Reviewer's report

Title: Planning a cluster randomized trial with unequal cluster sizes: practical issues

Version: 1 Date: 17 November 2005

Reviewer: Allan Donner

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1. The recommended sample size approach based on "minimum variance weights" may to be more sensitive to the guessed value of the ICC than the other methods, since the ICC appears in four separate terms. In this case, for situations where there is little prior knowledge available concerning the value of the ICC, one or more of the other approaches considered may be preferable in practice. Therefore it would be interesting to compare the robustness of the different approaches to misspecification of this parameter.

2. On a related point, would the recommended approach also be expected to show optimality for non-normal distributions in which the response variance depends on the mean? In particular it is important to know whether the authors’ recommendation would hold for binary outcome measures, since they are so common in practice.

3. The authors assume in their development that the underlying design involves unrestricted randomization. However for studies in which the cluster sizes are expected to be highly imbalanced, matching or stratification on cluster size is often built into the design. How does this affect the authors’ recommendations?

4. The differential ability of physicians to recruit subjects within each cluster may not only result in imbalance in cluster size, as stated on page 3, but could also seriously threaten validity. As discussed by Puffer et al (2003), the characteristics of subjects in the two groups may then be systematically different.

5. The median number of 34 trials referred to on page 5, does not come from a review of cluster randomized trials in general, but rather from a review only of trials in primary care settings.

6. With respect to the discussion in Section 2.2, it should be pointed out that in the balanced case considered, an analysis at the individual level using ANOVA is algebraically equivalent to an analysis of the cluster means using a two-sample t-test.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions