Author’s response to reviews

Title: A Systematic Review and Meta-Analysis of Interventions to Increase Stroke Thrombolysis

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Author’s response to reviews:

Dear Reviewers,

Thank you for your comments and recommendations which have significantly improved our manuscript. Herein we have addressed each comment individually. We have provided copies with and without changes tracked. Each page number included below refers to the manuscript without tracked changes.

Reviewer #1: This is a meta-analysis testing the effect of different interventions to increase the rate of rtPA treatment in community. There are only some minor comments. I suggest to insert a table showing all relevant data for the studies included into the meta-analysis. Currently, the forest plot (Figure 4) is not sufficient enough. I would like to see the data for all categories separately (public education, telemedicine etc). Currently, the numbers are shown only in the figure, but they are mixed up and it is difficult to follow and find the relevant studies only by authors’ names. Alternatively, I suggest to include references into the text for all these categories (number of studies in subcategory with references).

RESPONSE: We now include a table that lists studies by intervention approach (Table 1, page 24).

The legends for figures should be more detailed.

RESPONSE: We have added detail to three of the four figure legends (page 17) included in our original manuscript.
Please use whole words for abbreviations used for the first time (as EMS).

RESPONSE: We now define EMS in both the abstract and methods (page 5).

One punctuation missing online 41, page 8.

RESPONSE: We now include a period after Target:Stroke (page 8).

Reviewer #2: The authors have submitted a systematic review and meta-analysis of interventions aimed at improving rates of stroke thrombolysis. The methods and the associated weakness, as well as possible publication bias, are well written and acknowledged. Minor comments include that many systematic reviews are now a priori registered with services such as PROSPERO which was not done in this case in order to reduce bias.

RESPONSE: Thank you for your comments. At the time that we undertook this project, pre-registration was not widely performed. Were we to perform this meta-analysis today, we would certainly wish to pre-register with a service such as PROSPERO. We have now included this as a limitation in our discussion section (page 11).

The interventions appear to be only effective targeted at EMS, while the others were not statistically significant. The comments in the discussion on whether to improve thrombolysis should therefore be guided by local barriers are sensible but not supported by the data in this manuscript - ie the studies in this analysis were not designed under those hypotheses.

RESPONSE: We realize now that our discussion previously failed to adequately distinguish between two key concepts. Because the point estimates across intervention types are quite similar — this suggests similar efficacy across intervention types. However, given that EMS-based interventions have been trialed more commonly, the statistical evidence is considerably most robust for EMS-based interventions. We’ve spelled out this logic in the second and third paragraphs of the discussion section (page 9).

It is also important to note which ones were significant or not and displaying those within the summary of effect sizes separately (eg the figure with interventions "stratified" by the specific "target" with the references for those). Otherwise the interventions are so heterogeneous that comparing them has less clinical utility.
RESPONSE: We now include three additional figures (Figures 4-6) showing the effect sizes of specific interventions across studies (pages 21-22).

Again, thank you very much for your kind attention and comments.

Sincerely,

Mollie McDermott