Protocol
Version 2
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1. Contributors' Roles and Responsibilities:

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Responsibilities: Devise and design the study. Responsibility for overall project delivery: Contributing to the statistical analysis plan; interpretation of data and analyses; drafting the manuscripts.
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Responsibilities: Contributing to the statistical analysis plan; data management, overseeing data collation, storage, backup, archiving and sharing, interpretation of data and analyses; drafting the manuscripts.
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Responsibilities: Preparing the statistical analysis plan, data extraction plan, interpretation of data and analyses; drafting the manuscripts.
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Responsibilities: Preparing the statistical analysis plan; data extraction plan, interpretation of data and analyses; drafting the manuscripts.
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1.2 Steering Group
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People with aphasia as a consequence of stroke and their carers recruited from the community.

Responsibilities of the steering committee: To review the use of research data, dissemination planning and reporting of research findings.

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Responsibilities of co-applicants: Contribute IPD data to the RELEASE database Agreement of the final protocol; review progress of the study and, if necessary, agree changes to the protocol to facilitate the smooth running of the project. Regular formal project management team meetings to include co-applicants, collaborators and steering committee will be held at project start and months 12, 16 and 22 in order to share study progress to date, issues arising, analyses, interpretation of results, dissemination plans. Telephone or video conferencing will be used to facilitate communication with international co-applicants.

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Responsibilities of collaborators: contribute IPD data to the RELEASE database, Agreement of the final protocol; review progress of the study and, if necessary, agree changes to the protocol to facilitate the smooth running of the project. Regular formal project management team meetings to include co-applicants, collaborators and steering committee will be held at project start and months 12, 16 and 22 in order to share study progress to date, issues arising, analyses, interpretation of results, dissemination plans. Telephone or video conferencing will be used to facilitate communication with international co-applicants.

2. Overview

2.1 Rationale:

Aphasia affects a third of stroke survivors annually and impacts on the ability to speak, understand speech, read and write. This language impairment detrimentally impacts on many aspects of social functioning, emotional wellbeing, hospital discharge destination and returning to work. Systematic review evidence indicates that speech and language therapy (SLT) aids language recovery in people with aphasia, however, the specific patient and intervention factors which predict optimal recovery and rehabilitation are unclear.

2.2 Aim:

The aim of this study is to investigate the contribution individual characteristics, stroke and aphasia profiles and therapy components make to the recovery and rehabilitation of people with aphasia.

2.3 Design:

Anonymised clinical datasets at the level of individual patient data (IPD) l (collected during the course of various research designs (including randomised controlled trials (RCTs), cohorts, registers) will be collated and where possible, pooled and meta-analysed. Data sets have been volunteered from researchers and aphasia groups internationally, for example from the Predicting Language Outcome and Recovery After Stroke (PLORAS) study, Aphasia Bank (USA), the Clinical Centre for Research Excellence in Aphasia Rehabilitation (Australia) and other members of the Collaboration of Aphasia Trialists (CATs) as well other published and unpublished datasets from aphasia researchers.

2.4 Study Outcomes:

Outcomes of relevance to this review include therapy regimen (timing, intensity, frequency, duration) intervention approach (e.g. repetition and home practice) measures of language use or ability (communication activity, communication impairment, functional communication across speaking, understanding, reading and writing) and descriptions of the individuals' demographic, stroke and aphasia profiles.

2.5 Summary:

Our international, multidisciplinary collaboration will conduct secondary data analyses to inform our understanding of the optimal approach to the delivery of SLT delivery to individual patients' profiles in a time and cost-effective manner using secondary IPD data analysis.

3. Introduction

3.1 Aphasia and Impact

Of the estimated 1.1 million stroke survivors living in the UK[1] , 385,000 are likely to have a stroke related language impairment known as aphasia[1]. Aphasia is one of the most common and most devastating long term consequences of stroke[2] impacting 35% of stroke survivors[3]. This affects not only their language abilities (ability to speak, understand, read and write words) but also their ability to tell the time, use money and perform simple mathematical calculations. Of those that experience aphasia, 61% continue to have communication problems a year later [4]. While spontaneous recovery appears to be limited from that time point[5, 6] focused therapeutic interventions may continue provide benefit [7].

The impacts of aphasia extend beyond the communication domain. Aphasia is associated with poorer performance on measures of functional recovery [p = 0.007] [8] (comprehension deficits in particular impacting on activities of daily living[9] [OR = 5.38, 95% CI = 2.35–12.34; p<0.001]), incontinence [p=0.003][10] and emotional well-being after stroke [*r=0.51; P=0.001*] [11]. Aphasia also affects hospital discharge destination [p =0.002] [8] and the likelihood of successful return to work [p = 0.0009][12]. As communication is a fundamental self-defining activity[13] it is perhaps unsurprising that aphasia directly influences a person's perception of their own identity[14] . Aphasia isolates the person with the communication impairment from their spouse, family and wider social networks[14]. Family members have also described feeling isolated. Aphasia intensifies social problems more generally associated with a stroke, restricting or altering social activities[15]. This leads to fewer friendships[14, 15] and smaller social networks[16] compared to before stroke and in comparison to healthy peers[15]. With restricted opportunities for social participation, people with aphasia become socially isolated[17] impacting severely on their emotional wellbeing[18]. Clinical and cost effective rehabilitation for people with aphasia is therefore a priority.

3.2 Evidence Limitations for Predictors of Language Recovery

Clinical guidelines recommend that stroke teams (particularly speech and language therapists) should provide patients with aphasia with 'realistic recovery prospects' [19]. However, people with aphasia are a highly heterogeneous group varying in demographic, stroke and aphasia profiles making accurate prognosis difficult. Several factors are thought to relate to language recovery but little definitive evidence exists. For example, conflicting evidence exists in relation to impact of age[5, 20,4, 21], handedness and educational background [5, 22] on language recovery. Patient sex appears linked to initial aphasia profile but not recovery[4, 20]. Our insight into the relationship of mood, socioeconomic status and social support and language recovery outcomes is also limited. Stroke severity[21], location, time since onset of the stroke and related impairments (e.g. cognition) are also thought to predict recovery rates. Others suggest the initial aphasia profile (severity, modalities involved) may be related to the pattern of language recovery[4, 20]. Robust exploration based on large, comprehensive, aphasia specific datasets of these potential predictors of recovery would inform therapists' prognostic abilities (in turn benefiting patients and families). In addition, better insight into the prognostic indicators would inform the development of predictive models where specific patient subgroups most likely to benefit from specific therapeutic interventions might be identified early in their recovery.

3.3 Gaps in Evidence Base for Rehabilitation Interventions

While our 2016 Cochrane systematic review (n=57 RCTs, 3002 people with aphasia) and meta-analyses of pooled summary data highlights the effectiveness of SLT compared to no SLT, it provides little insight to inform therapist choice of therapeutic approach, rehabilitation regimen or suitability of patient subgroups for a specific intervention. [4] Using multidisciplinary data from 27 published and unpublished randomised comparisons involving 1620 participants we demonstrated that people

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with aphasia experienced significant clinical and statistical benefits as a result of SLT on functional communication (standardised mean difference (SMD) 0.28, 95% CI 0.06 to 0.49, P = 0.01), reading, writing and expressive language compared to those that received no therapy.

Despite this evidence supporting SLT in general, there is limited high quality research available to optimise the delivery of SLT interventions to the benefit of patients. Much of aphasia rehabilitation research has been limited in size (largest RCT n=191 reported) and scope. Despite evidence from 38 randomised comparisons (1242 participants) of two different approaches to the provision of SLT for aphasia after stroke, robust, evidence-based information to guide therapists in the choice of effective therapeutic approaches or regimens best suited to specific patient subgroups with aphasia (and their families) does not currently exist.

Aphasia rehabilitation interventions are truly complex and there is much uncertainty around the key 'active ingredients' and optimum delivery. These key ingredients might for example include the intensity, the therapeutic mechanisms (e.g. task repetition, functional relevance, conversational practice), theoretical approach to language and timing of intervention after stroke.

Intensity
While intensive SLT interventions are beneficial for many people after stroke,[23] the optimum level of intensity of SLT is less clear. Eight randomised trials compared SLT at different rates of intensity – high-intensity (4-15 hours weekly) observed on measures of functional communication, and severity of aphasia were confounded by a significantly higher number of drop outs from groups that received the higher intensity therapy. Thus high-intensity approaches to therapy may not be suited to all patients.

Dosage
Current recommendations are conflicting in the minimum weekly requirements for SLT intensity and range from 3.75 hours [6] to 2 hours [19]. A limited review of 10 English language publications (MEDLINE search 1975 to 2002) suggested that significant SLT treatment effects were observed when patients received a minimum of nine hours SLT weekly but not for two hours (or less) SLT weekly [24]. Thus there is little consensus about the optimum (minimum and maximum boundaries of) weekly provision of SLT for people with aphasia.

Theoretical approach
A number of theoretically based approaches to language rehabilitation therapy exist including for example Constraint Induced Language (or Aphasia) Therapy (CILT/CIAT), cognitive-linguistic approach, functional, language orientated, language enrichment, melodic intonation, phonological and semantic therapies. Some limited systematic reviews have reported partial evidence to support the use of CIAT which involves the 'forced-use' of language through manipulation of the communication context to ensure that communication can only occur via spoken language production and comprehension[25].

Timing of therapy
The optimum timing for aphasia rehabilitation intervention remains elusive. The term 'brain plasticity' has been used to describe a window of neuronal reorganisation in the brain subsequent to the stroke lesion [26] during which recovery can be augmented through enhanced rehabilitation environments and stimulation. [27-29] Generally early rehabilitation intervention results in more functional benefits for the stroke survivor than delayed intervention.[30] However the evidence for the timing of language rehabilitation has resulted in some uncertainties. Historically RCTs of aphasia rehabilitation interventions randomise people with chronic aphasia (where reported, an average of 20 months but extending up to

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28 years after stroke). More recent RCTs have recruited within clinical timelines (days to weeks after stroke) some demonstrating benefits and some not

Thus the mechanisms of therapy delivery and other 'active ingredients' are likely to interact with each other and with other factors such as the prognostic indicators highlighted above. Quantifying such interactions is imperative in order to highlight clinically effective and affordable approaches to language rehabilitation therapy.

3.4 Rationale
Effective management and rehabilitation of aphasia is vital[23]. Each year almost 17 million people worldwide acquire their first stroke while 152,000 people in the UK experience a stroke[31]. With aphasia affecting up to a third of people with stroke, we know that an estimated 5.6 million people worldwide, or 50,000 in the UK, will acquire aphasia every year. After the age of 55 the risk of stroke almost doubles with each successive decade[32]. Improved stroke survival rates and an aging European population mean that the incidence of aphasia, the numbers caring for and communicating with people with aphasia and the cost of aphasia rehabilitation will increase exponentially. This growing patient need for rehabilitation occurs in parallel with increasingly constrained NHS therapy budgets. Thus, there is currently a window of opportunity to develop novel, cost effective interventions in order to address this problem and aid services in their management of these growing numbers.

3.5 Current Evidence Based Guidelines and Recommendations
Recent research recommendations from the National Institute for Clinical Excellence (NICE) called for more evidence to support intensive approaches to stroke rehabilitation in general, and with reference to the patient subgroups most likely to tolerate such approaches. Specifically, communication therapy recommendations were unable to indicate which SLT approach or dosage might be optimal in the delivery of impairment based rehabilitation approaches (section 1.8 Communication). Two previous reviews have concluded that early[33, 34] and high-intensity SLT[24] are most effective. However these reviews were limited (time bound, English language only, small number of studies included, summary data analysis only). The recent Cochrane review (57 RCTs; n=3002) found that the potential benefits of high-intensity SLT were confounded by a significantly higher dropout rate from intensive SLT groups (2016 in press) [23]Evidence is also emerging of interactions between the chronicity of the aphasia and intensity of therapy. In subgroup analyses trials that randomised people who were within a few months of stroke to receive high-intensity SLT found benefit to the participants (compared to those randomised to a low-intensity therapy) but trials that randomised patients who were years after their stroke did not. Importantly, the findings from trials that recruited participants within a few months after their stroke onset were confounded as those participants who experienced the high-intensity SLT were significantly more likely to drop out of the trial than those receiving therapy at a lower level of intensity. There was no significant difference between the participants recruited years after their stroke in relation to drop outs.

3.6 Research Priority for Stroke Survivors and Carers
Within the recent James Lind Alliance Priority Setting Partnership aphasia intervention research was highlighted twice within the top 10 "life after stroke" research priorities by stroke survivors, carers and healthcare professionals. Effective aphasia interventions for people with aphasia and their families were considered an urgent unmet research need. However, rather than moving forward with many large, costly, logistically challenging, prospective trials we believe that a future programme of aphasia intervention research should be informed through a thorough exploration of information already collected and available via existing aphasia research datasets. The pooled data of international studies which specifically evaluate different populations and interventions will have immediate impact by developing our insight into prognostic indicators and effective components of SLT intervention for people with varying aphasia type and severity.

3.7 Synthesising Pre-Existing Research Data

International collaborative initiatives amongst researchers are becoming more frequent together with an increasing awareness of the benefits of data sharing, particularly at the level of anonymised IPD[35]. The Cochrane review methodology makes comparisons based on pooled summary data [23]. In contrast IPD will provide us with full access to all available data (not limited to summary values and those reported in publications), balanced interpretation of results, wider application and validation of findings and better clarification of key clinical and research questions.

Investing research resources on exploration of existing aphasia research data is a cost effective way to inform our understanding of aphasia recovery and rehabilitation. By pooling our multidisciplinary, international, aphasia research datasets we believe we can synthesise and analyse high quality, pooled IPD from pre-existing aphasia research datasets.

Creation of such a dataset would permit detailed analyses of pooled IPD to inform the predictors for language recovery outcomes after stroke and to explore the optimum SLT interventions for specific subgroups of people with post-stroke aphasia. Similar work conducted within the field of motor rehabilitation after stroke demonstrated the importance of intensive, task specific, functionally relevant, repetitive rehabilitation activities[36] while in occupational therapy it highlighted the value of focused therapy interventions [37]. Our study findings will provide invaluable insights into the development and design of the next generation of aphasia rehabilitation RCTs.

3.8 Objectives

To explore the contribution that individual characteristics (including stroke and aphasia profiles) and intervention components make to the natural history of recovery and rehabilitation of people with aphasia following stroke and to inform future research design by utilising pre-existing aphasia to explore:

- the natural history of language recovery
- the patient, aphasia, stroke and environmental characteristics which are linked to good language recovery
- the components of effective therapy interventions

3.9 Research Questions

1. What is the natural history of language recovery following stroke related aphasia?
   (a) When is language recovery most likely to occur?
   (b) Which components of language are most/least likely to recover (spoken language/ language comprehension/reading/writing)
   (c) Does this vary by language?

2. What are the predictors of language recovery outcomes following aphasia in relation to:
   a) Aphasia profile (the degree to which language comprehension, expression, reading and written language comprehension have each been affected in one or more languages)?
   b) Individual characteristics (age, education, cognition, mono or multi-lingual)?
   c) Rehabilitation environment (social support, socio-economic demographics, ethnicity)?
   d) Stroke profile (severity, lesion type, size, location)?

3. What are the components of effective aphasia rehabilitation interventions in relation to:

a. Timing of intervention?
b. Intensity, frequency and duration of intervention?
c. Repetition and adherence to home based therapy tasks?
d. Functional relevance and theoretical approach?

4. Are some interventions (or intervention components) more beneficial for some patient subgroups (individual, stroke or aphasia characteristics) than others?

4. Methods: Data Management

4.1 Data Management Overview
Data management is being undertaken by LW (Research Fellow) and KV (Data Co-ordinator) who will ensure that data management systems are in place from the start of the study, and are reviewed and revised as appropriate. The Data Co-ordinator will be in charge of data collation, storage, backup, data archiving and data sharing. LW and KV will liaise with the statisticians who will oversee the planned analyses to ensure that data are available in an appropriate format for analysis. Existing infrastructure at GCU will readily accommodate the proposed data management systems.

Data will be processed in two stages. Stage 1; which provides an overview of processes preparing for (4.2.1) the systematic data recruitment process, (4.2.2) application of the inclusion and exclusion criteria (4.2.3) data management and administration process and (iv) the creation of a data overview of availability leading to Stage 2: (4.3.1) the mapping of analysis variables to data availability (4.3.2) formatting data and data conversions and (4.3.3) the planned data analyses.

4.2 Stage 1

4.2.1 Systematic Data Recruitment
 Raw data from primary research studies will be sought; truncated versions of datasets will not be included, nor will data where only mean values ±standard deviations are recorded. Initial development work for the purposes of informing this proposal identified 52 eligible international data sets (comprising 3181 IPD). We will continue to seek additional contributions to further strengthen our analyses and so we anticipate that this figure may grow further.

We will seek to maximise the availability of IPD data for our analyses through the systematic identification of additional national and international aphasia research datasets. Researchers with data eligible for inclusion in the RELEASE study will be identified via the following routes and invited to contribute their data:

Systematic Review of Existing Literature
The comprehensive search strategy recently employed in the Cochrane Systematic Review of SLT for Aphasia after Stroke (2016)[23] encompasses a thorough search of several relevant electronic databases, hand searching from inception of the databases to Sept 2015. As a result over 5000 records relevant to aphasia and stroke were identified (see Figure 1). Utilising this existing search we will review the references for additional relevant dataset and invite the researchers to participate in our collaborative efforts.

Datasets Listed in the Cochrane Review
In tandem with the literature search described above, we are attempting to contact all researchers with eligible datasets listed in the 2016 Cochrane Review and inviting them to participate in the RELEASE project by contributing theses (and any other eligible datasets to RELEASE).

- International open invitation to collaborate

Contributions will be encouraged through the ongoing dissemination of the project's development to leading international aphasia researchers. Additional dissemination forums include the international, multidisciplinary Collaboration of Aphasia Trialists (CATs) and national and international conferences relating to stroke or aphasia.

- Records in public domain

Some eligible RCT IPD datasets are available in the public domain. After securing access to these datasets we will enter this data into formal statistical software (SPSS) facilitating planned analyses and their contribution to the overall database.
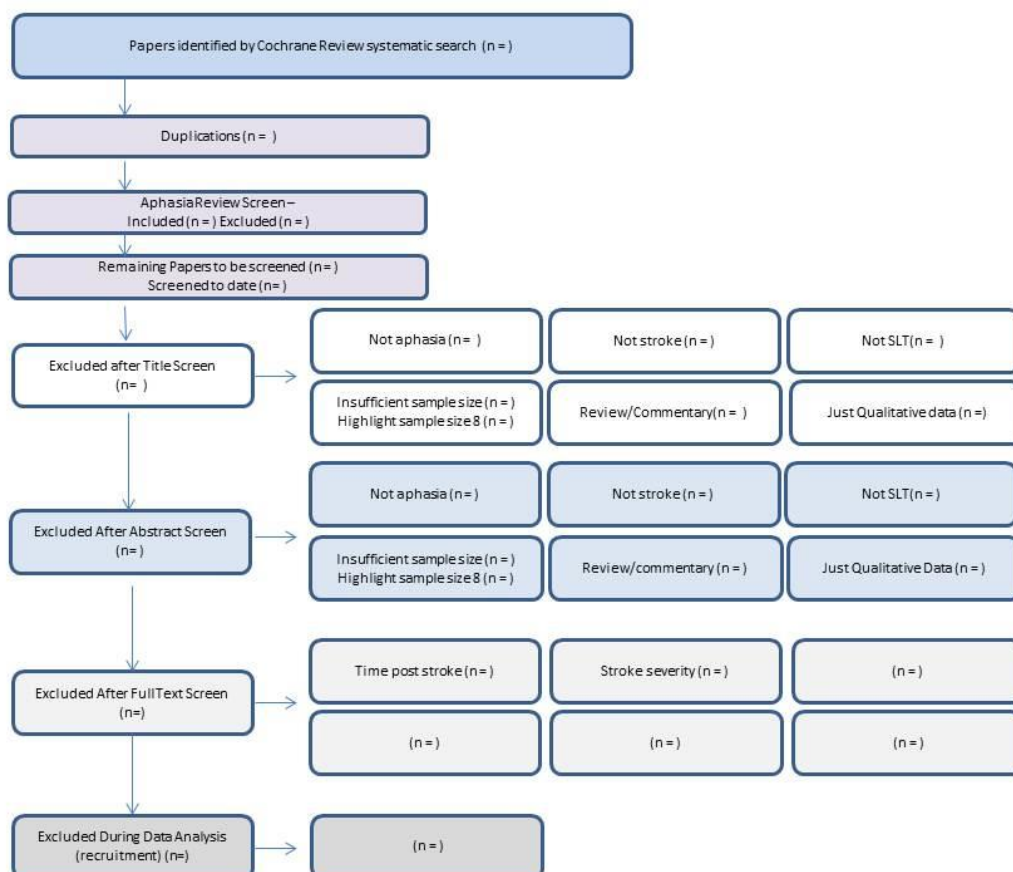
Figure 1. Screening process of literature identified in the systematic search for the Cochrane Systematic Review of SLT for Aphasia after Stroke (2016)

A recruitment record of communication with prospective PIs/research teams will detail all invitations to participate and subsequent expressions of interest in contributing data. A tracking process summary for these four streams of dataset identification and recruitment will be maintained throughout the project (see Figure 2).

Figure 2 RELEASE dataset identification and recruitment

4.2.2 Inclusion and Exclusion criteria

Inclusion Criteria
The criteria to contribute data to the RELEASE study are:
- Anonymised datasets collected as part of a research study (trial or other design) or clinical registers.
- A minimum dataset of 10 individual patients with aphasia as a consequence of stroke
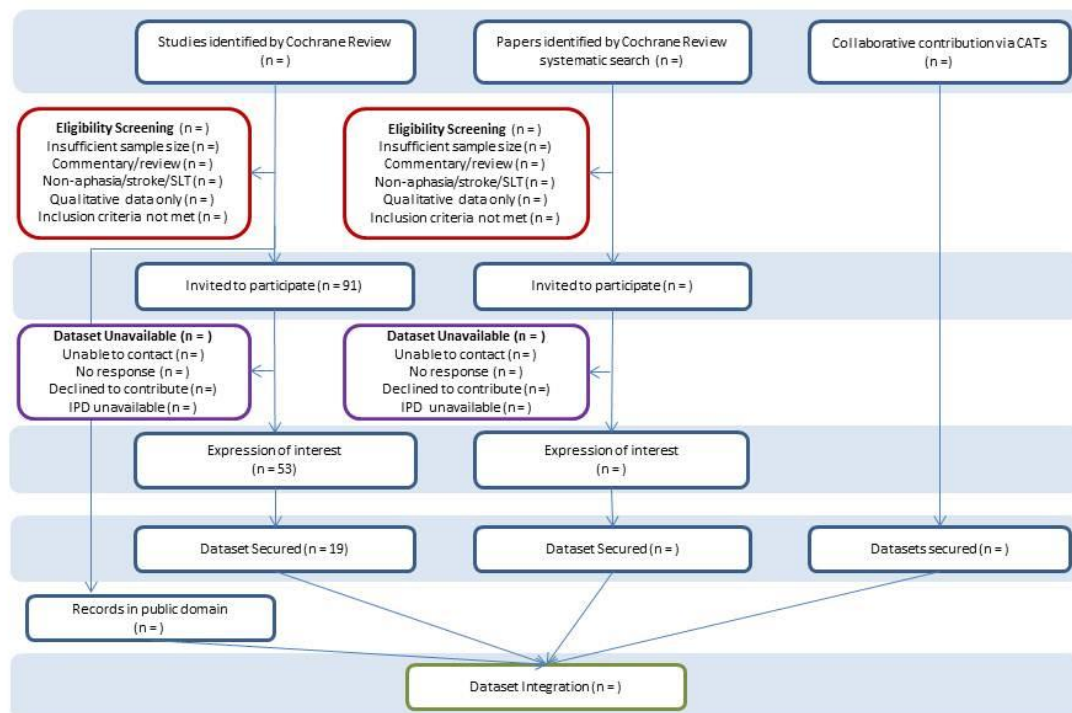- Data on aphasia severity for each individual
- Date of stroke or time of initial assessment post onset.
- Any outcome measurement or assessment tools and in any language and language modality (expression, comprehension, reading or writing

Exclusion Criteria
- Studies using only qualitative data
- Studies involving interventions other than SLT
- Studies where individual patient level data is unavailable.

4.2.3 Data Management and Administration Process

Data Documentation
Each dataset that is contributed electronically will be (where possible) accompanied by a data dictionary, evidence of ethical approval to collect the original data, gatekeeper approval(s) to share the data, an annotated Data Collection Form which will detail each of the variables collected, the

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time points for collection and the codes used for each of these variables. Where available, a funders report or a full publication will also be requested along with the dataset. These documents will be used to clean the data and apply standard data labels to the datasets. These documents will also be available as data descriptors on a common drive which can be accessed by the analyst/statistician.

Anonymisation
We will seek the contribution of anonymised patient data only. Collaborators will be reminded to ensure datasets are anonymised prior to submission. Where datasets are inadvertently contributed with identifiable data still present, any mention of names, addresses, contact phone numbers, post codes, CHI numbers (or equivalent hospital numbers) or sites will be removed prior to encryption and storage. A database-wide unique identifier will be allocated for each patient, comprising their unique study number and patient number. This will ensure that the inclusion of specific patients in subsequent analysis datasets can be traced back to the original trial source for quality assurance and data verification.

Data Encryption and Storage
Data will be stored at the NMAHP Research Unit, Glasgow Caledonian University, UK, according to university procedures. All original study datasets will be stored on a secure, encrypted, hard drive; a 1TB IronKey Enterprize H300 encrypted external hard drive with centralized management. The hard drive will be secured in locked storage in a password protected room. Separate, anonymised and password protected databases will be generated from these original datasets and will be stored on the NMAHP Research Unit's designated portion of the University server. Adjustments to these databases will not affect the original study data. Analyses datasets will be generated from the research question specific datasets and will be stored as password protected files on the University server.

Security and Access Control
Original study datasets, datasets created for this project and analyses datasets will be accessed only by the RELEASE project management group as set out in the RELEASE, IP and NIHR contract agreements. Access to data will be governed through a RELEASE Steering Committee comprising contributing principal investigators and co-applicants of the current proposal. Data will not be accessible to those outside of the project collaboration without prior application. The RELEASE Steering Committee will govern use of research data, participate in analyses and review manuscripts based on the planned analyses. These contributing researchers will thereby retain control of use of their own data and have an opportunity to contribute to the planned secondary analyses. The statistical analysis plans will be pre-specified and the contributing researchers will retain the option to join the research group and contribute to the peer-reviewed publication.

Data Retention and Disposal
After the RELEASE funding period, researchers who have contributed data may choose to lodge their data in a central repository hosted by the Collaboration of Aphasia Trialists (CATs) at Glasgow Caledonian University, UK for additional data sharing activities. Where the dataset is of a RCT design, they will also have an option to lodge their data with the rehabilitation section of the Virtual International Stroke Trials Archive (VISTA-Rehab www.vista.gla.ac.uk). Selected data will then be transferred to the Robertson Centre for Biostatistics, University of Glasgow, UK for storage on a secure server as part of the VISTA initiative. In this way, data can be reused beyond the scope of the current application, and will be made available to a wider community of aphasia and stroke researchers for the purposes of novel exploratory analyses. The RELEASE Steering Committee members from this project will also be invited to join the relevant steering committees. Anonymised data will be preserved within these databases for a period of at least 15 years for further re-use.

These potential secondary analysis activities might include re-use in validation studies, teaching, exploratory analyses and prognostic modelling.

Adherence to Data Sharing Standards

The International Committee of Medical Journal Editors' (ICMJE) has recently proposed requirements for ethical clinical trial data sharing[38]. It states that clinical data sharing is "an ethical obligation…because participants have put themselves at risk" and consequently it proposes that researchers conducting clinical trials must be required to include a data sharing plan as part of their registration. In order to meet the needs of authors requesting data and to protect the rights of researchers and trial sponsors, the ICMJE proposes that certain safeguards should be adhered to. The first of these is that deposition of data in a registry does not constitute prior publication. Secondly, researchers using secondary analyses must stipulate, at the time of receipt, that the use of the data is in accordance with any agreed terms. Thirdly, that due credit is given to the providers of the clinical trial data by using a unique identifier which will also enable studies it has supported to be located. Fourth, that researchers conducting secondary analyses provide full details of how their own analyses differs from previous analyses. The ICMJE also states that the efforts of the researchers who create and share clinical trial data should be credited and additionally, as data sharing is a shared responsibility, collaboration between these researchers and those using the collected data should be sought. In addition to ICMJEs proposals consensus activities are currently in progress around the principles and guidelines for good practice in data sharing activities (for example Knoppers: Framework for Responsible Sharing of Genomic and Health-Related Data, 2014[39]). The foundational principles for data sharing should set out to "promote health and wellbeing, respect individuals, families and communities, advance research and the fair distribution of benefits and foster trust, integrity and reciprocity". Elements essential for responsible data sharing include transparency, accountability, data security and quality, privacy, data protection and confidentiality, minimising harm and maximising benefits, recognition and attribution, sustainability, accessibility and dissemination. We will ensure that our data sharing activities adhere to these and any new guidelines or framework once available.

4.3 STAGE 2:

4.3.1 Feasibility of Planned Analyses

As data are contributed to the study, study level information will be recorded and mapped on a matrix of common variables identified as important to the research questions, such as those relating to participants, stroke and aphasia, and the SLT intervention. A Map of Availability and Placement (MAP) of data will be required for our planned analyses. The MAP will function as a reference document, providing oversight of acquired datasets. It will collate and describe the quality and quantity of data pertaining to each variable in each dataset. The MAP will enable us to assess the viability of planned analyses and pooling common variables.

While much of the data in this proposal relates to demographics or outcome measures recorded within the context of an RCT or other quantitative report we will also aim to capture, quantify and compare the aphasia rehabilitation interventions delivered within the research context. Detailed descriptions of the SLT interventions for aphasia rehabilitation after stroke will be extracted using all available (published and unpublished) material and information relating to the research. Based on the 12 items described within the recently published Template for Intervention Description and Replication[40] the MAP will record the interventions delivered in relation to the theoretical approach, provider, materials used, delivery mechanism(s), context of intervention, the duration, intensity, frequency (or dose), fidelity, and where available, the tailoring of treatment to the individual and adherence.

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4.3.2 Formatting Data and Data Conversions

The research fellow (LW) and statisticians (AE & JG) will oversee the conversion of datasets into compatible formats, liaise with trialists to ensure the completeness of contributed data and check variable ranges for accuracy. Data will be contributed in various formats including SAS, SPSS, Excel and Access. Access to SAS may be required for pre-processing data sets received in SAS and other format.

4.3.3 Data Extraction Plan

The Data Extraction Plan describes the process by which the quality, specific measures and compatibility of the various IPD datasets will be profiled. The Data Extraction Plan is a project document created and agreed collectively by project collaborators. It will be a living document which will be a record of decisions made by the collaboration to support the planned analyses.

The Data Extraction Plan identifies the appropriate format and structure for IPD in preparation for its use in RELEASE analyses. It informs the conversion of IPD from their existing source format to a standardised format ensuring compatible integration for analysis.

Quality Assurance

Quality assurance and verification of variables will be performed by cross-checking the dataset against the trial source, published papers and other outputs, checking the acceptable ranges of variables and through correspondence with the trial representatives. Some translation of variable labels will be required for international datasets. We will confirm the accuracy and completeness of translations with contributors.

Version Control and Backups

Version control will be applied to the data management procedures. The datasets specific for each research question and the datasets containing information which will be used across different analyses will be identified and updated as necessary in the MAP document versions (eg. <Filename version 1.0date>), kept in a separate folder from the analysis datasets. Each variable within the MAP will be coded to allow a steering file to produce the relevant comparisons appropriate for each research question. Each steering file will be given a unique identifying code (e.g. <steeringfile number>) and all data management and analyses datasets will be backed up daily according to University practice.

Statistical Methods

We will provide a statistical summary describing the RELEASE database and an overview of all included studies and the available data within these studies, including a report of which data are used in subsequent analyses for each research question. Full details of the analysis are described in the Statistical Analysis Plan which will be pre-specified and agreed by investigators prior to any analysis being conducted.

Briefly, we will produce summary statistics of variables used in each analysis, with continuous variables summarised with means and standard deviations (or medians and interquartile ranges if skewed), and summaries of categorical, binary and ordinal data reported as proportions.

- The total numbers of patients and the distributions of randomisation age, time from stroke to randomisation, gender, stroke type, stroke laterality, handedness and status measure(s) at randomisation will be checked for any significant imbalance between treatment groups.
- Where time to follow-up is available, checks are made for biased censoring and life-table curves are also produced.
- A tabulated breakdown of variables is produced for each trial, together (where relevant) with lists of patients in 'problematical' categories such as those with lapsed follow-up and uncertain final status. Before trial data are finally incorporated into the overview, the

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analyses described above are sent to the participating trialist(s) for checking and approval, accompanied if necessary by questions to resolve any misunderstandings or problems detected.

- Aphasia recovery outcomes relating to severity, functional communication and participation will be investigated. We will present study-level forest plots to summarise outcome data.
- Our planned analyses will be individual patient data meta-analyses using a one-step approach and we will analyse the data using generalised mixed effect linear models where possible.
- We will adjust for potential confounders (and baseline values if applicable), with individual study treated as a fixed effect. Statistical significance will be at the 5% level, with the exception of subgroup analyses where there will be a stricter level of 1%.
- We will examine study-level heterogeneity and explore the effect of publication bias. Sensitivity analyses will be conducted to investigate the effect of missing data and assumptions made around pooling outcome data from multiple sources. Statistical modelling will be performed using Stata (StataCorp, College Station, TX, USA).

We will describe the natural history of language recovery with respect to individual, stroke and aphasia variables (RQ1), potential prognostic variables and intervention components. Statistical models will be used to investigate predictors of language recovery with respect to individual, stroke and aphasia (RQ2), components of aphasia rehabilitation with respect to intervention components (RQ3), and potential intervention by subgroup interactions (RQ4).

5. Project Management
The Project Management Team comprises Marian Brady (MB; Chief Investigator), Myzoon Ali (MA; Project Manager), Louise Williams (LW; Research Fellow), Kathryn VandenBerg (KV; Data Co-Ordinator), Jon Godwin (JG; Senior Statistician) and Andrew Elders (AE; Statistician). Please see The Project Management Plan for full details of each team member's responsibilities, methods of communication, project work plan and deliverables, project schedule and dates of key milestones.

5.1 Intellectual Property Rights
Our proposed research builds upon previously conducted research where the study results and data gathered in relation to those primary research studies (Background IP) belongs to each individual study sponsor and investigators. All co-applicants and collaborating partners contributing data to the RELEASE database are aware of the plans to re-use this historical data for the purposes of the investigations described in this protocol. Our proposed research study will, through the pre-specified secondary analysis of the RELEASE database, develop and build upon substantial background IP from each of the contributing studies. All RELEASE study results will be newly generated (Foreground IP), this will be led by GCU and shared amongst the collaborators and co-applicants. While we do not anticipate any new statistical data analysis techniques or data management procedures it is possible that new methodologies may arise from the work. Any new developments will be disseminated in the public domain and shared with other researchers for wider research and public health benefit.

5.2 Intellectual Property and Co-Authorship
Each dataset contributor to this proposed project has been contacted prior to the submission of this proposal to ascertain whether they have any intellectual property issues. These details are requested in full within the on-line contribution form. Output will be presented "by the RELEASE Study Group, on behalf of the Collaboration of Aphasia Trialists." Each researcher, funder or research group will also be named as a co-author or acknowledged in subsequent publications from the RELEASE Study as appropriate (more details below in Section 8: Publication Policy) . Any future

contributor of datasets will also be asked to declare any Background IP issues in advance of data sharing.

6. Ethical Approval

6.1 Confirmation of Approvals for the Primary Research
Eligibility for inclusion in the RELEASE database requires that all contributed datasets were gathered subject to the national or regional ethical agreements in place at the time of the individual studies.

6.2 Approval for Anonymised Data Sharing
More recent datasets have consent processes which include permission for sharing of anonymised datasets (e.g. VERSEII). Some datasets are already in the public domain (in anonymised formats) via publications or other dissemination routes. In such cases additional ethical permission have not been required. In other cases national ethical review standards have required additional approvals for data sharing retrospective extension to ethical approval in place at the time of the primary investigation.

6.3 Local Approval for RELEASE
RELEASE staff will contact researchers who have agreed to contribute datasets for the RELEASE project. As part of complying with Glasgow Caledonian University's ethical regulations the contributors of each dataset will be asked to a) provide evidence of the ethical agreements in place for the collection of the primary dataset, b) confirm that they as gatekeeper are willing to share these data, c) inform the RELEASE team of any additional regulatory approvals that are required (and if so has that approval been granted) prior to sharing of the anonymised data. Ethics permissions will be communicated to GCU as and when new datasets arrive, or monthly, depending on the rate of new contributions.

7. Dissemination
Our findings will be shared with:
- People with aphasia and their families via the supporting organisations – The Tavistock Trust for Aphasia, Speakeasy, Dyscover, Australian Aphasia Association, the Stroke Association and Chest, Heart and Stroke Scotland, as well as via our contacts, newsletters and more formal presentations.
- Health and social care professionals responsible for the rehabilitation, care and support of people with aphasia including neurologists, stroke clinicians, nurses, speech and language therapists (via the Royal College of Speech and Language Therapists), occupational therapists, physiotherapists and social care workers. Findings will also be disseminated to students of these disciplines via relevant vocational trainers and organisations.
- Clinical Commissioning Groups. Dr Ted Turner supported by SLT and Prof Emeritus Pam Enderby will lead the dissemination of findings to the Clinical Commissioning Groups.
- Stroke groups and community rehabilitation programmes will also be targeted to disseminate our findings which will facilitate the participation and re-integration of people with aphasia following stroke.
- Voluntary services and education; those working in the non-profit and voluntary sectors with a role in the support and care of people with aphasia and their families (e.g. Speakeasy). In particular we include those organisations supporting this application which includes some patient and carer support groups
- International equivalents within the above listed categories and academics and researchers within the field which will inform the further development of this field of research (both via the Collaboration of Aphasia Trialists detailed below).

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Our methods will include open access, high impact, web-based and peer-reviewed publications, contributions to relevant guidelines and consensus statements, presentations (platform and poster) at national and international meetings and conferences including (but not restricted to) the European Stroke Organisation Conference, the UK Stroke Forum, Aphasia Alliance, British Aphasiology Society, International Aphasia Rehabilitation Conference. Working within an established COST funded international multidisciplinary CATs (IS1208) findings arising from the work will be effectively disseminated across 26 countries via seminars, training schools, website, social media, network meetings to patient and carer groups, relevant charities or other third sector organisations, professional groups and research communities.

8 Publication Policy
8.1 Authorship
The RELEASE core publication group comprises MB, MA, LW, KV, AE and JG. In addition to this group the co-applicants and other collaborators who have provided datasets (which are not already publicly available) to the RELEASE study will also have the opportunity to participate as co-authors on research outputs. For each output details of the contributions made by each author will be held on a contribution matrix and will include analysis and interpretation of data, drafting the article, and critical revision of manuscript.

8.2 Publication Categories
There will be three publication levels for the RELEASE group:

Level 1 will consist of the pre-specified research outputs (as outlined to NIHR in our application), utilising the combined IPD from the database created for RELEASE and reporting our key findings. In such cases (and subject to specific journal (or abstract) submission requirements and publication style) the authorship will be attributed to "the RELEASE Collaborators" with all those contributing to the RELEASE database and manuscript listed by name in an extended authorship listing. Where journals require specific details of individual contributions we will use the contribution matrix described for this purpose. We will ensure that all RELEASE collaborators are individually named in PubMed.

Level 2 will be for documents which do not report pre-specified research findings, do not utilise the IPD database created for RELEASE and where the majority of the work has been done by a small number of RELEASE collaborators. Such documents might for example include reporting specific aspects of the project set-up or management (for example the statistical analysis or data management plan). In such situations draft manuscripts will be circulated to the RELEASE group for commentary or input. Authorship in these cases would be "X, Y and Z on behalf of the RELEASE Group". The whole RELEASE collaboration would be listed in full in an extended section at the manuscript end.

Level 3 will be for reports that did not form part of the pre-specified RELEASE research output plan but were identified as an important dissemination activity and approved by the RELEASE group. RELEASE collaborators could be invited or requested to join the drafting group for level 2 and 3 reports and be listed as authors. Those listed as author must make a significant contribution to the paper. It will be for the lead author of the Level 2 and 3 reports to judge whether a contribution is sufficient to merit authorship. All other members of the RELEASE collaboration will be listed in full in an extended section at the manuscript end.

All reports arising directly or indirectly from the RELEASE project will follow the International Committee of Medical Journal Editors criteria, whereby authorship credit is based on:

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1. substantial contributions to conception or design, or acquisition, analysis or interpretation of data for the work; and

2. drafting the work or revising it critically for important intellectual content; and

3. final approval of the version to be published; and

4. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.'

RELEASE authors will meet all four conditions. Additionally, all RELEASE authors should be able to identify which co-authors are responsible for specific parts of the work and have confidence in the integrity of their contributions as co-authors. RELEASE will not condone 'gift authorship' and acquisition of funding, collection of data, or general supervision of the research group alone will not constitute authorship.

8.3 Chief Investigator Approval

The Chief Investigator of RELEASE (MB) is responsible for approving the submission of all scientific outputs (manuscripts, abstracts, presentations, workshops and posters or other scientific dissemination activities) on the advice of the project management team, co-applicants, collaborators and steering group. This includes agreeing both content and structure and where it is to be submitted.

8.4 NIHR funding

All publications acknowledge the funding from the NIHR programme grant for Health Services and Delivery Research and the Collaboration of Aphasia Scientists.

All publications and other outputs (whether in oral, written or other form) should be submitted to the NIHR at the same time as submission for publication, or at least 28 days before the date intended for publication/presentation, whichever is earlier to comply with NIHR obligations. This includes abstracts, conference presentations and press releases.

(1) The Stroke Association. Aphasia. *http://www stroke org uk/aphasia [Last Accessed 15th April 2014]* 2014.

(2) Lam JMC, Wodchis WP. The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related quality of life in Ontario hospital-based long-term care residents. Medical Care 48, 380-387. 2010.

(3) Dickey L, Kagan A, Lindsay MP, Fang J, Rowland A, Black S. Incidence and Profile of Inpatient Stroke-Induced Aphasia in Ontario, Canada. Arch Phys Med Rehabil 91, 196-202. 2010.

(4) Pedersen PM, Vinter K, Olsen TS. Aphasia after stroke: type, severity and prognosis. The Copenhagen Aphasia Study. Cerebrovasc Dis 17, 35-43. 2004.

(5) Ferro JM, Mariano G, Madureira S. Recovery from aphasia and neglect. Cerebrovascular Diseases 9[Suppl], 6-22. 1999.

(6) Prepared by the Intercollegiate Stroke Working Party. National Clinical Guidline for Stroke. Royal College of Physicians London[4th Edition]. 2012.

(7) Meinzer M, Djundja D, Barthel G, Elbert T, Rockstroh B. Long-Term Stability of Improved Language Functions in Chronic Aphasia After Constraint-Induced Aphasia Therapy. Stroke 36, 1462-1466. 2005.

(8) Gialanella B, Prometti. Rehabilitation Length of Stay in Patients Suffering from Aphasia After Stroke. Topic in Stroke Rehabilitation 16, 437-444. 2009.

(9) Paolucci S, Matano A, Bragoni M, Coiro P, De Angelis D, Fusco F.R, Morelli D, Pratesi L, Venturiero V, Bureca I. Rehabilitation of Left Brain-Damaged Ischemic Stroke Patients: The Role of Comprehension Language Deficits. Cerebrovasc Dis 20, 400-406. 2005.

(10) Gelber DA, Good DC, Laven LJ, Verhulst SJ. Causes of urinary incontinence after acute hemispheric stroke. Stroke 24, 378-382. 1993.

(11) Thomas SA, Lincoln NB. Predictors of emotional distress after stroke. Stroke 39, 1240-1245. 2008.

(12) Black-Schaffer RM, Osberg JS. Return to work after stroke: development of a predictive model. Archives of physical medicine and rehabilitation 71, 285-290. 1990.

(13) Clarke P, Black SE. Quality of life following stroke: Negotiating disability, identity and resources. The Journal of Applied Gerontology 24, 319-336. 2005.

(14) Parr S, Byng S, Gilpin S, Ireland C. *Talking About Aphasia: Living with Loss of Language after Stroke*. Buckingham; 1997.

(15) Cruice M, Worrall L, Hickson L. Quantifying aphasic people's social lives in the context of non-aphasic peers. Aphasiology 20, 1210-1225. 2006.

(16) Davidson B, Howe T, Worrall L, Hickson L, Togher L. Social participation for older people with aphasia: the impact of communication disability on friendships. Top Stroke Rehabil 15, 325-340. 2008.

(17) Parr S. Living with severe aphasia: Tracking social exclusion. Aphasiology 21, 98-123. 2007.

(18) Cruice M, Worrall L, Hickson L, Murison R. Finding a focus for quality of life with aphasia: Social and emotional health, and psychological well-being. Aphasiology 17, 333-353. 2003.

(19) The Royal College of Speech and Language Therapists. RCSLT Clinical Guidelines. *http://www rcslt org/members/publications/rcslt_clinical_guidelines* 2005.

(20) Laska AC, Hellblom A, Murray V, Kahan T, Von Arbin M. Aphasia in acute stroke and relation to outcome. Journal of Internal Medicine 249, 413-422. 2001.

(21) Ali M, Lyden P, Brady M on Behalf of the VISTA Collaboration. Aphasia and dysarthria in acute stroke: recovery and functional outcome. International Journal of Stroke DOI: 10.1111/ijs.12067. 2013.

(22) Berthier ML. Poststroke aphasia: epidemiology, pathophysiology and treatment. Drugs Aging 22, 163-182. 2005.

(23) Brady M, Kelly H, Godwin J, Enderby P. Speech and language therapy for aphasia following stroke. Cochrane Database of Systematic Reviews Art. No.: CD000425. DOI: 10.1002/14651858.CD000425.pub3.[5]. 2012.

(24) Boghal SK, Teasell R, Speechley M. Intensity of Aphasia Therapy, Impact on Recovery. Stroke 34, 987-993. 2003.

(25) Cherney LR, Patterson JP, Raymer A, Frymark T, Schooling T. Evidence-based systematic review: effects of intensity of treatment and constraint-induced language therapy for individuals with stroke-induced aphasia. Journal of Speech, Language and Hearing Research 51, 1282-1299. 2008.

(26) Johansson BB. Brain Plasticity and Stroke Rehabilitation: The Willis Lecture. Stroke. Stroke 31, 223-230. 2000.

(27) Wahl AS, Schwab ME. Finding an optimal rehabilitation paradigm after stroke: enhancing fiber growth and training of the brain at the right moment. Frontiers in human neuroscience 8, 381. 2014.

(28) Janssen H, Bernhardt J, Collier JM, Sena ES, McElduff P, Attia J, Pollack M, Howells DW, Nilsson M, Calford MB, Spratt NJ. An enriched environment improves sensorimotor function post-ischemic stroke. Neurorehabil Neural Repair. 24, 802-813. 2010.

(29) Janssen H, Ada L, Bernhardt J, McElduff P, Pollack M, Nilsson M, Spratt NJ. An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: a pilot non-randomized controlled trial. Disability and rehabilitation. 36, 255-262. 2014.

(30) Paolucci S, Antonucci G, Grasso MG, Morelli D, Troisi E, Coiro P, Bragoni M. Early Versus Delayed Inpatient Stroke Rehabilitation: A Matched Comparison Conducted in Italy. Arch Phys Med Rehabil 81, 695-700. 2000.

(31) Scottish Stroke Care Audit. National Report of Stroke Services in Scottish Hospitals. http://www strokeaudit scot nhs uk/Downloads/2012_report/SSCA-annual-report-2012-web pdf [Last Accessed 15th September 2014] 2012.

(32) What is stroke? http://www strokeassociation org/presenter jhtml?identifier=2528 [Last Accessed on 13th May 2009] 2002.

(33) Robey R. A meta-analysis of clinical outcomes in the treatment of aphasia. Journal of Speech, Language and Hearing Research 41, 172-187. 1998.

(34) Robey RR. The efficacy of treatment for aphasic persons: a meta-analysis. Brain Lang. 47, 582-608. 1994.

(35) Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan GA, Grotta J, Howard G, Kaste M, Kaga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren NG, Wardlaw J, Whiteley W, del Zoppo G, Baigent C, Sandercock P, Hacke W, for the Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 384, 1929-1935. 2014.

(36) Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clinical Rehabilitation 18, 833-862. 2004.

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(37) Walker MF, Leonardi-Bee J, Bath P, Langhorne P, Dewey M, Corr S, Drummond A, Gilbertson L, Gladman JR, Jongbloed L, Logan P, Parker C. Individual Patient Data Meta-Analysis of Randomized Controlled Trials of Community Occupational Therapy for Stroke Patients. Stroke 35, 2226-2232. 2004.

(38) Taichman DB, Backus J, Baethge C, Bauchner H, de Leeuw PW, Drazen JM, Fletcher J, Frizelle FA, Groves T, Haileamlak A, James A, Laine C, Peiperl L, Pinborg A, Sahni P, Wu S. Sharing Clinical Trial Data — A Proposal from the International Committee of Medical Journal Editors. NEJM 374, 384-386. 2016.

(39) Knopper BM. Framework for responsiable sharing of genomic and health-related data. 2014.

(40) Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, Altman DG, Barbour V, Macdonald H, Johnston M, Lamb SE, Dixon-Woods M, McCulloch P, Wyatt JC, Chen AW, Mitchie S. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. 2014. Report No.: 2014-03-07 10:29:06.

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