Reviewer's report

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

Version: 1 Date: 28 March 2014

Reviewer: ANTONI DAVALOS

Reviewer's report:

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.

Major Compulsory Revisions

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

Methods:

1. Clarify if best medical treatment followed published guidelines
2. Clarify if MCA M1 and M2 were included or only M1.
3. Confirm if patients’ enrolment was or not was 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?
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.
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?
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.
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.

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?

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.

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.

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?

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.

14. In my opinion the description of the other ongoing clinical trials is beyond the scope of this manuscript.

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

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

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?

I am the P.I of the REVASCAT trial funded by Covidien with an unrestricted grant. I have not received fees for this.

I received fees as member of the SC of the STAR trial

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? NO

Do you hold or are you currently applying for any patents relating to the content of the manuscript? NO

Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? NO

Do you have any other financial competing interests? NO

Do you have any non-financial competing interests in relation to this paper? NO