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: 28 Jun 2017

Reviewer: Nuria Porta

Reviewer’s report:

A very well written protocol. Some comments for clarification below:

-Following SPIRIT checklist, consider adding population of interest in the title.

-Pg.5, line 100, sentence starting "It aims to investigate…” seems unfinished.

-Pg.5, line 114, refer to Table 1 in the text (as Table may appear in different place in the published version)

-Pg.8, line 170, "We will compare HR…" - what does HR stand for?

-Exploratory objective: no prior reference or explanation of the Respiratory Motion ExSpiron Xi. There are no statistical methods of analysis for this objective in the SAP.

-Study period, pg.9: "the study infusion will be commenced within one hour of extubating the patient and continued until 8.00 the morning after surgery”. This is the period of follow-up of the patient. However, it would seem that different patients can have different periods of observation, i.e., presumably surgeries start/finish at different times (different schedule, complications during surgery). Please can you clarify? It is also said that the collection of postoperative observations is standardised to allow sufficient data to be collected…". I assume this means that the follow-up is the same in both arms?

-How do you achieve concealment of allocation to treatment (i.e. avoid predictability of the randomisation sequence), given it is single centre and the size of the blocks is known to the investigators?

-Does the study have an (external/independent) Data Monitoring Committee? (to review the safety/efficacy of the trial during its conduct and advise the trial team). If not, please state so (following SPIRIT item 21a)

-Pg.13, line 288, section "Study objectives and endpoints" - the contents of this section do not match its title, it seems a brief summary n statistical methods, which is further elaborated in pg.15, "Statistical Analysis Plan". To avoid repetition, I suggest harmonising into the SAP
section. Further, I don't think an empty CONSORT diagram is needed; maybe explain in words what will be reported.

-Sample size does not account for dropout - is there any chance that a patient who has been randomised does not receive the medication, due for instance of complications at surgery?

-Pg.16: a couple of references to adjustment for covariates "(see below)", but below there is no list of such covariates.

-Section "Safety Monitoring" refers simply to analysis of safety endpoints in the SAP, I don't think a section is needed. Safety monitoring seems to imply a DMC exists which regularly review the safety and efficacy data. If not DMC exists, I think the title of the section is misleading.

-Current status: aim is to complete recruitment "within 18 months" of start of recruitment? From now?

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