NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

External Assessment Centre correspondence

HumiGard Surgical Humidification System for the prevention of inadvertent perioperative hypothermia

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

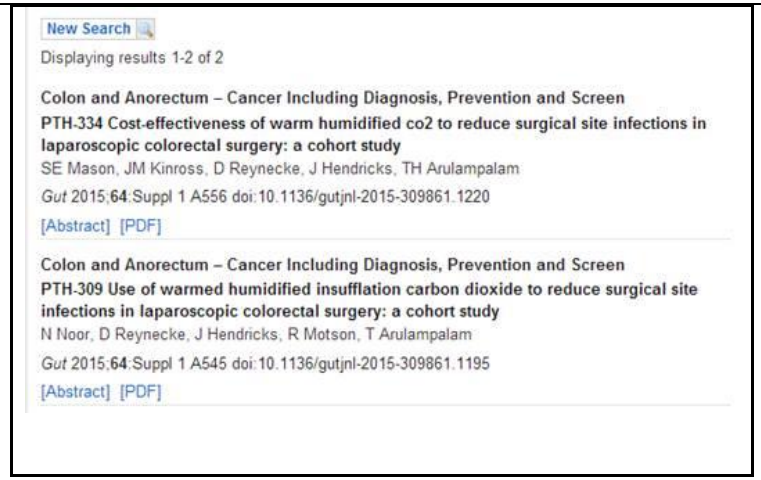
These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
General	17/09/2015 Teleconference between EAC and manufacturer EAC asked for statement of equivalence between models MR860 and SH860 and manuscripts marked as academic in confidence.	**From:** Jess Fogarin **Sent:** Thu 03/12/2015 02:43 Hi Carole and Liesl, In addition to the response provided last night I have also attached a manuscript in confidence related to some of the previous economic analysis. The other manuscripts in confidence discussed (Frey and Mason) were provided with the clinical submission. Please let me know if you would like an additional copy. With regards to the evidence of equivalence between the two models. Our engineering team is putting together a summary which we will have to you close of business Monday 7th of December 2015. Please let me know if we can provide any additional details. Kind Regards, Jess. --- **From:** Jess Fogarin **Sent:** Mon 07/12/2015 20:45 Hi Carole, Please find attached the statement of equivalence	Noted by the EAC. Paul Dimmock forwarded the unpublished studies as academic in confidence.  1. RE HumiGard - contact details .msg  2. Statement of equivalence.msg  3. RE HumiGard - contact details .msg

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		between the MR860 and the SH870 model. Please let me know if you require any additional information. Kind Regards, Jess.	
General	- Requested copy of the email confirmation from the authors of the Cochrane review acknowledging the errors in the publication - Requested timeline for publication of the two unpublished manuscripts (Frey et al and Mason et al) submitted	**From:** Jess Fogarin **Sent:** Wed 09/12/2015 19:37 Hi Liesl, Please find attached the original email from the Cochrane authors. With regards to the Frey paper we have recently had confirmation that the paper has been accepted to the International Journal of Colorectal Disease so we expect publication as “online first” in the next few weeks. Once a link is available I will send it through. Once published on line you are welcome to make the information from this paper public in the submission document. I will follow up on the status of the Mason paper and get back to you as soon as possible. Kind Regards, Jess.	Noted by the EAC.  1. RE HumiGard Evaluation.msg  2. RE HumiGard Evaluation.msg

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		_____ **From:** Jess Fogarin **Sent:** Wed 09/12/2015 20:33 Hi Liesl, Just had a response from the Mason research group. They expect submission in January 2016. Kind Regards, Jess.	
Economic submission	**Sponsor contacted** Queries regarding the Humigard economic submission to the NICE MTEP: 1) The unpublished paper by Mason et al looks to be an early draft and does not include any tables or figures. Is it possible to send us copies of the tables/figures and a more complete version if available? 2) We are unclear if the	**From:** Dean Reynecke **Sent:** Thu 07/01/2016 00:35 Hi Louise Please see the e-mail below, where I have responded per singula to your original request to Jess requesting further information. Please do not hesitate to be in touch if we can provide more information. Many thanks Dean Reynecke _____ 1) The unpublished paper by Mason et al looks to be an early draft and does not include any tables or figures. Is it possible to send us copies of the	Noted by the EAC.  RE MT257 Humigard evaluation.msg

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
	Mason paper and the abstract by Noor et al relate to the same study. Please can you clarify how the two studies relate to each other (e.g. are they the same study? Is there overlap in the patient populations?)? 3) There is limited detail provided in the abstract by Noor et al. Please could you send further details if available (e.g. a technical report)? 4) Please can you provide copies of the correspondence detailing the additional information on the proportion of patients with/without hypothermia from the authors of the paper by Sammour et al?	tables/figures and a more complete version if available? >> This is correct, as the draft that we sent through is indeed an early version of the manuscript. The manuscript has been in preparation until very recently, and recent correspondence from the authors suggests that the final version is pending. We hope to have it available in the next 10 -14 days. We will forward this to you as soon as we have it – it would be good if you could give us an indication of the urgency required if necessary. 2) We are unclear if the Mason paper and the abstract by Noor et al relate to the same study. Please can you clarify how the two studies relate to each other (e.g. are they the same study? Is there overlap in the patient populations?)?>> I can confirm that this is one study, covering the same patient population. Originally, the study results were presented in two abstracts and both of these are available on the GUT website:	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		 New Search Displaying results 1-2 of 2 **Colon and Anorectum – Cancer Including Diagnosis, Prevention and Screen** **PTH-334 Cost-effectiveness of warm humidified co2 to reduce surgical site infections in laparoscopic colorectal surgery: a cohort study** SE Mason, JM Kinross, D Reynecke, J Hendricks, TH Arulampalam *Gut* 2015;**64**:Suppl 1 A556 doi:10.1136/gutjnl-2015-309861.1220 [Abstract] [PDF] **Colon and Anorectum – Cancer Including Diagnosis, Prevention and Screen** **PTH-309 Use of warmed humidified insufflation carbon dioxide to reduce surgical site infections in laparoscopic colorectal surgery: a cohort study** N Noor, D Reynecke, J Hendricks, R Motson, T Arulampalam *Gut* 2015;**64**:Suppl 1 A545 doi:10.1136/gutjnl-2015-309861.1195 [Abstract] [PDF] The Noor *et al*. abstract dealt with the clinical aspects of the study, while the Mason *et al*. abstract addressed the incremental cost-effectiveness ratio per surgical site infection avoided, for the same study. The final Mason *et al*. manuscript is the amalgam of both abstracts and is the description of the entire study. 3) There is limited detail provided in the abstract by Noor et al. Please could you send further details if available (e.g. a technical report)? >> As mentioned above, the Noor *et al*. abstract is simply the clinical aspect of the study. Please note that neither the Noor nor the Mason abstracts address the temperature differences between the pre and post-intervention groups. The Mason *et al*. manuscript (which is close to	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		completion as discussed above) is thus the fullest possible technical and scientific description of the study, and we will forward it to you as soon as we obtain a copy from the authors. Should this not suffice please let me know and we will prepare a complete report of the study. 4) Please can you provide copies of the correspondence detailing the additional information on the proportion of patients with/without hypothermia from the authors of the paper by Sammour et al?>> Yes, this will be no problem, as this author was recently contacted by Michelle Jenks at YHEC, during the process of collating data and evidence for the HumiGard economic submission. I am including a snip of the economic submission detailing this, and I will also request a copy of the correspondence with Sammour *et al*. in order to forward this to you: SNIP REDACTED	
Economic submission	**Sponsor contacted** Updated version of the Mason paper - need it Wed next week at the latest to give it consideration.	**From:** Dean Reynecke **Sent:** Thu 07/01/2016 20:01 Dear Louise 1. Please find attached a later draft of the Mason *et*	Noted by the EAC.  RE MT257 Humigard evaluation.msg

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
	Alternatively, forward the tables and figures referred to in the current draft and get an indication from the authors as to whether they expect these to change in their updated version. Thanks for clarifying that the Noor and Mason articles relate to the same study. We note the numbers included in the two studies don't match. Mason: n=276 with 30 exclusions (246 in final analysis). Noor: n=252. Please can you clarify why this is? Thank you for agreeing to forward the correspondence from Dr Sammour.	*al*. manuscript, along with Table 1 and one figure which we currently have. As I have mentioned, this is also an early version of the manuscript, but it succeeds the version that you currently have. I have e-mailed the authors for the final version, along with figures and tables, and hope to have a response over the weekend. If it does not arrive in the time frame that you have available then we trust that this will suffice. 2. As far as differing sample sizes are concerned – this is due to the fact that the data are from an active laparoscopic teaching and research centre (ICENI, in Colchester), and new data is continually added to the patient case-note data base. HumiGard is in use at the hospital, and the scope of the study has increased as more data have become available. For instance, in the two abstracts, temperature was not discussed, but temperature is discussed in the manuscript, which was written after the DDF conference abstracts. 3. We will forward Dr Sammour's correspondence with YHEC as soon as it is available. Kind regards Dean --- **From:** Dean Reynecke **Sent:** Thu 07/01/2016 20:01	 RE MT257 Humigard evaluation.msg

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Hi Louise Here is the requested correspondence, along with a side-note from YHEC, who we contracted to carry out the economic research. The side-note is as follows: "The correspondence from Dr Sammour includes the number of patients with hypothermia at the end of surgery defined at both 35°C and 36°C . Therefore, for completeness a scenario combining the 35°C data from Sammour and the Billeter data should have been included and results reported within Table C13. This scenario would use a consistent definition of hypothermia (at 35°C) across the two studies. Using these data result in an incremental cost of £10 per patient, as opposed £5 per patient when the Sammour 36°C data are used. We are very sorry for this oversight. This additional scenario result falls within the range of results previously presented within Table C13. The other scenario analyses using clinical event data from Kurz and Flores-Maldonado are valid in using the 36°C data." Re the Table and Figure sent last week, from the Mason paper – will this level of detail suffice? Kind regards Dean	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
Economic submission	**Sponsor contacted** Please forward other tables if received from the authors. In the previous draft the authors referred to a multivariate analysis, but this is no longer mentioned in the current version. If the authors have conducted a multivariate analysis it would be helpful for us to have sight of it.	**From:** Dean Reynecke **Sent:** Tue 12/01/2016 01:45 Hi Louise That should be no problem, the multivariate analysis has been carried out and we hope to have it with you on Wednesday in the UK for you to have a sight of it. Regards Dean	Noted by the EAC.  RE MT257 Humigard evaluation.msg
Economic submission	**Expert advisers contacted** Clarification regarding several aspects of the economic submission sought from all expert advisers.	**From:** Mark Harper **Sent:** 11 January 2016 10:23 1. The manufacturer's analysis suggests that the proportion of patients experiencing hypothermia during surgery without HumiGard is much greater in patients undergoing laparoscopic surgery (57%) compared to open surgery (18%). Do you think this is reasonable? **2. This does not reflect my experience. In externally warmed (** 3. In the economic analysis the risks of complications (sepsis, surgical site infection, MI, stroke, pneumonia, mortality) associated with hypothermia compared to no hypothermia are derived from a US study of open surgery (Billeter et al). a. Would you expect the risks of these complications	Noted by the EAC.  FW NICE MTEP review of HumiGard.m  FW NICE MTEP review of HumiGard.m

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		associated with hypothermia to be similar regardless of surgical type (laparoscopic or open)? b. Would you expect the data on risks of complications associated with hypothermia (compared to those without hypothermia) from the USA to be generalisable to the UK? c. The Billeter et al study is not restricted to patients undergoing abdominal surgery (it also includes patients undergoing orthopaedic, general, thoracic, obs and gyne, and urology surgeries). Would you expect the risks of complications associated with hypothermia in all elective surgeries to be similar to abdominal surgery? **d. I don't think it's reasonable to apply an American economic analysis to a UK population. For both the NICE CG65 and the Inditherm TA, NICE have conducted economic analyses which would be relevant.** 4. One of the studies of HumiGard had an imbalance in the number of patients who underwent surgery for malignancy. Would you expect patients with malignancy to be more/less susceptible to hypothermia compared to those without malignancy? **5. As far as I know, malignancy is not an independent risk factor for IPH. However cancer surgery generally takes longer and this is a risk factor. Also need to look carefully at ASA grade.** 6. The manufacturer's model assumes that complications as a result of hypothermia may occur	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		both during the patient's hospital stay or after they have been discharged. Is this a reasonable assumption? **7. they are correct that complications occur after discharge but this is a relatively small number and, because they can often be treated in the community, does not impact financially in the same way as an extended hospital stay.** 8. The manufacturer estimates that an average of 75 patients would use the HumiGard System in abdominal surgery in each centre per annum in the UK. Do you think this is reasonable? **9. This is almost impossible to answer. In our hospital we would definitely use more than that because we are a big cancer centre. However, many places will probably do less.** 10. Are there any patients undergoing abdominal surgery for whom you would not consider using the HumiGard System? **11. While there are no conditions that I would exclude, for financial reasons we limit its use to patients undergoing surgery that is likely to last more than 60 minutes as for shorter surgical durations it does not seem to confer much benefit.** 12. The manufacturer has advised that the use of HumiGard system in laparoscopic and open surgery within the UK NHS has a ratio of around 70:30. However, the two clinical experts who advised the sponsor stated that HumiGard is currently only used	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		for laparoscopic surgery in their centres. Do you agree that the split of 70:30 represents current practice? Do you think this is likely to change in the future? **13. No and no. We also only use it for laparoscopic surgery and I think we should only consider it in this context for now and review any change in practice in the future.** 14. The manufacturer estimates that training requirements for the implementation of Humigard in a centre would include the training of one senior nurse (7.5 hours) who would then pass on training knowledge to groups of nurses (2.5 hours total time). a. Is it reasonable that only one nurse would receive training directly? b. Is the time estimate for the senior nurse appropriate? c. How many other nurses would receive in-house training from the senior nurse and how long would this be expected to last? d. Would you expect the training to be a 'one-off' event? If not, how often would you expect it to be re-administered? **e. I'm currently in theatre with a couple of nurses who both think that the 10 minutes training they received was perfectly adequate and they do not think they would need retraining. It really is very simple to use. In fact none of us can work out how they could possibly extend the training to**	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		7.5h. I hope that answers you questions. Kind regards, Mark _____ **From:** tan arulampalam **Sent:** 09 January 2016 21:52 1. The manufacturer's analysis suggests that the proportion of patients experiencing hypothermia during surgery *without HumiGard* is much greater in patients undergoing laparoscopic surgery (57%) compared to open surgery (18%). Do you think this is reasonable? **This data appears to be accurate and our centre is now analysing more data. The difference is quite marked.** 2. In the economic analysis the risks of complications (sepsis, surgical site infection, MI, stroke, pneumonia, mortality) associated with hypothermia compared to no hypothermia are derived from a US study of open surgery (Billeter et al). a. Would you expect the risks of these complications associated with hypothermia to be similar regardless of surgical type (laparoscopic or open)? **There is data suggest that there is a difference in SSI. It is difficult to state whether there is a similarity as the mechanisms of heart loss are**	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		different in lap and open surgery. However, the net difference may still be marked when using humigard. I therefore think it is a reasonable model based on data from our unit and the Karolinska b. Would you expect the data on risks of complications associated with hypothermia (compared to those without hypothermia) from the USA to be generalisable to the UK? **Yes** c. The Billeter et al study is not restricted to patients undergoing abdominal surgery (it also includes patients undergoing orthopaedic, general, thoracic, obs and gyne, and urology surgeries). Would you expect the risks of complications associated with hypothermia in all elective surgeries to be similar to abdominal surgery? **We understand that the impact and cost of SSI to be much greater for Colorectal surgery. There is an association with hypothermia.** 3. One of the studies of HumiGard had an imbalance in the number of patients who underwent surgery for malignancy. Would you expect patients with malignancy to be more/less susceptible to hypothermia compared to those without malignancy? **I have o data on this however our data is mainly for patients with malignancy. We have observed that if the temperature drops intraoperatively and is not salvaged within the first 30 minutes then hypothermia is generally seen in the recovery**	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		area. 4. The manufacturer's model assumes that complications as a result of hypothermia may occur both during the patient's hospital stay or after they have been discharged. Is this a reasonable assumption? **With laparoscopic surgery superficial SSI may present after discharge so this is a reasonable assumption.** 5. The manufacturer estimates that an average of 75 patients would use the HumiGard System in abdominal surgery in each centre per annum in the UK. Do you think this is reasonable? **This is a difficult figure to reach. We are a medium sized DGH carrying out about 150 elective colorectal resections a year. We serve a population of 350,000 people. We have standardised our practice so that all the colorectal surgeons use Humigard. If the assumption is that there are units where teams may have a variable adoption of the technology then 75 may be a reasonable figure for use in the elective setting. I think this is conservative.** **Of course this does not take into account the use of humigard in the emergency setting where heat loss and consequences of the same may be profound.** 6. Are there any patients undergoing abdominal surgery for whom you would not consider using the HumiGard System? **We use this device for all comers.**	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		7. The manufacturer has advised that the use of HumiGard system in laparoscopic and open surgery within the UK NHS has a ratio of around 70:30. However, the two clinical experts who advised the sponsor stated that HumiGard is currently only used for laparoscopic surgery in their centres. Do you agree that the split of 70:30 represents current practice? Do you think this is likely to change in the future? **The open device has not been adopted widely but this is due to lack of knowledge and experience as well as staff training. The latter is key to reaping the benefits of the device in our experience at Colchester.** 8. The manufacturer estimates that training requirements for the implementation of Humigard in a centre would include the training of one senior nurse (7.5 hours) who would then pass on training knowledge to groups of nurses (2.5 hours total time). a. Is it reasonable that only one nurse would receive training directly? **I would suggest pairs who are team leaders** b. Is the time estimate for the senior nurse appropriate? **yes** c. How many other nurses would receive in-house training from the senior nurse and how long would this be expected to last? **The training with appropriate supervision should be around 2.5 hours with a background talk, practical assessment and possible e**	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		learning. d. Would you expect the training to be a 'one-off' event? If not, how often would you expect it to be re-administered? **I think this is a one off training**	
Mason paper	**Sponsor contacted** Query on date for submission for publication of the Mason paper	**From:** Dean Reynecke **Sent:** Thu 14/01/2016 00:40 Hi Paul (*et al*.), many thanks for the message and the update on the process. We've just been sent the latest draft manuscript from the authors of the Mason paper, and it, as well as the figures and tables, have been forwarded to Louise directly from Mason *et al*. This is almost certainly the final draft, and it is for all intents ready for submission to a publisher pending formatting etc., for the appropriate journal. Just as a matter of interest – I am not an author on the paper; I was only an author on the original abstracts which was in the very early stages of the work, due to supplying data on HumiGard. Paul, if there are others that need a copy of this then I can forward it to them as needed. We will notify you as soon as the manuscript is submitted. Kind regards Dean	Noted by the EAC.  RE NICE evaluation of HumiGard.msg

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
Mason paper	**Author of Mason paper contacted** Query on date for submission for publication of the Mason paper and updated version of the paper	**From:** Sam Mason **Sent:** Wed 13/01/2016 22:19 Dear Louise, Dean asked me to send you some of the analysis we have conducted regarding the HumiGard CO2 conditioner for the EAC. I have attached our manuscript and tables. Please be aware this is a draft manuscript and is as yet unpublished. It is currently being prepared for submission for publication and we ask it is not circulated further until in the public domain. Many thanks, Sam Mason --- **From:** Tan Arulampalam **Sent:** Tue 19/01/2016 08:48 Dear Louise I am writing to confirm that the last piece of information that we need to make the paper robust and allow us to submit will be finally available by the end of this week. Although we could submit now, we believe the data	Noted by the EAC.  FW CO2 Conditioning analysis.  {Filename } FW CO2 Conditioning analysis.  RE CO2 Conditioning analysis.msg

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		specifying organ space and superficial infection will add value to the paper. As always deadlines are tight but I am confident that we will achieve this. Yours sincerely Tan Arulampalam	
Koninckx et al. (2013)	**Author of Koninckx et al. (2013) paper contacted** Query on study groups to confirm if the study would meet inclusion criteria	**From:** Philippe Koninckx **Sent:** Thu 14/01/2016 12:47 Dear Dr Duarte, In the control group standard humidification was used at 37°C. In the conditioning group a modified Fisher and Paekel was used in order to deliver fullky humidified gaz at 31° while the abdomen was cooled by sprinkling Sincerely PK	Noted by the EAC.  Re A quick question on your publication J
Clinical submission	**Sponsor contacted** Query on sponsor's clinical submission	**From:** Dean Reynecke **Sent:** Fri 15/01/2016 00:37 Hello Rui – thanks for the e-mail. I have inserted comments below: Could you please clarify the following regarding the submission on clinical evidence:	Noted by the EAC.  RE MT257 Humigard evaluation - Clinical e

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		- How were the mean differences on core temperature change, and on wound area temperature change at end of surgery calculated for the Frey et al. 2012 FPH device study (page 65 of your report submission)? - *This is an interesting question which should be addressed in any study where there is the nuisance factor of autocorrelation; i.e. a lack of independence between successive longitudinal readings or measurements. The simplest way to determine if time has a significant effect is to conduct a repeated measures analysis of variance. This was not the method used in the Frey et al. (2012) paper, however. These authors used an alternative method as stated in the publication: "The mean group temperatures were calculated by using the mean temperature for each patient during the operation, i.e., the area under the curve.* *Thus, the problems of analyzing repetitive measurement as well as differences in operation time between the patients were avoided."* *Basically, each patient has their own temperature response, which can be plotted as temperature against time. The actual area under the curve (AUC) has no meaningful interpretation until the value is divided by the time period (which does not have to be equal for each patient, hence the authors' reference to "differences in operation time between patients*	 RE MT257 Humigard evaluation - Clinical e

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		were avoided"). That is then the average temperature over a given time period lapsed. - Should the hypothermia data provided in the correspondence with Dr Sammour be treated as academic in confidence since this is not reported in the published paper? - *Yes, this should absolutely be treated as academic in confidence since the data were obtained directly from Dr Sammour by Michelle Jenks at YHEC. A copy of this correspondence has been forwarded to Louise Longworth, but I could forward it to you as well, if requested. You could also obtain this data directly from Dr Sammour.* Kind regards Dean et al. _____ **From:** Dean Reynecke **Sent:** Mon 18/01/2016 03:36 Hi Zulian, thanks for clarifying. We have included the information about the Frey et al. (2012) publication you are seeking below, referring to then Frey et al. (2012) study on pg. 65 of the submission: Outcome 1: Core temperature change (primary) *The value of -0.40 was calculated using the values "Core temperature during surgery °C (mean AUC)" in table 1*	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		(Frey paper). That is, 36.1-36.5. The CI was calculated in Revman5 which calculates the 95% CI for the mean difference of 36.1-36.5. The unit is "mean differences during surgery". Outcome 2: Wound area temperature change (primary) *The -1.70 was calculated using "Wound area temperature during surgery °C (mean AUC)" in table 1 (Frey paper). That is, 29.6-31.3. The CI was also calculated in Revman5. The confusing text is the "mean differences at end of surgery" which is incorrectly labelled and should say "mean differences during surgery".* Re: clarification of why those values were chosen. The "Core temperature during surgery °C (mean AUC)" was chosen to best capture the core temperature of patients during surgery with single standard error values. The temperature change could have been calculated using the core temperature values at start of surgery and at end of surgery however the P-value given by the authors could not have been accurately represented in the NICE table. To this end we chose the area under the curve values. The "Wound area temperature during surgery °C (mean AUC)" were chosen to be consistent with the core temperature value. As AUC was chosen prior we wanted to do the same with would area temperature.	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Apologies for our incorrect interpretation of the values you were referring to. Kind regards Dean et al.	
Economic submission	**Expert advisers contacted** Clarification regarding SSI costs and HRG codes used for SSI sought from expert advisers (Mark Harper, Tan Arulampalam)	**From:** Mark Harper **Sent:** Wed 20/01/2016 12:47 Dear Matt, I have to confess that, as I have nothing to do with entering HRG codes, I am no expert on the ones you have presented. However, the first four certainly look correct. E-G may apply to diagnostic laparoscopy but these procedures usually last less than 30 minutes and wouldn't usually justify the use of the Humiguard, I know both the CG65 and MTG7 did costings for SSIs. Can you get hold of these? It may save you some trouble. Kind regards, Mark	Noted by the EAC.  Re NICE MTEP review of HumiGard.n
Mason paper	**Author of Mason paper contacted**	**From:** Sam Mason **Sent:** Wed 20/01/2016 20:40	Noted by the EAC.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
	Request to clarify several queries on the study.	Dear Rui, Sorry for the delayed reply, I have had a rather busy few days at work. I will try to answer your questions in order: 1. The LOS of 8.3 vs 6.4 compares the 123 in the intervention group to the 123 in the control group 2. The Noor paper was a preliminary analysis of our database covering the same timeframe. I have since updated it and performed the comprehensive analysis you see in the manuscript, with slightly different numbers of patients eligible. I would consider the Noor patients a duplicate of those in my study. 3. Again, the Noor study was a preliminary analysis and I have since completed the final data collection, with the accurate LOS presented in the manuscript. 4. With regards to the odds ratio, sorry for the confusion.. the multivariate analysis has been confused for the OR in the manuscript. The correct OR is 0.40 (0.16-1.02, p=0.055). The data for this is 7 of 123 getting SSI in intervention group and 16 of 123 in the control group. The multivariate analysis shows effect size 0.34 (0.12-0.95, p=0.04) 5. Hypothermia numbers were 40 of 70 in the control group and 13 of 101 in the intervention group. Hope these points answer your questions! Thanks,	 Re MT257 Humigard evaluation - Mason pa

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Sam	
Mason paper	**Author of Mason paper contacted** Request to clarify number of patients with hypothermia.	**From:** Sam Mason **Sent:** Fri 22/01/2016 08:43 Dear Jes, The data I gave you for hypothermia is correct. Unfortunately there are less patients in each arm because we were unable to use some of the temperature measurements (they were not strictly taken in recovery). Therefore the analysis for SSI has 123 in each arm and for hypothermia has 70 and 101. Any further data I will need to pull from my database which I won't have access to until later. Hope this helps, Thanks, Sam	Noted by the EAC.  Fwd MT257 Humigard evaluation ·
Clinical submission	**Sponsor contacted** Query on sponsor's clinical submission (Herrmann & De Wilde (2015) paper)	**From:** Dean Reynecke **Sent:** Mon 25/01/2016 03:21 Hi Rui The Herrmann & De Wilde (2015) paper does not mention MEDD. Thank you for highlighting this oversight in our submission. Accordingly, the submission should	Noted by the EAC.  RE HumiGard - morphine equivalent (

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		refer to morphine use only, as we are uncertain of the units of consumption (i.e. absolute dose or dose in mg/kg body weight). We have not obtained any information from the authors. The unit of use referred to in the paper is mg/day (per patient), according to Table 2. Kind regards Dean	