech and language interventions for aphasia after stroke. *International Journal of Speech-Language Pathology*, *22*(3), 302–312. https://doi.org/10.1080/17549507.2020.1762000

RELEASE Collaborators. (2021, May). Rehabilitation and recovery of people with aphasia after stroke (RELEASE) collaborators. Predictors of poststroke aphasia recovery: A systematic review-informed individual participant data meta-analysis. *Stroke*, *52*(5), 1778–1787. https://doi.org/10.1161/STROKEAHA.120.031162

Robey, R. (1998). A meta-analysis of clinical outcomes in the treatment of aphasia. *Journal of Speech, Language, & Hearing Research*, *41*(1), 172. https://doi.org/10.1044/jslhr.4101.172

Rose, M. L., Nickels, L., Copland, D., Togher, L., Godecke, E., Meinzer, M., Rai, T., Cadilhac, D. A., Kim, J., Hurley, M., Foster, A., Carracher, M., Wilcox, C., & Steel, G. (2022). Results of the COMPARE trial of constraint-induced or multimodality aphasia therapy compared with usual care in chronic post-stroke aphasia. *Journal of Neurology, Neurosurgery & Psychiatry*, *93*(6), 573–581. https://doi.org/10.1136/jnnp-2021-328422

Silkes, J. P., Fergadiotis, G., Graue, K., & Kendall, D. L. (2021). Effects of phonomotor therapy and semantic feature analysis on discourse production. *American Journal of Speech-Language Pathology*, *30*(1s), 441–454. https://doi.org/10.1044/2020_ajslp-19-00111

Skivington, K., Matthews, L., Simpson, S. A., Craig, P., Baird, J., Blazeby, J. M., Boyd, K. A., Craig, N., French, D. P., McIntosh, E., Petticrew, M., Rycroft-Malone, J., White, M., & Moore, L. (2021). A new framework for developing and evaluating complex interventions: Update of Medical Research Council guidance. *BMJ*, *374*, n2061. https://doi.org/10.1136/bmj.n2061

Thompson, C. K. (2014). Establishing the effects of treatment for aphasia using single-subject-controlled experimental designs. *Aphasiology*, *29*(5), 588–597. https://doi.org/10.1080/02687038.2014.987043

Wallace, S. J., Worrall, L., Rose, T. A., Alyahya, R. S. W., Babbitt, E., Beeke, S., de Beer, C., Bose, A., Bowen, A., Brady, M. C., Breitenstein, C., Bruehl, S., Bryant, L., Cheng, B. B. Y., Cherney, L. R., Conroy, P., Copland, D. A., Croteau, C.Cruice, M. . . . Whitworth, A. (2023). Measuring communication as a core outcome in aphasia trials: Results of the ROMA-2 international core outcome set development meeting. *International Journal of Language & Communication Disorders*, *58*(4), 1017–1028. https://doi.org/10.1111/1460-6984.12840

Wallace, S. J., Worrall, L., Rose, T., Le Dorze, G., Breitenstein, C., Hilari, K., Babbitt, E., Bose, A., Brady, M., Cherney, L. R., Copland, D., Cruice, M., Enderby, P., Hersh, D., Howe, T., Kelly, H., Kiran, S., Laska, A.-C.Marshall, J. . . . Webster, J. (2019). A core outcome set for aphasia treatment research: The ROMA consensus statement. *International Journal of Stroke*, *14*(2), 180–185. https://doi.org/10.1177/1747493018806200

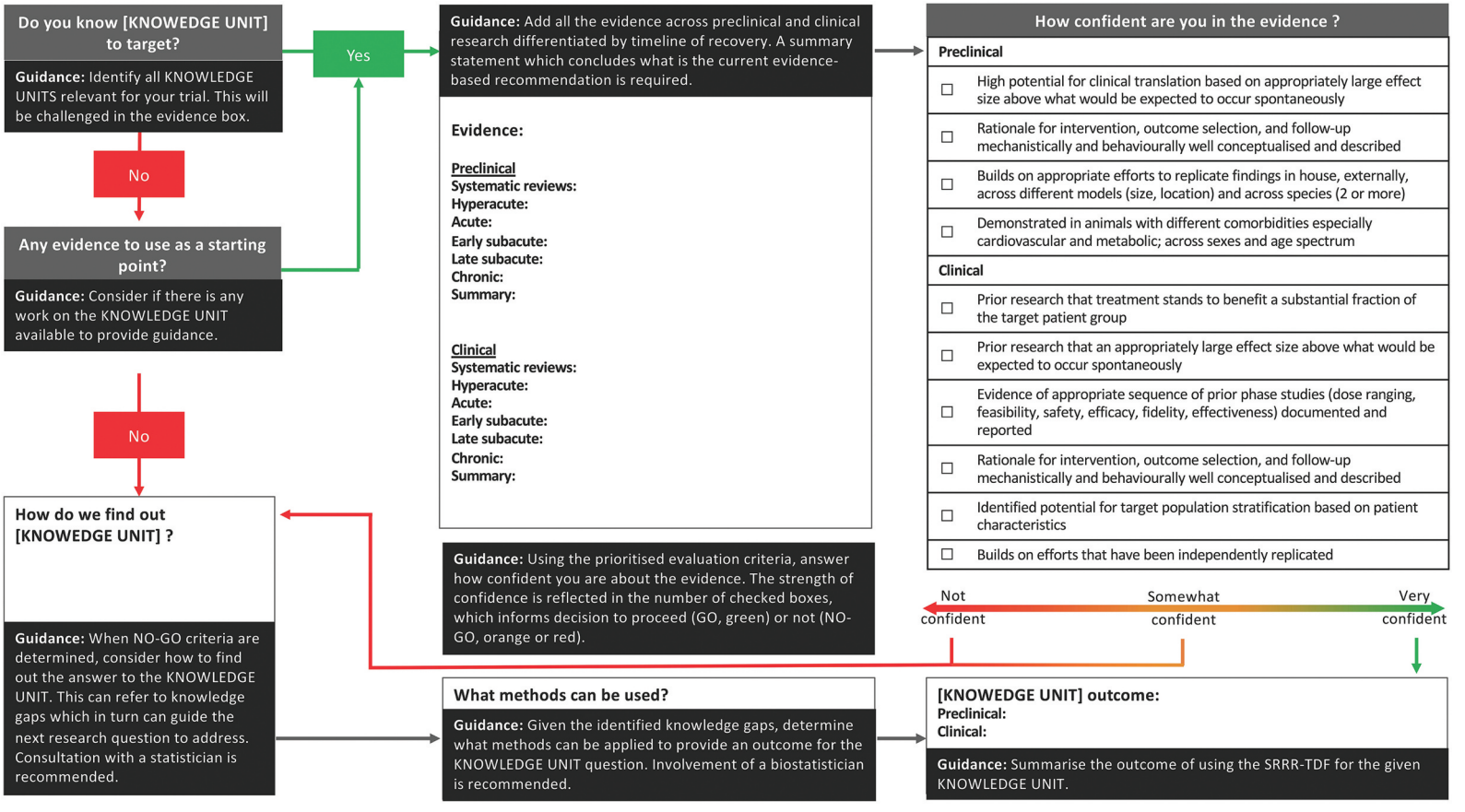
Wallace, S., Worrall, L., Rose, T., & Le Dorze, G. (2014). Measuring outcomes in aphasia research: A review of current practice and an agenda for standardisation AU - Wallace, Sarah J. *Aphasiology*, *28*(11), 1364–1384. https://doi.org/10.1080/02687038.2014.930262

Woldag, H., Voigt, N., Bley, M., & Hummelsheim, H. (2017). Constraint-induced aphasia therapy in the acute stage: What is the key factor for efficacy? A randomised controlled study. *Neurorehabilitation and Neural Repair*, *31*(1), 72–80. https://doi.org/10.1177/1545968316662707

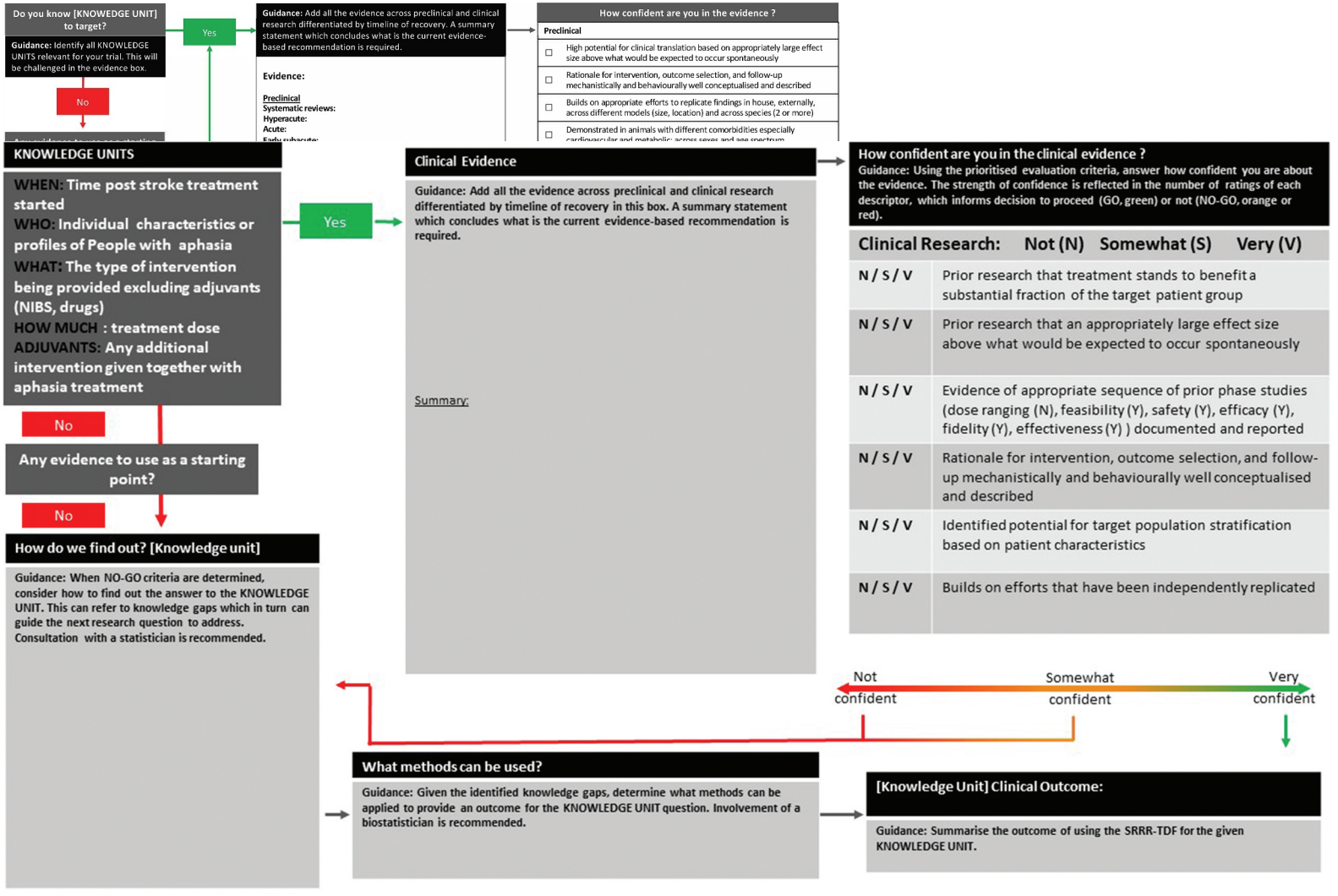
Yang, L., Armijo-Olivo, S., & Gross, D. P. (2023, May). Single-case experimental design in rehabilitation: Basic concepts, advantages, and challenges. *American Journal of Physical Medicine & Rehabilitation*, *102*(5), 454–460. https://doi.org/10.1097/PHM.0000000000002215

Appendices

Appendix A



Appendix B


Do you know [KNOWEDGE UNIT] to target?
Guidance: Identify all KNOWLEDGE UNITS relevant for your trial. This will be challenged in the evidence box.
Yes
No
Guidance: Add all the evidence across preclinical and clinical research differentiated by timeline of recovery. A summary statement which concludes what is the current evidence-based recommendation is required.
Evidence:
Preclinical
Systematic reviews:
Hyperacute:
Acute:
How confident are you in the evidence ?
Preclinical
High potential for clinical translation based on appropriately large effect size above what would be expected to occur spontaneously
Rationale for intervention, outcome selection, and follow-up mechanistically and behaviourally well conceptualised and described
Builds on appropriate efforts to replicate findings in house, externally, across different models (size, location) and across species (2 or more)
Demonstrated in animals with different comorbidities especially
KNOWLEDGE UNITS
WHEN: Time post stroke treatment started
WHO: Individual characteristics or profiles of People with aphasia
WHAT: The type of intervention being provided excluding adjuvants (NIBS, drugs)
HOW MUCH : treatment dose
ADJUVANTS: Any additional intervention given together with aphasia treatment
Yes
No
Any evidence to use as a starting point?
No
How do we find out? [Knowledge unit]
Guidance: When NO-GO criteria are determined, consider how to find out the answer to the KNOWLEDGE UNIT. This can refer to knowledge gaps which in turn can guide the next research question to address. Consultation with a statistician is recommended.
Clinical Evidence
Guidance: Add all the evidence across preclinical and clinical research differentiated by timeline of recovery in this box. A summary statement which concludes what is the current evidence-based recommendation is required.
Summary:
How confident are you in the clinical evidence ?
Guidance: Using the prioritised evaluation criteria, answer how confident you are about the evidence. The strength of confidence is reflected in the number of ratings of each descriptor, which informs decision to proceed (GO, green) or not (NO-GO, orange or red).
Clinical Research: Not (N) Somewhat (S) Very (V)
N / S / V Prior research that treatment stands to benefit a substantial fraction of the target patient group
N / S / V Prior research that an appropriately large effect size above what would be expected to occur spontaneously
N / S / V Evidence of appropriate sequence of prior phase studies (dose ranging (N), feasibility (Y), safety (Y), efficacy (Y), fidelity (Y), effectiveness (Y)) documented and reported
N / S / V Rationale for intervention, outcome selection, and follow-up mechanistically and behaviourally well conceptualised and described
N / S / V Identified potential for target population stratification based on patient characteristics
N / S / V Builds on efforts that have been independently replicated
Not confident
Somewhat confident
Very confident
What methods can be used?
Guidance: Given the identified knowledge gaps, determine what methods can be applied to provide an outcome for the KNOWLEDGE UNIT question. Involvement of a biostatistician is recommended.
[Knowledge Unit] Clinical Outcome:
Guidance: Summarise the outcome of using the SRRR-TDF for the given KNOWLEDGE UNIT.

Appendix C. Expert group members and description of their clinical trials expertise

"How much" Working Group	Discipline	Expertise
Group Lead Erin Godecke (EG)	Speech and Language Pathology	Designing and leading multicentre clinical trials on early intervention and including people with aphasia in stroke clinical trials https://orcid.org/0000-0002-7210-1295
Emily Brogan (EB)	Speech and Language Pathology	Designing and measuring treatment fidelity and therapeutic dose in clinical trials https://orcid.org/0000-0001-9604-4558
Marian Brady (MB)	Speech and Language Pathology	Designing and evaluating complex multidisciplinary interventions in stroke rehabilitation including multiple clinical trials, systematic reviews and meta-analyses including Cochrane Reviews https://orcid.org/0000-0002-4589-7021
Caterina Breitenstein (CB)	Cognitive Neuroscience	Designing and leading multicentre clinical trials that bridge the gap between controlled experimental research and real-world clinical practice https://orcid.org/0000-0002-6408-873X
Kate Hayward (KSH)	Physiotherapy	Designing and leading stroke recovery research, with a strong focus on early-phase and adaptive clinical trial design. Specialist application of SRRR-TDF in clinical trials https://orcid.org/0000-0001-5240-3264
Katerina Hiliari (KH)	Speech and Language Pathology and Psychology	Designing and leading clinical trials in stroke rehabilitation, aphasia, aphasia outcome measures and health-related quality of life https://orcid.org/0000-0003-2091-4849
Paola Marangolo (PM)	Neuropsychology and Cognitive Neuroscience	Expertise in language rehabilitation and neuromodulation in aphasia clinical trials https://orcid.org/0000-0002-1516-9832
Argye Hillis (AH)	Neurology and Speech and Language Pathology	Stroke neurologist and speech language pathologist with expertise in aphasia, and hemispatial neglect. Clinical trial expertise in neuroimaging, diagnosis, treatment, and recovery outcomes https://orcid.org/0000-0002-5192-1171
Shirley Thomas	Psychology	Designing and leading clinical trials in psychological interventions in rehabilitation and aphasia https://orcid.org/0000-0003-0704-9387
"What" Working Group		
Erin Godecke (EG) – Group Lead	Speech and Language Pathology	Designing and leading multicentre clinical trials on early intervention and including people with aphasia in stroke clinical trials https://orcid.org/0000-0002-7210-1295
Emily Brogan (EB)	Speech and Language Pathology	Designing and measuring treatment fidelity and therapeutic dose in clinical trials https://orcid.org/0000-0001-9604-4558
Rebecca Palmer (RP)	Speech and Language Pathology	Designing, managing and delivering aphasia clinical trials in healthcare settings https://orcid.org/0000-0002-2335-7104
Julius Fridrikkson (JF)	Speech and Language Pathology and Neuroscience	Designing, managing, and delivering aphasia clinical trials in aphasia and neuroimaging in healthcare settings
Kate Hayward (KSH)	Physiotherapy	Designing and leading stroke recovery research, with a strong focus on early-phase and adaptive clinical trial design. Specialist application of SRRR-TDF in clinical trials https://orcid.org/0000-0001-5240-3264
Sonia Brownsett (SB)	Speech and Language Pathology	Designing, managing, and delivering aphasia clinical trials in neuroimaging and computer-based intervention in aphasia https://orcid.org/0000-0003-1569-2014

(*Continued*)

"How much" Working Group	Discipline	Expertise
Miranda Rose (MR)	Speech and Language Pathology and Psychology	Designing and leading multicentre clinical trials in chronic aphasia rehabilitation https://orcid.org/0000-0002-8892-0965
Donna Tippett (DT)	Speech and Language Pathology	Designing and leading clinical trials in healthcare settings https://orcid.org/0000-0001-9485-9745

*All authors have conducted multiple aphasia and stroke related clinical trials, included consumer and community involvement in trial development, received national and international competitive funding and contributed new knowledge to aphasia evidence-based guidelines. Authors Becker F and Bernhardt J were involved in the manuscript but did not participate in the working groups.

Appendix D. "HOW MUCH" therapy example evidence summary table

Study	Study Design	TPO*in study	Samples	Aphasia therapy duration/ intensity	Findings/Outcomes	WHO (Population)	WHAT (Therapy type)
Bakheit et al., (2007)	Prosective longitudinal study	< 1 week to 24 weeks post stroke	62 participants recruited; 52 participants completed final assessment	Treatment started immediately after assessment (<1 week) and continued for 12 weeks. Exact amount, intensity and dose of treatment was not recorded.	Progressive increase noted from baseline in all aphasia types. Largest improvements noted in the first 4 weeks with smaller (but statistically significant) incremental increases in subsequent weeks.	PWA post stroke with a WAB score <93.8 at baseline; 50.4% female; Age M (SD) years: 71 (2.3)	Conventional speech language therapy targeting verbal and non-verbal, expressive and receptive communication
Bowen et al., (2012)	Pragmatic, Multicentre Randomised Controlled Trial	2 weeks to 16 weeks post stroke	170 participants recruited; 153 included in primary analysis.	Treatment started immediately after assessment (2 weeks) and continued for up to 16 weeks. *Intervention group* (average): 22 contacts (18 hours) over 13 weeks; *Control group*: 19 contacts (15 hours) over 13 weeks.	Overall improvement in functional communication in both arms of the study. No significant difference in scores between groups at baseline or at 6 month follow up.	PWA post stroke screened to determine if participant would potentially benefit from treatment.	Enhanced communication therapy; typically impairment based approach (aphasia and or dysarthria) by trained SLT *or* social contact from employed staff

(*Continued*)

(Continued).

Brady et al. (2016) Aphasia Cochrane Review.	Systematic Review with meta-analysis	< 1 week to 8 years post	Cochrane Systematic review 57 trials 3002 participants	Highly varied	These studies included people in acute, subacute and chronic recovery. Based on 27 studies (N=1620) benefits of SLT were seen in functional language, language comprehension and language production when compared to no language therapy. Thirty-eight studies (N=1242) compared two different types of SLT provided at varied regimens (intensity, dosage duration), delivery models and approach. More intensive (more hours over short time periods) appeared to help participants' language in daily life and reduce aphasia severity however more people stopped attending high intensity treatments than those who had lower intensity therapy.	PWA	Conventional speech language therapy approaches

(*Continued*)

(Continued).

Godecke et al., (2012)	Randomised controlled trial	3-11 days post stroke	59 randomised	Treatment started immediately after assessment and continued for their acute hospital stay. *Intervention group* (median): 8 contacts (4.75 hours) over 3 weeks; *Control group*: 1 contacts (47 minutes) over 3 weeks.	After controlling for initial aphasia severity those randomised to daily therapy scored 15.35 points higher on WAB at hospital discharge than those who were randomised to usual care treatment. This was a statistically significant difference. At six month follow up there was no difference between the groups.	PWA post stroke with a WAB score <93.8; 60% had severe aphasia at baseline; 51% female; Age M(SD) years: 69.1 (13.9)	Treatment was individually tailored and included sematic feature analysis, BOX therapy and mapping therapy.
Godecke et al., (2020)	Multicentre Randomised controlled trial	<2 weeks post stroke	246 randomised	Treatment started immediately after assessment and continued for up to 25 days. *Usual care Control group* (median): 3.1 contacts (9.5 hours) over 4 weeks; *Intervention: Higher intensity group*: (Usual Care-Plus & VERSE groups combined) 6.4 contacts (22.7 hours) over 4 weeks.	No difference between those randomised to usual care (9.5 hours) verses higher intensity treatment (22.7 hours) at 12 weeks post stroke.	PWA post stroke with a WAB score <93.8; 32% had severe aphasia at baseline; 55% female; Age M(SD) years: 75.5 (17.5)	Usual care treatment was individually tailored and included conventional speech and language approaches. Higher Intensity approaches had impairment based treatment approaches; VERSE used an 'error-free' approach to producing verbal output.

(*Continued*)

(Continued).

Laska et al., (2011)	Randomised controlled trial	3 (2-4) days post stroke	123 randomised	Treatment started immediately after assessment and continued for 21 days. *Usual care Control group* (median): no treatment over 21 days; *Intervention: Therapy group*: minimum of 600 minutes (10 hours) over 21 days.	No difference in ANELT scores at 21 days or six month follow up.	PWA post stroke; 55% female; Age M(SD) years: 75.5 (17.5)	Treatment was Language Enrichment Therapy focussed on comprehension and naming.
Nouwens et al., (2017)	Multicentre Randomised controlled trial	<2 weeks post stroke	152 randomised	Treatment started immediately after assessment and continued for 4 weeks. *Usual care Control group* (median): no treatment over 4 weeks; *Intervention: Therapy group*: 24.5 hours in 4 weeks.	No statistically significant differences between groups on ANELT at treatment completion, 3, 6 months post stroke. Per protocol analyses showed	PWA post stroke; 56% female; Age M(SD) years: 66 (12)	Semantic therapy (BOX program) or Phonological therapy (FIKS Program) targeting verbal output.
RELEASE et al., (2021)	Individual participant data meta-analysis from RCTs, comparative studies (non-randomised), registries, case-reports/cohort studies	321 days post stroke (IQR, 30-1156)	5928 individual participants	Insufficient data on participants who had no treatment. Treatment intensity ranged depending on the study.	Predictors of overall improved language recovery: • Age <55 years • Enrolment <1 month post stroke	PWA post stroke; 60% female; Age M(IQR) years: 63(53-73)	Treatment type ranged depending on the study.

(*Continued*)

(Continued).

Robey et al., (1998)	Meta-analysis of RCTs, comparative studies (non-randomised), registries, case-reports/cohort studies to determine treatment effect sizes	0 months - 24 years	1555 individual participants	Treatment intensity ranged depending on the study.	In acute stage of recovery high intensity (2+ hours per week) treatment effect (Cohen's *d*) was 1.39. The effect size for no treatment in acute stage was 0.77	PWA post stroke; Sex and Age were not reported	Treatment type ranged depending on the study.
Woldag et al., (2017)	Randomised controlled Trial	19 days post stroke	60 participants	Treatment intensity: Group 1: CIAT (30 hours over 10 work days) Group 2: Conventional aphasia therapy (30 hours over 10 work days) Group 3: Twice daily therapy & Group therapy (14 hours over 10 work days)	No significant difference between groups at treatment completion; Similar gains in language function were noted for those who received 30 hours of treatment to those who received 14 hours of treatment within the first 10 working days of stroke.	PWA post stroke; 60% female; Age M(IQR) years: 63(53-73)	CIAT; Conventional speech and language therapy approaches; Group therapy.

Appendix E. "WHAT" therapy example evidence summary table

Study	TPO* at study	Samples	Aphasia therapy duration/ intensity	Findings/Outcomes	WHO (Population)	WHAT (Therapy type)
Quique et al. Acquistition and generalisation Responses in Aphasia Naming treatment. Metanalysis (2019) American Journal of Speech Langauge Pathology	6–384 months =Chronic	Metanalysis 12 single subject tudies. 35 PWA Includes Boyle (2010) systematic review	2–3 treatment sessions per week	SFA intervention promoted increased naming accuracy. Increased dose associated with increased naming accuracy. Treatment gains greater for treated compared to untreated items. Language impairment variables were related to changes in naming performance.	Mean age 60 years 15 female, 21 male	SFA therapy
Brady et al. (2016) Aphasia Cochrane Review.	<1 week to 8 years post	Cochrane Systematic review 38 trials 1242 participants	Highly varied	There was little evidence of any difference between group SLT and one-to-one SLT, computer-facilitated, or volunteer-facilitated SLT versus professional SLT, although these comparisons were based on limited numbers of trials involving small numbers of participants. The available evidence, however, indicates there is no evidence of a difference in the provision of SLT interventions facilitated by volunteers or computers (under the direction of professional therapists and with appropriate access to relevant therapy materials and therapeutic intervention plans) compared with direct therapy provision by a professional therapist.	PWA	Conventional speech language therapy approaches
Efstratiadou et al. (2018) A systematic review of SFA, Journal of Speech Language and Hearing Research	4–384 months	Sytematic reivew 21 studies 55 PWA	Highly varied	Naming of trained items improved for 81% of participants. High quality single case designs. Small treatment effect size.	Mean age 55 years 31 men 24 women	SFA therapy
Kendall et al. (2019) Phonomotor versus SFA treatment for anomia in 58 persons with aphasia. Journal of Speech Language and Hearing Research	Chronic	RCT 58 participants	56–60 hrs treatment over 6 weeks	No significant difference on untrained nouns between groups. Significant improvement within groups for trained items. Treatment specific generalisation effects for confrontation naming for both groups.	Average age 63 years 18 men, 12 women	SFA vs. Phonomotor treatment

(*Continued*)

(Continued).

Study	TPO* at study	Samples	Aphasia therapy duration/ intensity	Findings/Outcomes	WHO (Population)	WHAT (Therapy type)
Evans et al. (2021) Effects of semantic feature type, diversity, and quantity on SFA treatment outcomes in Aphasia. American Journal Speech Language Pathology	Chronic	Multiple baseline design 44 participants	1:1 therapy, 4–5 days a week for 4 weeks, in two daily sessions of 120 minutes each	Producing more participant generated features was found to improve treatment response for trained but not untrained items in SFA.	Mean age 62 years 5 female 39 male	Individual SFA treatment

*Time Post Onset.