Author’s response to reviews

Title: The effect of implementing an aseptic practice bundle for anaesthetists to reduce postoperative infections. Protocol for a stepped wedge, cluster randomised, multi-site trial. The Anaesthetists Be Cleaner (ABC) Study.

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Reviewers’ comments to ABC manuscript

1. Can you please justify why you think it is not necessary to take informed consent from patients (their data will be used in an anonymous form, the intervention is low risk and having to take individual level consent would render the study infeasible, perhaps).
We have added the following sentence to line 211. “because, patient data will be used in an anonymous form, and the intervention is low risk.”

2. It is really admirable that you are taking consent from the health care practitioners. Can you expand a little of the level and type of this consent. What will happen if someone declines to participate? You might be interested in looking at the Ottawa statement on the ethics of cluster trials - they have recommendations for from whom you should take consent in cluster trials and you are following their advice, which is commendable.

We have added the following reference (see line 213) “as recommended by Weijer et al (2012) [41]”

3. Line 219 to 220: "Quite substantial differences in practices and case mix may exist between departments, but intra-cluster correlation is likely to be quite high.". I think you mean "so" rather than "but" here.

   Changed - see line 222

4. Line 221 can you clarify if this is 4*5 clusters or just 4 clusters (wording unclear)

   Changed - see line 223 (deleted: ‘five departments in four hospitals’) and line 224 (added: ‘with five clusters’)

5. Could you justify your design more please? I understand and it is clear why you use cluster randomisation. But, please can you clarify the justification for using a SW design. You mention it is to do with the ICC, is this because you expect the SW design will be more statistically efficient due to the high ICC?

We have added the following sentence to line 226 “The stepped wedge design is ideal for progressive implementation of quality improvement initiatives such as in this study, and will also be more statistically efficient than alternative cluster designs because of our anticipated high inter-cluster correlation.”
6. Inclusion and exclusion criteria - can you please clarify these at the individual level? What are these criteria for the clusters and for the health care participants?

We have made the following changes to the inclusion and exclusion criteria (lines 265-276).

"Inclusion criteria

All hip or knee arthroplasty or cardiothoracic surgery (as defined by the Surgical Safety Infection Improvement programme [43]) procedures carried out in the five clusters under general anaesthesia with or without regional anaesthesia, or under regional anaesthesia with sedation. Participant anaesthetists, anaesthetic technicians and perfusionists who consent to be part of the study will be included.

Exclusion criteria

Patients receiving organs for heart and lung transplants will be excluded from the study because of their complexity and the use of immunosuppression in these cases. Likewise, patients donating organs for these purposes (i.e. patients who are ASA 6) will be excluded. Participant anaesthetists, anaesthetic technicians and perfusionists who decline to be part of the study will be excluded."

7. Under withdrawal - are anaesthetists also free to withdraw?

We have added the following sentence to line 280, “Participants will be free to withdraw from the study.”

8. In table 3 you provide the schematic for the study. But, it looks like the order of the transitions has already been revealed - as the clusters are named on each of the rows. Can you clarify when the clusters were told when they would transition? And, can you clarify how this order was determined under a section subheading of randomisation.

We have added the following sentences.
Lines 420 to 422:

“Each department will be told of the date of the implementation of the bundle in the weeks leading up to that date. This is to reduce the likelihood of a change in practise prior to the bundle implementation.”

Line 422: please change ‘initiation’ to ‘implementation’.

Line 402:

“Randomisation of departments

The five departments were placed in a random sequence and then sequentially allocated to the five possible dates of the bundle implementation, as shown in Table 3 [see Additional file 2].”

9. Do you need to include a transition period during which the intervention will be embedded into practice? During this period observations could not be treated as either fully exposed or unexposed to the intervention, and so they would be excluded from the analysis. (I see you say this later, but please mention it earlier under the design).

We have moved the following sentence to line 229 “We will exclude data from our analysis for one week following transition from baseline to active phases of the study at each site to allow for the influence of progressive uptake of the bundle and the required changes in participating anaesthetists’ practice.”

10. Within cluster contamination: your outcome is 90 day survival essentially. How will you treat patients who are still on the ward when the hospital transitions to the intervention condition?

We have added the following sentence to line 579 “Patients whose initial operation was prior to the implementation of the bundle but are still in hospital during the implementation of the bundle will be included in the analysis of baseline data.”
11. You intend to use a non-parametric approach. Jennifer Thompson has developed and published a permutation test for SW trials which you might be interested in. Using your approach can you clarify how you will present the treatment effect and its associated uncertainty? Simply reporting a P-value is unlikely to be informative.

We have added the following to this section (see lines 479-492).

“Although our preference would be to use permutation testing methods, our five-cluster, five-sequence design only allows for 120 permutations. We consider this too low a number for a precise estimation of the significance of the difference between control and intervention cases. We will thus use a single Wilcoxon-Mann-Whitney U (WMWU) ranked-sum test as our omnibus test to ascertain whether intervention patients have significantly higher DAOH90 than control patients. This WMWU test will also be sensitive to prevailing trends in patient outcomes, so we will further investigate the difference using quantile regression. Models will be fitted at quantiles 0.1, 0.25, 0.5, and 0.75, with DAOH90 as the outcome, and time, intervention, and site as the predictors. We will characterise any differences in distribution between groups by reporting differences associated with the intervention term in each model, and their significance.”

12. You sample size justification needs a lot more detail. What method have you used, how did you implement it? Does it correspond to your proposed analysis? What is your event rate and your treatment difference? (It might be useful to consult the CONSORT for SW where there is a table of items to report in a sample size calculation). It might be OK to remove the power calculation for the secondary outcome.

We have added the following to this section (see lines 493-503).

“We have used simulations to estimate our statistical power. Data sets were synthesised using distributions generated from four of our sites (excluding Starship Children’s Hospital) with different step lengths. Starship Children’s Hospital data was synthesised on the basis of the distribution from Auckland City Hospital’s cardiac unit. Distributions for each site were tweaked by increasing or decreasing the relative likelihood of higher DAOH scores until the desired magnitude of difference appeared at quantile 0.25. We found that a step length of 180 days (i.e. 6 months) would give us 100% power to detect a 2 DAOH difference at quantile 0.25 between groups using the WMWU, and 77.7% power to detect an intervention effect using quantile regression (both two-tailed α<0.05), with just over 10,000 patients. The intra-cluster correlation coefficient was measured as 0.02. Cluster sizes in the simulation depended on the ratio of caseload between sites (see Table 3).”
13. Your section on "structure" needs to come much earlier. This is essential information that is needed before you justify your sample size.

We have moved this section to line 232 and changed line 241 to the following. “(see Statistics and sample size section)”

14. You have a section on data collection on analysis, but you have already seemingly outlined the analysis earlier.

We have moved this information to line 530.

Line 511: please delete ‘and analysis’

15. Can you expand on the interim analysis? How will you analyse the outcomes, and what outcomes will you look at? Will you make any multiplicity adjustments?

We have explained this in line 531 and have made the following change to line 532. “We will also verify the completeness of the study data.”

16. What will happen if one of the sites doesn't adhere to your allocation?

We have added the following sentence to line 256 “We will be seeking approval for the study from senior hospital leadership and agreement in principle from participating departments to participate in the study, so it seems unlikely that an individual department will not adhere to the implementation of the bundle.”