

HumiGard Surgical Humidification System for the prevention of inadvertent perioperative hypothermia: Addendum to the EAC report: Additional Analysis by Birmingham and Brunel Consortium EAC

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Following the committee meeting of 19th February 2016, NICE requested the BBC EAC performed some additional work, to inform the economic analysis of the potential cost savings associated with HumiGard.

1. Summary of data on complications associated with hypothermia

The EAC reviewed the NICE Clinical practice guideline on management of inadvertent perioperative hypothermia in adults (CG65, 2008) to identify additional empirical data on complications associated with hypothermia. One additional study by Frank et al (1997) was cited in CG65, alongside two studies referenced in the EAC report: Kurz (1996) and Flores-Maldonado (2001). The EAC's concerns regarding the appropriateness of these studies for the NICE review are briefly summarised below. For completeness, information is also provided on the two further studies included in the EAC report: Billeter (2014) and Anannamcharoen (2012).

Kurz et al (1996)

RCT assessing the hypothesis that hypothermia increases post-operative wound infection and lengthens hospitalisation in 200 patients undergoing elective colorectal surgery for cancer or inflammatory bowel disease.

Generalisability to current NHS practice may be limited due to:

- Age of the study: data collected between 1993 and 1995
- Setting: hospitals in Vienna, Graz and Rudolfstiftung in Austria¹
- Study protocol: temperature of patients in the control group allowed dropping to 34.5 degrees without intervention.

Frank et al (1997)

RCT to assess the relationship between body temperature and cardiac morbidity during the perioperative period in 300 patients undergoing peripheral vascular, abdominal and thoracic surgery.

Generalisability to current NHS practice may be limited due to:

- Age of the study: data collected between 1992 and 1995
- Setting: single centre in Baltimore USA
- Age of population: all patients aged over 60 years (mean age 71 years)
- Gender balance of population: 85% male

¹ This study was incorrectly stated as having been conducted in USA in the EAC report

- High risk of Coronary Artery Disease (CAD): all patients had documented CAD or high risk of CAD (approximately 50% had documented CAD).
- Study protocol: patients in the control group were allowed to develop mild hypothermia without intervention
- Outcomes reported: doesn't report data on surgical site infections (SSIs); focus is on cardiac outcomes.

Flores-Maldonado (2001)

Prospective cohort study to test the hypothesis that mild perioperative hypothermia is associated with surgical wound infections in 290 patients undergoing cholecystectomy surgery.

Generalisability to current NHS practice may be limited due to:

- Age of the study: data collected between 1999 and 2000
- Setting: single centre in Yucatan, Mexico
- Gender balance of population: 85% female
- Age of population: mean age of 40 years.

Anannamcharoen (2012)

Prospective cohort study of open colon and rectal resections in 229 patients.

Generalisability to current NHS practice may be limited due to

- Setting: single centre army hospital in Phramongkutklao, Thailand

Billeter (2014)

Retrospective observational study of 1405 patients undergoing elective surgery in the USA. Patients identified as having hypothermia were matched with controls for type of procedure, Diagnosis Related Group, demographics, severity of illness at admission, pre-existing co-morbidities and blood transfusions.

Generalisability to current NHS practice may be limited due to

- Setting: Multiple hospitals in USA
- Type of surgery: includes all surgeries and is not restricted to abdominal surgery.

Conclusions

Overall the EAC considers the study by Billeter and colleagues to be most relevant to the NICE decision problem. It is a recent, large and well conducted study in which cases were closely matched with controls. We accept that a limitation in applying the data to the NICE decision problem is that the study was not limited to abdominal surgery. Also, clinical practice in the USA may not be generalisable to the English NHS. The EAC acknowledges the Committee's concerns regarding the high rates of stroke reported in the study. Upon request, Dr Billeter kindly provided the EAC with

data for a comparable, more recent sample of patients restricted to those who had undergone abdominal surgery. The proportion of strokes was lower in this sample [REDACTED] It was not possible to use these data in the economic model as they were only available for the hypothermic group. Therefore the EAC has conducted a range of sensitivity analyses varying the estimates of the risk of stroke along with other data sources.

2. Updated data on clinical effectiveness of HumiGard

Two sources of data on the clinical effectiveness of HumiGard for laparoscopic surgery were available to the EAC: a published RCT conducted in New Zealand (Sammour et al, 2010) and an unpublished retrospective 'before and after' cohort study conducted in the UK (Mason et al, unpublished).

Upon request by the EAC, the authors of the unpublished UK study kindly provided the EAC with the outputs of a multivariate analysis of the data, including regression coefficients, details of missing data and the results of some statistical tests. The EAC used these results to estimate the predicted risks of hypothermia and SSIs taking into account the population characteristics in each study arm. Unfortunately, following clarification with the authors regarding a discrepancy in the models provided, the study authors confirmed an error in the analysis. The authors provided the EAC with revised tables of regression coefficients for the corrected analysis; however full details for the corrected analysis, including number of events and results of statistical tests were not provided. The precise proportions of missing data in the models is not known; however based on the output provided for the incorrect analysis and previous correspondence with the authors, the EAC expects it to be in the region of [REDACTED] for the model of hypothermia. This relatively high proportion of missing cases indicates a risk of bias which cannot be explored by the EAC without further information on the characteristics of the missing cases.

The models were estimated using logistic regression. The EAC notes that that a number of different logistic regression models of the risk of hypothermia and SSIs are possible and that the submitted models may not be optimal given that some of the variables included are likely to occur in association with other variables, for example, BMI is likely to be related to diabetes, and operation for a neoplasm increases the risk of conversion to open surgery which is associated with SSI. Hence residual confounding raises questions on the validity of the models submitted. Following peer review of the submitted paper, the final published models may be different to those considered here.

Results of the multivariate analyses are presented in

XXXXXX and XXXXXX.

Based on pooled characteristics from the patients in both groups of the study (Table 3), predicted risks of hypothermia and SSI with and without the use of HumiGard were estimated and are presented in Table 4.

Table 3: Hypothetical cohort - pooled patient characteristics

██████████	██
██████████	██
██████████	██
██████████	██
██████████	██
██████████	██
██████████	██
██████████	██
██████████	██

The exponentiated coefficient (β) for each variable in the fitted logistic models was multiplied by the pooled characteristic (X) to calculate the odds when HumiGard dummy =0 and HumiGard dummy =1. The odds were then converted into a probability [P = (odds/1+odds)]. The resultant risks were as follows:

Table 4: Predicted risks of hypothermia and SSI

	No HumiGard	HumiGard
<u>Risk of hypothermia</u>	██████████	██████████
<u>Risk of SSI</u>	██████████	██████████

The difference in estimated risk of SSIs between HumiGard and no HumiGard based on the fitted models was similar to the unadjusted data used in the sponsor de novo cost analysis ██████████. However the estimated difference in risk of hypothermia between HumiGard and no HumiGard was less than the unadjusted data ██████████

3. Additional sensitivity analyses conducted by the EAC

We conducted a range of additional analyses to assess the impact of varying stroke rates, SSI costs and sources of effectiveness data on the potential cost savings of HumiGard. All analyses are based on the EAC analysis described in Table 27 of the EAC report.

The following analyses were conducted:

- I. Open surgery: As for the EAC analysis (including effectiveness data from Frey et al and data on complications from Billeter), varying the rate of stroke and using the upper and lower range of the reference cost codes for 'Infections and Other Complications of Procedures'.
- II. Laparoscopic surgery: As for the EAC analysis (including effectiveness data from Sammour et al and data on complications from Billeter), varying the rate of stroke and using the upper and lower range of the reference cost codes for 'Infections and Other Complications of Procedures'.

- III. Laparoscopic surgery: As for the EAC analysis (including data on complications from Billeter), using the predicted risk of hypothermia from the Mason multivariate analysis, varying the rate of stroke and using the upper and lower range of the reference cost codes for 'Infections and Other Complications of Procedures'.
- IV. Laparoscopic surgery: As for the EAC analysis, using the predicted risk of SSIs from the Mason multivariate analysis and using the upper and lower range of the reference cost codes for 'Infections and Other Complications of Procedures'. Note that stroke risk is not varied as the only complications included in this analysis are SSIs.

Table 5: Cost differences (HumiGard minus Control) from analysis I for open surgery (Frey, Billeter)

		SSI cost (£)										
		10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	
		£1,080	£1,886	£2,692	£3,499	£4,305	£5,111	£5,917	£6,723	£7,530	£8,336	£9,142
Stroke risk (diff hypo/no-hypo)	0.25%	£51	£49	£46	£44	£42	£39	£37	£34	£32	£29	£27
	0.50%	£39	£37	£34	£32	£29	£27	£24	£22	£19	£17	£14
	0.75%	£27	£24	£22	£19	£17	£14	£12	£10	£7	£5	£2
	1.00%	£15	£12	£10	£7	£5	£2	£0	-£3	-£5	-£8	-£10
	1.25%	£2	£0	-£3	-£5	-£8	-£10	-£13	-£15	-£18	-£20	-£22
	1.50%	-£10	-£13	-£15	-£17	-£20	-£22	-£25	-£27	-£30	-£32	-£35
	1.75%	-£22	-£25	-£27	-£30	-£32	-£35	-£37	-£40	-£42	-£45	-£47
	2.00%	-£35	-£37	-£40	-£42	-£45	-£47	-£49	-£52	-£54	-£57	-£59
	2.25%	-£47	-£49	-£52	-£54	-£57	-£59	-£62	-£64	-£67	-£69	-£72
	2.50%	-£59	-£62	-£64	-£67	-£69	-£72	-£74	-£77	-£79	-£81	-£84
	2.75%	-£72	-£74	-£76	-£79	-£81	-£84	-£86	-£89	-£91	-£94	-£96
	3.00%	-£84	-£86	-£89	-£91	-£94	-£96	-£99	-£101	-£104	-£106	-£108
	3.25%	-£96	-£99	-£101	-£104	-£106	-£108	-£111	-£113	-£116	-£118	-£121
	3.50%	-£108	-£111	-£113	-£116	-£118	-£121	-£123	-£126	-£128	-£131	-£133
	3.75%	-£121	-£123	-£126	-£128	-£131	-£133	-£136	-£138	-£140	-£143	-£145
	4.00%	-£133	-£135	-£138	-£140	-£143	-£145	-£148	-£150	-£153	-£155	-£158
	4.25%	-£145	-£148	-£150	-£153	-£155	-£158	-£160	-£163	-£165	-£168	-£170
	4.50%	-£158	-£160	-£163	-£165	-£167	-£170	-£172	-£175	-£177	-£180	-£182
4.75%	-£170	-£172	-£175	-£177	-£180	-£182	-£185	-£187	-£190	-£192	-£195	
5.00%	-£182	-£185	-£187	-£190	-£192	-£195	-£197	-£199	-£202	-£204	-£207	
5.25%	-£194	-£197	-£199	-£202	-£204	-£207	-£209	-£212	-£214	-£217	-£219	
5.50%	-£207	-£209	-£212	-£214	-£217	-£219	-£222	-£224	-£227	-£229	-£231	

Table 6: Cost differences (HumiGard minus Control) from analysis II for laparoscopic surgery (Sammour, Billeter)

		SSI cost (£)										
		10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	
		£1,080	£1,886	£2,692	£3,499	£4,305	£5,111	£5,917	£6,723	£7,530	£8,336	£9,142
Stroke risk (diff hypo/no-hypo)	0.25%	£50	£49	£48	£47	£45	£44	£43	£42	£41	£39	£38
	0.50%	£44	£43	£42	£41	£39	£38	£37	£36	£35	£33	£32
	0.75%	£38	£37	£36	£35	£33	£32	£31	£30	£29	£27	£26
	1.00%	£32	£31	£30	£29	£27	£26	£25	£24	£23	£21	£20
	1.25%	£26	£25	£24	£23	£21	£20	£19	£18	£17	£15	£14
	1.50%	£20	£19	£18	£17	£15	£14	£13	£12	£11	£9	£8
	1.75%	£14	£13	£12	£11	£9	£8	£7	£6	£5	£3	£2
	2.00%	£8	£7	£6	£5	£3	£2	£1	£0	-£2	-£3	-£4
	2.25%	£2	£1	£0	-£1	-£3	-£4	-£5	-£6	-£8	-£9	-£10
	2.50%	-£4	-£5	-£6	-£7	-£9	-£10	-£11	-£12	-£14	-£15	-£16
	2.75%	-£10	-£11	-£12	-£13	-£15	-£16	-£17	-£18	-£20	-£21	-£22
	3.00%	-£16	-£17	-£18	-£19	-£21	-£22	-£23	-£24	-£26	-£27	-£28
	3.25%	-£22	-£23	-£24	-£26	-£27	-£28	-£29	-£30	-£32	-£33	-£34
	3.50%	-£28	-£29	-£30	-£32	-£33	-£34	-£35	-£36	-£38	-£39	-£40
	3.75%	-£34	-£35	-£36	-£38	-£39	-£40	-£41	-£42	-£44	-£45	-£46
	4.00%	-£40	-£41	-£42	-£44	-£45	-£46	-£47	-£48	-£50	-£51	-£52
	4.25%	-£46	-£47	-£48	-£50	-£51	-£52	-£53	-£54	-£56	-£57	-£58
4.50%	-£52	-£53	-£54	-£56	-£57	-£58	-£59	-£60	-£62	-£63	-£64	
4.75%	-£58	-£59	-£60	-£62	-£63	-£64	-£65	-£66	-£68	-£69	-£70	
5.00%	-£64	-£65	-£66	-£68	-£69	-£70	-£71	-£72	-£74	-£75	-£76	
5.25%	-£70	-£71	-£72	-£74	-£75	-£76	-£77	-£78	-£80	-£81	-£82	
5.50%	-£76	-£77	-£78	-£80	-£81	-£82	-£83	-£84	-£86	-£87	-£88	

Table 7: Cost differences (HumiGard minus Control) from analysis III for laparoscopic surgery (Mason, Billeter)

		SSI cost (£)										
		10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	
		£1,080	£1,886	£2,692	£3,499	£4,305	£5,111	£5,917	£6,723	£7,530	£8,336	£9,142
Stroke risk (diff hypo/no-hypo)	0.25%	-£8	-£11	-£15	-£19	-£23	-£27	-£31	-£35	-£38	-£42	-£46
	0.50%	-£27	-£31	-£34	-£38	-£42	-£46	-£50	-£54	-£58	-£61	-£65
	0.75%	-£46	-£50	-£54	-£58	-£61	-£65	-£69	-£73	-£77	-£81	-£85
	1.00%	-£65	-£69	-£73	-£77	-£81	-£84	-£88	-£92	-£96	-£100	-£104
	1.25%	-£84	-£88	-£92	-£96	-£100	-£104	-£108	-£111	-£115	-£119	-£123
	1.50%	-£104	-£107	-£111	-£115	-£119	-£123	-£127	-£131	-£134	-£138	-£142
	1.75%	-£123	-£127	-£131	-£134	-£138	-£142	-£146	-£150	-£154	-£158	-£161
	2.00%	-£142	-£146	-£150	-£154	-£157	-£161	-£165	-£169	-£173	-£177	-£181
	2.25%	-£161	-£165	-£169	-£173	-£177	-£181	-£184	-£188	-£192	-£196	-£200
	2.50%	-£180	-£184	-£188	-£192	-£196	-£200	-£204	-£207	-£211	-£215	-£219
	2.75%	-£200	-£204	-£207	-£211	-£215	-£219	-£223	-£227	-£230	-£234	-£238
	3.00%	-£219	-£223	-£227	-£230	-£234	-£238	-£242	-£246	-£250	-£254	-£257
	3.25%	-£238	-£242	-£246	-£250	-£253	-£257	-£261	-£265	-£269	-£273	-£277
	3.50%	-£257	-£261	-£265	-£269	-£273	-£277	-£280	-£284	-£288	-£292	-£296
	3.75%	-£276	-£280	-£284	-£288	-£292	-£296	-£300	-£303	-£307	-£311	-£315
	4.00%	-£296	-£300	-£303	-£307	-£311	-£315	-£319	-£323	-£327	-£330	-£334
	4.25%	-£315	-£319	-£323	-£326	-£330	-£334	-£338	-£342	-£346	-£350	-£353
4.50%	-£334	-£338	-£342	-£346	-£350	-£353	-£357	-£361	-£365	-£369	-£373	
4.75%	-£353	-£357	-£361	-£365	-£369	-£373	-£376	-£380	-£384	-£388	-£392	
5.00%	-£373	-£376	-£380	-£384	-£388	-£392	-£396	-£399	-£403	-£407	-£411	
5.25%	-£392	-£396	-£399	-£403	-£407	-£411	-£415	-£419	-£423	-£426	-£430	
5.50%	-£411	-£415	-£419	-£422	-£426	-£430	-£434	-£438	-£442	-£446	-£449	

Table 8: Cost differences (HumiGard minus Control) from analysis IV for laparoscopic surgery (Mason)

	SSI cost (£)									
	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
£1,080	£1,886	£2,692	£3,499	£4,305	£5,111	£5,917	£6,723	£7,530	£8,336	£9,142
£1	-£55	-£111	-£167	-£223	-£279	-£335	-£390	-£446	-£502	-£558

Conclusions

For open surgery (Table 5), HumiGard appears to be associated with a cost saving for scenarios where the difference in risk of stroke between hypothermic and normothermic patients is greater than 0.75-1.25% (depending on cost of SSI). Where the difference in stroke risk falls below this range, HumiGard is associated with a modest mean cost per patient increase.

For the analysis of laparoscopic surgery (using data from Billeter and Sammour; Table 6), HumiGard is cost saving only if the difference in stroke risk is greater than 1.75%-2.25% (depending on the cost of treating SSIs). The additional analyses using the data from the unpublished study by Mason et al (Table 7 and Table 8), suggest that HumiGard is cost saving across the range of SSI costs and differences in stroke risks when using information on a range of complications using data from the Billeter study (Table 7) and cost saving or cost neutral when using only direct data on SSI complications (Table 8). The EAC has not been able to fully review these models due to a lack of information on the extent of missing data and how this was handled, the results of statistical tests of the models and information on how they were developed.

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