Reviewer's report

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.

Version: 2 Date: 9 April 2010

Reviewer: Gordon Doig

Reviewer's report:

This is a very well written protocol paper. Congratulations on your undertaking. Could you please address the following issues:

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."

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.

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'. 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. 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. 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.

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?