Author's response to reviews

Title: Bayesian Methods to Determine Performance Differences and to Quantify Variability among Centers in Multi-center trials: The IHAST Trial

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Author's response to reviews: see over
Referee 2

1. The change to the model description is appreciated and brings the model description into line with the WinBugs model.

We thank the reviewer for the comments.

2. I can see that the revised paper places more weight on the quantification of variability rather than focusing exclusively on outliers. Nevertheless the impression is still given in places that variation that is consistent with a normal distribution is somehow unimportant. To me, when comparing institutions, it is the extent of variation that is important, not its distributional form. It may just be a matter of the wording used in places. See my point under “Major compulsory revisions” for more specific details.

We agree, thank you. We have removed unnecessary references to being consistent with a normal distribution and focused on identifying outliers.

3. Regarding the outlier detection methodology, I still find it odd that a centre with negligible posterior probability of being an outlier can be considered a “potential outlier”. However I realize you are following the prescription of an accepted methodology. Perhaps some comment or additional clarification of the logic of the method could be added, acknowledging the apparent anomaly that centres with low posterior probability for being an outlier can still be considered “potential outliers.”

The following paragraph is added to page 20 to clarify that Bayes Factor should be evaluated to decide whether a center is identified as an outlier.

“Under the normality assumption, the prior probability of any one center to be an outlier is low and is 0.0017 when there are 30 centers. In this case, any center with a posterior
probability of being an outlier larger than 0.0017 would be treated as a potential outlier. It is therefore possible to identify a center with a low posterior probability as a “potential outlier”. The Bayes Factor (BF) can be used to quantify whether the relative change from the prior probability of being outlier to the posterior probability is large enough to categorize a center as an outlier.”

Note that in reference [22] a residual with a mean close to zero but a large posterior standard deviation can be potential outlier -- sometimes they do meet the criterion and sometimes they do not. In regression (as in [22]) a large posterior standard deviation corresponds to a large leverage value.

**Major Compulsory Revision**

As noted above, you seem almost to dismiss variation that that is consistent with a normal distribution. For example at the bottom of page 19, I read: “There is no indication that, when center, sample size and patient characteristics are accounted for, as well as the normal variability between centers, outcomes differed among any of the centers.” The italics are my addition. I just do not think that normal variability between centers should be “accounted for” as quantifying variation is, or should be, the point of the analysis. To me it seems incorrect for a summary of the analysis to conclude that there is no indication of outcomes variation between centers. Note that we are not talking about random variation here. That is accounted for by the first stage of the model. We are talking about variation between the $\delta_{k}$, i.e. variation between the true centre effects. I suggest either deleting that sentence or rewording to emphasise the extent of the variation, noting the consistence with a normal distribution, if necessary. Alternatively, if you genuinely regard variation that is consistent with a normal distribution as unimportant please provide a coherent justification for that stance. I think attending to this issue would considerably strengthen the paper.
We completely agree with the referee and have removed the sentence in page 19 (now 20). Thank you.

**Minor Discretionary Revisions**

1. Abstract, page 4, last line, omit “of the variability” or omit “sd of the.”

“sd of the” is deleted.

2. Page 21, last line omit “with mean zero” (the \delta_k have prior mean 0; I doubt that holds necessarily in the posterior and, in any case, the mean of the center effects should include the main part of the model in addition to the “random effects”).

*The sentence on page 21 (now on page 22) is edited as follows:

“*In summary, the observed variability among centers in IHAST has a moderately large standard deviation (*σ_e* = 0.538, 95% credible interval for *σ_e* 0.397 to 0.726).”*

3. Page 25, penultimate sentence. It is very hard to know what this sentence means and suggest it could just be deleted.

*This sentence is deleted.*