Reviewer’s report

Title: The NAPRESSIM Trial: The use of low dose prophylactic naloxone infusion to prevent respiratory depression with intrathecal morphine in elective hepatobiliary surgery: study protocol and statistical analysis plan for a randomised controlled trial

Version: 0 Date: 22 Jun 2017

Reviewer: Pilar Hereu

Reviewer’s report:

Comments:

1) The morphine intrathecal dose is missing in different sections of the manuscript. The morphine dose is very important information to correctly interpret the study. The morphine dose should be defined in the information of the previous studies (Background). The morphine intrathecal dose and the iv fentanyl dose as a supplemental analgesia during the surgery should be included in the Participants description.

2) The exclusion criteria "treating clinicians feels it is not in patient's best interest to be randomized" should be described in a more objective way.

3) Intervention. The intervention and the standard anaesthetic management should be described in a more detailed way to allow the replication.

4) The participant timeline should be described and justified. The follow up of the patient is adequate to answer in a good way the main question of the trial in terms of the main outcome? Also, it should be clarified if a follow-up of the patients is expected after the end of infusion of naloxone?

5) Outcomes.
   a. The definition of the primary outcome should be the same along the manuscript.
   b. It should be specified the time point of the primary and secondary outcomes.

6) Sample size:
   a. The assumption about the percentage of patients that develop respiratory depression without treatment is based on an audit of 29 patients, and the confidence interval of the estimate should be included.
   b. All the parameters necessary to assess the sample size should be described, including the expected losses in the follow up.
7) The statistical analysis main population should be clarified.

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**Statistical review**
Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

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