Author's response to reviews

**Title:** Effects of the dose of erythropoiesis stimulating agents on cardiovascular events, quality of life, and health-related costs in hemodialysis patients: The Clinical Evaluation of the DOSe of Erythropoietins (C.E. DOSE) trial protocol.

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

Thank you for providing a very thorough revision of our manuscript entitled “Effects of the dose of erythropoiesis stimulating agents on cardiovascular events, quality of life, and health-related costs in hemodialysis patients: The Clinical Evaluation of the DOSe of Erythropoietins (C.E. DOSE) trial protocol”. This revision has provided an opportunity to address the reviewer’s comments on our article, which we believe has improved the manuscript. Below please find a point by point answer to all comments.

We hope that our manuscript, in its revised form, is now acceptable for publication on Trials Journal.

Regards
Valeria Saglimbene,
on behalf of all authors.

Answers to reviewer’s comments

Comment no.1
Page 8, sentence reading “Patients who are already receiving treatment with any ESA may participate in the trial and will be directly allocated to the experimental ESA dose without a wash-out period.” This sentence reads as if patients already receiving treatment with ESA will be directly allocated to one specific arm of the trial (the 'experimental' ESA dose arm). This would violate your randomization pattern and may raise internal validity issues. Did you mean to write that “Patients who are already receiving treatment with any ESA may participate in the trial and will be directly enrolled and randomized into the trial without a wash-out period.”

Reply: Yes, and we have modified this sentence as appropriately suggested by the Reviewer.

Comment no.2
Please provide sufficient detail in your Randomization section such that the reader can determine how you intend to maintain allocation concealment. For example, were sequentially numbered opaque sealed envelopes provided to each site? Was randomization conducted via the web? Etc.

Reply: We have added the following sentence in the randomization section: “To achieve concealment, randomization will be carried out centrally by the coordinating study center”.

Comment no.3
Please consider re-writing your Data Analysis section.
a) Please provide appropriate references to support the use of each type of statistical test. For example, I was unaware that the log-rank test referred to in the second sentence could be used to assess incidence. I understood it was used to assess ‘time to event’.
**Reply:** Kaplan-Meier curves estimate “time to event” of a group of patients. More precisely, in the survival context, the measure of incidence has to take into account not only the number of events, but also their timing. Consequently, we have revised our manuscript by replacing the world “incidence” with the more appropriate “incidence rate”, as suggested by the Reviewer.

The log-rank test was used to compare the two Kaplan-Meier curves. The sentence in the manuscript has been re-written accordingly to avoid misinterpretations, as suggested by the Reviewer.

Finally, we have provided appropriate references to the relevant statistical tests used, as requested by the Reviewer.

**b) Please provide a list of variables that will be assessed for baseline imbalance, the decision rule that will be employed to identify imbalance and report the analytic technique that will be used to control for imbalance by outcome type.**

**Reply:** The Reviewers’ suggestion has a two-fold interpretation.
1. The request to provide a list of variables to be assessed for baseline imbalance. With respect to this interpretation of the Reviewers’ request, we note that a list of baseline variables has been provided in the previous version of the manuscript (data analysis section-page 13). Furthermore, within the context of a properly powered and designed randomized trial, we confute the need for any assessment of baseline imbalance which, if at all present, could be due to chance. The concept has been broadly appreciated in the literature; p values for comparisons of baseline covariates are no longer reported in Table 1 of randomized trials according to the Consolidated Standards for Reporting Trials (CONSORT) statement, as any existing differences could well be due to chance.
2. Most probably the Reviewer is requesting the need for adjustment for potential confounding variables which may be distributed unevenly. This should be of course (as we did) be declared in advance, independent of potential lack of balance in some of the baseline covariates (i.e. subgroup and other type of analysis stated ‘a priori’). With respect to such approach, we clarified in the Data Analysis section that a multivariate Cox proportional hazards models will be used to address potential confounding.

c) Provide an explicit reference to support the use of the Cox P-H model and state how the fundamental assumptions of the model will be tested.

**Reply:** We have appropriately referenced the use of the Cox model in the revised version as suggested by the Reviewer. We also added a sentence relating to underlying assumptions of the Cox model.

d) Report the exact number of sub-group analyses that will be conducted and how your findings will be controlled for the problem of multiple comparisons.

**Reply:** The full list of subgroup analyses that we plan to conduct is provided on page 13 of the revised manuscript. Data will be presented as a forest-plot with any meaningful subgroup analysis being reported, primarily for the sake of addressing potential concerns from the clinicians requesting to see analyses for different subgroups. Clearly we have not powered the trial for detecting existing differences in any of the specific subgroups, i.e. these are not ‘powered pre-planned analyses’, nonetheless we believe important that these information should be provided. In this view, we do not plan any adjustment for multiple comparisons. The impact of any relevant covariates will also be explored within the multivariate regression model.
Comment no.4
Please provide a reference to support the analytic decision threshold of the interim analysis. Is this the Haybittle-Peto approach? How does this impact on your final p-value of your primary analysis? If possible, please provide concrete decision thresholds with regards to the interim analysis to modify sample size. For example, if projected power drops below 80%, will you extend follow-up?

Reply: As the Reviewer appropriately suggested, we clarify the strategy for our interim analysis. The study, as stated in the protocol, is event-driven. Based upon standard methodology, we plan to perform our interim analysis at 2 years following completion of recruitment, to assess whether assumption (expected event rates and expected risk reduction with experimental intervention) have been met, have not, or have be exceeded. The duration of follow-up will be modified accordingly.