Author’s response to reviews

Title: The CASCADE trial: Effectiveness of ceramic versus PEEK cages for anterior cervical discectomy with interbody fusion; protocol of a blinded randomized controlled trial

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Response to Reviewer Carl J. Lombard’s report:

First comment - no page numbers! We have added page numbers.

1. Methods. under this section it is stated that the blinding will be maintained for the full period of follow-up (24 months). Under the randomisation section it is stated that blinding will be maintained until 1 year. This does not make sense. Patients will be blinded for one year only. We have corrected this mistake.

2. Was a fixed block size used for randomisation blocks? Were the envelopes numbered? We have added explanations that the block size is variable in units or 4, 6, or 8, and that the envelopes are numbered and opened in sequence.

3. Surgical intervention. No information is given regarding the surgeons performing the procedures. What level of experience is required? is it a single surgeon per operation? Are there more than one surgeon?. How is this factor controlled for? We added detail explaining that the two surgeons are very experienced. This is a very common procedure, so experience is not an important factor. Each procedure has only one surgeon participating.

4. Main outcome: NDI. At what time point will the primary outcome be used for comparison - 24 months?. Is 24 months is moderate follow-up time for assessing the success of this procedure? Is the NDI self-administered? The primary comparison of NDI is at 12 months, which is typical for cervical fusion studies. We also follow the patients for one additional year to make sure that the effect and the product are durable. The NDI is self-administered.
5. Who sees the participant at each of the visits? il it the same person? What happens when a participant misses a visit? The surgeon who operated sees the patient at each visit. The staff makes sure that patients do not miss an appointment.

6. What happens to the data? We have added a discussion of data management. The data is entered into an online data capture (EDC) system as it is received. The paper CRFs (source documents) will be kept in the hospitals where the patients are treated.

7. What about safety of the patients? How is adverse events recorded and handled? The operating surgeon or PA completes the adverse event form. Does the participants have insurance and who carries the risk of special investigations and long term care? The patients are covered under their normal insurance for the procedure and the cost of the product. The sponsor has special insurance to cover any problems created during the investigation. The sponsor is paying for the extra imaging and radiologist fees. We have added this info to the manuscript.

8. How is informed consent done (not when and where)? Patients are asked to read and sign an informed consent document that is written in Dutch. They can take it home and consider it carefully.

9. What is the involvement of the companies that produce the implants? Does the participant have to pay for their implant? Normal insurance pays for the implant. Patients get a small stipend to cover their travel expenses for returning to the clinic for follow-up. This has been added to the manuscript.

10. The safety and care aspects of the participants are lacking in the protocol. We have added a discussion of the patient’s freedom to withdraw from the study at any time. We have also added discussion of handling of adverse events.

11. One of the major concerns of the protocol is that the sample size is based on a superiority hypothesis (improvement) whereas it should have been formulated and calculated as a sample size for a non-inferiority hypothesis. It is not clear if the 7.5 NDI points is the equivalence limit specified. The study may therefor be underpowered. We agree that this part of the manuscript was confusing. We have changed the text to this:

Sample Size and Data Analysis

Sample size for this equivalence trial has been established using power analysis incorporating data from journal article reports of similar ACDF studies. For sample size calculations, we have used the change in NDI from pre-op to one year post-op improvement rate cited in the literature for ACDF with carbon fiber reinforced PEEK cages: 10% reduction (improvement) with a standard deviation of 22%. The Minimal Clinically Important Difference (MCID) for the NDI is 7.5
points or 15\%[31], which is the equivalence interval for sample size calculation.
The 46-patient Valeo C enrollment has a power of .90 when compared with a
PEEK study arm of the same size. Incorporating a one-year estimate of 6\% loss
to follow up, a total of 100 patients need to be enrolled.

12. The statistical inference outlined for evaluating equivalence does not any
make sense. It has been changed as follows: The two groups will be considered
equivalent if the mean NDI improvement for the silicon nitride cage group is
within a range from the mean of the PEEK group minus the NDI MCID to the
PEEK mean plus the MCID.

13. The repeated measures of NDI within participants can be of benefit in
improving the precision of the estimated difference at say 24 months and using
this improved precision in the confidence interval for the inference of
non-inferiority. This will be an important issue since the study might be
underpowered. We have added this sentence: A repeated measurements
analysis of variance for the primary outcome measure will also be performed in
order to compare the evolving patterns over time.

14. I would advise the study team to consult a medical statistician to ensure that
the statistical section of this protocol is corrected. We have taken his advice.

15. It seems that the enrolment of participants have been completed. Could not
calculated a revised sample size from the information provided in the protocol.
Enrollment has not been completed yet.