National Institute for Health and Care Excellence

Medical Technologies Evaluation Programme

MT257 HumiGard for preventing inadvertent perioperative hypothermia

Consultation Comments table

MTAC date: 18 November 2016

There were 26 consultation comments from 2 consultees (1 Sponsor, 1 Other). The comments are reproduced in full in guidance section order.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
1	1. Sponsor	1.1 Page 2	The consultation document states that “HumiGard shows promise for preventing hypothermia during abdominal surgery. There is however, insufficient robust evidence to support the case for routine adoption across all abdominal surgery, particularly on how using HumiGard may avoid important adverse outcomes and its impact on resource use in open and laparoscopic surgery”. The sponsor agrees that more robust evidence is required for a recommendation for all abdominal surgery. The sponsor recommends that the scope be narrowed to consider only colorectal surgery where the evidence assessing resource use is strongest. Please see the supplementary economic analysis provided by the sponsor specific to colorectal surgery.	**MTEP team note:** Thank you for your comment. The scope sets the boundaries for assessing the evidence and for the Committee's decision-making. A draft version of the scope was made available to all stakeholders, including the sponsor for comment. No stakeholder suggested varying the scope and the company, in its submission, did not propose any variation to the decision problem. The economic model submitted in support of this comment, which is further referred to in the responses to comments 24 and 25, has inputs which are different to those in the EAC’s revisions to the sponsor’s model which were accepted by the committee. In particular: the additional modelling uses evidence on colorectal surgery only and thus does not rely on the EAC’s preferred source of inputs from the study by Billeter (2014) where 25% of the population had

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				surgery for gastrointestinal diseases, including bowel, pancreatic and hepato-biliary surgery; the additional model uses the cost of surgical site infection from Jenks (2015) which is higher than the EAC's estimate. The additional model contains no new evidence; all of the studies used were previously assessed by the EAC. The additional modelling contains inputs from the Mason (2016) study which was published during the guidance consultation period. During the development of final guidance, the committee considered the full publication and the EAC's critical appraisal of it. The committee noted that the paper acknowledges that the study design could not fully account for confounding factors and the EAC's concerns about the poor statistical reporting. The committee was also advised by a clinical expert that the methods used to measure patient temperature could be prone to significant error. Overall, it considered that there remained a lack of high-quality comparative evidence on the impact of HumiGard on adverse outcomes such as surgical site infection (section 3.14 of the guidance). **The Committee gave careful consideration to the additional modelling presented, to the Mason (2016) study and discussed making a recommendation for a sub-group of patients having colorectal cancer surgery. However, it judged overall that the evidence remains insufficiently robust to support a recommendation for routine adoption and decided not to change section 1.1.**

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2	1. Sponsor	1.2 Page 2	The consultation document states that further research should report on the comparative rate of surgical site infections and other complications associated with hypothermia and normothermia, as well as related resource use. The sponsor agrees that further research is required on direct outcomes for all abdominal surgery. However the sponsor recommends that the scope be narrowed to consider colorectal surgery where direct outcomes for laparoscopic surgery are reported and follow up data on open surgery are available. Supplementary analysis provided by the sponsor demonstrates that for colorectal surgery use of HumiGard is cost-saving in a high proportion of instances where it is used in laparoscopic surgery. The probability of cost-effectiveness is higher than 95% in these iterations, with cost-savings in the order of £200 - £300 per patient on average. In open surgery, there is also a reasonable case for cost-effectiveness, with cost-savings in the order of £15 - £20 per patient on average, or, alternatively it can be considered that the use of HumiGard is cost-neutral in the open application.	Thank you for your comment. Please see the response to comment 1.

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3	1. Sponsor	2.6 Page 4	The consultation document states that NICE's inadvertent perioperative hypothermia guideline does not make any specific recommendations about the warming of insufflation gas. The sponsor would like to highlight that no measures currently referenced in this guideline consider evaporative heat loss. Preventing evaporative heat loss is the aim of warm humidified insufflation. Currently recommended warming solutions are primarily focused on convective heat loss and do not address heat loss directly from the incision and exposure of the organs to cool dry air in open surgery, or from the evaporative heat loss caused by standard CO2 insufflation gas in laparoscopic surgery. Data reporting on an audit after instituting the recommendations in the current guideline revealed that 53% of patients had a post-operative temperature of < 36 °C (Lavies, 2011). In addition Frey et al, 2012 reported on a RCT in laparotomy, where it was shown that despite traditional warming measures in the control group, 18% of patients were below <36 °C compared to none in the group that received warm humidified insufflation of the abdominal wound. Since the 2008 assessment of CG65, 7 studies consider heated dry and 14 assess heated humidified insufflation. The sponsor recommends that evaporative heat loss be considered in CG65.	Thank you for your comment. NICE guideline 65 was published in December 2016. Any information relevant to the future review of the guideline can be sent by registered stakeholders via https://www.nice.org.uk/process/pmg22/chapter/introduction
4	1. Sponsor	3.2 Page 5	The consultation document states that the EAC considered that humidification systems other than HumiGard were beyond the scope of the evaluation and that 16 investigations should be excluded. The sponsor agrees that investigations encompassing the therapy are outside of the scope of the medical technology guideline, however NICE's inadvertent perioperative hypothermia guideline does not consider evaporative heat loss or make any specific recommendations about warming and	Thank you for your comment. Please refer to the response to comment 3.

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			humidification of insufflation gases. The sponsor recommends that the therapy of warm humidified insufflation to prevent inadvertent hypothermia is considered in a clinical guideline.	
5	1. Sponsor	3.3 Page 6	The consultation document states that there is no statistically significant difference in any other outcome measures specified in the scope. There were however significant differences in morphine use on operation day (p= 0.027), morphine use 24h postoperatively (p=0.030), total morphine consumption (p=0.0127), as well as a 3-fold reduction in rejected bolus 24h postoperatively (p=0.016). All of these pain differences are in favour of HumiGard.	Thank you for your comment. The comment refers to findings from the study by Hermann and de Wilde (2015) which was assessed by the EAC and which reports on multiple outcomes related to pain and morphine use. Patient reported outcomes for pain are the primary outcomes and morphine consumption outcomes are secondary outcomes. The paper quotes both one sided p values where significant and two sided p values. The EAC has stated that good practice in statistical reporting would report only two sided p values in this context. “Morphine use on operation day (p= 0.027), morphine use 24h postoperatively (p=0.030)” quotes one sided p values and the two sided p values were not statistically significant: these results should not therefore be considered as statistically significant. However, “Total morphine consumption (p=0.0127)” and “rejected bolus 24h postoperatively (p=0.016)” report one sided p values but the two sided values were p=0.0253 and p=0.032 respectively, so these results can be considered statistically significant if taken in isolation. Taking all of the report results into account, the EAC’s view was that in this study the intervention did not have a substantial impact on pain. **The committee decided not to change the section 3.3.**

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6	1. Sponsor	3.7 Page 7	The consultation document states with regards to Mason et al, The study was submitted as an unpublished manuscript which was available to the committee as academic in confidence. The Mason et al, 2016 study is now in press with Surgical Endoscopy, and can be referenced as peer-reviewed, manuscript number SEND-D-16-00631R1. All of the other included literature was designed to assess pain as the primary outcome with the acceptation of Mason et al, which was designed to assess hypothermia and associated outcomes. In addition Mason et al, is the only included investigation to assess hypothermia and associated complications directly in the context of the NHS.	Thank you for your comment. Relevant sections of the guidance have been updated to refer to the study as published.
7	1. Sponsor	3.10 Page 9	The consultation document states the cohort Mason et al, 2016 should be interpreted with caution, because it was submitted as unpublished data. Since the EAC assessment Mason et al, has been peer reviewed and accepted for publication in Surgical Endoscopy Manuscript number SEND-D-16-00631R1.	Thank you for your comment. The EAC noted that the Mason cohort retrospectively reports a before-after single site study. The Cochrane Collaboration Effective Practice and Organisation of Care (EPOC) group considers that “These studies have a high risk of bias because there may be unidentified differences between the intervention and control groups that may affect changes in the outcome measure.” The EAC’s main reservations centred on the study design, not the publication status of the article. **The committee decided to revise section 3.10 to further clarify the critical appraisal of the Mason study.**
8	1. Sponsor	3.14 Page 26	The consultation document states that the committee also noted the lack of high quality direct evidence supporting the use of HumiGard in avoiding adverse outcomes of hypothermia. Mason et al, 2016 is a peer	Thank you for your comment. Please refer to the responses to comment 1 and 7.

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			reviewed cohort of NHS based data demonstrated reduced complications with the introduction of HumiGard.	
9	1. Sponsor	3.17 Page 26	The consultation document states that the experts expressed concerns about the use of HumiGard in circumstances where thermogenesis may occur (such as in ablation surgery) or when cooling is needed (such as neurosurgery). HumiGard is not indicated for use in Neurosurgery. For abdominal surgery the temperature output of the system is ≤ 37 °C, therefore cannot warm a patient beyond body temperature. There is no risk of thermogenesis related to the use of the HumiGard Surgical Humidification System.	Thank you for your comment. The highlighted section related to circumstances when use of HumiGard would not be appropriate. It is agreed that HumiGard is not indicated for use in neurosurgery and that this use is out of scope. **The Committee decided to delete this phrase from section 3.17.**
10	1. Sponsor	3.18 Page 10	The consultation document states that the only evidence submitted showing a reduction in the incidence of surgical site infection using HumiGard was from a single observational study which was unpublished. Mason et al is a peer reviewed cohort that has been accepted for publication in Surgical Endoscopy manuscript number SEND-D-16-00631R1. Well-designed observational studies have been shown to provide results similar to randomised controlled trials (Song and Chung, 2010). The FDA recently issued draft guidance on the use of real world data to support regulatory decision making (July, 2016).	Thank you for your comment. Please refer to the responses to comments 1 and 7.
11	1. Sponsor	5.8 Page 14	The consultation document states that for open surgery, using data from Sammour et al, 2010, HumiGard was associated with a modest cost. Sammour et al did not include open surgery and was specific to laparoscopic surgery. In addition the sponsor did not report on the Sammour incidence of hypothermia as this data was provided by the author to the EAC and was not peer reviewed. This section may have been intended for	Thank you for your comment. Sammour et al (2010) reports on laparoscopic colonic surgery and the sponsor used data from Frey et al 2012. Section 5.8 has been amended to clarify this.

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			section additional work by the assessment centre (Section 5.10 +).The sponsor recommends that the probability of complications related to hypothermia in open surgery to be linked to the data from Frey et al, 2012.	
12	1. Sponsor	5.11 Page 15	The consultation document states that the EAC took hypothermia data from Sammour et al, 2010 and risk of complications data from Billeter et al, 2014. It should be noted that the information from Sammour was provided via correspondence with the author and is unpublished and not undergone peer review. The sponsor suggests that published data as per Mason et al with direct outcome measures be used to establish the economic model for laparoscopic surgery. This also removes uncertainty that is caused by the incidence of stroke. Scenario analysis is provided in the comment on the consultation document as a whole.	Thank you for your comment. Please see comment 7 regarding the Mason study. The EAC noted that it is common practice to request further information from authors of published studies, and that the Sammour RCT had undergone peer review. The RCT design is less susceptible to bias and confounding than data from a retrospective cohort. The EAC can find no mention of stroke in the Mason paper and does not know whether stroke was unrecorded or did not occur. A single study provides only an estimate of incidence; outcomes not mentioned cannot be assumed to be zero. **The committee decided not to change the guidance.**
13	1. Sponsor	5.13 Page 15	The consultation document states that the EAC used data from Sammour et al, 2010 rather than Mason et al, 2016. While the analysis remains cost saving it should be noted that the data obtained from Sammour et al, 2016 was via correspondence with the author and was unpublished and has not undergone peer review. The sponsor suggests that published data as per the Mason et al with direct outcome measures be used to establish the economic base cost. However for completeness the sponsor has submitted a cost analysis based on Mason	Thank you for your comment. Please refer to the responses to comments 1, 7 and 12.

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			and/or Sammour. Additional analysis is provided in the comments on the consultation document as a whole.	
14	1. Sponsor	5.15 Page 16	The consultation document states that the risk of stroke during abdominal surgery is very low. The sponsor agrees that stroke may be low in abdominal surgery and the addition of stroke to the economic model introduces uncertainty. The Billeter data considers a range of surgical procedures which may not be relevant to abdominal surgery. The sponsor recommends that the Billeter data be omitted from analysis and data specific to the incidence of complications in abdominal surgery be utilised such as Kurz et al, 1996, Flores-Maldonado et al, 2001 or Anannamcharoen et al, 2012. Scenario analysis considering this case is provided in the comments on the consultation document as a whole.	Thank you for your comment. The EAC noted that the risk of stroke is likely to be low, but there is not conclusive comparative data for hypothermic patients and non-hypothermic patients undergoing abdominal surgery to confirm this. The EAC acknowledged the Billetter (2014) study included all types of elective surgery (25% were gastrointestinal diseases, including bowel, pancreatic, and hepato-biliary surgery) but it is a contemporary study with a large sample (mean age = 61) and appropriate analytical techniques to determine effect size (differences in complications rates in hypothermic and non-hypothermic patients) The EAC also had serious concerns regarding the generalisability of the studies referred to in comment 14, as described in the Assessment Report Addendum and summarized here: **Kurz et al (1996)** RCT assessing whether hypothermia increases post-operative wound infection and lengthens hospitalisation in 200 patients undergoing elective colorectal surgery. Generalisability to current NHS practice may be limited due to: data being collected between 1993 and 1995 from hospitals in Austria and a protocol which involved dropping the temperature of patients in the

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				control group to 34.5 degrees without intervention. **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 data being collected between 1999 and 2000 from mostly female Mexican patient with a mean age of 40. **Anannamcharoen (2012)** Prospective cohort study of open colon and rectal resections in 229 patients. Generalisability to current NHS practice may be limited due to the setting: a single centre army hospital in Thailand. **The Committee considered each of the 3 cited studies and judged that, despite some concern over the generalisability of the data from Billeter (2014), it remains the best available source. The Committee concluded that the 3 studies were unlikely to provide better estimates and decided not to change section 5.15.**
15	1. Sponsor	5.17 Page 16	The consultation document states that the EAC used 2 sources of clinical effectiveness data to reduce uncertainty in the cost model Sammour et al, 2010 and Mason et al, 2016. The EAC used personal communication from Mason et al, 2016 to calculate adjusted risks. It should be noted that the data collected from Sammour et al, was also from personal communication. The sponsor recommends that the	Thank you for your comment. Please refer to the responses to comments 1, 7 and 12. For clarity, the EAC suggested 5.17 in the guidance may be amended: “The EAC used 2 sources of clinical-effectiveness data to perform

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			Mason data be used as a preference as this is now peer reviewed data and accepted for publication in Surgical Endoscopy, manuscript number SEND-D-16-00631R1. However for completeness the sponsor has submitted additional analysis which includes cost benefit scenarios with either Mason and/or Sammour. For scenario analysis please see the comments on the consultation as a whole.	further analyses and better characterise remaining uncertainties". **The Committee decided to change section 5.17 to clarify the data sources but not to update the cost benefit scenarios due to uncertainty in the Mason data (see comment 7).**
16	1. Sponsor	5.19 Page 17	The consultation document states that 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% to 1.25% (depending on the cost of surgical site infections). At a stroke risk difference below this range, HumiGard is associated with a modest increase in mean cost per patient. The sponsor agrees that in the recommend model stroke rates significantly affect the cost effectiveness and introduces uncertainty to the model. The sponsor recommends that the Billeter data be removed from the cost model. Billeter et al, covers all surgery and may not be the best reference for the decision problem. The sponsor recommends that for open surgery economic evaluation be made with Kurz et al, 1996, Flores-Maldonado et al, 2001 and Anannamcharoen et al, 2012 which are directly relevant to abdominal colorectal surgery. Scenario analysis is provided on the comments on the consultation document as a whole.	Thank you for your comment. Please refer to the response to comment 14.
17	1. Sponsor	5.20 Page 26	The consultation document states that the EAC has been unable to fully appraise these models due to incomplete information from the unpublished Mason et al, 2016. This investigation has been peer reviewed peer and accepted for publication in Surgical Endoscopy	Thank you for your comment. Please refer to the response to comment 7.

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			manuscript number SEND-D-16-00631R1. A full copy of the accepted manuscript is available on request to the author.	
18	1. Sponsor	5.21 Page 26	The consultation document states that the 5.5% stroke risk extrapolated from Billeter et al. 2014 in the company's cost model was an overestimate of the risk in current UK NHS practice, and that this is more likely to be less than 1%. The committee concluded that this distinction is likely to be very influential in the outcome of cost modelling. The sponsor agrees that the incidence of stroke as represented by the published US data set by Billeter et al, 2014 may not accurately represent abdominal surgery in the NHS population as the data is both US based and includes many surgery types in the analysis. Based on this the sponsor recommends that the cost considerations exclude stroke and consider an economic case based on data published by Mason et al, 2016 and associated direct outcomes for laparoscopic surgery. For open surgery the sponsor recommends outcome data to be taken from Kurz et al, 1999, Flores-Maldonado et al, 2001 and Anannamcharoen et al, 2012 removing stroke as a confounder. Scenario analysis considering these cases is provided in the comment on the consultation document as a whole.	Thank you for your comment. Please refer to the responses to comments 1, 7 and 14.
19	1. Sponsor	5.22 Page 26	The sponsor agrees that the average cost for SSI reflects current practice. The sponsor has taken the suggested value from the EAC to include in the updated economic case considered in the comments on the consultation documents as a whole.	Thank you for your comment. Note: the cost of an SSI used in the EAC model was £1,858. The additional model submitted by the consultee uses £5,164 from Jenks et al. 2014.

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20	1. Sponsor	6.1 Page 26	The consultation document states that the committee considered that there is insufficient evidence to demonstrate that HumiGard has a substantial effect on reducing adverse outcomes. At the time of submission the publication Mason et al, 2016 which demonstrates a substantial effect on reducing adverse outcomes was under review and presented as academic in confidence. Since that time the publication has been peer reviewed and accepted for publication in Surgical Endoscopy (SEND-D-16-00631R1). In addition data demonstrating warm humidified insufflation in open surgery reduced the incidence of hypothermia and that intraoperative hypothermia was associated with improved survival (p = 0.050) was presented as academic in confidence. Since that time this publication has been published in International Journal of Colorectal disease 2016. doi: 10.1007/s00384-015-2467-4. Epub 2015 Dec 23. PubMed PMID: 26694927; PubMed Central PMCID: PMC4773499.	Thank you for your comment. Please refer to the responses to comments 1 and 7 on the study by Mason (2016). The other study referred to is by Frey (2016) and is a post hoc retrospective analysis of two RCTs, both of which were already in the list of included primary studies of the sponsor's clinical evidence review, with one being on HumiGard (Frey et al. 2012a) and the other on another humidification device (Frey et al. 2012b). **The committee considered this comment carefully and decided not to change section 6.1.**
21	1. Sponsor	General	References for comments: Mason S, Kinross J, Hendricks J, Arulampalam T. Postoperative hypothermia and surgical site infection following peritoneal insufflation with warm humidified carbon dioxide during laparoscopic colorectal surgery: a cohort study with cost effectiveness analysis. Surg Endosc. 2016 [ahead of print]. SEND-D-16-00631R1. Keenan JE, Speicher PJ, Thacker JM, Walter M, Kuchibhatla M, Mantyh CR. The Preventive Surgical Site Infection Bundle in Colorectal Surgery: An Effective Approach to Surgical Site Infection Reduction and Health Care Cost Savings. JAMA Surg.	Thank you for your comment.

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			2014;149(10):1045-1052. doi:10.1001/jamasurg.2014.346 Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med. 1996 May 9;334(19):1209-15. PubMed PMID: 8606715. Hart, S. R., Bordes, B., Hart, J., Corsino, D., & Harmon, D. (2011). Unintended Perioperative Hypothermia. The Ochsner Journal, 11(3), 259–270. Mu Y, Edwards JR, Horan TC, et al. Improving risk-adjusted measures of surgical site infection for the National Healthcare Safety Network. Infect Control Hosp Epidemiol 2011;32:970– 986. Mehta OH, Barclay KL. Perioperative hypothermia in patients undergoing major colorectal surgery. ANZ J Surg. 2014 Jul-Aug;84(7-8):550-5. doi:10.1111/ans.12369. Epub 2013 Sep 5. PubMed PMID: 24004440. Frey JM, Janson M, Svanfeldt M, Svenarud PK, van der Linden JA. Local insufflation of warm humidified CO_2increases open wound and core temperature during open colon surgery: a randomized clinical trial. Anesth Analg. 2012 Nov;115(5):1204-11. doi: 10.1213/ANE.0b013e31826ac49f. Epub 2012 Aug 10. PubMed PMID: 22886839. Sammour T, Kahokehr A, Hayes J, Hulme-Moir M, Hill AG. Warming and humidification of insufflation carbon dioxide in laparoscopic colonic surgery: a double-blinded	

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			randomized controlled trial. Ann Surg. 2010 Jun;251(6):1024-33. doi: 10.1097/SLA.0b013e3181d77a25. PubMed PMID: 20485147. Billeter AT, Hohmann SF, Druen D, Cannon R, Polk HC Jr. Unintentional perioperative hypothermia is associated with severe complications and high mortality in elective operations. Surgery. 2014 Nov;156(5):1245-52. doi: 10.1016/j.surg.2014.04.024. Epub 2014 Jun 16. PubMed PMID: 24947647. Flores-Maldonado A, Medina-Escobedo CE, Ríos-Rodríguez HM, Fernández-Domínguez R. Mild perioperative hypothermia and the risk of wound infection. Arch Med Res. 2001 May-Jun;32(3):227-31. PubMed PMID: 11395189. Anannamcharoen S, Vachirasrisirikul S, Boonya-Assadorn C. Incisional surgical site infection in colorectal surgery patients. J Med Assoc Thai. 2012 Jan;95(1):42-7. PubMed PMID: 22379740. J. Frey, M. Holm, M. Janson M. Egenvall & J. van der Linden. Relation of intraoperative temperature to postoperative mortality in open colon surgery—an analysis of two randomized controlled trials. 2015. Int J Colorectal Dis. DOI 10.1007/s00384-015-2467-4 Song, J. W., & Chung, K. C. (2010). Observational Studies: Cohort and Case-Control Studies. Plastic and Reconstructive Surgery, 126(6), 2234–2242. http://doi.org/10.1097/PRS.0b013e3181f44abc. Frey, J., Holm, M., Janson, M., Egenvall, M., & van der Linden, J. (2016). Relation of intraoperative temperature	

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			to postoperative mortality in open colon surgery—an analysis of two randomized controlled trials. International Journal of Colorectal Disease, 31, 519–524. http://doi.org/10.1007/s00384-015-2467-4	
22	1. Sponsor	General	Has all of the relevant evidence been taken into account? The sponsor thanks the EAC and the Committee for their thorough analysis. We agree that all of the relevant information has been taken into account. One major change that has taken place is that at the time of submission and during the evaluation of data by the EAC Mason et al. 2016 was provided as academic in confidence. The Mason et al. 2016 paper has now been accepted for publication in Surgical Endoscopy and can be referenced as a peer-reviewed manuscript number SEND-D-16-00631R1.	Thank you for your comment. Please refer to the response to comment 7.
23	1. Sponsor	General	Are the provisional recommendations sound, and a suitable basis for guidance in the NHS? The sponsor considers the recommendations sound for the included scope. The sponsor would additionally like to highlight the strength of the clinical and cost evaluations for colorectal surgery in particular. Accordingly, the sponsor would like to recommend that the scope be narrowed and a recommendation be made which is specific to colorectal surgery. Due to the complexity and length of the surgery, colorectal patients are at a high risk of operative hypothermia. Also, due to the nature of the surgery including exposure of bowel contents, length of surgery and co-morbidities, colorectal surgery has a	Thank you for your comment. Please refer to the responses to comments 1, 7 and 14.

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			disproportionate rate of surgical site infection (Keenan et al. 2014). Published literature reports a threefold increase in the frequency of surgical site infections in colorectal surgery patients who experience perioperative hypothermia (Kurz et al. 2008). General anaesthesia has a characteristic pattern of an initial rapid decrease in core temperature which is exacerbated by evaporative heat losses experienced due to the dry cool nature of the gas used in laparoscopic surgery, and evaporative and convective heat losses experienced due to the ambient theatre conditions in open surgery (Hart et al. 2011). During colorectal surgery the procedures are long, with a co-morbid population, all of which are independent risk factors for SSI (Mu et al. 2011). Data from Frey et al. 2012 demonstrate that in a RCT of open colorectal surgery utilising currently available warming methods, 18% of patients are hypothermic at the end of surgery. Mason et al. 2016 report the incidence of hypothermia as measured on entry to recovery as 57% after laparoscopic colorectal surgery with traditional warming methods. Mehta and Barclay. 2014 reported on perioperative hypothermia in patients undergoing major colorectal surgery and demonstrated that 74% of patients experienced mild hypothermia which was most common intra-operatively despite preventative measures. These data highlight that maintaining normothermia during colorectal surgery remains a challenge. Mason and colleagues audited the incidence of hypothermia in 123 colorectal patients in a single specialist laparoscopic centre and found that the	

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			incidence of hypothermia, defined as < 36 °C on entry to recovery, was 57%. After warm humidified insufflation was introduced to the unit an audit on an additional 123 patients demonstrated that the incidence of hypothermia was significantly reduced to 13% (P = <0.001). The data also demonstrated that the incidence of SSI was also significantly reduced from 13% in the control group to 5.7% in the warm humidified group. The incidence of hypothermia significantly increased the risk of developing a SSI with an OR of 4.0 (95% CI 1.25-12.9, P = 0.02). Kurz et al. 1996 also demonstrated in colorectal surgery in a double blind Randomised Controlled Trial (RCT) of patients undergoing colorectal surgery that the incidence of SSI was higher in patients who experienced hypothermia with 6% in the normothermia group and 19% in the hypothermia group (P = 0.009). Meta data looking at the incidence of hypothermia in colorectal surgery as presented by the EAC including an assessment of data provided by Sammour et al. 2010 and Mason et al. 2016 demonstrates a significant benefit in favour of HumiGard. Similarly Frey et al. 2012 demonstrated in a RCT in open colon surgery that the incidence of hypothermia in the control group was 18% compared with the treatment group (i.e. warm-humidified insufflation) at 0% (P = 0.005). This was despite following current warming recommendations including active warming, pre-warming and fluid warming. Local insufflation of warm humidified CO2 also significantly improved both wound and core temperature (P = < 0.001, P = 0.001 respectively). A long term follow up of these patients demonstrated that final core temperature was associated with better overall survival (P = 0.050) highlighting the	

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			importance of maintaining normothermia during colorectal surgery (Frey et al. 2010). The sponsor considers that both the economic and clinical evidence currently evaluated support the use of HumiGard in colorectal surgery.	
24	1. Sponsor	General	Are all of the summaries of clinical effectiveness and resource savings reasonable interpretations of the evidence? All of the summaries of clinical effectiveness are reasonable for the current scope. The sponsor would like to recommend that the scope of the recommendations be narrowed specifically to colorectal surgery. For open surgery the cost models provided by the sponsor and the appraised models proposed by the EAC in the original submission are more uncertain due to the reliance of the models on the proposed incidence of stroke in Billeter et al. 2014 publication. For laparoscopic surgery the limitation was that the Mason et al. (2016) data was unpublished at the time of submission and that effectiveness data from Sammour et al. 2010 was obtained via personal communication with the author and not included in the publication. In addition, the primary endpoint for the Sammour et al. 2010 data was pain and the investigation was powered to detect a 20% difference in morphine equivalent daily dose during the hospital stay with an alpha of 0.05 and power of 0.8. The sponsor would therefore like the committee to consider some alternative cost scenarios specific to colorectal surgery that address the uncertainty pertaining to stroke for open surgery and publication concerns for laparoscopic surgery. Accordingly, the outcome data for	Thank you for your comment. Please refer to the responses to comments 1, 7, 12 and 14. The consultee has proposed alternative parameters to the EAC's revisions to the sponsor's original model. The consultee's proposed alternative parameters are described in table 1 of comment 25. The SSI cost used in the EAC's revisions, based on DH reference costs 2013/14, was £1,858 and not £5164.00. The EAC has reviewed the inputs used in the additional model presented in the company consultation comments in the original assessment and the addendum to the AR (April 2016); . Please also refer to the response to comments 1, 7 and 14. **The committee considered the additional information carefully but decided not to change the guidance.**

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
			open surgery related to Billeter et al. 2014 has been removed for the following reasons: • Reference cut off for hypothermia was 35 °C compared to the NICE recommended cut off of 36.5 °C for mild hypothermia and 36.0 °C for moderate hypothermia. • Data includes all surgery types and is not restricted to abdominal surgery or more specifically colorectal surgery. • Higher recorded incidence of stroke than reported by expert advisors, as well as the fact that incidence of stroke inflated cost savings in longer term time horizons. Furthermore, data from Flores-Maldonado et al. 2001 was provided in the original analysis. This data source has been removed in the amended model as it was specific to laparoscopic cholecystectomy and not colorectal surgery. For laparoscopic surgery the source of complications has been amended to Mason et al. 2016 as this data has been peer reviewed and accepted for publication in Surgical Endoscopy, manuscript number SEND-D-16-00631R1. The sponsor proposes a sensitivity analyses to be discussed based on the revised model submitted by the sponsor, which includes the published data sources discussed above. In the revised model the cost for SSI	

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
			has been amended to match the EAC recommended value of £ 5164.00.	

<table>
<tr>
<td>25</td>
<td>1. Sponsor</td>
<td>General</td>
<td>Sources of data for sensitivity analysis:

Table 1. Sources of data for sensitivity analysis

<table>
<tr><th>Scenario</th><th>Surgery type</th><th>Source of complications (Temperature)</th><th>Speciality for complication data</th><th>Source of effectiveness (SSI data)</th><th>Specialty fo effectivene data</th></tr>
<tr><td>1</td><td>Open</td><td>Frey</td><td>Colorectal N = 83</td><td>Kurz</td><td>Colorectal N = 200</td></tr>
<tr><td>2</td><td>Open</td><td>Frey</td><td>Colorectal N = 83</td><td>Anannamcharoen</td><td>Colorectal = 229</td></tr>
<tr><td>3</td><td>Laparoscopic</td><td>n/a</td><td>n/a</td><td>Mason</td><td>Colorectal N = 246</td></tr>
<tr><td>4</td><td>Laparoscopic</td><td>Sammour</td><td>Colorectal N = 74</td><td>Kurz</td><td>Colorectal N = 200</td></tr>
<tr><td>5</td><td>Laparoscopic</td><td>Mason</td><td>Colorectal N = 246</td><td>Kurz</td><td>Colorectal N = 200</td></tr>
</table>

Results of sensitivity analysis:

Scenario 1: OPEN (Frey, Kurz, Colorectal)

For open surgery, the results suggest that HumiGard is cost saving compared with standard care, with an average saving per patient of -£16 over a one year time horizon. The probabilistic analysis found that HumiGard was cost saving 51.4 % of iterations.

Scenario 2: OPEN (Frey, Anannamcharoen, Colorectal)

For open surgery, the results suggest that HumiGard is cost saving compared with standard care, with an average saving per patient of £ -18 over a one year time horizon. The probabilistic analysis found that HumiGard was cost saving 52.3 % of iterations.

Scenario 3: LAPAROSCOPIC (Mason, Colorectal)

This scenario utilises Mason complication data directly. For laparoscopic surgery, the results suggest that HumiGard is cost saving compared with standard care, with an average saving per patient of £ -301 over a one</td>
<td>Thank you for your comment.

Please also refer to the response to comments 1, 7 and 14.

The EAC commented that the sensitivity analyses presented are concordant with data presented to the committee; for laparoscopic surgery using comparative data from Mason (2016) either directly or indirectly, the economic model suggests HumiGard is cost saving. When using other sources of effectiveness data (Sammour, 2010) this is only true under certain input parameter combinations (higher SSI costs). For open surgery the economic model suggests the use of HumiGard is cost incurring except at higher SSI cost. The EAC's preferred SSI cost was £1,858 from NHS reference costs and not £5164, which was quoted in the Jenks et al paper.

The committee considered the additional information carefully but decided not to change the guidance.</td>
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Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
			year time horizon. The probabilistic analysis found that HumiGard was cost saving 96 % of iterations. Scenario 4: LAPAROSCOPIC (Sammour, Kurz, Colorectal) The scenario is provided for completeness as the Kurz complication data is based on open surgery. For laparoscopic surgery, the results suggest that there is a small cost incurred with HumiGard compared with standard care, with an average cost per patient of £ 17 over a one year time horizon. The probabilistic analysis found that HumiGard was cost saving 35 % of iterations. Scenario 5: LAPAROSCOPIC (Mason, Kurz, Colorectal) The scenario is provided for completeness as the Kurz complication data is based on open surgery. For laparoscopic surgery, the results suggest that HumiGard is cost saving compared with standard care, with an average saving per patient of £ -220 over a one year time horizon. The probabilistic analysis found that HumiGard was cost saving 99 % of iterations. Conclusion: The use of HumiGard is cost-saving in a high proportion of instances where it is used in laparoscopic surgery. The probability of cost-effectiveness is higher than 95% in these iterations, with cost-savings in the order of £200 - £300 per patient on average. In open surgery, there is also a reasonable case for cost-effectiveness, with cost-savings in the order of £15 - £20 per patient on average, or, alternatively, use of HumiGard is cost-neutral in the open application.	

<table>
<tr><th>Com. no.</th><th>Consultee number and organisation</th><th>Sec. no.</th><th>Comments</th><th>Response</th></tr>
<tr><td></td><td></td><td></td><td>Sensitivity analysis for provided scenarios</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Table 2: Cost differences (HumiGard minus control) from scenario 1 and 2 for open surgery.
<table>
<tr><th></th><th></th><th colspan="11">SSI cost (£)</th></tr>
<tr><th>Source of complication (Temperature)</th><th>Source of effectiveness (SSI data)</th><th>£1080</th><th>10% £1886</th><th>20% £2692</th><th>30% £3499</th><th>40% £4305</th><th>50% £5111</th><th>60% £5917</th><th>70% £6723</th><th>80% £7530</th><th>90% £8336</th><th>100% £9142</th></tr>
<tr><td>Frey</td><td>Kurz</td><td>£79</td><td>£60</td><td>£42</td><td>£23</td><td>£4</td><td>-£15</td><td>-£34</td><td>-£53</td><td>-£72</td><td>-£90</td><td>-£109</td></tr>
<tr><td>Frey</td><td>Anannamcharoen</td><td>£79</td><td>£60</td><td>£41</td><td>£22</td><td>£3</td><td>-£17</td><td>-£36</td><td>-£55</td><td>-£74</td><td>-£93</td><td>-£112</td></tr>
</table>
Table 3: Cost differences (HumiGard minus control) from scenario 3, 4 and 5 for laparoscopic surgery.
<table>
<tr><th></th><th></th><th colspan="11">SSI cost (£)</th></tr>
<tr><th>Source of complication (Temperature)</th><th>Source of effectiveness (SSI)</th><th>£1080</th><th>10% £1886</th><th>20% £2692</th><th>30% £3499</th><th>40% £4305</th><th>50% £5111</th><th>60% £5917</th><th>70% £6723</th><th>80% £7530</th><th>90% £8336</th><th>100% £9142</th></tr>
<tr><td>n/a</td><td>Mason</td><td>-£3</td><td>-£62</td><td>-£121</td><td>-£180</td><td>-£239</td><td>-£297</td><td>-£356</td><td>-£415</td><td>-£474</td><td>-£533</td><td>-£592</td></tr>
<tr><td>Sammour</td><td>Kurz</td><td>£63</td><td>£54</td><td>£45</td><td>£36</td><td>£26</td><td>£17</td><td>£8</td><td>-£1</td><td>-£10</td><td>-£20</td><td>-£29</td></tr>
<tr><td>Mason</td><td>Kurz</td><td>-£14</td><td>-£32</td><td>-£78</td><td>-£125</td><td>-£171</td><td>-£217</td><td>-£263</td><td>-£309</td><td>-£355</td><td>-£401</td><td>-£447</td></tr>
</table></td></tr>
<tr><td>26</td><td>2. Other - Department of Health</td><td>General</td><td>Dear NICE

Thank you for the opportunity to comment on the evaluation programme documents for the above medical technology.

I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.

Many thanks and best wishes</td><td>Thank you for your comment.</td></tr>
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