Reviewer’s report

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

Version: 1 Date: 27 May 2019

Reviewer: Ferrán Catalá-López

Reviewer's report:

Thank you for this revised version of the manuscript. I would encourage authors to consider the following additional comments:

Abstract
p.3 Methods. Lines 52-54. Where: "We designed a search strategy to be used to address all three systematic reviews, which were each registered with PROSPERO. We will implement our search strategy in (…) should be "We designed three systematic reviews, which were each registered with PROSPERO. Searches will be conducted in MEDLINE, EMBASE, and Cochrane Controlled Register of Trials. (…)"

p.3 Methods. Lines 59-62. Where: "Clinical measures of motor recovery will be investigated (primary measure Fugl Meyer Upper Limb assessment), as well as measures of health-related quality of life (primary measure EQ-5D) and cost analyses." Please, be more explicit here and provide all outcomes of interest including prioritization. For example: "Primary outcomes will be recovery of upper limb impairment, health-related quality of life and costs (please, include a cost-effectiveness measure such a incremental cost-effectiveness ratio in terms of cost per quality-adjusted life years). Secondary outcomes will include adverse events and serious adverse events".

p.3 Methods. Lines 59-62. Why did you mention "adverse events and serious adverse events" in PROSPERO, but not here. Please clarify, and include: "Secondary outcomes will include adverse events and serious adverse events".

p. Methods. Line 62 and 63. Where: "If possible, we will conduct review specific meta-analyses that pool effects across studies". Should be: "If feasible, we will conduct random-effects meta-analyses where appropriate".

Background
p.6 Lines 129. Where: "We have designed a search strategy to address three (…)" should be "We have designed a systematic review protocol to address three (…)".

p.6. Please, delete lines 131 and 131. "This is important as (…) such issues".

p.6. Line 133. Where: "The comprehensive search strategy will address the following study objectives (…)" should be "We plan to conduct a systematic review to address the following study objectives (…)".
Methods

p.7. Lines 146-148. Where: "(...) (PROSPERO): timing (registration number: CRD42018019367), therapy efficacy (registration number: include valid number), and cost-effectiveness (registration number: CRD42018111628)" should be: "(...) (PROSPERO): timing (registration number: CRD42018019367), therapy efficacy (registration number: CRD42018111629), and cost-effectiveness (registration number: CRD42018111628)".

p.7. Lines 173. Please, delete figure 1. In my opinion, this figure is uninformative.

Page 8. Interventions. Please, be more explicit and report a full description of "upper limb motor therapy only". List some examples, if appropriate. Some of this information is reported in p.13, and should be placed here. Please, revise.

Page 9. Outcome measures. Lines 197-218. This subsection should be extensively revised. Authors should be more explicit and provide all outcomes of interest including definitions and outcome prioritization. Please, include as primary outcomes "recovery of upper limb impairment, health-related quality of life", but also a cost per health outcome measure for the cost-effectiveness analysis (e.g. incremental cost-effectiveness ratio in terms of cost per quality-adjusted life years). Why did you mention "adverse events and serious adverse events" in PROSPERO and in p.11 line 255, but not as an outcome of interest? Please clarify, and include: "Secondary outcomes will include adverse events and serious adverse events".

Page 10-11. Data extraction. This section should be extensively revised. For example:

P.10 Line 244. The term stroke is duplicated. Please, include number of participants, comorbidities…

P.10 Line 256-257. For economic evaluations (not "cost analyses"), please, report main methods and characteristics such as: setting, location, study perspective (e.g. health system, societal), time horizon, discount rate, estimating resources and costs, currency, price data, assumptions, etc…

P.10 Line 260-261. Please revise and include "Main clinical and cost measures: For all outcomes considered (benefits, harms and costs), we will abstract and present for each study: simple summary data for each intervention group and effect estimates and confidence intervals".

Pages 12-14. Strategy for data synthesis. Again, this section should be extensively revised.

Page 12. Line 281. Where: "A narrative synthesis will be used for each review to describe quality and content of the evidence" should be: "Our systematic review results will be reported by describing study characteristics, patient characteristics, and outcome results. We will also describe our literature search results, as well as the methodological quality and risk of bias results using tables, figures, and text."

Page 12. Lines 283-287 should be replaced by: "We will evaluate whether we have sufficient data to conduct random-effects meta-analysis. We will also ensure that the body of literature is sufficiently homogenous in terms of clinical (e.g., patient characteristics), methodological (e.g.,
study design), and statistical (e.g., forest plot consistency) characteristics. For example, we will use our clinical insight to assess for clinical heterogeneity, methodologists will assess for methodological heterogeneity, and statistical heterogeneity will be calculated using the I2 statistical test. We will try to explain potential heterogeneity via subgroup analysis and meta-regression analysis, as described below.


Page 13. Lines 314-319. Please, revise as follows: "If data are appropriate, we will attempt conducting a network meta-analysis (NMA). This analysis is particularly useful when there is a lack of head-to-head studies or when both relevant head-to-head and standard treatment controlled studies exist. The network meta-analysis approach allows the ranking of effectiveness and safety of interventions. Key considerations that will be evaluated on completion of data extraction for NMA will be handling of multi-arm trials, variance structures, and assessment of fit and consistency. This analysis will be conducted in [PLEASE INCLUDE SOFTWARE] and median rankings (or point estimates) will be calculated using a random effects model that makes use of all available direct and indirect data. The degree of uncertainty for all point estimates will be reported as 95% credible intervals (CIs)."

Page 14. Lines 321-322. Please, revise as follows: "We will use the CHEERS statement to examine the reporting quality of the identified economic evaluations."

**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

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