Reviewer's report

Title: Efficacy of prescribed injected diacetylmorphine in the Andalusian trial: responders and non-responders evaluated using a multi domain outcome index

Version: 1 Date: 27 May 2009

Reviewer: U Frick

Reviewer's report:

General Comments:
A well written paper dealing with a special technical detail on Bayesian analysis of smaller clinical trials when there is relevant a priori information on treatment effects available. The application in the field of heroin assisted treatment seems not to add too much knowledge from a substantive point of view. Results on the trial were already available, and the currently described multi-domain index seems hardly acceptable as a new major study endpoint for future trials, because its interpretation is too difficult. But the statistical technique offers important advantages that can be demonstrated with the data in use.

An article whose findings are important to those with closely related research interests

Recommendation:
Accept after minor essential revisions (which the authors can be trusted to make)

Specific Questions:
1. Is the question posed by the authors new and well defined?
There are various clinical trials on injected DAM substitution for severe opioid addiction. Results for the Andalusian trial had already been published in 2006. The current manuscript deals with a specific outcome measure (multi domain outcome index MDO) and a specific statistical technique (Bayesian analysis) to evaluate a clinical trial with a dichotomous study endpoint. From a methodological point of view, this seems to represent a “classical” example to evaluate a smaller sized clinical trial integrating a priori knowledge on the study endpoint from a Bayesian perspective.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
Using a non-informative a priori estimate of the distribution of the treatment difference parameter seems clear, as well as using the Dutch study to determine the a priori Beta-distributions of the two parameters for various treatment differences. But what is the rationale for the scenario called “partial use” of the existing Dutch study, and how were the a and b parameters (table 1) for this scenario derived? The methods section gives only a technical description, how this “partial use scenario” was calculated by dividing the parameters derived from
the CI-fitting Beta-distribution by 5. What is the substantial meaning of this procedere?

3. Are the data sound and well controlled?
Using the data of the Dutch trial as a priori information for a Bayesian analysis of the Andalusian study would require, that outcome evaluation of the Dutch and the Andalusian had been performed in identical manner. This seems true with respect to the outcome measure (multi-domain outcome index MDO).

But with respect to the number of study participants used for statistical calculations, the van den Brink article in BMJ reports an ITT-analysis including all randomized patients (Fig.1) and using multiple imputation techniques for missing values (Table 2). The current paper – by contrast – reports an analysis based on only 27 (instead of 31 patients randomized) in the experimental group and 23 patients in the control group that were available for follow up examination. This is called “intention to treat” analysis, but does not correspond to the Dutch estimate of the treatment difference. The paper should be presented with a clear method dealing with this missing value problem. (= Major Compulsory Revision)

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes.

6. Do the title and abstract accurately convey what has been found?
I would prefer to read about the Bayesian analysis already in the title of this study.

7. Is the writing acceptable?
Yes.

Minor comments:

Page 7: The parameters of the two beta distributions (first paragraph) are given with underscores? need some editing?

Table 1: Why is “b” for the a priori distribution of THETA_2 here given in capital letter? (“B”), what is “y” (hispanic for “and”?) ?

Title of figure 1: “non parametric distribution” of success rate differences. This nomenclature for the simulated posteriori distribution for the difference between to rates has never been explained before and would need some more details in the methods section.

Level of interest: An article whose findings are important to those with closely related research interests
Declaration of competing interests:

I declare that I have no competing interests