Author's response to reviews

Title: Endoscopic Saphenous harvesting with an Open CO2 System (ESOS) Trial. Study design and rationale of a prospective randomized trial for coronary artery bypass grafting surgery

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Author's response to reviews: see over
Reviewer's report

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Trial. Study design and rationale of a prospective randomized trial for coronary artery bypass grafting surgery

Version: 2 Date: 1 April 2011

Reviewer: lawrence friedman

Reviewer's report:

I have revised this manuscript and I have a point-by-point response to the concerns:

a) In this unblinded trial, are there any procedures for assuring that outcome assessment is unbiased?

Answer: Outcome events will be assessed by an independent “adverse-events” clinical committee (outside observers of ESOS trial).

b) It is unclear how the projected sample size is adequate for the 2-year endpoint. What are the expected MACE event rates? Is this being planned as a superiority or a noninferiority trial? If the former, what difference in MACE will be likely to be detected with 80% power? If the latter, what is the delta of noninferiority and why?

Answer: The expected MACE events are: death; repeat revascularization; recurrent angina and/or myocardial infarction. About the primary end-point of freedom from leg wound complications, ESOS trial is being planned as a superiority trial. About the secondary end-points of freedom from MACE, ESOS is being planned as a non-inferiority trial.

In our trial, as far as the short-term outcome is concerned, previous studies suggest a six-week leg wound complication rate of about 20% in the CVH arm and less than 4% in the EVOH arm. With this risk/prevalence difference of 16%, and the predicted sample size of 100, the power based on normal approximation is about 94% (91% if we apply the continuity correction), and thus very good: a power of about 80% would be reached already with a sample size around 80.

The situation changes dramatically when we consider the mid- and long term outcomes. Previously quoted studies' suggest a first-year vein-graft failure rate of about 20% with an annual occlusion rate of 1% to 2% in the first six years, with practically no difference between the EVH and OVH approaches. Similarly, the results on event-free survival rates for the two arms have barely a 2-3% gap. The 80% test power goal, with such a small risk prevalence
difference requires sample sizes of at least 3000 for each cohort, values well beyond any practical implementation in a single medical centre, at least in a lifetime.

On the basis of these considerations, the initial recruitment number of 115 patients per cohort, with endpoint number of about 100 patients, sustainable from the point of view of human and financial resources, looks fully acceptable.

I look forward to receiving your comments of our revised manuscript. Please don’t hesitate to contact me if you have any problems or questions regarding our manuscript.

With best wishes,

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