Author's response to reviews

Title: MR CLEAN: design and protocol of a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands

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Author's response to reviews: see over
Dear editors,

Thank you for considering our manuscript. We thank the reviewer, dr Davalos for his critical and helpful remarks. Below, we list all remarks with our response, which includes a summary of the changes we made to the manuscript. Our response is delayed, for which we apologize.

Finally, we updated the trial status. Very recently, we included our last patient. We were well ahead of schedule. The trial database is still open as follow-up continues. Soft lock and partial unblinding will take place after a final review by our DMSC on July 18, 2014.

Sincerely,

Diederik Dippel

Puck Fransen,

For the MR CLEAN investigators and writing committee.

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Reviewer remarks

A General remark

This paper describes the methodology of probably the third endovascular treatment trial for acute stroke that will appear in literature. So the results are highly expected although the methodology used in this trial constitutes a big challenge for obtaining positive results. There are several points that the authors should clarify in order to make easier comparison with other similar trials.

Response:

The design of a trial is always a compromise between generalizability and power. We take the viewpoint that when not much is known of effect modifiers, generalizability and broad inclusion criteria should be preferred.

B Major Compulsory Revisions

Background

1. The background of the manuscript should be shortened since the detailed description of previous trials is not needed.

Response:
Indeed the background section is very detailed; it was taken from the original protocol.

Changes to the manuscript:

We now briefly refer to these trials on page 5.

Methods:

1. Clarify if best medical treatment followed published guidelines

Response:

Best medical treatment was provided according national and international guidelines. This includes IV alteplase when indicated.

Changes to the manuscript:

We added the phrase “according to national and international guidelines” to the Design section on page 7.

2. Clarify if MCA M1 and M2 were included or only M1.

Response:

Both M1 and M2 occlusions are allowed as an inclusion criterion, but not M3 occlusions.

Changes to the manuscript:

We added information about the exact location of the occlusion to the sentence on page 8: “General inclusion criteria are: a clinical diagnosis of acute stroke with a deficit on the NIH stroke scale of at least 2 points, CT or MRI ruling out intracranial hemorrhage, occlusion of distal intracranial carotid artery or middle or anterior cerebral artery demonstrated with CT angiography (CTA), MR Angiography (MRA), digital subtraction angiography (DSA) or transcranial Doppler ultrasound (TCD), the possibility to start treatment within 6 hours from onset, age 18 or over and informed consent given in writing.” with: “General inclusion criteria are: a clinical diagnosis of acute stroke with a deficit on the NIH stroke scale of at least 2 points, CT or MRI ruling out intracranial hemorrhage, occlusion of distal intracranial carotid artery or middle (M1 of M2) or anterior cerebral artery (A1) demonstrated with CT angiography (CTA), MR Angiography (MRA) or digital subtraction angiography (DSA), the possibility to start treatment within 6 hours from onset, age 18 or over and informed consent given in writing. “

We also deleted referral to the use of TCD, see the response to point 4.

3. Confirm if patients’ enrolment was or not was limited according to the ASPECTS score or extension of early signs of infarction at baseline.

Response:
Our inclusion criteria do not refer to the ASPECTS score. Whether a patient with extensive early CT signs of ischemia should be included was left to the discretion of the local investigators. However, all baseline CTs are being evaluated with the ASPECTS score, in order to analyze any effect modification.

**Changes to the manuscript:**

We added the following sentence to the section on exclusion criteria on page 8: “Enrolment was not limited according to the ASPECTS score or extension of early signs of infarction at baseline.”

4. Confirm if TCD was an optional tool for the diagnosis of arterial occlusion. This is stated on page 8 but not mentioned in the table of page 26. If TCD was used, the authors must clarify diagnostic criteria of arterial occlusion and expertise of investigators. Also, they should discuss if a poor correlation between conventional angiography and TCD results in those patients assigned to the IAT arm could warn trial validity. How was baseline TCD evaluated by the imaging committee?

**Response:**

When we designed the trial we approved occlusion detection with TCD, but during the trial all centers intended to make use of CT angiography or MRA. TCD was never used.

**Changes to the manuscript:**

We have removed any reference to TCD from the manuscript, to avoid further confusion.

5. Intervention: Please, define policy about intubation or conscious sedation. Specify if time from picture to puncture (image to groin) was recorded and limited. Also specify if there was a window from onset to revascularization or if the procedure was as long as indicated by the local interventionists.

**Response:**

The choice for intubation or conscious sedation was left to the local interventionist. Time from picture to puncture was recorded and limited by the fact that treatment should be started within 6 hours after stroke onset. The trial steering committee has advised the investigators that the procedure should be as quick as possible and terminated at last 8 hours from onset of symptoms.

**Changes to the manuscript:**

We added the following sentences to the description of the intervention on page 8: “The decision for intubation or conscious sedation was left to the treating physicians. Time from onset to treatment (needle in groin) was recorded. The trial steering committee has issued recommendations that interventional procedures should be stopped at 8 hours from onset of symptoms.”

6. mRS evaluation (primary endpoint) by assessors masked to treatment allocation should be better defined: did they use a structured interview? Were they local or central assessors? Was evaluation performed in a face-to-face interview or by a telephone call?

**Response:**
All patients were approached by the research nurse at 3 months, who was not aware of treatment allocation. She did a telephonic interview with standardized questions. Afterwards the question forms were blinded and assessed by 2 different outcome assessors who were not aware of the assigned treatment allocation. In case of disagreement between the two assessors, a final judgment was made by third blinded assessor.

Changes to the manuscript:

We added to the section on blinding on page 9: “with standardized forms and procedures in a structured telephone interview by an experienced research nurse at the central trial office, who is not aware of treatment allocation. “

7. Confirm on the text that the trial statistician was not a member of the trial SC. If this is the case, define the interaction with the DMC statistician. Also, the authors should clarify the number of interim analyses reported to the DMC, if they were or not predefined and if reports were masked or unmasked to treatment allocation.

Response:

The trial statistician was not a member of the trial SC. The trials statistician had access to the treatment allocation codes and combined these with other trial data to prepare the DMC report. Trial reports were predefined and contained an unmasked section, which was accessible only to the trial DMC members, one of whom is a biostatistician.

We argued in the section describing our interaction with the data monitoring committee that the exact number of interim analyses is of little importance. However, we report to the DMC every half year which coincides with an accrual of 100 patients.

While we were critically reviewing our own text, we saw that it suggests that we report only serious adverse events believed to be due to treatment. This is not the case, as we report all serious adverse events.

Changes to the manuscript:

In the second sentence in the section “Data monitoring committee”, we replaced the word “procedure” by “allocated treatment”. We decided to leave out the words “.. believed to be due to treatment” .

We added that “.. the DMC at least annually, and is provided with structured unmasked reports, prepared by the trial statistician, for their eyes only.”

8. Clarify if safety parameters included arterial rupture, dissections, distal emboli in non-involved arteries, and SAH. The roles of the adverse event and outcome assessment committees in adjudicating those events should be mentioned.

Response:
Our description of safety parameters is indeed a little brief. The trial protocol that has been available at our website throughout the trial (and still is) defines serious adverse events, which lead to death, disability, or to extended hospital stay or are life threatening. We defined neurological deterioration as increase in NIHSS score at follow up of 4 points or more. Adverse events, such as

Changes to the manuscript:

We added a subsection, headed “Safety aspects” which contains the following text:

“Adverse events are undesirable experiences occurring to subjects during the study, whether or not they are considered to be related to the experimental treatment. All adverse events reported spontaneously by the subject or observed by the investigators are recorded. A serious adverse event is any untoward occurrence or effect that causes death, is life-threatening, requires prolonged hospitalization or results in persistent significant disability. The primary safety parameter will be neurologic deterioration during the first 24 hours from inclusion. This is defined as an increase in NIHSS of 4 points or more. Expected serious adverse events are neurologic deterioration, symptomatic intracranial hemorrhage, extracranial hemorrhage, technical complications or vascular damage at the target lesion, such as perforation or dissection, distal emboli in non-involved arteries, aspiration pneumonia, allergic reactions to contrast agents.

9. DMC had some rules for halting the trial as a result of efficacy, but were there rules for safety stopping? Who did report safety data to the DMC? Were there a CRO and an electronic CRF?

Response:

The DMC received safety data from the trial statistician, after they were reviewed by the adverse event committee. We have a central trial office where a trial coordinator reviewed all incoming data. Data were entered into a web-based trial management system, which allowed for edit and audit trails, by trained local research nurses. All local data were carefully reviewed by the central trial office and the first 3, as well as every 10th patient’s CRF was fully checked against source data.

The “stopping rule” for the DMC to rely on speaks of “proof beyond reasonable doubt” … “one particular treatment is clearly indicated or clearly contra-indicated...” This includes the possibility that there is a safety issue that clearly favors standard treatment. This formula has been used in many trials and in our view worked very well. We did however, formulate safety criteria, for individual centers.

Changes to the manuscript:

We added the following to the section on trial organization:

“All incoming data were reviewed by the trial coordinator at the central trial office. Imaging data were reviewed at the secondary imaging center. All data were entered into a web-based trial management system that allowed for edit and audit trails, by trained local research nurses. All local data were carefully reviewed and first 3, as well as every 10th patient’s CRF was fully checked against source data.”
We added the following sentences to the section on Data monitoring committee:

“There are no detailed safety stopping rules. Safety criteria for individual centers were: If the local investigator or other member of the team at a trial centre has a concern about the outcome of their trial procedures, they should inform the MR CLEAN trial office, which will organize a blinded assessment of the relevant outcome events. This will be submitted by the central office to the chairman of the data monitoring committee, who may recommend further action, such as suspending randomization at the centre. Similarly, the database manager at the trial office will monitor outcome events and if there are three consecutive deaths or three consecutive serious adverse events at a single centre within 30 days of treatment in the same arm of the study, then assessment of the events will be triggered. A cumulative death rate of more than 50% or a cumulative serious adverse event rate exceeding 20% over 10 cases during hospital admission would also trigger careful assessment of the relevant outcome events.”

10. The DMC paragraph seems to mention that the study protocol could be modified according to the interim analyses. Please, clarify. If this was the case, did investigators make any changes? Since this fact may introduce a bias, please discuss.

Answer: The DMC paragraph states that the DMC will advise the chairman of the Steering Committee. It suggests that a difference of 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting or modifying the study prematurely. The present paper does not report on the conduct of the study, but on the study protocol. However, we can assure the reviewer that during patient accrual the DMC has never made a recommendation as halt the study or modify the study protocol.

Changes to the manuscript: None.

11: Criteria for vessel patency classification on CTA/MRA/DSA follow-up should be defined. I imagine that the central Corelab reviewed the angio runs performed during the procedure. If so, complete revascularization after the procedure should be a secondary endpoint and the definition should be provided.

Response:

Angio runs are evaluated by a separate independent central Corelab, (chaired by dr Albert Yoo from Mass Gen Hosp, Boston, USA), because the assessors of DSA will not be blind for treatment allocation. We will provide a detailed report of revascularization immediately after the procedure, as assessed from the final angio run. We did not include DSA results as a secondary outcome as they are only available in patients who underwent the intervention. Although MRA was also allowed, all centers followed the recommendation of the trial executive committee to use CTA. Follow-up CTA at 24 hours will be available in the majority of patients. We used the Clot Burden score to describe vessel patency.

Changes to the manuscript:
12. The study sample size calculation seems to accept 10% crossovers. This may seriously affect the validity of the trial since an ITT principle for analyses is used. What are the actions done by the SC members for monitoring and preventing this important drawback during the trial?

Response:

We do not regard the possibility of cross-overs as a drawback of the trial, but merely as an inconvenient and undesirable aspect of clinical care, which has to be avoided and prevented as much as possible. The intention to treat principle is in our view the only way to deal with this phenomenon. The occurrence of cross-overs merely requires a larger sample size, which is what we planned.

We did the following to prevent cross-overs: we held once or twice yearly work shops where we trained investigators with video and role playing about including and randomizing patients with much emphasis on good communication and preventing cross-overs. The cross-over percentage has to be analyzed yet, but we are confident that our policy led to a much lower than 10% cross-over rate.

Changes to the manuscript:

None.

13. In the discussion the authors comment that they gathered information on consecutive patients before the trial, but did they monitor consecutive enrolment of all eligible patients? This is an important point for external validity and should be discussed.

Response:

We do not agree with the reviewer that monitoring of all eligible patients is essential to judge external validity. External validity should in our opinion be apparent from the baseline characteristics of the trial population. Moreover, when the ongoing trials demonstrate a treatment effect, major changes in the population of eligible patients can be expected, because of changing work-up and referral patterns.

However, participating centers did not treat patients outside the context of the MR CLEAN trial. All centers had registries of patients who underwent intra-arterial treatment and we will use these to describe the whole study population. We will refer to the CONSORT statement.

Changes to the manuscript:

We added the following text to

All participating centers register consecutive patients with acute ischemic stroke and record treatments given outside the trial protocol. These will be reported (ref: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Trials 2010, 11:32. (24 March 2010).
14. In my opinion the description of the other ongoing clinical trials is beyond the scope of this manuscript.

Response:

We agree.

Changes to the manuscript:

We shortened the text describing other trials in the discussion on page 14 by now only mentioning the following:

“Several randomized clinical trials of intra-arterial therapy for acute ischemic stroke are ongoing. One trial exclusively concerns the treatment of patients with basilar artery occlusion. [ref] Several other studies compare mechanical thrombectomy with standard treatment including or preceded by iv alteplase (refs). Several other studies compare mechanical thrombectomy with standard treatment in patients who are ineligible for iv alteplase treatment exclusively [ref] of additionally. [refs] Several trials have an upper age limit, [refs] some exclude patients with a large ischemic core (refs), and some require perfusion mismatch on baseline imaging (refs).”

Minor Essential Revisions

Update the REVASCAT reference. It was published in Int J Stroke

Response:

We updated the reference to REVASCAT in the discussion on page.

Changes made to the manuscript:
inserted reference to REVASCAT in the new text on page 14 of the discussion.