NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

MT257 HumiGard

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Birmingham and Brunel EAC to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 4pm, **Wednesday January 27th 2016** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

25th January 2016

Issue	Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
1	Page 25, Table 5. Characteristics of the 7 relevant trials on HumiGard. Numbers reported are the number recruited not the number of patients analyzed. Specifically Herrmann et al. report n = 48 (HumiGard) and n = 49 (standard gas) as opposed to n= 52 for both.	Change reported n-values to those patients analysed in the study so that they match the numbers in the meta-analysis or report both values.	Accuracy of values and conclusions.	Table 7 in our report included both number of patients recruited and number of drop-outs for all the studies. It also contains information on whether ITT analysis was performed. For clarification we have now added a footnote to table 5 stating that the number of patients reported in this table is the number of patients randomised.
2	Page 33, Section 3.6 Results, 1st Bullet point. Primary outcome measures were reported by the sponsor to reflect the primary outcome of the NICE submission and not the primary outcome of the individual papers.	Perhaps change bullet point to reflect context.	Clarification	In the NICE scope there is no specification of a primary outcome measure. Nevertheless, it is inappropriate to report a secondary outcome measure of a study as the study's primary outcome measure. No change needed.
3	Page 34, Section 3.6 Results, 4th Bullet point. Temperature values should fit within a normal distribution	Amend the report to include mean values reported in Birch, or perhaps contact the	Data accuracy	In Figure 3 of the sponsor's submission, the data in the meta-analysis

	and so mean values should have been reported by the sponsor. Birch et al. (Cochrane) retrieved the values used in the meta-analysis (0.64+/-0.48 heated, 0.48+/-0.66 standard) from communication with the author.	author for accurate mean values.		for the study Sammour et al. (2010) are the median (IQR) reported in the paper, i.e. 0.4 (IQR 0.7) for the HumiGard and 0.6 (IQR 0.9) for the control group. There is no indication in the Cochrane review by Birch et al. that the authors of the Sammour et al. paper were contacted to obtain the mean (SD). As Sammour et al. used non-parametric statistics, we cannot assume that the data were normally distributed. For information, we re-ran the analysis using the data from the Cochrane review and result did not change. Therefore no changes are needed.
4	Page 43, Section 3.8, Incidence of hypothermia in the intra- and post-operative period. The report quotes “HumiGard group had a slightly but statistically lower incidence of hypothermia both perioperative and postoperatively [redacted]	Remove “slightly” as the sponsor believes that a probability of 0.1 of becoming hypothermic is more than slight.	Remove subjective statement for clarity.	Suggestion is accepted and now we have deleted ‘slightly but’ in the text.

5	Page 45, Section 3.8, Incidence of surgical site infections. The report quotes [redacted]Page 10 of Mason et al, 2016 (manuscript final version) [redacted])" There is a difference in the reported abstract and the finalised manuscript in significance due to the final manuscript utilising multi-variate analysis, where the abstract only reported the significance of the odds ratio.	Amend to show statistical significance.	Data accuracy.	The EAC has now put both the univariate analysis result and the multivariate analysis result in table 11 and in the text on page 45. The authors of the Mason et al. study provided the results for the univariate OR. The EAC considered that it is important to also present this result in the report.
6	Page 46, Section 3.8, Analgesic use. The report quotes "No statistically significant differences in analgesic use were observed in the studies between patients in which HumiGard was used and those that did not use HumiGard." This result is influenced by Sammour et al. It is worth noting that this paper shows large within treatment variation. No within treatment (longitudinal) assessment using repeated measures for autocorrelation was done in this paper. (See Table 3 Where: MEDD use increases from 12 to 22 in "study group", and 9 to 36 in "control"; clearly a large difference in pain response favouring "study group". It is also not clear why MEDD use is reported as medians and IQRs, as this data should be normal. It is also not clear why MEDD data analysed was with Mann-Whitney, as opposed to t-tests.	Discuss potential non-normality of the Sammour data.	Data interpretation.	The EAC's meta-analysis presented on page 46 (figure 4) is for analgesic use after laparoscopic surgery in the recovery room. The study Sammour et al. is not included in this meta-analysis because the study reported this outcome in median (IQR). The EAC cannot make assumptions regarding the distribution of the MEDD data. Therefore no changes are needed.
7	Page 80, Table 27.	Proportion of patients with	For accuracy when	Table 27 has been

	Proportion of patients with hypothermia: HumiGard = 13% and No HumiGard = 57%. Within the sponsor submission the model was also run using the values from Sammour (14%/23%). See Table C10.2b and C13 in submission.	hypothermia: 1. [redacted]HumiGard = 14% and No HumiGard = 23% (Sammour)	reporting the submission.	amended to clarify this.
8	Page 80, Table 27. Stroke costs. The sponsor's stroke costs estimates are not reported correctly.	Sponsor's stroke costs (with discounting): Year 1 = £6,537 Year 2 = £3,622 Year 3 = £3,500 Year 4 = £3,381 Year 5 = £3,267	For accuracy when reporting the submission.	The EAC and sponsor estimates were presented in the wrong columns. Table 27 has been amended.
9	Page 84, Section 4.10: "The study also found no statistically significant association between SSIs and hypothermia, which is a key assumption in the sponsor's model."	"The study also found no statistically significant association between SSIs and hypothermia, which is a key assumption in the sponsor's base case deterministic analysis. However, this uncertainty is reflected within the deterministic and probabilistic sensitivity analysis whereby the association is not assumed	Whilst the deterministic base case analysis assumes there is a significant association between hypothermia and SSI, the uncertainty is reflected in both the univariate sensitivity analysis and the PSA. Hence, in the model as a whole the association is not assumed to be	We have amended the sentence to read "The study also found no statistically significant association between SSIs and hypothermia, which is a key assumption in the sponsor's base case deterministic analysis of open surgery". The inclusion of differential rates of SSIs between

		to be significant."	significant.	hypothermic and normothermic patients in the deterministic basecase has a substantial impact on the results for open surgery. This is highlighted in the tornado diagram presented in Fig 8 of the EAC report. If differential rates are not included, the results change from HumiGard being cost saving to being (marginally) cost increasing. Therefore we have not added the additional sentence suggested by the sponsor.