Author’s response to reviews

**Title:** MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in The Netherlands: study protocol for a randomized controlled trial.

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**Author’s response to reviews:** see over
Re: 2nd resubmission of manuscript 1112083911118592 - MR CLEAN: design and protocol of a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands

Dear dr Cobo and TRIALS editorial team,

Hereby we submit the second revision of our manuscript and appendices, both with TRK and without. Below we list the remark of referee 1 and the editorial requests, point by point, with our responses. We separately indicated any changes to the manuscript.

Referee 1.

Comment: “The authors have appropriately addressed most of the requested points. However, point #11 should be completed (Minor Essential Revisions). The response of the authors to this point should be summarized in the text. It is important to clarify how potential revascularization will be studied and classified. The Clot Burden score is not a common classification for recanalization, but for the clot length. Why investigators do not use TIMI score on CTA? These points should be addressed.”

Response: We now added our response to the text of the manuscript. We agree that Clot Burden score is not a common classification for recanalization, but it is a static measure, and in dichotomized form, along with the collateral flow score, serves the purpose. We did not use TIMI or TICI on CTA because these scores require information concerning flow, which is not provided by CTA. Of course, all pre- and post-intervention DSA-runs are available, and scored by an independent core lab, but DSA is only available in patients who underwent the intervention, and therefore cannot be used to estimate the effect of treatment, because the comparison with controls cannot be made.

Changes to the manuscript: We added the following sentence to the methods section paragraph on Study outcomes, on page 10: “DSA runs are evaluated by a separate independent central core lab, because the assessors of DSA will not be blind for treatment allocation.”

We added the following sentence to the discussion on page 14: “We assess recanalization on CTA, which will be available in intervention and control patients. We will use a combination of Clot Burden Score and Collateral Flow Score to assess the presence and extent of recanalization, because TIMI or TICI scores do not apply, as they require information concerning flow, which is not provided by CTA. We do not repeat DSA at 24 hours, as this would pose an additional risk to the patients in the study.”
Editorial requests:

Comment 1: Please ensure the title conforms to journal style for study protocol articles. The title should follow the format “___________: study protocol for a randomized controlled trial.”
Response: We changed the title as requested.
Changes to the manuscript: The title now reads as: “MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in The Netherlands: study protocol for a randomized controlled trial.”

Comment 2: Please include the date your study was registered with your trial registration number at the end of your Abstract.
Response: We included the date and registration number of the Dutch and International registries at the end of the abstract.
Changes to the manuscript: We deleted the trial registration number from the title, and added the following to the end of the abstract: Trial registration: NTR1804; May 7, 2009)/ISRCTN10888758; July 24, 2012.

Comment 3: Please include the names of all ethical bodies that approved your study in the various centres involved, along with the reference numbers given, in the Methods section. If you do not wish to list them all in the Methods section, please include the list as an additional file and refer to this in the methods section.
Response: In the Netherlands, government–approved Medical Ethics Committees act for all participating centers. Once a study protocol is approved by one (central) Medical Ethics Committee, only administrative permission is needed to start the trial in one of the collaborating centers. We therefore mention only the reference number of the central medical ethics committee approval in the Methods section.
Changes to the manuscript: We replaced the text under the heading “Ethical considerations” with: “The MR CLEAN trial protocol has been approved for the Netherlands by the central medical ethics committee and research board of Erasmus MC University Medical Center (MEC-2010-041).”

Comment 4: Please remove your Conclusion and incorporate this section into your Discussion.
Response: Done.
Changes to the manuscript: We removed the conclusion header and incorporated this section into the discussion. The text was reduced to: “We expect that MR CLEAN will increase our knowledge of the effects of IAT for acute ischemic stroke, and facilitate the further development and implementation of this potentially beneficial treatment.”

Thank you again for considering our manuscript.

Yours sincerely,

Diederik Dippel