Reviewer's report

Title: Distress and quality of life after autologous stem cell transplantation: a randomized clinical trial to evaluate the outcome of a web-based stepped care intervention

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Reviewer: Andrew Vickers

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A few comments on the protocol:

1. Is it intended for randomization to be stratified by study center (university hospital vs teaching hospital), as is common for multicenter studies?

2. More step-by-step details for how randomization will be carried out are required. I'd expect at least a paragraph on the practical implementation of randomization. How will the clinicians be informed of the randomization assignment? What steps will be taken to ensure that allocation cannot be guessed before treatment or changed afterwards?

3. The study is powered to detect a difference in quality of life from baseline to T30 (30 weeks following randomization). This suggests that the primary endpoint is the improvement in outcome at 30 weeks post-treatment. However, the analysis planned is a mixed model, which would estimate the mean improvement in outcome over duration of the study (from baseline through 42 weeks post-treatment). A couple of comments on this:
   a. If the main outcome of interest is the improvement at 30 weeks, then the analysis could be simplified as an ANCOVA model with the 30 weeks score as the dependent variable.
   b. If the main outcome of interest is the mean improvement over the duration of the study, then why doesn't the power calculation take into account the 3 post-treatment measurements?

4. The background states that there is a large decrease in quality of life immediately after auto-SCT, with gradual improvement during the first year. This suggests that a non-linear treatment effect may exist, in which case, a mixed model could be used to test for a difference in treatment effect over time, by entering a group x time interaction term into the model.

5. The ANCOVA models should include the randomization stratification variables as covariates, since this has been shown to increase power.

6. Page 16, middle paragraph, states that if baseline differences between treatments are found, then these variables may be entered as covariates in the ANCOVA model. Instead of this method, the investigators should pre-specify any baseline variables which they believe will predict outcome and include them as covariates, regardless of whether baseline differences between groups are
detected.