Reviewer’s report

Title: COMMENTARY: Should treatment effects be estimated in pilot and feasibility studies?

Version: 0 Date: 19 Jul 2019

Reviewer: Alex Mitchell

Reviewer’s report:

I would like to thank the editors for giving me the opportunity to review this paper, which is an interesting and well-written commentary. However before the paper is published I have some concerns that I would like to see addressed.

Major revisions

* 'However, assuming that a 95% CI were chosen, this would be equivalent to a hypothesis test at a 5% significance level, which would thereby prejudge the conclusion of the main trial.' I think for clarity this sentence could be expanded on, as I'm not entirely sure what you mean by prejudging the conclusion of the main trial. Do you mean that as the null hypothesis of the test is that the true treatment effect is equal to the MID, and therefore if the pilot has an identical design to the main trial it follows that the researchers have assumed the true treatment that will be looked for in the main trial is equal to the MID?

* 'Additionally, studies that satisfy the previous criterion of requiring the MID to lie on or below the lower bound of the CI will also satisfy this less demanding criterion, as all plausible values of the true treatment effect would be at least as large as the MID.' I think this sentence needs to be in a different paragraph to the one it is currently in. The paragraph begins and ends with a discussion of the scenario where the MID lies within the CI, however the aforementioned sentence briefly discusses the scenario where the MID lies on or below the lower bound of the CI, which I think has the potential to confuse the reader.

* 'Thus, in a typically small pilot study, generating a wide CI, if a judgment is made on the basis of the MID lying within the CI, a decision to proceed to the main trial might be made too readily, whereas when the MID is required to lie below the CI, a decision not to proceed with the main trial might also be made too readily.' I think figure 2 backs up the second point made in this sentence. However I do not believe it backs up the first point, as all 20 confidence intervals contain the MID and indicate the main trial should proceed, which based on the assumptions made in the simulation scenario would be the correct decision! I think there needs to be a second simulation to back up the first point.

* 'Biased estimates may also arise in particular through substantial baseline imbalance in a small pilot study.' I think when you discuss bias in your paper you need to distinguish between systematic bias, which you touch upon when discussing the importance of the
external pilot study being run in exactly the same way as the main trial, and chance bias, which is due to the variance of the treatment effect estimator. See the paper by Roberts and Torgerson titled 'Baseline imbalance in randomised controlled trials'.

* 'One purpose of using a pilot or feasibility study in this way might be to seek reassurance that a new untested intervention is effective in its own right, before proceeding to compare it with standard therapy or placebo.' I strongly disagree with this. There are various biases that can affect the results of single-group studies which means the results cannot be said to have been caused by the treatment.

* 'This approach would not pre-empt the conclusion of the main trial, in the way that estimating a between-group effect might, as it is answering a different question - one of absolute rather than relative effectiveness.' See comment above.

* 'However, if the size of the pilot or feasibility study has not been formally calculated to provide an appropriate level of precision, these estimates are based on relatively meagre evidence and are therefore unreliable, and may result in inappropriate decisions either to proceed or not to proceed to a main trial.' Some would argue that estimates of the standard deviation obtained from the pilot that are then used in the sample size are also based on relatively meagre evidence, how would you argue that what you have said for effect sizes does not apply to the use of standard deviations in sample size calculations?

Minor revisions

* 'Lee et al add the requirement that the point estimate of the treatment effect should be greater than zero'. Is there a point to be made here that for some interventions, negative treatment effects can also be interesting and indicate that a main trial should be carried out?

* 'The highest confidence level at which the MID is excluded from the CI is 75%, and it is therefore with this level of confidence that progression to the main trial could be recommended.' I think a point could be made here that this method takes the word 'confidence', which in the context of the confidence interval is a statistical term equal to the percentage of times the confidence interval is expected to contain the true value, and translates it to the 'confidence' more commonly used in the non-statistical world. In my opinion this is inappropriate as the percentage obtained is not based on any person's 'confidence' that the main trial could be recommended to proceed.

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