RELEASE

**RE**habilitation and recovery of peop**LE** with **A**phasia after **S**trok**E**

# Protocol
# Version 3
# December 2016

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**1. Contributors' Roles and Responsibilities:**

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Responsibilities of co-applicants (1.2) and collaborators (1.4): contribute IPD data to the RELEASE database, act as the sole representative for their dataset with the option for co-authorship on publications (8), agree 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 and collaborators 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) 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(Australia) and other members of the Collaboration of Aphasia Trialists (CATs) as well other published and unpublished datasets from aphasia researchers. We also adopted a systematic approach towards the identification of additional eligible datasets through a systematic search of the literature and invited data contribution and participation. IPD in the public domain meeting our eligibility criteria has also been identified.

### *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[56] 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) 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[2,22] 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 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*

Recent systematic review and meta-analyses of pooled summary data (n=57 RCTs involving 3002 people with aphasia) highlighted the effectiveness of SLT compared to no SLT. Multidisciplinary data from 27 published and unpublished randomised comparisons involving 1620 participants demonstrated that people 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. It provided limited evidence to inform therapist choice of therapeutic approach, rehabilitation regimen or suitability of patient subgroups for a specific intervention[4].
Much of aphasia rehabilitation research has been limited in size (largest RCT in Cochrane review was n=191[23]). Despite 38 randomised comparisons (1242 participants) of two approaches to the provision of SLT for aphasia after stroke, therapists continue to lack evidence to guide their choice of therapeutic approaches or regimens best suited to specific patient subgroups with aphasia (and their families).

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 to 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 or 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 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 randomise people with chronic aphasia (where reported, an average of 20 months but extending up to 28 years after stroke). More recent RCTs have recruited within clinically relevant timelines (days to weeks after stroke) however we continue to lack evidence of the effectiveness of early SLT versus delayed SLT after stroke.

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, 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[33] and Recommendations*

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[34,35] 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)[23]. Evidence is also emerging of interactions between the chronicity of the aphasia and intensity of therapy. In post-hoc subgroup analyses trials that randomised people who were within three months of stroke onset 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[23]. 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*

Aphasia intervention research was highlighted twice within the James Lind Alliance 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[36]. The Cochrane review methodology makes comparisons based on pooled summary data[23]. In contrast IPD will provide us with 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[37] while in occupational therapy it highlighted the value of focused therapy interventions[38]. 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 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?
    (d) How does access to SLT impact on this recovery profile

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*

Full details of the data management process are described in the RELEASE data management Plan (Version 1, November 2016). Briefly, 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 extraction, data archiving and data sharing. LW, KV and MA 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. Full details of data management and data processing are available in the Data Management Plan which provides a comprehensive description of the following:

- The two stage data processing system.
    - Stage 1 covers the systematic search, screening and recruitment of eligible datasets; the inclusion and exclusion criteria; data management and administration processes covering anonymization, data encryption and storage, security and access control, data retention and disposal and adherence to data sharing standards.
    - Stage 2 encompasses feasibility mapping of planned analyses utilizing two documents specifically designed for this – (1) the matrix of availability and placement 'MAP' which lists information from each dataset appropriate for the four research questions, and (2) the data extraction table which details study details not available within the numeric IPD data but extracts that information from primary sources (e.g. researchers or journal articles). All relevant documents are used in tandem with primary sources and datasets to ensure quality assurance and to inform conversion of IPD from their existing format to the standardized SAS format in preparation for statistical analyses.
- We will ensure that all datasets provided for the RELEASE database are tracked and saved on Ironkey. A working copy of each dataset will be created and saved using a unique ID along with supporting documents in a unique ID folder accessible on to the Project Management Team. In accordance with University practice, all files will be backed up daily.

### *4.2 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 our planned analysis are described in the RELEASE Statistical Analysis Plan (Version 2, November 2016) 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 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 (Version 2, May 2016) 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 our on-line contribution form. Output will be presented "by the RELEASE

Collaborators." Each researcher, funder (for example the Collaboration of Aphasia Trialists) 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 researchers contributing datasets confirm that these 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 IPD 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 sought. 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) confirm that the primary dataset was collected with relevant ethical agreements in place

b) confirm that they, as gatekeeper and acting on behalf of the primary data research team, are willing to share these data with the RELEASE project,

c) confirm that any additional regulatory approvals required for sharing of the anonymised primary dataset have been secured.

An update of all dataset contributions and the associated approvals will be communicated School of Health and Life Sciences Research Ethics Committee 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).

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 and Dissemination Policy

*8.1 Output Categories*
We anticipate three levels of outputs arising from the RELEASE project:

**Level 1**; the primary outputs described within the RELEASE funding application, for example, those publications reporting the findings for each of the research questions.

**Level 2;** outputs describing or reporting more specific elements of the project, e.g. the development of the database, the statistical analysis plan or the data management plan. These papers will not include results from the primary hypotheses.

**Level 3;** outputs that were not identified within the funding application for the RELEASE project but develop during the course of the project.

All outputs will be in keeping with the RELEASE publication and dissemination policy and plans as described (above and in the GCU contractual agreement). Level 1 outputs will take priority. Level 3 outputs will only occur once Level 1 outputs have been published. Level 2 outputs by nature (e.g. Protocol paper) may precede Level 1 publications. RELEASE collaborators will only publish or otherwise disseminate the conclusions of the Study, including any part of the Results of the Study with the prior written consent of GCU (as per GCU contractual agreement), who will in turn need to seek approval of the Funder prior to any such publication. A draft copy of any planned output should be submitted to GCU RELEASE team at least 30 days in advance of the dissemination date.

*8.2 Authorship*
The RELEASE study will adhere to the International Committee of Medical Journal Editors (ICMJE) recommendations on authorship[39] which recommend that authorship should be based on:

1. "Substantial contributions to the conception or design of the work; or the 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. "

*8.3 Core authorship team*

The RELEASE core authorship team will be comprised of RELEASE staff based at Glasgow Caledonian University (MB, MA, LW, KV, AE and JG). They will lead on the development and drafting of Level 1 and Level 2 outputs associated with the RELEASE project and will also have overall responsible for the integrity of any output.

*8.4 RELEASE authors*

All collaborators and co-applicants who have contributed IPD datasets to the RELEASE database have clearly made a 'substantial contribution to …acquisition… of data' for the RELEASE project. Additionally, we expect that most RELEASE collaborators and co-applicants will make substantial contribution to the analysis and interpretation of data. Thus most RELEASE collaborators will fulfill the first of the ICMJE authorship criteria (8.2 above). In keeping with the ICMJE recommendations we will also ensure that

- all RELEASE collaborators will have "the opportunity to participate in the review, drafting and final approval of" RELEASE outputs.
- Acquisition of funding as a co-applicant, collection of data, or general supervision of the research group alone will not constitute authorship.
- RELEASE will not support 'gift authorship'.

We will detail authors' contributions to drafting and revision of outputs with 'important intellectual content' on a contribution matrix (authorship criteria 2). We will also request and record final approval of outputs prior to dissemination (authorship criteria 3) and agreement to be accountable for the output (authorship criteria 4) on the matrix. Similarly, where RELEASE collaborators specifically request that they are not listed as authors on a particular output we will also record that on the contribution matrix. In this way the RELEASE collaborators will be able to identify which co-authors were responsible for specific elements of the work and have confidence in the integrity of their contributions as co-authors. Lead authors of the outputs will judge whether a contribution is of sufficient intellectual content to merit authorship.

**Level 1** All authors meeting the four authorship criteria (as identified in the contribution matrix and confirmed in advance of submission) will be listed by name, with the byline 'on behalf of the RELEASE Collaborators' where all members of the Collaboration are listed on the final page. Some publishers or conference organisers may request that our large multi-author group designate authorship by a group name with or without the names of individuals. We will comply with such requests, exploring alternative methods of listing all co-authors (e.g. via a weblink). Where individuals are listed they will be listed alphabetically by order of surname.

**Level 2** A small specialist author subgroup of the RELEASE Collaboration will draft and prepare such outputs relating to specific elements of the project (e.g. the statistical analysis plan). A draft will be circulated to the whole group prior to dissemination. Authorship would be "X, Y and Z on behalf of the RELEASE Group". The whole group would be listed at the end, but the work would be clearly attributed to the named authors.

**Level 3** will be for papers that were not part of the RELEASE protocol but develop during the course of the project.

All RELEASE authors will

- meet all four of the ICMJE recommendations for authorship
- approve the final output or manuscript
- take public responsibility for the output
- be responsible for the accuracy and integrity of the work
- complete conflict of interest disclosure forms

*8.5 Contact author and approvals*

The Chief Investigator of RELEASE (MB) will be responsible for approving the submission of all scientific outputs (manuscripts, abstracts, presentations, workshops and posters or other dissemination activities) on the advice of the project management team, co-applicants and collaborators. This includes agreeing both content and structure and where it is to be submitted. Where contact details are required on manuscript submission, the CI details will be fulfil this role on behalf of the RELEASE Collaboration.

*8.6 Acknowledgements:*

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*8.7 Notifying funders of planned outputs*

As required by the NIHR, all publications and other outputs (as described in section 7) will be submitted to the NIHR funders at the same time as submission for publication, or at least 28 days before the date intended for the output dissemination, whichever is earlier. As requested by NIHR, when presenting ongoing RELEASE research activities the terminology “emerging findings” will be used instead of “results”, particularly if the work has not been peer reviewed.

*8.8 Publication Access:*

A copy of the final manuscript of any research papers supported in whole or in part by the NIHR will be deposited with UK PubMed Central upon acceptance for publication, to be made freely available as soon as possible and in any event within six months of the journal publisher’s official date of final publication to meet the NIHR’s open access commitment.

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