Review report of MTG31: HumiGard for preventing inadvertent perioperative hypothermia

This medical technology guidance was published in 8th February, 2017.

All medical technology guidance is usually reviewed 3 years after publication, unless NICE become aware of significant new information before the expected review date.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance will be updated, amended, remain unchanged (static list) or withdrawn.

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1. Original objective of guidance

To assess the clinical and cost effectiveness of HumiGard for preventing inadvertent perioperative hypothermia.

2. Current guidance recommendations

1.1 HumiGard shows promise for preventing hypothermia during abdominal surgery. There is, however, insufficient robust evidence to support the case for routine adoption, particularly on using HumiGard to avoid important adverse outcomes and on how it affects resource use in open and laparoscopic surgery.

1.2 Research is recommended on HumiGard compared with standard insufflation gases in patients having laparoscopic or open surgery alongside general measures to reduce the risk of perioperative hypothermia described in section 2.5. 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.

3. Methods of review

3.1 Aims of review

The initial review of HumiGard (*Review of MTG31: HumiGard for preventing inadvertent perioperative hypothermia*) identified a relatively large body of literature that has been published since the publication of MTG31 in February 2017 (NICE, 2017). The aim of this review report is to summarise this evidence and to evaluate the requirement for full review. Key areas of uncertainty that were identified by the Medical Technologies Advisory Committee (MTAC) during the development of MTG31 were the lack of direct evidence on HumiGard in preventing complications (and related healthcare resource use such as length of stay) and a lack of evidence in children and high-risk groups (NICE, 2017). The EAC notes that evidence from meta-analyses described in the Assessment Report did not unequivocally show that HumiGard improves temperature control or prevents hypothermia (Duarte *et al.*, 2016). Evidence was particularly lacking in patients undergoing open surgery. Therefore, the EAC has focussed on how new evidence addresses the following issues:

- The impact of HumiGard on core body temperature and prevention of hypothermia in patients undergoing laparoscopic or open abdominal surgery.
- The use of HumiGard in children and high-risk patient groups.
- Direct evidence showing HumiGard reduces peri- and post-surgical complications.
- Direct evidence on the impact of HumiGard on healthcare resource use.

This review will not assess the evidence base linking inadvertent hypothermia with surgical complications (indirect evidence of the effectiveness of HumiGard), as this is beyond the scope of the review.

3.2 Literature sifting and searching

The NICE Information Services (IS) identified 2,139 potentially relevant studies from their literature search (detailed in Appendix D). The EAC used a semi-automatic method to de-duplicate these studies and identified 1,333 studies potentially in scope. A single reviewer (IW) sifted these studies and identified 32 records as being potentially in scope based on their title and abstract (see Table 3.1). Full records were retrieved for these studies and after further sifting 11 studies were identified and included as being in scope (Figure 3.1). Reasons for exclusion of full papers are reported in Table E1 (Appendix E).

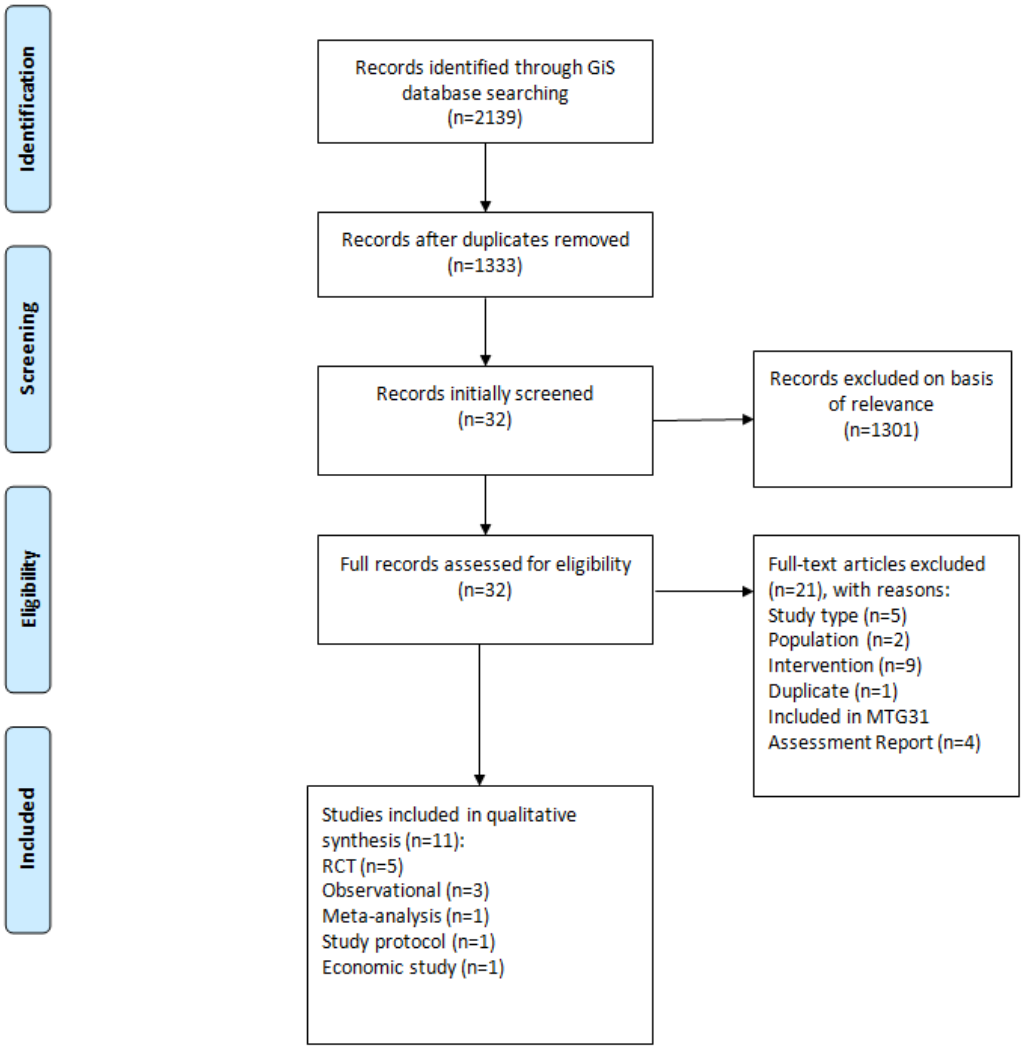
Table 3.1. *Selection criteria used for sifting.*

	Inclusion criteria	Exclusion criteria
Population	People undergoing abdominal surgery, as an open or laparoscopic procedure	Non-abdominal surgery
Intervention	HumiGard surgical humidification system for open or laparoscopic abdominal surgery	Other surgical humidification systems Non-abdominal surgery
Comparator	Standard care Open abdominal surgery: • No insufflant Laparoscopic abdominal surgery: • Unheated, unhumidified insufflant gas	No comparators explicitly excluded. Single-armed studies to be included
Outcomes	The outcome measures to consider include: • Incidence of hypothermia in the intra- and post-operative period (defined as a core body temperature <36°C) • Incidence of surgical site infections • Length of stay in post-operative recovery • Total length of hospital stay • Device-related adverse events • Patient-reported pain	Other outcomes to consider if relevant to the decision problem or economic analysis.
Subgroups to be considered	• People receiving adjunctive warming, such as from forced air warming devices or warming mattresses • High-risk groups as described in NICE guideline 65 (any 2 of: ASA grades II-V, preoperative temperature below 36°C, combined general and regional anaesthesia, major or intermediate surgery or at risk of cardiovascular complications)	
Study design	• Primary research involving human participants • Systematic review with meta-analyses	• Bench tests and animal studies • Non-systematic reviews, editorials, letters, commentaries.
Abbreviations: ASA, American Society of Anesthesiologists Physical Status.		

In addition to the IS literature search, studies identified by the company were considered. All the studies identified in the IS search were also identified by the company. The company also identified an additional 4 studies that were not considered to be in scope by the EAC. Two were excluded because they were bench tests not involving human participants (Kokhanenko et al., 2017, Baumann and Cater, 2018); one was a narrative review (Cheong *et al.*, 2017); and one was a systematic review that was not specific to HumiGard (Cheong *et al.*, 2018). The company also identified two studies not identified by the IS search. One was a prospective cohort study, published in abstract form only, that was included by the EAC (Dimache *et al.*, 2018). The other study was a conference video, to which the EAC did not have access (https://vimeopro.com/soba/key-issues-2018/video/309715056).

The clinical experts identified no additional relevant studies.

Figure 3.1. *PRISMA diagram illustrating search and sifting results.*



4. New evidence

4.1. Changes in technology

The company has confirmed that the HumiGard is currently available to the NHS. Current models are the SH870 Surgical Humidification System used with ST320 Humidified Insufflation kit (consumables). These have superseded the MR860 Surgical Humidifier and ST310 kits, which are no longer available. The product has a valid CE certificate until May. The company states there are no significant changes to the technology between current and predecessor systems.

4.2. Changes in care pathways

There is relevant NICE clinical guidance entitled *Hypothermia: prevention and management in adults having surgery* (CG65) (NICE, 2008). This guidance recommends using a mixture of methods to keep the patient warm prior to, during, and immediately after surgery to reduce the likelihood of discomfort and complications. Specifically, temperatures above 36.0 ºC should be maintained preoperatively; 36.5 ºC intra-operatively; and 36.0 ºC post-operatively. Methods to achieve this include regular temperature monitoring; adequate ambient temperature; use of warmed intravenous fluids and irrigation fluids; use of forced air warming devices; and use of actively warmed mattresses.

4.3. Results from the MTEP research commissioning workstream

Two projects have resulted from the MTEP research commissioning workstream, both awarded to Cedar EAC. The first of these was a technical evaluation, predating MTG31 (reported December 2015). It answered four questions from MTEP using a literature review, a user survey, and company documentation. The summary of findings was as follows:

- “There may be some tissue discolouration visible when using HumiGard in open surgery, but trained users do not find this problematic.
- There is no reason to believe that HumiGard adds undue complexity or restricts the field of vision during open surgery.
- The single use nature of the administration set and the use of filters makes it unlikely that HumiGard will cause bacterial contamination during surgery. The administration set is not entirely sterile, meaning that there is a possibility of contamination entering the system during setup. The company has submitted a test report to demonstrate that bacteria are not transmitted from the reservoir or sensor to the patient. No evidence has been identified that indicates any increase in infection rates.”

The second project was to design a randomised controlled trial (RCT) with the stated aims of determining if “insufflation with warmed, humidified CO_2 using the HumiGard device, alongside standard perioperative warming techniques, can improve patient recovery, including pain, surgical site infections, complications, and the use of analgesia compared with standard care alone”. The protocol for this study has been published in *JMIR Research Protocols* (Ryczek *et al.*, 2019). A pilot study, the *HumiGard Evaluation Study* (HEAT), registered with ClinicalTrials.gov (NCT04164706), intends to recruit 40 participants and randomise them to HumiGard or sham (HumiGard with no heating). This study was due for completion in October 30th 2020, but no results have been published yet.

4.4. Description of new studies

The 11 new studies consisted of 5 RCTs, 3 observational studies, a meta-analysis, a cost-utility study, and a study protocol.

Randomised controlled trials

Table B1 shows the characteristics of the 5 included RCTs. Two RCTs enrolled patients receiving abdominal laparoscopic procedures (Oderda *et al.*, 2019, Matsuzaki *et al.*, 2017), and 3 were in patients receiving open abdominal surgery (Weinberg *et al.*, 2017, Kalev *et al.*, 2020, Cheong *et al.*, 2019). The RCT by Weinberg *et al.* (2017) had been previously included as a poster abstract in the original Assessment Report (Duarte *et al.*, 2016), but has since been published in full, so is included in this review report.

The study by Oderda *et al.* (2019,) was done in a single centre in Italy that evenly randomised 64 men undergoing robot-assisted radical prostatectomy (a laparoscopic procedure) to treatment with standard insufflation (cold, dry CO_2) or insufflation mediated by HumiGard. Both groups also received forced air warming. The randomisation procedure appears to have been adequate, but the study did not conceal allocation and was open-label, so there was a risk of bias (selection, performance, detection). The primary outcome of the study was core body temperature. Secondary outcomes included biochemistry, pain scores, procedural times, and clinical complications.

The study by Matsuzaki *et al.* (2017) was a prospective parallel RCT enrolling women undergoing laparoscopic subtotal hysterectomy in a single centre in France. The study adopted a 2x2 factorial design to measure the effects of CO_2 pressure as well as warmth and humidity (through the use of HumiGard); with about 20 participants in each of the 4 groups The primary outcome of the study was the expression levels of 12 genes (4 adhesion-formation-related genes, 4 inflammation-related genes, and 4 hyaluronan [HA]-related genes), which is not in the scope of this review. Secondary outcomes were mainly in scope and consisted of the quality of postoperative recovery: postoperative pain, intraoperative core body temperature; and intraoperative and postoperative complications. The main limitation of this study was the small sample size, with around 20 participants in each arm.

The study by Kalev *et al.* (2020) was published in German and only available in English as an abstract. Fifty patients undergoing open resection for colorectal cancer were randomised to receive HumiGard or control (unspecified, presumed standard care). The risk of bias in this study could not be assessed. Outcomes included body core temperature and wound temperature. The proportion of patients with surgical complications was also reported.

The study by Cheong *et al.* (2019) enrolled 40 patients undergoing elective resection of the colon via a midline laparotomy (an open surgical procedure). The indication for surgery was varied and not restricted to colon cancer. Patients were randomised to receive warm gas insufflation with HumiGard or standard care (no insufflation). Patients and investigators were blinded to allocation; treating clinicians were not. The primary objective of the study was to detect differences in cytokine and chemokine concentrations and detection of peritoneal tissue apoptosis (out of scope). Secondary outcomes included surgical outcomes, complication rates, and hospital length of stay (LoS).

The study by Weinberg *et al.* (2017) had been available to the authors of the original Assessment Report as an abstract, but has since been published in full, and thus is described here. The study, described as a pilot study, was conducted in patients undergoing orthotopic liver transplantation, which is known to affect patient thermoregulation. Twenty-two patients were evenly randomised to receive standard care alone (which included the use of an underbody warming blanket) or standard care combined with HumiGard. A computer generated random block allocation system was used, with concealment of allocation. All parties were blinded where practical (including patients, postsurgical clinicians, and investigators). The primary endpoint was defined as core temperature measured with a nasopharyngeal temperature probe 5 minutes prior to reperfusion of the donor liver. Secondary outcomes were core temperature at other stages of the operation. No clinical outcomes were reported.

Comparative observational studies

Four non-randomised comparative studies were identified, all of which were in patients receiving some form of laparoscopic surgery.

The study by Wittenborn *et al.* (2019) was a retrospective cohort study that aimed to compare patients who were undergoing laparoscopic surgery who had received HumiGard after its introduction in a single hospital with those who had not (before its introduction). Patients were matched (n = 33 in each group) for surgical duration and smoking status. The primary outcome of the study was change on core temperature and the proportion of hypothermic patients.

Liu *et al.* (2019) performed a retrospective observational study in patients undergoing laparoscopic colon resection in the treatment of colonic cancer. The intervention group (n = 125) received standard care combined with HumiGard whereas the control group received standard care with cold, dry CO_2 (n = 120). The groups were not statistically matched, although no differences in patient characteristics were apparent. Outcomes were derived from routine data and included intraoperative hemodynamic data, arterial blood pH, and lactic acid levels. Additionally, limited post-operative clinical data was analysed. However, clinical outcomes relevant to the scope and body core temperature changes were not reported.

The study by Dimache *et al.* (2020) was described as a prospective cohort study, but was available in abstract form only. The study enrolled 120 women undergoing gynaecological laparoscopic surgery expected to last more than 90 minutes. Sixty patients were assigned to the HumiGard group and 60 to the control group. The mean core temperature loss was measured and compared in each group, as well as LoS in the Anaesthesia Care Unit.

The study by Mason *et al.* (2017) was available to Birmingham and Brunel (B&B) EAC (the authors of the original Assessment Report) as an abstract and unpublished manuscript only. It has since been published in full and thus is included in this review. This was a retrospective observational study set in a single centre in the United Kingdom (Colchester Hospital). Patients were enrolled if they were undergoing elective laparoscopic colorectal resection, and assigned to the intervention group (peritoneal insufflation with HumiGard, n = 123) or control group (cold, dry, CO_2 peritoneal insufflation, n = 123) for analysis. The control group were historical from a period before the service provision changed to include HumiGard. No statistical matching was performed, although no significant differences in patient characteristics were reported. The study had two principal endpoints; the proportion of patients in each group with postsurgical hypothermia and the proportion diagnosed with surgical site infections. A cost analysis was also reported.

Meta-analyses

In 2016, Frey *et al.* reported a meta-analysis of two RCTs on HumiGard (Frey *et al.*, 2016). Both the included studies, which were by the same author, had been included in the original Assessment Report by B&B EAC, with data being collected from the same single-centre in Sweden (Frey et al., 2012a, Frey et al., 2012b). Patients from the RCTs had undergone elective major open colon surgery and been randomised to a group receiving HumiGard (n = 80) or control (n = 78). The aim of the study was to evaluate if HumiGard affected long-term all-cause mortality and morbidity, and the factors affecting this. The principal outcome was mortality measured using survival analysis. Univariate and multivariate analysis was performed in order to calculate hazard ratios in the cohort overall.

Economic analysis

The cost-utility analysis by Jenks *et al.* (2017) had been identified in the original Assessment Report, but was only available as an abstract. It has since been published in full and so is included in this review (Jenks *et al.*, 2017). The authors of this study, York Health Economics Consortium (YHEC), were also the authors of the *de novo* economic model used in the company's submission. The study by Jenks *et al.* (2017) reported on the same model, but adapted it from a cost-consequence to a cost-effectiveness framework, introducing quality of life (QoL) utilities to the heath states. These values were derived by applying disutilities to patients experiencing complications.

Study protocol

The sole relevant study protocol identified by the literature search was from Cedar EAC as part of the MTEP facilitation programme (Section 4.3). Other ongoing studies are described in Section 4.6.

4.5 Results of new studies

This section reports on results from the recently published studies according to the outcomes outlined in the scope. Additional outcomes not in scope are also briefly discussed.

Incidence of hypothermia

The incidence of hypothermia was defined as patients having a core body temperature of less than 36ºC in the intra- and post-operative period, consistent with NICE clinical guidelines, CG65 (NICE, 2008).

Two studies directly reported on this outcome. The principal study of interest was by Mason *et al.* (2017), as it was set in the UK. This study was available as an Academic in Confidence (AiC) abstract in the original Assessment Report by B&B, but has since been published in full. The EAC has validated the data reported with those used in the economic model and confirmed they are similar, but not identical (Section 4.7). This was a retrospective cohort study (n = 246) that reviewed the records of patients undergoing laparoscopic resection of the colon who received either warm, humidified peritoneal CO_2 insufflation with HumiGard or cold, dry peritoneal insufflation with CO_2. The patients' post-surgical core body temperature in both groups was measured in the recovery suite. In the intervention group, 16/123 (13%) were reported as hypothermic compared with 70/123 (53%) in the control group ($p \leq 0.001$). However, this study had several limitations, including:

- This was a retrospective cohort study of patient records and was therefore prone to confounding. The intervention and control groups were not matched, although both were consecutively recruited during similar durations.

- Only the post-surgical temperature was taken, because "temperature intraoperatively was not standardised and therefore could not be included in this analysis". The temperature that was reported used a tympanic probe which lacks the accuracy of other methods of temperature measurement, and exhibits inherent intra-patient variability (Giuliano *et al.*, 1999).

- The authors did not report the actual temperatures of the cohorts (mean and median average, and distributional data), and instead reported only dichotomised data, with values below 36°C considered hypothermic. The justification for this threshold was not reported.

During the study by Wittenborn *et al.* (2019), temperature was measured pre-procedurally using an oesophageal probe. Hypothermia was defined as temperature ≤ 36 ºC. The authors reported that in the study group (HumiGard), the proportion of patients with hypothermia fell from more than 54% at the start of surgery to 36% immediately after surgery. The proportion of patients with hypothermia in the control increased from 36% to 42%. The statistical significance of this was not reported. It is

unclear why the proportion of hypothermic patients was so high at the start of surgery, particularly in the HumiGard group. The authors speculated that it was probably due to inadequate pre-warming in the study group. One concern about this study was selection bias, because it focused on a particular subgroup (long operations, no other warming methods), and it was not clear whether results can be generalised.

In the absence of other studies directly reporting the incidence of hypothermia, the EAC has extracted all temperature data reported in the included studies (Table B3). Four RCTs reported on temperature as an outcome: 2 on patients undergoing laparoscopic surgery (Matsuzaki *et al.*, 2017, Oderda *et al.*, 2019); and 2 on patients undergoing open surgery (Kalev *et al.*, 2020, Weinberg *et al.*, 2017).

The study by Oderda *et al.* (2019) recorded core body temperature before, during, and after surgery using an oesophageal probe (an accurate measurement of core body temperature). Mean temperature was non- significantly higher in the HumiGard group at all time-points. The largest difference in mean temperature reported was 0.27°C 4 hours into the operation. Matsuzaki *et al.* (2017) reported similar outcomes using an oesophageal probe. There were mainly slight differences in body core temperature in patients insufflated with HumiGard compared with cool, dry CO_2 (typically 0.1 °C).

Kalev *et al.* (2020) reported only a marginal difference in body core temperature between HumiGard and control following surgery (0.2 °C). However, there was a significant increase in wound temperature (0.9 °C, $p < 0.001$), although the clinical importance of this is not clear. Weinberg *et al.* (2017) made extensive observations of temperature throughout liver transplant operations. There were no significant differences in core body temperature measured centrally (pulmonary artery catheter). There were significant increases in temperature associated with HumiGard at some, but not all, time points when peripheral temperature via a nasopharangeal probe were compared.

Two additional studies reported body core temperatures during and after laparoscopic procedures. Wittenborn *et al.* (2019) reported an upwards trend in temperature during surgery when HumiGard was used, in contrast to a downward trend associated with the control (cool, dry CO_2 insufflation). These results are difficult to interpret because the control group had higher mean core body temperature at baseline, and there was only 0.3 °C difference at the end of the procedure. Limited data from Dimache *et al.* (2018) reported greater heat loss in the control group compared with the HumiGard group (0.1 °C vs. 4 °C, $p = 0.005$).

One meta-analysis of two RCTs in patients undergoing laparoscopic colonic resection (Frey *et al.*, 2016) reported 0.3 °C higher mean core temperature at the end of surgery in the HumiGard group compared with the control (36.2 ± 0.6 °C [SD] vs. 35.9 ± 0.5 °C, $p = 0.005$). There was a greater proportion of normothermic

patients (patients ≥36 °C); with 64.6% in the HumiGard group compared with 42.7% in the control group (p = 0.006). Wound temperatures were also significantly higher in the HumiGard group.

Incidence of surgical site infections

The incidence of surgical site infections (SSIs) was reported in one primary study (Mason *et al.*, 2017). In patients undergoing laparoscopic resection of the colon, 16 patients (13.0%) in the control group (cool, dry CO_2 insufflation) developed SSIs compared with 7 (5.7%) in the intervention group (HumiGard). This was reported as statistically significant using the Chi-squared test ($p < 0.05$). The odds ratio (OR) for developing an SSI with the intervention was 0.34 (95% CI 0.12 to 0.95) compared with the control (p = 0.04). Additionally, it was noted that hypothermic patients had increased probability of developing an SSI in the cohort overall compared with non-hypothermic patients (OR 4.0, 95 %CI 1.25 to 12.9, p = 0.02).

Secondary evidence from the meta-analysis by Frey *et al.* (2016) reported 13/80 patients in the HumiGard group (16.3%) had an SSI compared with 13/78 in the control group (16.7%). This difference was not significant (p = 0.944).

Length of stay in post-operative recovery

This outcome was reported in the study by Liu *et al.* (2019). In the intervention group (HumiGard), the mean amount of time spent in the post-anaesthesia care unit (PACU) was 25.17 minutes (± 5.45 minutes [SD]). This compared with 36.74 ± 9.02 minutes in the control group, which was reported as significantly longer (p = 0.012). However, differences in high-dependency recovery suites were not observed in two RCTs. One RCT reported there was no difference in the “duration of stay in ICU [intensive care unit]” between intervention and control groups (Weinberg *et al.*, 2017). Another RCT did not identify any differences in PACU LoS in any of the patient arms (Matsuzaki *et al.*, 2017).

Total length of hospital stay (LoS)

Three RCTs reported on LoS. Oderda *et al.* (2019) reported there was no significant difference in LoS between intervention and comparator groups, with a mean LoS of 3.5 ±1.3 days in the HumiGard group compared with 3.5 ± 1.7 days in the control group (p = 0.529). Cheong *et al.* (2017) reported a mean LoS of 15.1 days in the HumiGard group compared with 16.6 days in the control group (p = 0.76). Matsuzaki *et al.* (2017) stated “[there was] no significant difference in the length of hospital stay between the 12-mmHg IPP [intraperitoneal pressure] and 8-mmHg IPP groups or between the WH [warm humid] gas and CD [cold dry] gas groups”. The authors highlighted that LoS was related to many factors other than the use of insufflation technologies.

The UK retrospective observation study reported that patients receiving HumiGard had a shorter median LoS (6.4 days) than those receiving the control (8.3 days). However, this difference was not significant (p = 0.11) (Mason *et al.*, 2017). However, the authors did report that the presence of SSI was associated with longer LoS (p = 0.002).

Device-related adverse events

Two RCTs reported on adverse events of outcomes. One study reported that 3 patients (9.3%) experienced adverse events in the intervention group, 2 of which were serious (Clavien-Dindo [CD] grade III); these were intraoperative small bowel perforation (n = 1) and intraoperative haemorrhage (n = 1). This compared with 1 case of intraoperative ureteral injury in the control group (CD grade III) (Oderda *et al.*, 2019). Another RCT reported a similar incidence of complications in both arms (Cheong *et al.*, 2019). In both these studies, it is unlikely the adverse events documented were directly attributable the technology.

Patient-reported pain

Two studies, both RCTs, reported pain scores. The study by Oderda *et al.* (2019), reported extensively on patient perceptions of pain using a numeric rating scale (NRS) system. The following pain scores were measured on awakening; at 12 hours; at 24 hours; and at 48 hours:

- Pain at rest: no significant difference (p = 0.160).
- Pain on coughing: no significant difference (p = 0.205).
- Pain on walking: no significant difference (p = 0.582).
- Shoulder pain: no significant difference (p = 0.687).

Oderda *et al.* (2019) also reported there were no significant differences between groups in shivering (p = 0.925) or Aldrete score (p = 0.931) on waking.

Matsuzaki *et al.* (2017) measured pain perception using the pain domain of the QoR-40 system (which assesses quality of recovery from surgery) and the visual analogue scale (VAS). There was a small reduction in pain in the HumiGard groups relative to the control groups of -0.2 (95% CI -0.6 to 0.2), but this was not significant (p = 0.23). The proportion of people with a VAS score ≥30 was 68% in the HumiGard groups compared with 71% in the control groups, giving an OR 0.83 (95% CI 0.32 to 2.13, p = 0.70).

The RCT by Cheong *et al.* (2017) included postoperative pain (morphine equivalent daily dose score) and duration of patient-controlled analgesia use (measured in days) as outcomes. However, actual results were not reported,.

None of the other studies reported on pain.

Other outcomes

The RCT by Oderda *et al.* (2019) reported there were no significant differences between groups in the following outcomes: serum interleukin-6 (IL-6); serum tumour necrosis factor alpha (TNFα); intraoperative blood gas parameters (pH, pCO_2, HCO_3, potassium, calcium, and lactate); and patient satisfaction. Matsuzaki *et al.* (2017) reported some significant differences between the arms in gene expression suggesting that HumiGard may help suppress an inflammatory response; however the primary outcome was a surrogate measure and its relationship to clinical outcomes has not been demonstrated. Cheong *et al.* (2017) reported greater "oxidative damage" (3-chlorotyrosine/tyrosine ratio) in the control group compared with the HumiGard group, but this is a surrogate outcome and its relationship with clinical outcomes was not demonstrated. Weinberg *et al.* (2017) did not identify any significant differences in procedural outcomes between groups.

The principal outcome of interest in the identified meta-analysis was mortality (Frey *et al.*, 2016). The authors reported the cumulative survival was not significantly different between HumiGard and control groups over 8 years follow up ($p = 0.508$). However, the cumulative survival rate was significantly lower in patients who had hypothermia following surgery compared with those who with normothermia ($p = 0.035$). Final wound edge temperature and age were also associated with death over the period of the study.

Economic outcomes

The retrospective observational study by Mason *et al.* (2017) reported that HumiGard was associated with costs of £171 compared with £391 for the control group (average saving of £155). The main driver of this saving was the greater incidence of SSIs in the control group compared with the HumiGard group, with estimated associated costs of £48,093 compared with £21,033. It is not possible to appraise this analysis based on the data reported.

The cost-utility analysis by Jenks *et al.* (2017) reported that for laparoscopic surgery, savings of £345 and incremental QALYs of 0.001 per patient were estimated in favour of HumiGard. Cost savings were related to the lower incidence of SSIs. For open surgery, savings of £20 and incremental QALYs of 0.013 were estimated per patient. Savings related to a lower rate of a variety of complications, such as stroke and myocardial infarction. Thus insufflation of warmed humidified CO_2 with HumiGard dominated standard care in both laparoscopic and open surgical scenarios.

Subgroups

Two subgroups were specified in the scope as being of special interest:

- “People receiving adjunctive warming, such as from forced air warming devices or warming mattresses”. All the primary studies identified compared HumiGard against standard care, which typically included adjunctive warming methods.

- “High-risk groups as described in NICE guideline 65 (any 2 of: ASA grades II-V, preoperative temperature below 36°C, combined general and regional anaesthesia, major or intermediate surgery or at risk of cardiovascular complications)”. None of the studies identified focussed specifically on high-risk subgroups or reported subgroup analyses in these groups.

4.6. Ongoing trials

One ongoing trial was identified directly from the literature. This was the protocol from Cedar EAC, from the MTEP research commissioning work stream (Section 4.3). Results from this study would be instrumental in informing the clinical effectiveness and cost-effectiveness of HumiGard in the NHS of England and Wales.

A top-level search of ClinicalTrials.gov identified one study that had not been otherwise identified by the literature search (also identified by the company). The Temperature and Pain in Laparoscopy (TePaLa) trial is an ongoing parallel, double-blinded RCT that has three treatment arms (NCT02781194). Patients are eligible if they are females undergoing laparoscopic surgery scheduled to last ≥ 1 hour. Patients will be randomised to receive a forced-air warming blanket ("Bair Hugger", 3M); warm, humid CO_2 insufflation with HumiGard; or both interventions. One hundred and fifty patients are expected to be enrolled. The primary outcome is intra-operative core temperature, stratified into 3 categories of hypothermia severity (Mild [core temperature 35.0 °C to 35.9 °C], Moderate [34.0 °C to 34.9 °C], or Severe [≤33.9°C]). Secondary outcomes will include pain perception using VAS, morphine equivalent daily dose, perioperative fluid use, and fibrinolytic activity. The trial was due for completion in September 2018; however, its results have not been published on the ClinicalTrials.gov protocol website. However, the company provided raw data from this study; this has not been analysed by Newcastle EAC.

A top-level search of the Australian New Zealand Clinical Trials Registry (ANZCTR) returned 10 hits for "HumiGard"). These records were examined and 6 were excluded for the following reasons:

- Two studies were on patients receiving open thoracic surgery, which is out of scope (ACTRN12618001613291 and ACTRN12618000473268).
- One study did not report relevant outcomes (ACTRN12618000818235)
- One study had been withdrawn (ACTRN12618001419257).
- Two studies (ACTRN12616001631493, ACTRN12619001570178) had been published and have already been included in this review (Cheong *et al.*, 2019, Weinberg *et al.*, 2017).

Possibly the study with the most potential to impact on MTG31 is the study by Arachchi (ACTRN12620000269932), which describes the protocol for an RCT enrolling patients undergoing elective open surgery (n = 298) to be randomised to management with or without HumiGard. The primary outcome of this study is the incidence of SSIs, the reduction of which is an important claimed benefit of HumiGard, and a key factor in the economic analysis. However, no patients have yet been recruited, no anticipated completion date has been reported, and the protocol

has not been updated for over 1 year (November 2019). The study by Hii, an RCT enrolling patients undergoing laparoscopic or elective surgery (n = 120) may also be informative (ACTRN12617000850370). This study is anticipated to complete patient recruitment presently (December 2020), although the protocol has also not been updated for over 1 year (November 2019).

A summary of all the relevant ongoing trials is reported in Table C1.

4.7. Changes in cost case

Clinical effectiveness parameters

The *de novo* economic model, produced by YHEC EAC, the structure of which has been peer-reviewed and published (Jenks *et al.*, 2017), reported on costs associated with complications arising as a result of intra- and post- operative hypothermia. The model was a blend of two scenarios reflecting costs associated with laparoscopic and open surgery. These scenarios were separated by B&B EAC and were considered separately. See Figure 4.1a and b.

For the laparoscopy cohort of the model, the complications were the incidence of SSI and pneumonia, the value for which was derived directly from a retrospective observational study. This was available as an abstract only at the time of MTG31 (Noor *et al.*, 2015), but has since been published in full (Mason *et al.*, 2017). In the abstract, the incidence of SSI was reported as reducing from 12% to 4.7% with HumiGard (p=0.047). This differs slightly from the full publication, which reports a reduction from 13.0% (16/123) to 5.7% (7/123), $p < 0.05$. For the incidence of pneumonia, the authors of the abstract reported a "non-significant reduction in pneumonia was observed using HumiGard (4 patients vs 1 patient, $p = 0.21$)". These data were not reported in the full study. Newcastle EAC notes that the study did not involve a randomised design and confounding factors, not included in their multivariate analysis, may have influenced the measured effect size. The data used to inform pneumonia in particular was not robust, as it was based on very low event numbers.

Figure 4.1a. *Laparoscopic surgery cohort of de novo model.*

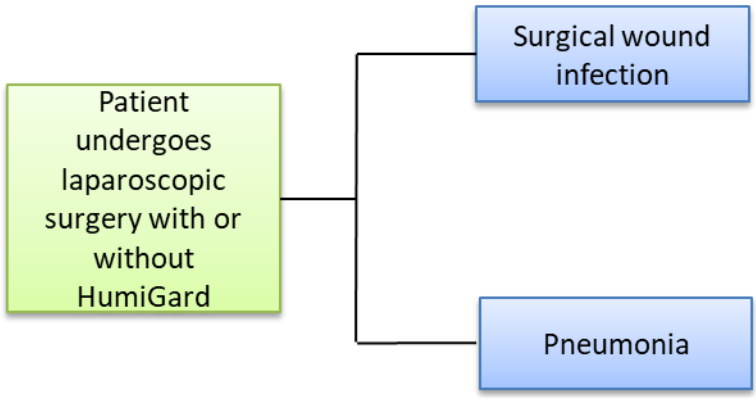
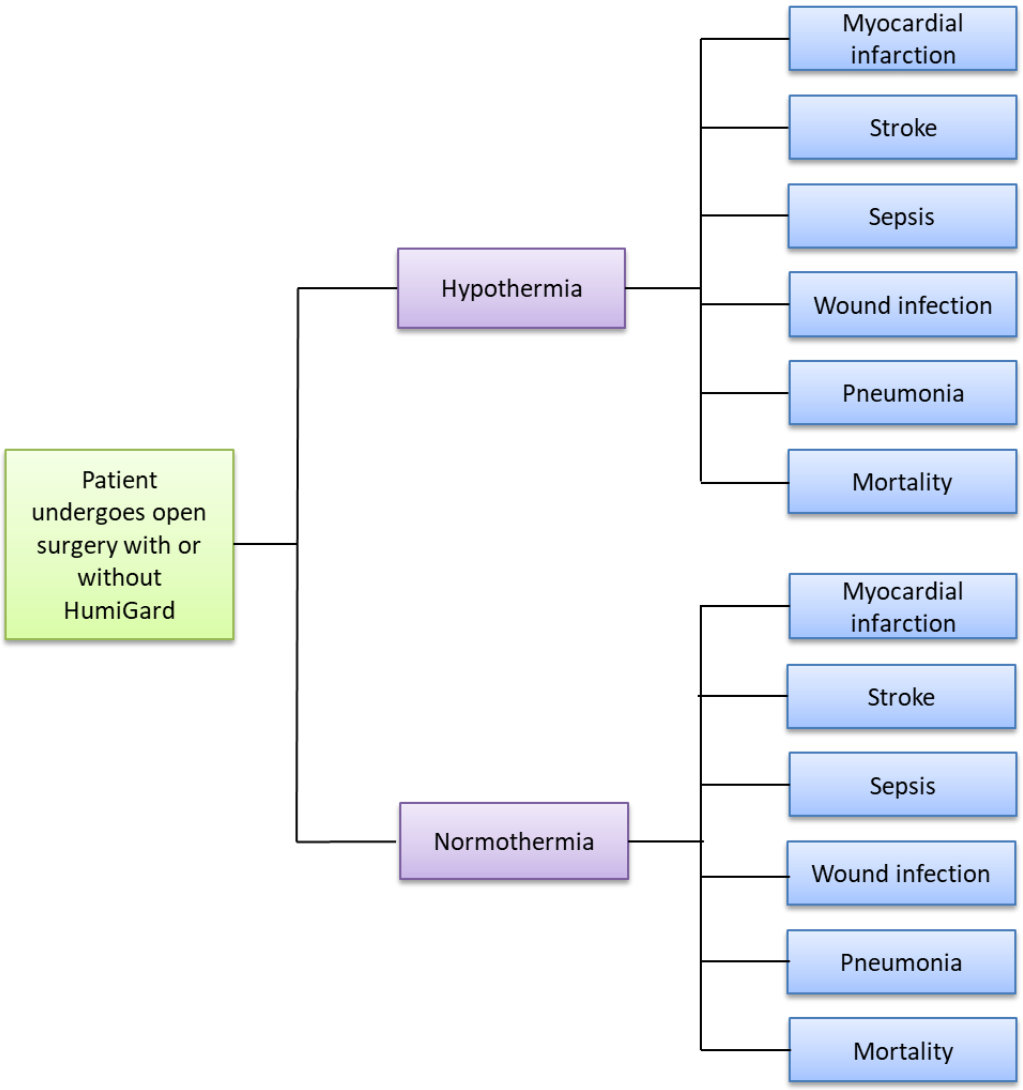


Figure 4.1b. *Open surgery cohort of de novo model.*



For the open surgery cohort of the model, complications were derived through linkage to a retrospective observational study of routine data sources (Billeter *et al.*, 2014). This approach of economic analysis required some assumptions and has limitations. As a general point, the most fundamental assumption was that the incidence complications observed in the Billeter *et al.* (2014) study were exclusively related to hypothermia, and not to other factors: that is, it was a causal relationship, and complications would be prevented through corporeal warming in a linear manner. In line with this, the model assumes that HumiGard is effective at preventing hypothermia in open surgery. However, there is little experimental evidence from RCTs to demonstrate this. Specific limitations of the study by Billeter *et al.* (2014) include the definition of hypothermia used was core body temperature ≤35°C in patients in post-surgical recovery. However, this is relatively severe hypothermia which was not in line with the studies of HumiGard, or NICE clinical guidelines, which define patient hypothermia as a core body temperature ≤36°C (NICE, 2008). It is likely that patients with severe hypothermia are more likely to suffer complications

than those with mild hypothermia, and may have additional comorbidities. An additional limitation of the generalisability of this study was that only a minority of patients had abdominal surgery, in line with the scope. Other forms of surgery may be more susceptible to complications.

The clinical experts at MTAC appeared to be in agreement that the data from the Billeter *et al.* (2014) study was unlikely to be generalisable. For instance, the experts stated "risk of stroke during abdominal surgery is very low", and would not approach the levels of 1% (HumiGard patients) or 6.5% (standard care patients) used in the model. It was beyond the scope of this review to identify other studies reporting on the association between inadvertent hypothermia and complications; nevertheless in the opinion of Newcastle EAC this probably remains the biggest source of uncertainty (see Implications for update).

Cost parameters

The company has informed that there have been no changes to the costs of the technology and consumables since the publication of MTG31. This has not been verified, since the HumiGard system is not on the NHS Supply Chain.

The complications, which were costed assuming a 1 year timeframe in the company's base case, and up to 5 years in sensitivity analyses, were myocardial infarction (MI); stroke; sepsis; wound infection; pneumonia; and mortality. The costs associated with these complications are briefly summarised:

- Surgical site infections: these were derived from a weighted average of NHS reference costs, "Infections or Other Complications of Procedures, with Multiple Interventions", codes WH07A to 7G. An alternative estimate based on a UK observational study (Jenks *et al.*, 2014, conference abstract) was also included by B&B EAC in sensitivity analysis.

- Myocardial infarction (non-acute): long-term management costs were derived from NICE clinical guidelines on *Hypertension*, inflated to 2013/2014 prices using the Hospital & Community Health Services pay and Prices Index. It was recognised by B&B EAC that the components of this cost included micro-costing of drugs which have substantially reduced in price due to the availability of generics. These were corrected for by B&B using up-to-date data.

- Stroke (non-acute): B&B adopted stoke costs based on a UK population-cohort study (Luengo-Fernandez *et al.*, 2012). This differed from the estimate used by the company which was based on NICE Technology Assessment on dabigatran etexilate (2012).

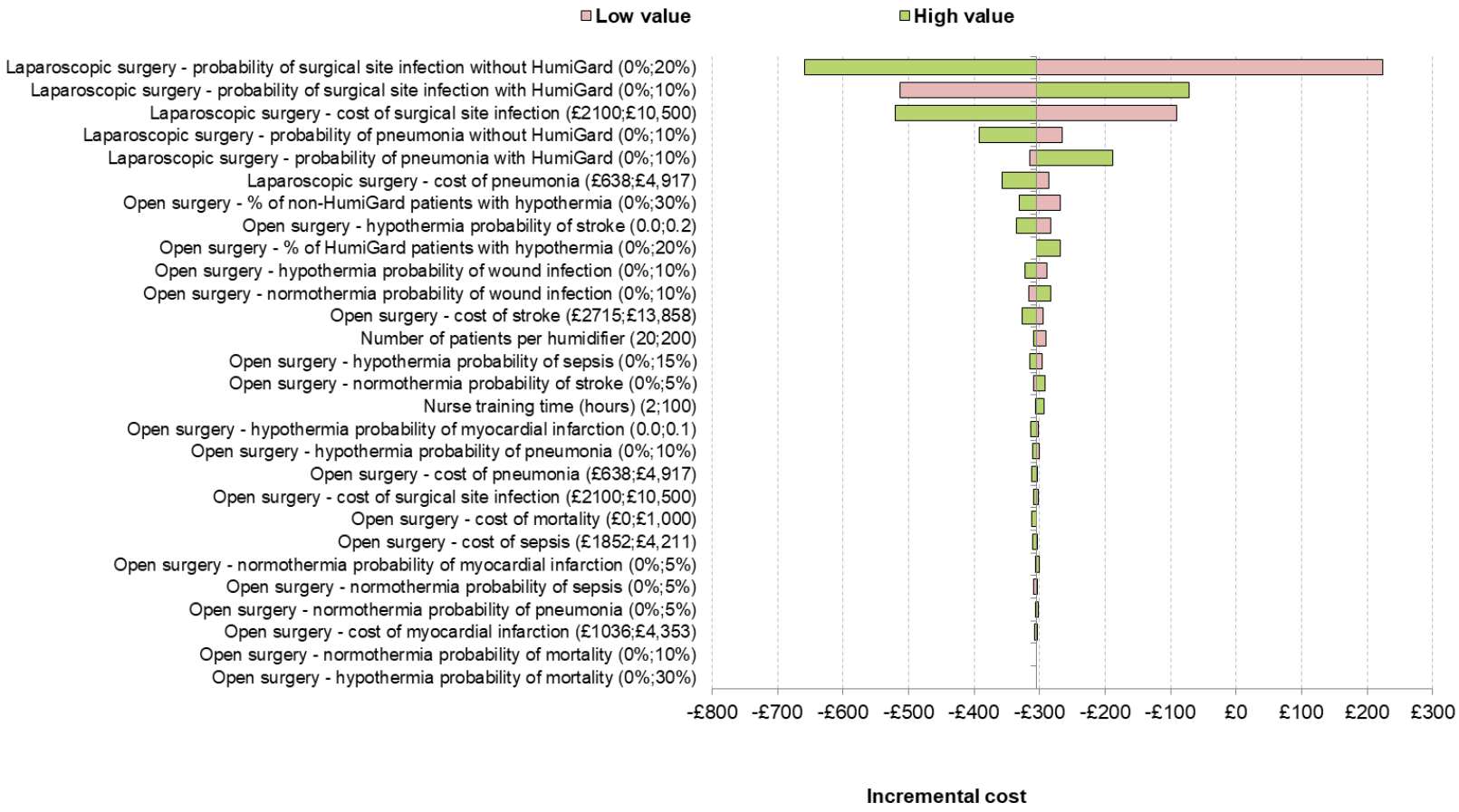
- Other complication costs: the company based costs of acute inpatient stays for MI; stroke; pneumonia; and sepsis were all based on weighted average values derived from NHS reference sources. B&B EAC did not re-evaluate these costs.

Estimating the cost of complications to the NHS and personal social services (PSS) is very challenging due to the heterogeneous nature of these conditions, the populations they affect, and the settings surgery is undertaken in. These issues are further compounded when longer-term perspectives are adopted. For instance, estimates for the total costs of stroke have been found to vary five-fold in magnitude (Xu *et al.*, 2018).

Implications for update

The company undertook univariate deterministic analysis to identify which inputs the *de novo* model was sensitive to. This is represented as a Tornado diagram (Figure 4.2). Note: the ranges used in these analyses was somewhat arbitrary, with the company stating “Range is assumed to assess the impact of this parameter on the results of the model” for most inputs. However, zero values were generally included for the lower limit.

Figure 4.2. *Tornado diagram illustrating univariate deterministic sensitivity analysis.*



It can be seen that the only input which had the potential to change the direction of the result was the probability of SSI with HumiGard (point estimate 4.7%, range in sensitivity analysis 0 to 20%).

Updated cost inputs and results

Newcastle EAC has updated the costs of complications by using the most up-to-date NHS reference data, as described in the original Assessment Report (Duarte et al., 2016). Model inputs are reported in Table 4.1, additionally more detailed information on the costs used are reported in Appendix D (Tables D1 to D6).

Table 4.1. *Revised cost parameters.*

Cost parameter	Company estimate	B&B EAC estimate	Revised estimate (December 2020)
MI (acute)	£1,608	£1469	£1478
MI (longer term/year)	£646	£43	£43
Stroke (acute)	£2,788	£2834	£2969
Stroke (longer term/year)	£3,749	Year 1: £9144 Year 2: £1618 Year 3: £2449 Year 4: £1775 Year 5: £2170 TOTAL: £17,126	Year 1: £9144 Year 2: £1655 Year 3: £2506 Year 4: £1816 Year 5: £2220 TOTAL: £17,341*
SSI	£6,300	£1858	£1793
Sepsis	£2,182	£2149	£2206
Pneumonia	£1,825	£1799	£1636
Mortality	£0	£0	£0

Abbreviations: MI, myocardial infarction; SSI, surgical site infection.

* Longer-term costs of stroke were derived from a UK-based observational study (Luengo-Fernandez et al., 2012) identified by B&B EAC. These were inflated to the relevant time periods by B&B EAC and again by Newcastle EAC.

These costing parameters were applied to the company's economic model. HumiGard remained cost saving in both laparoscopic and open surgery scenarios (Table 4.2).

Table 4.2. *Base case results using Company, B&B EAC, and revised costing input data.*

Surgery type	Source of estimate	HumiGard	Usual Care	Δ (per patient)
Laparoscopy	Company	£391	£819	**-£428**
	B&B EAC	£763	£840	**-£77**
	Revised estimate	£178	£272	**-£94**
Open surgery	Company (1 year)	£483	£503	**-£20**
	B&B EAC (5 years)*	£537	£746	**-£209**
	Revised estimate (1 year)	£381	£438	**-£57**
	Revised estimate (5 years)	£425	£525	**-£101**
* The base case time perspective for open surgery was 5 years in the B&B base case.				

4.8 Other relevant information

Audit studies

The company submitted three additional UK studies to inform on the effectiveness of HumiGard. The first of these was a service evaluation audit conducted at Russell's Hall Hospital (Dudley Groups NHS Trust). This study enrolled 11 patients undergoing laparoscopic colorectal cancer resection with an expected duration of over 3 hours to receive HumiGard with standard warming. These were compared with 10 patients received standard warming only. Temperature recordings were then taken at 15 minute intervals throughout each case (method not stated). The authors reported significant differences in temperature in favour of the HumiGard using area under the curve (AUC) analysis ($p = 0.04$). The incidence of hypothermia, defined as ≤ 36°C, was 29.5% in the HumiGard group compared with 50.4% in the control group (statistical significance not stated).

The second study (University Hospital of Bristol NHS Foundation Trust) compared 10 patients undergoing colorectal laparoscopic surgery receiving standard care with 7 patients receiving additional care with HumiGard. There was a significant difference in end of surgery temperature. At the end of surgery, the authors reported "HumiGard group was 0.63°C warmer than the control group ($p = 0.02$)". The nadir temperature was reported as significantly lower in the control group compared with the HumiGard group (0.47°C, $p = 0.01$).

The third study was set in Swansea Bay University Health Board. This was an audit of 72 patients scheduled to undergo laparoscopic gastric sleeve or bypass surgery with HumiGard insufflation or standard insufflation. The authors reported the mean LoS was 2 days in the control group compared with 1.6 days in the HumiGard group, and the pain score (measured using VAS) was reduced in the HumiGard group. No further information was reported.

These audit studies have not been published and cannot currently be adequately appraised or interpreted. No firm conclusions can be drawn.

Bench testing

The company also provided information of a bench test study on the effect of HumiGard in simulated open surgery. As this study was not conducted in human subjects and did not report outcomes relevant to the scope, it has not been considered further.

Usage

The company reported that 10 NHS providers currently use HumiGard as part of their clinical practice.

[redacted]

Safety information

The IS search did not identify any alerts or field notices concerning the HumiGard technology.

5. Conclusion

Clinical evidence

HumiGard received a recommendation for further research by NICE in MTG31 (NICE, 2017). This was primarily due to a lack of clinical evidence on its effectiveness and consequent uncertainty on its cost-saving potential. No specific research recommendations were made, although MTAC concluded "The committee recommended conducting research in collaboration with the company and with clinical and academic partners. NICE will update this guidance if new and substantive evidence becomes available". The purpose of this review was to identify new evidence that might warrant a full reappraisal of the evidence base.

Eleven studies were identified that were considered to be in scope. Five of the studies were RCTs; however, one was available as an abstract only (Kalev *et al.*, 2020) and one had been available to B&B EAC previously in abstract form (Weinberg *et al.*, 2017). Two of the RCTs were in patients receiving laparoscopic procedures (Matsuzaki *et al.*, 2017, Oderda *et al.*, 2019) with the remainder performed in patients receiving open surgery (Cheong *et al.*, 2019, Kalev *et al.*, 2020, Weinberg *et al.*, 2017). Four observational studies were also identified, the most relevant of which was the UK study by Mason *et al.* (2017). However, B&B EAC had also had access to the data from this study, which was used to inform the original Assessment Report and economic model.

On hypothermia, the UK study by Mason *et al.* (2017) reported that HumiGard was associated with significantly reduced cases of hypothermia compared with the control group, However, as discussed, this evidence had already been taken into account in the original Assessment Report. The effect size observed in this study was large, with the ratio of odds of hypothermia with HumiGard 0.10 (95%CI 0.04 to 0.23) compared with the odds without HumiGard. However, the study was not randomised, and the method of measuring temperature was not standardised. The authors themselves recommended that their findings should be confirmed by a prospective trial. Some RCTs showed that HumiGard is associated with modest increases in core body temperature (Table B3), and others reported non-significant increases. There remains a particular gap in the evidence concerning the efficacy of HumiGard in preserving temperature in patients undergoing open surgery. In conclusion, Newcastle EAC considers that the new evidence on hypothermia is of moderate quality, with some evidence that HumiGard has a moderate warming effect, particularly during laparoscopic surgery, but its effect on preventing hypothermia remains uncertain.

There was very little direct evidence identified that HumiGard reduces the rate of post-surgical complications, especially serious complications with long-term sequelae, such as stroke. In the open surgery cohort of the model, this lack of evidence meant a linked approach to quantify cost savings through reduction of complications was required (using data from a large retrospective database of surgical procedures). In the opinion of Newcastle EAC, this approach was unsatisfactory due to different definitions of hypothermia and uncertainties around the cause-effect relationship between postsurgical hypothermia and complication. The direct evidence that informed the laparoscopy cohort was taken from the Mason *et al.* (2017) study. The quality of evidence on SSI rates from this study can be considered as low because, despite steps being taken to reduce bias, the rate of SSI was low overall, and subject to potential confounding by improving surgical outcomes over time. Additionally, no new evidence was identified to corroborate these results. It is unclear whether the gaps in the current evidence base will be addressed by further research (Table C1).

Economic evidence

The principal uncertainties of the economic evidence were related to the gaps in the clinical evidence. There were no new data to satisfactorily update clinical effectiveness parameters. The company confirmed that the costs of the technology has not changed. The EAC updated the downstream costs on complications with the most up-to-date data available. The direction of effect was not changed in either the laparoscopic or open surgery cohorts, with HumiGard remaining ostensibly cost-saving.

Newcastle EAC notes that some of the new studies investigated the mechanistic effects of warmed and humidified CO_2 through measurement of inflammatory markers. Although these are surrogate outcomes not yet linked with clinical outcomes, the emergence of such articles suggests this is an active field of research.

Recommendation

In conclusion, Newcastle EAC has reviewed the uncertainties identified by MTAC in Table 5.1. In the opinion of the EAC, none of these areas of uncertainty has been unequivocally addressed by the new evidence identified. The EAC notes that the HEAT RCT is due for completion imminently, according to the trial registry, and is expected to add high quality UK evidence relating to quality of recovery, warming effect and length of stay for HumiGard in laparoscopic surgery. The TePaLa RCT (laparoscopic surgery) and trial by Hii *et al.* (open and laparascopic surgery) are relevant to the scope, and are due to complete recruitment and report their findings shortly. In addition, the authors of the three completed audit studies may be planning to report their

findings, or could be encouraged to do so. Until such time these studies, or other significant new studies, are published, the EAC recommends that MTG31 is placed on the static list.

Table 5.1. *Summary of the areas of uncertainty affecting MTG31 identified by MTAC.*

Issue	How was issue identified	Description of issue	Potentially relevant information identified by this review?
Lack of clinical evidence of HumiGard used in open surgery	MTAC considerations Section 3.14	"The committee considered that the clinical evidence supported the effectiveness of HumiGard in reducing hypothermia during laparoscopic and open abdominal surgery, noting that the evidence base was more substantial for laparoscopic surgery than for open surgery".	Three RCT were identified on the use of HumiGard in patients receiving open surgery (Cheong *et al.,* 2019, Kalev *et al.*, 2020, Weinberg *et al.,* 2017). However, these were small studies in heterogeneous populations that did not provide unequivocal evidence of the benefits of HumiGard .
Lack of direct evidence on adverse events of hypothermia	MTAC considerations Section 3.14	"The committee also noted the lack of high quality direct comparisons supporting the use of HumiGard to avoid the adverse outcomes of hypothermia following surgery".	No new evidence was identified to address this. There remains little direct evidence that HumiGard reduces post-surgical complications.
Lack of evidence on children	MTAC considerations Section 3.15	"The committee noted that only 1 of the included studies involved children, and that in this study outcomes did not improve. The clinical experts advised that heat loss is partly determined by the ratio of body surface area to body mass. Because this is larger in children, overheating through the use of warming strategies can also be a concern. The committee concluded that there was insufficient evidence to recommend the use of HumiGard in children".	No evidence for the use of HumiGard in children was identified.
Risk of stroke in patients with hypothermia	MTAC considerations Section 5.21	"The committee was informed by the clinical experts 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 committee was informed by the EAC that	No direct evidence was identified on the potential of HumiGard to reduce the incidence of complications such as stroke. An assessment of indirect evidence was beyond the scope of this review.

		reducing the stroke risk to 0% in the cost model would make the use of HumiGard cost incurring. The committee concluded that the use of HumiGard was unlikely to reduce stroke rates for patients having abdominal surgery in the NHS".	
Cost of SSIs	MTAC considerations Section 5.22	"The committee was informed that the NHS costs associated with surgical site infections were uncertain and that published estimates vary. The committee noted that the average cost used in the EAC cost analysis was reflective of current practice. Expert advice stated that surgical site infection costs vary considerably in colorectal surgery".	No evidence on the costs of complications was identified (and was out of the scope of the review). The complications included in the de novo model are likely to be heterogeneous in nature and consequently costs will be uncertain.
Abbreviations: MTAC, Medical Technologies Appraisal Committee; SSI, surgical site infections			

Appendix A – Relevant guidance

NICE guidance – published

Hypothermia: prevention and management in adults having surgery (2008 updated 2016) NICE guideline CG65

NICE medical technologies guidance – published

Inditherm patient warming mattress for the prevention of inadvertent hypothermia (2011) NICE medical technologies guidance 7. WITHDRAWN.

NICE Medtech innovation briefing

Bair Hugger for measuring core temperature during perioperative care (2017) NICE medtech innovation briefing 99

NICE guidance – in development

None identified.

NICE pathways

Inadvertent perioperative hypothermia (2017) NICE Pathway

Guidance from other professional bodies

None identified.

Appendix B – Clinical evidence

Table B1. *Characteristics of included RCTs.*

	Study reference	Design, sample size	Population	Intervention	Comparator	Outcomes
Laporoscopy	(Oderda *et al.*, 2019) (NCT02586974).	Parallel, single-blinded RCT (n=64)	Men with prostate cancer undergoing robot-assisted radical prostatectomy.	Insufflation with WHC (HumiGard) plus forced air warming blanket. (n=32)	Insufflation with CDC plus forced air warming blanket. (n=32)	Primary Core body temperature Secondary IL-6, TNF-α titres, Pain NRS, Procedural characteristics including LoS, Intra- and early postoperative complications
	(Matsuzaki *et al.*, 2017) (NCT01887028)	2x2 single-blinded, factorial RCT (n=93 ITT)	Women indicated for laparoscopic sub-total hysterectomy with promonto-fixation for uterine prolapse	HumiGard WHC IPP 12 mmHg (n=23) WHC IPP 8 mmHg (n=23)	Control CDC IPP 12 mmHg (n=23) CDC IPP 8 mmHg (n=24)	HRQoL, Pain VAS, Core body temperature, intraoperative and postoperative complications. "Quality of surgical condition", Gene expression of 12 mRNA

	Study reference	Design, sample size	Population	Intervention	Comparator	Outcomes
						inflammatory markers.
Open surgery	(Kalev *et al.*, 2020)*	Parallel RCT (n=50)	Patients undergoing open resection for colorectal cancer.	WHC with HumiGard (n=25)	Control (unspecified) (n=25)	Core body temperature, Wound temperature, IL-6, Wound healing complications
	(Cheong *et al.*, 2019) (NCT02975947)	Parallel, single-blinded RCT (n=40)	Patients receiving open elective laparotomy. Indications include potentially curable colorectal carcinoma; polyposis syndrome; diverticular disease; rectal prolapse and inflammatory bowel disease.	WHC with HumiGard and gas diffuser (n=20)	Standard practice (no gas insufflation) (n=20)	Primary "Increased degree of peritoneal inflammation and damage from the beginning to the end of operation" Secondary "Perioperative clinical result"
	(Weinberg *et al.*, 2017)†	Parallel, double-blinded RCT (n=22)	Patients undergoing orthotopic liver	Standard care with addition of WHC with	Standard care (includes body warming blanket	Primary Core temperature measured 5 mins

	Study reference	Design, sample size	Population	Intervention	Comparator	Outcomes
			transplantation. Indications were: •Hepatitis C •Non-alcoholic steato-hepatitis •Autoimmune hepatitis •Primary sclerosing cholangitis •Primary biliary cirrhosis •Hepatocellular cancer •Alcoholic cirrhosis	HumiGard and gas diffuser (n=11)	prior to procedure) (n=11)	prior to reperfusion of the donor liver Secondary Baseline patient characteristics, Duration of surgery, Core temperature at other time points

Abbreviations: CDC cool dry carbon dioxide; HRQoL, health-related quality of life; IPP, intraperitoneal pressure; IL, interleukin; ITT, intention to treat; LoS, length of stay; NRS, numerical rating system; RCT, randomised controlled trial; TNF-α, tumour necrosis factor alpha; VAS, visual analogue scale; WHC, warm humidified carbon dioxide.
* Published in German journal, abstract available only.
† Included as an abstract in MTG31 Assessment Report. Now published as full study.

Table B2. *Characteristics of non-RCT studies.*

Study reference	Design, sample size	Population	Intervention	Comparator	Outcomes
(Wittenborn *et al.*, 2019)	Retrospective observational study (n=110) 66 matched cases.	Women undergoing laparoscopic surgery. Main indications uterine myoma, endometriosis, ovarian tumour, bleeding disorder.	Operations in which WHC with HumiGard was used (n=33)	Operations without use of WHC with HumiGard	Intra-oesophageal temperature at start, middle, and end of operation.
(Liu *et al.*, 2019)	Retrospective observational study (n=245)	Patients with colorectal carcinoma undergoing laparoscopic colorectal surgery.	WHC insufflation with HumiGard (n=125)	Control group, insufflation with CDC (n=120)	Perioperative haemodynamic data, Clinical symptoms
(Dimache *et al.*, 2018)* Abstract	Prospective cohort study (n=120)	Women undergoing gynaecological laparoscopic surgery expected to last more than 90 min.	WHC insufflation with HumiGard (n=60) Forced-air warming blanket	Control group, Forced-air warming blanket only	Core body temperature, LoS
(Mason *et al.*, 2017)	Retrospective observational study (n=246)	Patients undergoing elective laparoscopic resection of the colon, rectum or	WHC insufflation with HumiGard (n=123)	Standardised care (use of CDC) (n=123)	<u>Primary</u> incidence of postoperative hypothermia <u>Secondary</u>

Study reference	Design, sample size	Population	Intervention	Comparator	Outcomes
		anus for malignant or benign disease.			Surgical complications, SSIs, Unplanned re-intervention, LOS, Readmissions, Operative time, Costs
(Frey *et al.*, 2016) †	Meta-analysis (N=2, n=158)	Patients attending elective major open colon surgery.	WHC insufflation with HumiGard (n=80)	Control (not specified) (n=78)	Peri-procedural outcomes including core and wound temperature, Mortality Cox regression analysis on mortality
(Jenks *et al.*, 2017)‡	Cost-utility analysis (200 simulated patients per year, 5 year time horizon)	Patients receiving laparoscopic or open surgery (2 models)	WHC insufflation with HumiGard	Standard care (CDC)	Costs, QoL utility, ICERs
(Ryczek *et al.*, 2019)	Trial protocol RCT (n=232 planned)	Patients undergoing laparoscopic colectomy	WHC insufflation with HumiGard	Standard care	<u>Primary</u> Change in QoR-40 <u>Secondary</u> Pain Scores Presence of hypothermia

Study reference	Design, sample size	Population	Intervention	Comparator	Outcomes
					Complications SSIs LoS Resource use CE analysis

Abbreviations: CDC, cold dry carbon dioxide; CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; LoS, length of stay; QoL, quality of life; QoR-40, quality of recovery; Surgical site infections; WHC, warm humid carbon dioxide insufflation

* Identified by the company.
† This study appears to have been identified in the bibliography of original Assessment Report as “Epub ahead of print” but does not appear to have been included or otherwise discussed.
‡ Identified as an abstract in MTG21.

Table B3. *Temperature outcomes reported in included studies.*

	Study	Surgery type	Outcome	HumiGard	Control	Difference Δ (HumiGard-control)
RCTs	(Oderda *et al.*, 2019)	Laparoscopy	Body core temperature (oesophageal probe) Mean ◦C	Start of surgery: 35.73 After 1 h: 35.78 After 2 h: 35.96 After 3 h: 36.11 After 4 h: 36.34 End of surgery: 36.26	Start of surgery: 35.70 After 1 h: 35.77 After 2 h: 35.90 After 3 h: 36.02 After 4 h: 36.07 End of surgery: 36.06	0.03 0.01 0.06 0.09 0.27 0.2 (p=0.997)
	(Matsuzaki *et al.*, 2017)	Laparoscopy	Body core temperature (oesophageal probe) Mean ◦C (SD)	<u>12 mmHg</u> Start: 36.0 (0.40) Minimum: 35.8 (0.60) Maximum: 36.0 (0.40) Final: 36.0 (0.40) <u>8 mmHg</u> Start: 36.0 (0.30) Minimum: 35.9 (0.30) Maximum: 36.0 (0.30) Final: 36.0 (0.30)	<u>12 mmHg</u> Start: 36.1 (0.40) Minimum: 35.8 (0.50) Maximum: 36.1 (0.40) Final: 36.0 (0.30) <u>8 mmHg</u> Start: 36.1 (0.36) Minimum: 36.0 (0.50) Maximum: 36.3 (0.40) Final: 36.2 (0.50)	<u>12 mmHg</u> -0.1 0.0 -0.1 0.0 <u>8 mmHg</u> -0.1 -0.1 -0.3 -0.2
	(Kalev *et al.*, 2020)	Open	Body core temperature Median °C (Q1 : Q3)	Start: 36.2 (35.7 : 36.4) End: 36.4 (36.0 : 36.7)	Start: 36.2 (36.0:36.4) End: 36.2 (35.9:36.45)	0.0 0.2 (p=0.08)
			Wound temperature Median °C (Q1 : Q3)	Start: 31.9 (30.25 : 32.95) End: 31.6 (30.25 : 31.85)	Start: 32.8 (31.85:34.05) End: 30.7 (29.85:32.15)	-0.9 0.9 (p=0.000475)

	Study	Surgery type	Outcome	HumiGard	Control	Difference Δ (HumiGard-control)
	(Weinberg *et al.*, 2017)	Open	Core body temperature (pulmonary artery catheter) Mean °C (SD)	Primary* 35.9 (0.16) Secondary Baseline: 35.8 (0.2) S1+60 min: 35.7 (0.2) S2+30 min: 36.2 (0.2) S3+5 min: 34.9 (0.21) S3+60 min: 35.8 (0.18) Closure: 36.8 (0.23)	Primary* 35.5 (0.24) Secondary Baseline: 35.9 (0.1) S1+60 min: 35.8 (0.2) S2+30 min: 35.6 (0.3) S3+5 min: 35.1 (0.28) S3+60 min: 35.7 (0.16) Closure: 36.3 (0.09)	0.4 (p=0.14) -0.1 (p=0.73) -0.1 (p=0.69) 0.6 (p=0.09) -0.2 (p=0.46) 0.1 (p=0.59) 0.5 (p=0.091)
			Core body temperature (nasopharangeal probe) Mean °C (SD)	Primary* 36.0 (0.13) Secondary Baseline: 36.0 (0.1) S1+60 min: 35.8 (0.2) S2+30 min: 36.4 (0.2) S3+5 min: 34.7 (0.23) S3+60 min: 35.8 (0.16) Closure: 36.7 (0.21)	Primary* 35.4 (0.22) Secondary Baseline: 35.9 (0.1) S1+60 min: 35.8 (0.2) S2+30 min: 35.6 (0.23) S3+5 min: 35.0 (0.22) S3+60 min: 35.7 (0.15) Closure: 36.1 (0.13)	0.6 (p=0.028) 0.1 (p=0.75) 0.0 (p=0.91) 0.78 (p=0.02) - 0.3 (p=0.41) 0.1 (p=0.77) 0.6 (p=0.04)
Observational studies	(Wittenborn *et al.*, 2019)	Laparoscopy	Body core temperature (oesophageal probe) Mean ◦C (SD)	Absolute Start: 35.94 (0.46) Middle: 35.98 (0.49) End: 36.04 (0.49) Change Start-end: -0.09 Start-middle: -0.03 Middle end: -0.06	Absolute Start: 36.10 (0.46) Middle: 36.07 (0.42) End: 36.01 (0.49) Change Start-end: 0.09 Start-middle: 0.04 Middle end: 0.05	-0.07 -0.09 0.03 (p=0.011) (p=0.122) (p=0.003)

	Study	Surgery type	Outcome	HumiGard	Control	Difference Δ (HumiGard-control)
				Proportion with hypothermia Start-end: 54.6% Start-middle: 42.4% Middle end: 36.4%	Proportion with hypothermia Start-end: 36.4% Start-middle: 39.4% Middle end: 42.4%	NR
	(Dimache *et al.*, 2018)	Laparoscopy	Body core temperature loss Mean ◦C (SD)	0.1 (0.5)	0.5 (0.5)	0.4 (p=0.005)
	(Mason *et al.*, 2017)	Laparoscopy	Proportion patients hypothermic† in post-anaesthetic recovery suite	13%	57%	(p≤0.001)
	(Frey *et al.*, 2016) †	Open	Core temperature Mean ◦C (SD)	Mean: 36.2 (0.6) Final: 36.5 (0.6)	Mean: 35.9 (0.5) Final: 36.1 (0.6)	0.3 (p=0.005) 0.4 (p<0.001)
			Core temperature ≥ 36.0 ◦C	Mean: 51 (64.6%) Final: 66 (82.5%)	Mean: 32 (42.7%) Final: 49 (65.3%)	(p=0.006) (p=0.015)
			Wound edge temperature Mean ◦C (SD)	Mean: 29.8 (1.2) Final: 29.7 (1.9)	Mean: 28.5 (1.1) Final: 28.5 (1.7)	1.3 (p<0.001) 1.2 (p<0.001)
			Wound area temperature Mean ◦C (SD)	Mean: 31.0 (1.2) Final: 31.2 (2.0)	Mean: 29.7 (1.1) Final: 30.1 (1.9)	1.3 (p<0.001) 1.1 (p=0.001)

Abbreviations: CDC, cold dry CO2; IQR, inter-quartile range; NR, not reported; SD, standard deviation; WHC, warm humid CO_2
*Primary outcome was core temperature measured 5 min prior to reperfusion of the donor liver (S3+5 min). Secondary outcomes: S1+60, 60 min after start of the dissection phase; S2+30, 30 min after start of the anhepatic phase; S3+60, 60 min post reperfusion.
† Hypothermia defined as a temperature of less than 36◦C, as measured by tympanic probe.

Appendix C – Details of studies and ongoing trials

Table C1. *Summary of relevant ongoing studies.*

Study identification	Study design	Population	Intervention Comparator	Outcomes	Status
HEAT study Cedar EAC (Ryczek *et al.*, 2019) (Also NCT04164706 feasibility study*) United Kingdom	Multicentre, blinded (patient, surgeon, and assessor), sham device-controlled, parallel RCT (n=258)	Adults (>18 years) scheduled for elective laparoscopic, segmental, or total colectomy.	I: Warm humid CO_2 insufflation using HumiGard. (n=129) C: Cool, dry CO_2 insufflation with sham device (HumiGard turned off). (n=129).	Primary QoR-40 scores from baseline to postoperative day 1. Secondary QoR-40 postoperative day 3. Pain (VAS) Incidence of hypothermia (temperature ≤36°C) Duration and depth of hypothermia Postoperative complications SSIs LoS Resource use	Unknown. Pilot feasibility study estimated completion date October 30, 2020. Results not published.
TePaLa study (NCT02781194) PI: Julia Wittenborn	Multicentre, parallel, double blinded (Care provider, investigator) RCT	Patients admitted to hospital for laparoscopic surgery with a planned	I: HumiGard (n=50) C1: Bair Hugger blanket (n=50)	Primary Intra-operative core temperature. Hypothermia stratified as mild, moderate, or severe.	Study date completion: September 2018

Study identification	Study design	Population	Intervention Comparator	Outcomes	Status
Germany	(n=150)	duration of more than 1 hour	C2 HumiGard plus Bair Hugger blanket (n=50)	Body temperature (tympanic), Pain (VAS), Morphine equivalent dose, Perioperative fluid load, Fibrinolytic activity.	Results not published.
Does utilisation of surgical humidification reduce surgical site infection in colorectal surgery patients? A randomised control trial ACTRN12620000269932 PI: Asiri Arachchi Australia	Single centre single blind parallel RCT (n=298)	Patients undergoing elective or emergency open colorectal resection	I: HumiGard system (n=149) C: standard care (in absence of HumiGard system). (n=149)	Primary SSI (14 and 30 days post-operation) Secondary LoS, Return to theatre for intervention of SSI, Antibiotic use for SSI.	Approved, not yet recruiting. Date of last data collection 02/04/2022. Last update March 2020
Efficacy of warm humidified insufflation for reducing post-operative ileus in patients undergoing acute general surgical laparotomy: A randomised single-blind controlled trial.	Single blind parallel RCT (n=226)	Patients undergoing an elective, expedited, urgent, or emergency laparotomy lasting at least 60 minutes	I: Insufflation with warm, humid, CO_2 (HumiGard) C: Insufflation with cool, dry CO_2	Primary Time from operation to recovery of bowel function as defined by tolerance of a solid diet and passage of stool. GCSI score Secondary Peritoneal inflammation	Submitted, not yet approved Last update November 2019

Study identification	Study design	Population	Intervention Comparator	Outcomes	Status
ACTRN12619001570178 PI: John Windsor New Zealand				GIQLI score	
Effect of warm humidified insufflated carbon dioxide on wound bacterial load in open elective gastrointestinal surgery: a pilot investigation ACTRN12617001558314 PI: John Windsor New Zealand	Single blind parallel RCT (n=10)	Patients scheduled to undergo upper gastrointestinal surgical procedures longer than 120 minutes involving an open midline laparotomy incision.	I: HumiGard system C: standard care (in absence of HumiGard system).	Primary Bacterial colonisation measured using qPCR Secondary Bacterial load as determined by taking swabs during surgery, Wound edge tissue response	Approved, recruiting. Date of last data collection anticipated: 28/02/2019. Last update July 2018
A randomised controlled trial investigating the effect of humidified warm carbon dioxide (CO2) insufflation during laparoscopic and open abdominal surgery.	Single centre single blind RCT. (n=120)	Patients undertaking elective Upper GI or hepatobiliary surgery of longer than 2 hours duration.	I: HumiGard C Laparoscopic: Cool, dry room temperature CO2 insufflation C Open: No intracorporeal warming.	Primary Intraoperative and postoperative temperature loss using a nasopharyngeal temperature probe. Secondary Postoperative pain (VAS)	Approved, recruiting. Date of last data collection anticipated: 24/12/2020.

Study identification	Study design	Population	Intervention Comparator	Outcomes	Status
ACTRN12617000850370 PI: Michael Hii Australia		Open or laparoscopic.		Histopathological changes	Last update November 2019

Abbreviations: C, comparator; GCSI, Gastroparesis Cardinal Symptom Index; GI, gastrointestinal; GIQLI, Gastrointestinal Quality of Life Index; I, intervention Los; QoR-40 quality of recovery); qPCR, quantitative polymerase chain reaction; randomised controlled trial, RCT; PI, principal investigator; SSI, surgical site infection; VAS, visual analogue scale.

* The HEAT trial was to follow on from a smaller pilot study, see Section 4.3.

Appendix D – Detailed costs

Table D1. *Calculation of surgical site infection cost using total activity from 2018/19 NHS reference costs.*

HRG code	Description	Activity	Unit Cost
WH07A	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+	1,748	£9,497.07
WH07B	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1	2,359	£5,451.72
WH07C	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+	1,814	£5,034.69
WH07D	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1	4,553	£3,131.44
WH07E	Infections or Other Complications of Procedures, without Interventions, with CC Score 4+	1,618	£3,311.39
WH07F	Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3	7,582	£1,908.49
WH07G	Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1	44,355	£949.18
	Weighted average		**£1,792.64**

Table D2. *Calculation of medication costs (using cost per pack from BNF online, and number of dispensed items from the Prescription Cost Analysis 2019).*

Medication	Cost per 28-tablet pack	Dispensed items	Weighted costs
Bisoprolol 5mg tabs	£0.97	5,560,342	
Bisoprolol 10mg tabs	£1.12	2,403,667	£1.02
Ramipril 1.25mg caps	£1.89	2,972,203	
Ramipril 1.25mg tabs	£1.14	248,442	
Ramipril 10mg caps	£1.20	10,105,424	
Ramipril 10mg tabs	£1.77	566,377	
Ramipril 2.5mg caps	£1.13	6,860,565	
Ramipril 2.5mg tabs	£1.79	733,283	
Ramipril 5mg caps	£1.11	7,221,787	
Ramipril 5mg tabs	£1.80	613,471	£1.27
Atorvastatin 10mg tabs	£0.97	6,757,220	
Atorvastatin 20mg tabs	£1.15	20,188,694	
Atorvastatin 40mg tabs	£1.42	13,016,830	

Atorvastatin 80mg tabs	£1.96	5,706,131	£1.30
		Total monthly cost	£3.59
		Annual cost	**£43.03**

Table D3. *Calculation of pneumonia cost using total activity from 2018/19 NHS reference costs.*

HRG code	Description	Activity	Unit Cost
DZ11K	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 14+	685	£9,989.39
DZ11L	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 9-13	3,080	£6,781.02
DZ11M	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 0-8	2,334	£4,527.96
DZ11N	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 13+	3,194	£5,940.28
DZ11P	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 8-12	10,661	£4,088.00
DZ11Q	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-7	9,890	£2,835.76
DZ11R	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 14+	11,399	£3,727.66
DZ11S	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10-13	66,256	£2,657.37
DZ11T	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9	97,309	£1,888.36
DZ11U	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-6	123,592	£1,478.31
DZ11V	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3	89,245	£1,054.85
DZ22K	Unspecified Acute Lower Respiratory Infection, with Interventions, with CC Score 9+	1,244	£5,194.09

DZ22L	Unspecified Acute Lower Respiratory Infection, with Interventions, with CC Score 0-8	2,063	£3,305.00
DZ22M	Unspecified Acute Lower Respiratory Infection, without Interventions, with CC Score 13+	2,655	£3,134.90
DZ22N	Unspecified Acute Lower Respiratory Infection, without Interventions, with CC Score 9-12	16,158	£2,110.49
DZ22P	Unspecified Acute Lower Respiratory Infection, without Interventions, with CC Score 5-8	45,592	£1,416.85
DZ22Q	Unspecified Acute Lower Respiratory Infection, without Interventions, with CC Score 0-4	64,635	£870.88
DZ23H	Bronchopneumonia with Multiple Interventions	303	£5,084.93
DZ23J	Bronchopneumonia with Single Intervention, with CC Score 11+	397	£4,743.99
DZ23K	Bronchopneumonia with Single Intervention, with CC Score 0-10	717	£3,135.04
DZ23L	Bronchopneumonia without Interventions, with CC Score 11+	2,949	£2,881.35
DZ23M	Bronchopneumonia without Interventions, with CC Score 6-10	7,019	£1,985.04
DZ23N	Bronchopneumonia without Interventions, with CC Score 0-5	5,634	£1,254.23
	Weighted average		**£1,635.66**

Table D4. *Calculation of myocardial infarction cost using total activity from 2018/19 NHS reference costs.*

HRG code	Description	Activity	Unit Cost
EB10A	Actual or Suspected Myocardial Infarction, with CC Score 13+	16,897	£2,582
EB10B	Actual or Suspected Myocardial Infarction, with CC Score 10-12	22,118	£1,805
EB10C	Actual or Suspected Myocardial Infarction, with CC Score 7-9	27,945	£1,382
EB10D	Actual or Suspected Myocardial Infarction, with CC Score 4-6	31,355	£1,162
EB10E	Actual or Suspected Myocardial Infarction, with CC Score 0-3	25,333	£954
	Weighted average		**£1478.17**

Table D5. *Calculation of stroke cost using total activity from 2018/19 NHS reference costs.*

HRG code	Description	Activity	Unit Cost
AA35A	Stroke with CC Score 16+	22,459	£6,869
AA35B	Stroke with CC Score 13-15	22,510	£4,712
AA35C	Stroke with CC Score 10-12	28,051	£3,296
AA35D	Stroke with CC Score 7-9	32,348	£2,484
AA35E	Stroke with CC Score 4-6	32,359	£1,963
AA35F	Stroke with CC Score 0-3	21,672	£1,602
AA29C	Transient Ischaemic Attack with CC Score 11+	5,070	£1,764
AA29D	Transient Ischaemic Attack with CC Score 8-10	5,205	£1,042
AA29E	Transient Ischaemic Attack with CC Score 5-7	7,772	£817
AA29F	Transient Ischaemic Attack with CC Score 0-4	10,775	£629
	Weighted average		**£2969.28**

Table D6. *Calculation of sepsis cost using total activity from 2018/19 NHS reference costs.*

HRG code	Description	Activity	Unit Cost
WJ05A	No longer available		
WJ05B	No longer available		
WJ06A	Sepsis with Multiple Interventions, with CC Score 9+	2,842	£9,289
WJ06B	Sepsis with Multiple Interventions, with CC Score 5-8	3,075	£7,360
WJ06C	Sepsis with Multiple Interventions, with CC Score 0-4	1,367	£5,870
WJ06D	Sepsis with Single Intervention, with CC Score 9+	5,688	£5,156
WJ06E	Sepsis with Single Intervention, with CC Score 5-8	8,680	£4,323
WJ06F	Sepsis with Single Intervention, with CC Score 0-4	4,738	£3,565
WJ06G	Sepsis without Interventions, with CC Score 9+	41,311	£2,632
WJ06H	Sepsis without Interventions, with CC Score 5-8	105,443	£1,968
WJ06J	Sepsis without Interventions, with CC Score 0-4	97,668	£1,436
	Weighted average		**£2205.65**

Appendix E – Literature search strategy

EPPI-R 5

Databases*	Date searched	No retrieved	Version/files
MEDLINE (Ovid)	28th Aug 2020	636	Ovid MEDLINE(R) <1946 to August 27, 2020>
MEDLINE In-Process (Ovid)	28th Aug 2020	212	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to August 27, 2020>
MEDLINE ePub ahead of print (Ovid)	28th Aug 2020	51	Ovid MEDLINE(R) Epub Ahead of Print <August 27, 2020>
EMBASE (Ovid)	28th Aug 2020	1033	Embase <1974 to 2020 August 27>
Cochrane	??	208	??
CDSR (Wiley)	31st Aug 2020	4	Issue 8 of 12, August 2020
CENTRAL (Wiley)	31st Aug 2020	204	Issue 8 of 12, August 2020
**Database of Abstracts of Reviews of Effects – DARE (CRD)	N/A		
HTA database (CRD)	N/A		
**NHS EED (CRD)	N/A		
Econlit (Ovid - for economic searches)	28th Aug 2020	0	Econlit <1886 to August 20, 2020>
Total		2,139	
Total after de-duplication		1,289	

Search strategies

Database:
Database: Ovid MEDLINE(R) <1946 to August 27, 2020>

Search Strategy:

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1 humigard*.mp. or insuflow*.ti,ab. (12)
2 Insufflation/ (3397)
3 humidif*.ti,ab. (3801)
4 insuffl*.ti,ab. (6489)
5 ((heat* or warm* or temperature*) adj2 (CO2 or carbon dioxide)).ti,ab. (1206)
6 exp Carbon Dioxide/ (87883)
7 Nitrous Oxide/ (14234)
8 6 or 7 (100750)
9 (heat* or warm*).mp. or temperature*.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (657017)
10 8 and 9 (10309)
11 2 or 3 or 4 or 5 or 10 (22054)
12 exp Minimally Invasive Surgical Procedures/ (518637)
13 Pneumoperitoneum/ (3801)
14 (laparoscop* or endoscop*).mp. or pneumoperitone*.ti,ab. (325467)
15 (open adj3 (surgery or procedure$)). ti,ab. (35122)
16 or/12-15 (626711)
17 11 and 16 (4633)
18 1 or 17 (4634)
19 limit 18 to ed=20151101-20200828 (671)
20 limit 19 to english language (636)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to August 27, 2020>
Search Strategy:

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1 humigard*.mp. or insuflow*.ti,ab. (2)
2 Insufflation/ (0)

3 humidif*.ti,ab. (577)
4 insuffl*.ti,ab. (657)
5 ((heat* or warm* or temperature*) adj2 (CO2 or carbon dioxide)).ti,ab. (600)
6 exp Carbon Dioxide/ (0)
7 Nitrous Oxide/ (0)
8 6 or 7 (0)
9 (heat* or warm*).mp. or temperature*.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (247031)
10 8 and 9 (0)
11 2 or 3 or 4 or 5 or 10 (1798)
12 exp Minimally Invasive Surgical Procedures/ (0)
13 Pneumoperitoneum/ (0)
14 (laparoscop* or endoscop*).mp. or pneumoperitone*.ti,ab. (42772)
15 (open adj3 (surgery or procedure$)).ti,ab. (4664)
16 or/12-15 (45600)
17 11 and 16 (328)
18 1 or 17 (328)
19 limit 18 to dt=20151101-20200828 (212)

Database: Ovid MEDLINE(R) Epub Ahead of Print <August 27, 2020>
Search Strategy:
---
1 humigard*.mp. or insuflow*.ti,ab. (1)
2 Insufflation/ (0)
3 humidif*.ti,ab. (71)
4 insuffl*.ti,ab. (111)
5 ((heat* or warm* or temperature*) adj2 (CO2 or carbon dioxide)).ti,ab. (49)
6 exp Carbon Dioxide/ (0)
7 Nitrous Oxide/ (0)

8 6 or 7 (0)
9 (heat* or warm*).mp. or temperature*.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (13388)
10 8 and 9 (0)
11 2 or 3 or 4 or 5 or 10 (221)
12 exp Minimally Invasive Surgical Procedures/ (0)
13 Pneumoperitoneum/ (0)
14 (laparoscop* or endoscop*).mp. or pneumoperitone*.ti,ab. (7509)
15 (open adj3 (surgery or procedure$)).ti,ab. (849)
16 or/12-15 (7973)
17 11 and 16 (51)
18 1 or 17 (51)

Database: Embase <1974 to 2020 August 27>
Search Strategy:
---
1 laparoscopic humidification system/ (15)
2 humigard*.mp,dv. or insuflow*.ti,ab,dv. (39)
3 1 or 2 (41)
4 Insufflation/ (13327)
5 humidif*.ti,ab. (6824)
6 insuffl*.ti,ab. (10047)
7 ((heat* or warm* or temperature*) adj2 (CO2 or carbon dioxide)).ti,ab. (2143)
8 Carbon Dioxide/ (96616)
9 Nitrous Oxide/ (33185)
10 8 or 9 (127849)
11 (heat* or warm*).mp. or temperature*.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1010925)
12 10 and 11 (18849)

13 4 or 5 or 6 or 7 or 12 (44591)
14 Minimally Invasive Surgical Procedures/ (37372)
15 exp laparoscopy/ (161341)
16 exp endoscopy/ (633681)
17 Pneumoperitoneum/ (10370)
18 (laparoscop* or endoscop*).mp. or pneumoperitone*.ti,ab. (642387)
19 open surgery/ (11126)
20 (open adj3 (surgery or procedure$)).ti,ab. (59329)
21 or/14-20 (924310)
22 13 and 21 (7156)
23 3 or 22 (7163)
24 limit 23 to dc=20151101-20200828 (2028)
25 limit 24 to (conference abstract or conference paper or "conference review") (995)
26 24 not 25 (1033)

Cochrane Library

ID	Search	Hits
#1	(humigard* or insuflow)	27
#2	MeSH descriptor: [Insufflation] this term only	300
#3	(humidif*):ti,ab,kw	1298
#4	(insuffl*):ti,ab,kw	1749
#5	((heat* or warm* or temperature*) near/2 (CO2 or carbon dioxide)):ti,ab,kw	147
#6	MeSH descriptor: [Carbon Dioxide] explode all trees	2776
#7	MeSH descriptor: [Nitrous Oxide] this term only	1462
#8	#6 or #7	4160
#9	((heat* or warm*) or temperature*):ti,ab,kw	33182
#10	#8 and #9	235
#11	#2 or #3 or #4 or #5 or #10	3145
#12	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees	27820

#13 MeSH descriptor: [Pneumoperitoneum] this term only 89
#14 ((laparoscop* or endoscop*) or pneumoperitone*):ti,ab,kw 45364
#15 (open near/3 (surgery or procedure*)):ti,ab,kw 6441
#16 #12 or #13 or #14 or #15 65922
#17 #11 and #16 1032
#18 #1 or #17 with Cochrane Library publication date Between Nov 2015 and Aug 2020 576
#19 "conference":pt or (clinicaltrials or trialsearch):so 498114
#20 #18 not #19 208

Database: Econlit <1886 to August 20, 2020>
Search Strategy:
---
1 humigard*.mp. or insuflow*.ti,ab. (0)
2 [Insufflation/] (0)
3 humidif*.ti,ab. (0)
4 insuffl*.ti,ab. (0)
5 ((heat* or warm* or temperature*) adj2 (CO2 or carbon dioxide)).ti,ab. (23)
6 [exp Carbon Dioxide/] (0)
7 [Nitrous Oxide/] (0)
8 6 or 7 (0)
9 (heat* or warm*).mp. or temperature*.ti,ab. [mp=heading words, abstract, title, country as subject] (29359)
10 8 and 9 (0)
11 2 or 3 or 4 or 5 or 10 (23)
12 [exp Minimally Invasive Surgical Procedures/] (0)
13 [Pneumoperitoneum/] (0)
14 (laparoscop* or endoscop*).mp. or pneumoperitone*.ti,ab. (29)
15 (open adj3 (surgery or procedure$)).ti,ab. (34)
16 or/12-15 (61)
17 11 and 16 (0)
18 1 or 17 (0)

Notes:
The original EAC strategy was run in Nov 2015 (here – see pg 99). Changes made to the original EAC search strategy are as follows: • The EAC ran 2 strategies, one for 'minimally invasive surgery' and one for 'open surgery'. In my search, I've combined the 2 strategies together in 1 search. • In the EAC strategy, line 3: 'humigard.mp. or insuflow.ti,ab' is combined to the minimally invasive surgery/open surgery terms with the AND Boolean operator. In my strategy, I search 'humigard.mp. or insuflow.ti,ab' as a standalone search line (i.e. I haven't combined it with anything else in the search strategy). This is because it's the name of the device (we don't usually combine device names to other search terms) and the line retrieves less than 40 results in each database.

Table E1. *Studies excluded (with reasons).*

Study name, date	Reference	Design	Company included?	Reason for exclusion
Balayssac, 2016	Balayssac D, Pereira B, Bazin JE, *et al.* Warmed and humidified carbon dioxide for abdominal laparoscopic surgery: Meta-analysis of the current literature. Surgical Endoscopy 2016;31(1):1-12. doi: http://dx.doi.org/10.1007/s00464-016-4866-1	SR/MA	No	Intervention*
Baumann, 2018	Baumann M, Cater JE. The Effect of Heated CO2 Insufflation in Minimising Surgical Wound Contamination During Open Surgery. *Annals of Biomedical Engineering* 2018;46(8):1101-11. doi: http://dx.doi.org/10.1007/s10439-018-2034-6	Bench test	Yes	Study type
Binda, 2015	Binda MM. Humidification during laparoscopic surgery: overview of the clinical benefits of using humidified gas during laparoscopic surgery.	Narrative review	No	Study type

	Archives of gynecology and obstetrics 2015;292(5):955-71. doi: https://dx.doi.org/10.1007/s00404-015-3717-y			
Birch, 2016	Birch DW, Dang JT, Switzer NJ, *et al.* Heated insufflation with or without humidification for laparoscopic abdominal surgery. *Cochrane Database of Systematic Reviews* 2016(10) doi: 10.1002/14651858.CD007821.pub3	Cochrane review	No	Intervention*
Cadeddu, 2017	Cadeddu JA. Re: Warmed and Humidified Carbon Dioxide for Abdominal Laparoscopic Surgery: Meta-Analysis of the Current Literature. *The Journal of urology* 2017;198(3):465. doi: http://dx.doi.org/10.1016/j.juro.2017.06.015	Letter	No	Study type
Cheong, 2017	Cheong J, Oliphant R, Richardson G, *et al.* The use of warmed, humidified CO2 during open abdominal surgery: a modified delivery technique. *Techniques in Coloproctology* 2017;21(4):309-10. doi: http://dx.doi.org/10.1007/s10151-017-1603-2	Narrative review	Yes	Study type
Cheong, 2018	Cheong JY, Keshava A, Witting P, *et al.* Effects of intraoperative insufflation with warmed, humidified CO2 during abdominal surgery: A review. Annals of Coloproctology 2018;34(3):125-37. doi: http://dx.doi.org/10.3393/ac.2017.09.26	SR	Yes	Intervention*
Dean, 2017	Dean M, Ramsay R, Heriot A, *et al.* Warmed, humidified CO2 insufflation benefits intraoperative core temperature during laparoscopic surgery: A meta-analysis. *Asian journal of endoscopic surgery* 2017;10(2):128-36. doi: http://dx.doi.org/10.1111/ases.12350	SR	No	Intervention*
Hermann, 2015	Herrmann A, De Wilde RL. Insufflation with humidified and heated carbon dioxide in short-term laparoscopy: a double-blinded randomized controlled trial. *Biomed research international* 2015;2015:412618. doi: 10.1155/2015/412618	RCT	No	Reported in MTG21 AR
Jiang, 2019	Jiang R, Sun Y, Wang H, *et al.* Effect of different carbon dioxide (CO2) insufflation for laparoscopic colorectal surgery in elderly patients: a randomized controlled trial. *Medicine* 2019;98(41):e17520. doi: 10.1097/MD.0000000000017520	RCT	No	Intervention
Kaloo, 2019	*Kaloo P, Armstrong S, Kaloo C, et al. Interventions to reduce shoulder pain following gynaecological laparoscopic procedures. Cochrane Database of Systematic Reviews 2019(1) doi: 10.1002/14651858.CD011101.pub2*	SR	No	Intervention*
Kendir, 2018	*Kendir V. Evaluation of intraperitoneal CO2 insufflation, given in different pressures, on hemodynamic parameters by USCOM (Non-Invasive Ultrasonographic Cardiac Output Monitor) in laparoscopic cholecystectomy operations. Medical Journal of Bakirkoy*	RCT	No	Intervention

	2018;14(2):176-82. doi: http://dx.doi.org/10.5350/BTDMJB.20170206081522			
Kocyigit, 2016	Kocyigit M, Gullu AU, Kocyigit OI, *et al.* Carbondioxide insufflation and outcomes in cardiac surgery. *Gogus-Kalp-Damar Anestezi ve Yogun Bakim Dernegi Dergisi* 2016;22(3):111-15. doi: http://dx.doi.org/10.5222/GKDAD.2016.111	OS	No	Intervention
Kokhanenko, 2017	Kokhanenko P, Papotti G, Cater JE, *et al.* Carbon dioxide insufflation deflects airborne particles from an open surgical wound model. *Journal of Hospital Infection* 2017;95(1):112-17. doi: http://dx.doi.org/10.1016/j.jhin.2016.11.006	Bench test	Yes	Study type
Lee, 2015	Lee SJ, Lee TH, Park SH, *et al.* Efficacy of carbon dioxide versus air insufflation according to different sedation protocols during therapeutic endoscopic retrograde cholangiopancreatography: prospective, randomized, double-blind study. *Digestive endoscopy* 2015;27(4):512-21. doi: 10.1111/den.12448	RCT	No	Population
Meng-Meng, 2019	Meng-Meng T, Xue-Jun X, Xiao-Hong B. Clinical effects of warmed humidified carbon dioxide insufflation in infants undergoing major laparoscopic surgery. *Medicine* 2019;98(27):e16151. doi: 10.1097/MD.0000000000016151	RCT	No	Intervention
Oderda, 2018	Oderda M, Cerutti E, Gontero P, *et al.* Effects of warmed, humidified CO2 insufflation on body core temperature and cytokine response: head-to-head randomized comparison vs. standard insufflation during RARP. *Minerva anestesiologica* 2018;84(10):1228-30. doi: 10.23736/S0375-9393.18.12695-2	RCT (abstract)	No	Duplicate
Sajid, 2008	Sajid MS, Caswell J, Bhatti MI, et al. Carbon dioxide insufflation vs conventional air insufflation for colonoscopy: a systematic review and meta-analysis of published randomized controlled trials. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 2015;17(2):111-23. doi: https://dx.doi.org/10.1111/codi.12837	SR/MA	No	Included in AR
Sammour, 2008	Sammour T, Kahokehr A, Hill AG. Meta-analysis of the effect of warm humidified insufflation on pain after laparoscopy. British journal of surgery 2008;95(8):950-56. doi: 10.1002/bjs.6304	SR/MA	No	Included in AR
Sammour, 2015	Sammour T, Hill AG. Five year follow-up of a randomized controlled trial on warming and humidification of insufflation gas in laparoscopic colonic surgery--impact on small bowel obstruction and oncologic outcomes.	RCT	No	Included in AR

	International surgery 2015;100(4):608-16. doi: 10.9738/INTSURG-D-14-00210.1			
Sutton, 2017	Sutton E, Bellini G, Grieco MJ, *et al.* Warm and Humidified Versus Cold and Dry CO2 Pneumoperitoneum in Minimally Invasive Colon Resection: a Randomized Controlled Trial. *Surgical innovation* 2017;24(5):471-82. doi: 10.1177/1553350617715834	RCT	No	Intervention
Abbreviations: RCT, MA, meta-analysis; randomised controlled trial; SR, OS, observational study; systematic review * Interventions other than HumiGard included in the review.				

Appendix F – References

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CHEONG, J., OLIPHANT, R., RICHARDSON, G., RICKARD, M. J. F. X. & KESHAVA, A. 2017. The use of warmed, humidified CO2 during open abdominal surgery: a modified delivery technique. *Techniques in Coloproctology,* 21**,** 309-310.

CHEONG, J. Y., CHAMI, B., FONG, G. M., WANG, X. S., KESHAVA, A., YOUNG, C. J. & WITTING, P. 2019. Randomized clinical trial of the effect of intraoperative humidified carbon dioxide insufflation in open laparotomy for colorectal resection. *BJS open*, 4, 45-58.

CHEONG, J. Y., KESHAVA, A., WITTING, P. & YOUNG, C. J. 2018. Effects of intraoperative insufflation with warmed, humidified CO2 during abdominal surgery: A review. *Annals of Coloproctology,* 34**,** 125-137.

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Body Core Temperature as well as on Wound Healing in Open Colorectal Surgery. *Zentralblatt fur Chirurgie,* 145**,** 188-199.
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