Reviewer’s report

Title: Single blind randomized Phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial)

Version: 1 Date: 7 October 2011

Reviewer: Andrew Vickers

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This is a nicely written protocol. Attention should be paid the following points in any resubmission.

1. Eligibility criteria. What is a WHO score >2? WHO score of what?

2. Justify the use of multiple overlapping questionnaires. It is very peculiar to have patients fill in so many questions, especially when most have nothing to do with prostate cancer or treatment side-effects. Questionnaires every 6 months for 10 years? This is a massive amount of data. It is probably 100 questions per time point, multiplied by 600 patients, times 20 questions, that is over 1 million data points. This huge burden for patients and research staff needs to be justified.

3. The sample size is peculiar for two reasons. First, the use of a one sided p value is very unusual, indeed, I cannot remember seeing it before in a Phase III trial of a new cancer intervention. Second, the analysis is based on time to event data (Cox modeling) but the sample size is based on binary comparison of proportions. A more standard sample size approach would be to take the time to event nature of the data into account, calculating the number of events expected within a given length of follow-up. Is it really the case that all patients will be followed for five years? State the length of follow-up after accrual of the last patient.

4. The QoL analysis is hugely underpowered. You are talking all that data from patients and then just saying "better or worse?". It might be that all patients get worse, so no difference between groups, but patients in one treatment group don’t get as bad as the other. Please use a standard approach such as ANCOVA, with baseline score as a covariate (see Vickers and Altman, BMJ)