Author’s response to reviews

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

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Version: 1 Date: 07 Sep 2017

Author’s response to reviews:

We thank the reviewers for their constructive comments and have addressed them in a point by point format below and revised the manuscript tracked accordingly. In addition we have updated the sample number, the approval documentation for this is attached.

The declarations section has been added as per the editorial advice. See Lines 524 – 540.

Responses to reviewer 1:

Question 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.

Response 1. We agree. Please see the revised Background section in tracked changes document as suggested. (Lines 83, 84, 92, 120, 135). Furthermore, the intrathecal morphine dose of 10mcg/kg – has been added to patient description in Figure 1. Please note that IV fentanyl dose intraoperatively is not standardised, and is administered as per clinician preference, with the dose recorded in the case report form. It is then analysed as part the process variable analysis, see revised lines 346–347.

Question 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.

Response 2. Revised to “treating clinician does not have equipoise to randomise this patient into the study ” in table 1.

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

Response 3. See revised Figure 1

Question 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?

Response 4. Due to the duration of surgery, all patients receive intrathecal morphine prior to 14.00 on the day of surgery. Therefore the follow up time between 18 and 24 hours after the administration of intrathecal morphine– At least 14.00 – 08.00 the following morning. We feel that this is an adequate duration of follow up to exceed the risk period for respiratory depression and would reflect real world clinical practice. As a pragmatic trial in a real clinical setting, this is the duration of monitoring that the patients routinely receive in the PACU and HDU prior to transfer back to a ward level setting. See clarification in line 166-168, 170-172, 229-232. There is no further follow up after completion of the study period, due to the short half life of naloxone, and the end of the risk period with intrathecal morphine. The time from injection of intrathecal morphine to end of study infusion is also compared as part of the analysis of process variables, see line 346.

Question 5. The definition of the primary outcome should be the same along the manuscript.
Response 5. See revision to Line 48 and 49.
Question 6. It should be specified the time point of the primary and secondary outcomes.

Response 6. Time period for recording of primary and secondary outcomes is specified in revised lines 166-168, 170-172, 229-232.

Question 7. Sample size: 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.

Response 7. The estimate regarding the percentage of patients is based on a number of independent pieces of data, one of which is a estimate based on a small retrospective study in our unit. Of the 29 patients, we found a rate of respiratory depression of 31% (95% CI: 14.2%-47.9%). – Confidence interval added for the estimate, line 370.

Question 8. All the parameters necessary to assess the sample size should be described, including the expected losses in the follow up.

Response 8. Losses to follow up were not included in the original sample size which was an oversight on our part. Since our original submission, we have altered the protocol to inflate the sample size to account for a possible 10% dropout rate, and this is reflected in the amended application and approval from the Irish Health Products Regulatory Authority, and the Research Ethics Committee. Both are attached as supplementary documents. This is reflected in the section on sample size, lines 385-386, also revised study number in line 41, line 119.

Question 9. The statistical analysis main population should be clarified.

Response 9. The main Statistical analyses of primary and secondary outcomes will be conducted following the modified intention-to-treat (ITT principle) on a full analysis set of patients, excluding those who withdrew consent to participate or have their data used in the study. A further per protocol analysis will be carried out on all primary and secondary outcomes for patients who received any dose of the study infusion. See revised lines 358–362.

Responses to reviewer 2:

Question 10. Following SPIRIT checklist, consider adding population of interest in the title.

Response 10. This has been added to the Trials paper and will be reflected in the final manuscript, however, the registered title of the trial with the regulatory authorities does not contain the reference to the study population, an oversight at the time of registering the trial. See revised line 2 (title).
Question 11. Pg.5, line 100, sentence starting "It aims to investigate…” seems unfinished.

Response 11. This typo has been corrected – see amended line 117-119.

Question 12. Pg.5, line 114, refer to Table 1 in the text (as Table may appear in different place in the published version)


Question 13. Pg.8, line 170, "We will compare HR…” - what does HR stand for?

Response 13. HR = heart rate – clarified line 199.

Question 14. 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.

Response 14. A description of the Exspiron monitor and its intended use has been added to lines 50-53, 127-130. Added some detail to this objective - Line 208-216. A plan for statistical analysis of exploratory outcomes has been added – lines 452-461.

Question 15. 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?

Response 15. It is true that there is a small variation in the duration of observation for individual patients within the trial but this will very likely be equally distributed cross both arms of the study. All patients will receive intrathecal morphine prior to 14.00 on the day of surgery, so the time from injection of intrathecal morphine to end of study is 18-24 hours in all patients, bringing them past the high risk period for respiratory depression. As a pragmatic trial in a real clinical setting, this is the duration of monitoring that the patients routinely receive in the PACU and HDU prior to transfer back to a ward level setting. Some of these covariates are process variables (e.g. duration of study infusion), that will also be compared between treatment groups – detail added on lines 343-350,. Also see revised lines 226-227.

Question 16. 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?
Response 16. While size of the blocks is known to the research staff it is unknown by the clinical staff, who treat the patients. Furthermore, randomisation is via variable block sizes of 4-6, in random order. Study infusion is prepared in the pharmacy isolator, which is distant from the patient care area, and those involved in preparation have no involvement in patient care. The 2 infusions are physically identical and are labelled identically. We feel that this method has removed any predictability in the sequence and achieves adequate concealment.

Question 17. 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)

Response 17. The study does not have an independent data monitoring committee. The sponsor has employed a data / safety monitor who reports directly to the sponsor. The HPRA as the regulator is also entitled to inspect the site and data at any time. Outcome analysis for efficacy will not be reviewed until the end of trial, due to the relatively small sample size and low risk of the intervention. In addition, all AE’s and SAE’s are reviewed by the director of quality in our University Clinical Research Centre and are reported to the institutional sponsor and the HPRA. See amended lines 464-468.

Question 18. 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 inn words what will be reported.

Response 18. See adjustment to formatting and title of this section. From line 333 onwards. Figure 3 removed, description included lines 333-339.

Question 19. 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?

Response 19. Losses to follow up were not included in the original sample size calculation which was an oversight on our part. Since our original submission, we have altered the protocol to inflate the sample size to include a possible 10% dropout rate, and this is reflected in the amended application and approval from the Irish Health Products Regulatory Authority, and the EudraCT database. Both are attached as revised approval documents. It is also addressed in line 385-386.

Question 20. Pg.16: a couple of references to adjustment for covariates "(see below)", but below there is no list of such covariates.
Response 20. Some of these covariates are process variables (e.g. duration of study infusion), that will also be compared between treatment groups – detail added on lines 339-347. Detail on the list of covariates to be adjusted for in sensitivity analysis has been added for the primary and secondary outcomes. See lines 404-412, 425, 432, 446-449.

Question 21. 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.

Response 21. This section has been revised. We have now stated in this section that we do not have a DMC, and our reasoning for this as per SPIRIT Item 21a. We have also added a description of the monitoring which is carried out by the sponsor. Revised lines 464-468.

Question 22. Current status: aim is to complete recruitment "within 18 months" of start of recruitment? From now?

Response 22. The projected end of trial is on or before December 2017. This is an extended trial duration due to the addition of patient numbers to account for dropout. This is reflected in the trial amended documentation supplied. Revised lines 493-496.