Author's response to reviews

Title: Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-acclerated Thrombolysis for thromboembolic infrainguinal disease (DUET): design and rationale [ISRCTN72676102]

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

Thank you for carefully reviewing our manuscript entitled: ‘Dutch randomized trial comparing standard catheter-directed thrombolysis versus Ultrasound-accelerated Thrombolysis for thromboembolic infrainguinal disease (DUET): design and rationale [ISRCTN72676102]’.

Herewith we would like to address the comments in a revised manuscript and by giving a point-by-point response to the concerns in this cover letter.

Reviewer: Roger Malcolm Greenhalgh

Reviewer’s report:
I would note that the crural arteries may cause significantly more difficulty and it should be important that equal numbers are allocated to each group. A stratification is advised. I note the various secondary endpoints and the patients to be included. Under eligibility criteria it becomes very plain that a mixture of thrombosed femoropopliteal or femorocrural bypass grafts will be used and also some will be vein and some prosthetic. It should be noted that prosthetic bypass to crural vessels is especially susceptible to primary thrombosis and also secondary thrombosis. Thus stratification for this is also to be considered. The numbers in the groups may not be large enough (30 v 30) to do this adequately and statistical advice is vital.

We believe that additional stratification for femoropopliteal versus femorocrural bypass grafts and venous versus prosthetic bypass grafts is not warranted because these groups will be equally distributed in both treatment arms. This is in contrast to the unequal distribution of native arteries versus bypass grafts. Furthermore, the disadvantage of additional stratification is the predictability of treatment allocation, especially in a trial with non-blinded treatment arms.

Reviewer: Allan Donner

Reviewer’s report:
1. It should be kept in mind that the primary outcome (duration in hours) is likely to be positively skewed, implying that a log transformation may be advisable for the purposes of analysis.

We apologize for the statistical analysis paragraph being too short. The reviewer is correct, and our intention is to analyze the primary outcome by means of Kaplan-Meier and Log-rank test. The sample size calculation was also based on this premise.

2. It is stated that the hypothesis of interest will be evaluated using a t-test. Since this a relatively small trial, substantive imbalances on important prognostic
characteristics (predictors of outcome) may well arise. To the extent possible, all such potential covariates should be specified in advance. The multivariable method (e.g. multiple linear regression) that will be used for adjustment purposes should also be specified.

The t-test was wrongly stated and should be the log-rank test. We will assess imbalance in prognostic factors as a secondary analysis by means of Cox-proportional Hazards multivariate analysis.

3. Aside from stratification by whether a native artery or bypass graft is used, stratification by centre will also presumably be employed.

The reviewer is correct.

Sincerely yours,

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