Reviewer’s report

Title: A systematic review protocol of timing, efficacy and cost effectiveness of upper limb therapy for motor recovery post-stroke.

Version: 0 Date: 04 Apr 2019

Reviewer: Ferrán Catalá-López

Reviewer's report:

According to the authors, this manuscript describes a study protocol for a systematic review on timing, efficacy and cost effectiveness of upper limb therapy for motor recovery post-stroke.

Overall, this a well written manuscript in an important subject. However, it appears this manuscript presents the methods for several systematic reviews of multiple research questions (some of them pre-registered in PROSPERO as single protocols). Although the reporting of planned methods is transparent (but somewhat complex - multiple review questions!), some aspects could be improved and clarified.

I was asked for an open peer review report of a revised version of this manuscript and this includes all aspects of the design and reporting of the study protocol.

Comments:

Abstract
Page 3. Background. Lines 7-22. Authors should provide an explicit statement of the pre-registered question(s) their review(s) will address with reference to participants, interventions, comparators, and outcomes (PICO). In my opinion, information in lines 7-12 should be deleted (e.g. "(1) determine how many upper limb therapy studies have been conducted; (2) describe the characteristics of included studies (therapy dose, schedule and content and outcome measures)" - to the best of my knowledge, Q1 and Q2 were not part of their PROSPERO protocols, and scoping review methods are clearly better suited for answering both questions. Please, clarify and revise/delete (if appropriate).

Page 3. Methods. Overall, methods section should report how the study will be performed, including study eligibility criteria (PICO), data screening, selection and extraction (e.g. "We will include randomised controlled trials and observational studies of adult stroke survivors with an average stroke onset < 6 moths, undergoing hospital-based therapy to improve upper limb function. Eligible interventions will be [please list study interventions]. Two reviewers will independently screen, select and extract data. The methodological quality (or risk of bias) of individual studies will be appraised using appropriate tools.). In addition, planned synthesis methods should be reported (e.g. "A narrative synthesis will describe quality and content of the evidence. If feasible, we will conduct random effects meta-analysis)."
Page 3. Methods. Lines 27-37. Authors state: "Any study design of adult stroke survivors with an average stroke onset <6 months, undergoing hospital-based therapy to improve upper limb function with a minimum of two waves of assessment will be included and form the evidence for aims one through three. Only randomised controlled trials will be used to address aim 4 and 5". Please, revise this section considering all the above. For the review question evaluating the "cost-effectiveness", why only randomised controlled trials will be used? Most of the published cost-effectiveness analyses in the biomedical literature are model-based analysis (e.g. deterministic decision analysis, Markov models, etc… populated with data from the literature). Please, clarify and/or revise.

Page 3. Methods. Lines 37-41. Authors state: "Clinical measures of motor recovery (i.e., impairment and activity) will be investigated, as well as measures of health-related quality of life. Please, be more explicit here and provide a summary (list) of outcomes for which data will be sought, including prioritization (e.g. primary and secondary outcomes), as per PRISMA-P recommendations.

Page 3. Methods. Lines 39-49. Authors state: "Should sufficient studies be identified we aim to proceed to stage of quantitative synthesis either at the level of individual patient data or study level". In my opinion, this statement should be rephrased or eliminated. If authors plan to conduct IPD meta-analysis, sources and methods for data identification, selection, contact/request of IPD etc.. should be revised, noting that IPD will be sought, as per PRISMA-IPD.

Page 3. Line 58. "Trial registration" should be "Systematic review registration". In addition, please, revise PROSPERO registration numbers and provide accessible links. Apparently, authors have included three different PROSPERO registration numbers: "CRD42018019367" (SR evaluating the "timing of upper limb motor training interventions post-stroke related to motor recovery"), "CRD42018111628" ("SR of the cost effectiveness of upper limb motor rehabilitation interventions post-stroke") and "CRD42018111162" (with no PROSPERO record, a typo/error? efficacy review?). Could you please clarify in methods section of the Abstract you plan to conduct several systematic reviews for different study questions? For example, first line of methods: "We designed and registered three study protocols for systematic reviews and meta-analysis of timing, efficacy and cost-effectiveness of upper limb therapy for motor recovery post-stroke".

Background
Overall, this section should be revised. Readers need to understand the rationale behind the decision to perform the systematic review(s) and what the results may add to what is already known. Authors should explain the impetus for presenting 1 protocol x 3 systematic reviews on timing, efficacy and cost-effectiveness (such as to support clinical guideline development, to address uncertainty or variation in practice in approaches to a specific clinical problem, to support policy development…) and briefly summarize how the review builds on and could add to prior knowledge.

Page 5. Lines 19-24. Authors' state: "To develop a better understanding of what might be possible, we propose a search strategy to identify relevant evidence that will advance knowledge across three domains of upper limb rehabilitation and recovery: (a) time to deliver upper limb
therapy that yields greatest functional gains, (b) therapy efficacy of investigated upper limb therapy intervention and (c) cost effectiveness of upper limb therapy approaches. The findings will support future studies to test novel data-driven hypotheses that aim to define a new therapy pathway to promote upper limb recovery." This paragraph presents the main objectives of the systematic review(s), and should be placed as the last paragraph of the "Background section", before the "Methods section" (in page 7). Last sentence "The findings will support future studies to test novel data-driven hypotheses that aim to define a new therapy pathway to promote upper limb recovery" should be placed in "Discussion section". Please, revise.

Page 6. Lines 49-59. Authors' state: "Statistical techniques are available (including comparisons of effect sizes and network meta-analysis) that may help to establish the relative efficacy of different intervention approaches. Such an approach has the potential to help identify the most promising therapy targets to test in future studies; providing important guidance for the field (14)." In my opinion, this section is confusing. This study protocol does not report planned methods for network meta-analysis. Please, delete and/or clarify.

Page 7. Lines 37-44. Authors' state: "With this (dosage) information will we be able to determine the resource implications and assess the health economic arguments for optimum upper limb therapy. At present there are few investigations of the cost per quality adjusted life years (QALY) of upper limb therapy approaches." Please, provide some rationale for cost-effectiveness component (not only that, to your knowledge "there are few investigations").

Methods
Page 7. Line 49. Please, delete "AND DESIGN".

Page 7. Lines 52-59. and Page 8. Lines 1-15. "Aims". Please, remove from this section this information. Study objectives should be placed at the end of "Background section". Please, see comments above. Scoping review Q1 and Q2 were not included in PROSPERO, and should be deleted. Please, clarify.

Page 8. Line 20. Please, delete "Study design:"

Page 8. Line 20-28. The authors' state: "This protocol covers several research questions that will be answered from one systematic search strategy. Outcomes will be reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA/-P/-IPD) statement (33-35)." Please, revise as follows:

"The present protocol is being reported in accordance with the reporting guidance the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [with reference] (see PRISMA-P checklist in Additional file 1). This protocol covers several research questions that will be answered from one systematic search strategy. Three substudy protocols were registered within the International Prospective Register of Systematic Reviews (PROSPERO) for specific research questions: timing (registration number: CRD42018019367"), therapy efficacy (registration number: include valid number), and cost-effectiveness (registration number: CRD42018111628)."
In addition, in "Discussion section" include: "The methods and results of our systematic reviews will be reported following PRISMA statement and their extensions [with references]."

Page 8. Line 25. The authors state the final review ("outcome") will be reported using PRISMA extension for Individual Patient Data (IPD). Please, clarify why PRISMA-IPD. Will you identify, extract, and synthesize IPD evidence? If Yes, methods section should be accommodated to PRISMA-IPD providing some rationale and integrity (example, the following)
* Whether there was a protocol for the IPD project, and where it can be found
* Why/when the IPD approach will be initiated
* How authors of relevant studies will be approached for IPD
* Details of any missing IPD within the available individual participant data for each study, and how this will be handled within the meta-analyses
* Description any qualitative or quantitative differences between those studies providing individual participant data and those studies not providing individual participant data (if appropriate)

Page 8. Line 44. Eligibility criteria. Please, include: "Studies will be selected according to the criterio outlined below".

Page 8. Lines 47-57. Study designs. The authors state: "The search strategy will include all study designs of randomised controlled trial (RCT), non RCT, cohort and observational, pre-post single group, which have a minimum of two waves of assessment i.e., pre/baseline and post intervention/follow up. Single case, case series, qualitative, surveys, protocols papers, conference proceedings, crosssectional, and review designs will be excluded." Please, be more explicit with the study designs (e.g. non RCTs? observational include case-control studies?). I suggest the following revisions, if appropriate: "Study designs: We will include randomised controlled trials (RCTs), including cluster RCTs, controlled (non-randomized) clinical trials or cluster trials, before-after studies, and observational studies (prospective and retrospective cohort studies, case-control or nested case-control studies). We will exclude cross-sectional studies, case series, case reports, qualitative studies and reviews".

Page 8. Line 1-3. The authors state: "only RCTs will be included in the therapy efficacy and cost effectiveness systematic reviews as outlined in Figure 1." Could you please clarify and provide some rationale? For the review question evaluating the "cost-effectiveness", why only randomised controlled trials will be used? Most of the published cost-effectiveness analyses in the biomedical literature are model-based analysis (e.g. deterministic decision analysis, Markov models, etc… populated with data from the literature). Could you please clarify which reports will be eligible (e.g. full economic evaluations including cost-effectiveness analyses, cost-utility analyses, cost-benefit analysis? Partial economic evaluations including cost-outcome descriptions? Both? A selection of the above?). Please, clarify and/or revise.

Interventions. Upper limb therapy could be considered complex and broad intervention. For interventions (and type of comparators), authors should be more explicit and report/describe eligible interventions for inclusion (eg. in a BOX/Table). Same as previous Cochrane reviews (ref. 21-24 in Background section? Only those in p.14 "(e.g., CIMT, robotics, task-specific practice)"). If appropriate, note whether any will be clustered or merged into the same group or class (with justifications).

Please, see Hoffmann et al/TIDieR team paper (in the BMJ 2017) on enhancing the usability of systematic reviews by improving consideration and description of interventions: https://www.bmj.com/content/358/bmj.j2998

Outcomes and prioritization. Please, define all outcomes for which data will sought, including rationale for prioritization for main and secondary outcomes. Authors could include a BOX/or Table with definitions and examples of (main) study outcomes. Please, note some discrepancies in data abstraction and outcome list (e.g. safety/adverse events not reported as outcome, but described in Data extraction p.10-11).

Search strategy. Please, clarify and/or report planned limits (e.g. publication status, language, years considered).

Data synthesis. This section should be revised. Please, see my comments on IPD justification, data collection, integrity, etc… (and follow PRISMA-IPD if appropriate, for methods used to synthesise IPD eg. specify any statistical methods and models used: one-stage or two-stage approach? how effect estimates will be generated separately within each study and combined across studies (where applicable), specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for; use of fixed or random effects models and any other model assumptions?) How studies providing IPD and not providing IPD were analysed together (where applicable)? How missing data within the IPD were dealt with (where applicable)? Are you interested in survival functions/only for timing outcomes?) Please, clarify and extensively revise.

Clinical efficacy. This section should be revised. Please, describe criteria under which efficacy data will be quantitatively synthesised. If data are appropriate for quantitative synthesis, describe planned summary measures (continuous or binary outcomes?), methods of handling data and methods of combining data from studies (random effects model?, including any planned exploration of consistency (such as I2 , Kendall’s τ). Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression). If quantitative synthesis is not appropriate, describe the type of summary planned.

Note: If you plan to conduct "network meta-analysis", please report methods following PRISMA NMA recommendations. If not, please delete information in p.14 "If not possible, we will allocate cohorts to therapy approach categories and complete statistical modelling within categories e.g., network meta-analysis. Categories of intervention approach will be driven by the included studies (e.g., CIMT, robotics, task-specific practice), and will include a standard therapy category that will serve as the reference group for all analyses".
Page 13-14. Please, report methods for quantifying statistical heterogeneity (such as I² and □ ² ). Please, report statistical software and version.

Page 14. Cost-effectiveness. Could you please clarify if a "de-novo" economic evaluation will be conducted and reported (please, consider the CHEERS statement to report main methods - available at EQUATOR Network website) or only a systematic review of previous economic evaluations will be conducted/reported, and how evidence synthesis of economic evidence will be reported?

Discussion
Page 15. Discussion. Please, discuss potential limitations at study (outcome) level, and at review level you anticipate.


Appendix. PRISMA-P checklist. Please, revise (considering all the above).

Level of interest
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

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5. Do you have any other financial competing interests?
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If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

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No