Author’s response to reviews

Title: Chlorhexidine Locking Device for Central Line Infection Prevention in ICU Patients: Protocol for an Open-Label Pilot and Feasibility Randomized Controlled Trial

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In the methods section, remove the term "prospective" from the study design. This is assumed in an RCT. Removed from the methods and the abstract

Please indicate how the "order of randomization will be concealed". This is later reported in the allocation and blinding section, but a few words would be appropriate here (line 124). We have added a line in the Study Design section about randomization concealment. (Page 7 line 126-7)
On line 135, correct the spelling of "Trial" from "Trail" Corrected

What is the justification of the maximum age of 100? This has been corrected to state greater than 18 years of age.

Please explain what a "Kardex" is for a wider audience. The term Kardex has been changed to nursing care plan

The sample size justification is insufficient. It is unclear how the cited references relate to the current trial. In other words, explain how 100 participants is enough to measure a consent rate of 80% and the level of precision that comes with it.

We have added the following justification for the sample size: It is not possible to know the standardized effect size of our proposed intervention. Our best guess is to refer to other trials, however trials that utilize our device does not exist. To err on the side of caution, we made the conservative assumption of having a very small effect size. A pilot study of such effect size is recommended to enroll 50-75 in each treatment arm as per the non-central t-distribution approach.

(reference: Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res. 2016 Jun;25(3):1057–73.) This is also confirmed in a publication by Teare et al Trials 2016 that suggests at a pooled sample size of 100 patients there is
still an increase in precision for future trials including a composite outcome of recruitment and consent rates.

Many ICU pilot studies run with less than 50 patients but set consent rates at 80% for feasibility as adequate for the full RCT. We were unable to find any literature to support this as a specific precision estimate.

Group differences can be reported descriptively but should not be measured statistically or tested since the study is not powered for such comparisons and any findings would be potentially misleading. This is important.

We agree that statistically analyzing the differences between groups should be mostly descriptive. We agree that any statistical analysis of group differences may not be adequately powered unless there is large effect size for bacterial growth (no patients in treatment arm have a central line infection) given this is a biological outcome of interest to the sponsor. We have added the following:

The two treatment arms will be compared by simple statistics as the study may not be powered for the secondary outcomes. However, we will test group differences with either the independent-samples t-test or the Mann-Whitney U test. Somer’s delta (d) will be used to identify and measure of the strength and direction of association that exists between two ordinal variables, particularly for the number of positive cultures. If there is a large treatment effect between groups, this may aid the sponsor in proceeding with larger RCT as required for regulatory approval within other countries.