HumiGard Surgical Humidification System for the prevention of inadvertent perioperative hypothermia

Produced by: Birmingham and Brunel Consortium External Assessment Centre

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Declared interests of the authors

No conflicts of interest.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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ABBREVIATIONS

Term	Definition
°C	Degrees Celsius
ASA	American Society of Anaesthesiologists
AUC	Area under the curve
BMI	Body mass index
BNF	British National Formulary
CI	Confidence interval
CO_2	Carbon dioxide
DH	Department of Health
EAC	External Assessment Centre
ECRI	Emergency Care Research Institute
hrs	Hours
IQR	Interquartile range
kg	Kilogram
MAUDE	Manufacturer and User Facility Device Experience
mg	Milligram
MHRA	Medicines & Healthcare products Regulatory Agency
MI	Myocardial infarction
MTEP	Medical Technologies Evaluation Programme
N	Number of patients
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised Control Trial
SD	Standard deviation
SS	Sponsor's submission
SSI	Surgical Site Infection
VAS	Visual Analogue Scale
vs	Versus
WHI	Warmed and humidified insufflation
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform

1 Summary

Scope of the sponsor's submission

The clinical context is the use of heated, humidified insufflation in people undergoing open or laparoscopic abdominal surgery. The sponsor considered that the other available humidification systems were comparable to HumiGard and thus included HumiGard as well as other humidification systems as the intervention in their submission. The comparator was no insufflant gas for open abdominal surgery, and unheated, unhumidified insufflant CO_2 gas for laparoscopic abdominal surgery. The outcome incidence of hypothermia in the intra- and post-operative period was specified in the report scope but was replaced by change in core-temperature in the sponsor's report as data were unavailable in published studies. The sponsor also considered analgesic use as an objective measure of patient reported pain. Additional outcomes included incidence of surgical site infections (SSIs), length of stay in post-operative recovery, total length of hospital stay, device-related adverse events, and patient-reported pain. Subgroups included people receiving adjunctive warming, and people considered at high-risk as described in NICE guideline 65. Only RCTs or prior meta-analyses were included.

Summary of clinical evidence submitted by the sponsor

The sponsor's submission included 16 RCTs and 3 published meta-analyses for laparoscopic surgery and 2 RCTs for open surgery.

Meta-analyses including studies using HumiGard as well as other humidification devices were conducted for the following outcome measures (measured as mean differences).

For laparoscopic surgery:

- Core temperature change during laparoscopic surgery (with adjunctive warming): -0.47; 95% CI -0.78 to -0.16; p=0.003
- Pain VAS scores from recovery to 48 hours after laparoscopic surgery: -0.16; 95% CI -0.31 to -0.02; p=0.03
- Shoulder tip pain from 12 to 24 hours after laparoscopic surgery: -0.41; 95% CI -0.75 to -0.06; p=0.02
- Analgesic usage from recovery to 72 hours after laparoscopic surgery: -0.15; 95% CI -0.25 to -0.05; p=0.003

- Total length of hospital stay after laparoscopic surgery: -0.07; 95% CI -0.24 to 0.10; p=0.42
- Total length of stay in postoperative recovery after laparoscopic surgery: -0.58; 95% CI -1.20 to 0.04; p=0.07
- Core temperature change for high-risk laparoscopic patients: -1.12, 95% CI -1.95 to -0.30; p=0.008
- Patient reported pain (VAS) for high risk laparoscopic patients: -0.17; 95% CI -0.32 to -0.02; p=0.03
- Patient reported pain (analgesic use) for high risk laparoscopic patients: -0.24; 95% CI -0.45 to -0.02; p=0.03
- Total length of hospital stay for high risk laparoscopic patients: -0.43; 95% CI -0.98 to 0.12; p=0.12

For open surgery:

- Core temperature change in open surgery: -0.89; 95% CI -1.22 to -0.55; p<0.00001
- Wound area temperature change in open surgery: -1.04; 95% CI -1.63 to -0.45; p=0.0006

Summary critique of clinical evidence submitted by the sponsor

The sponsor identified all studies using HumiGard that are relevant to the decision problem. However, of the 16 RCTs on laparoscopic surgery which were included in the sponsor's submission, 4 used HumiGard and the rest used humidification devices other than HumiGard. Of the 3 published meta-analyses on laparoscopic surgery, 2 included only studies that used devices other than HumiGard. In the third meta-analysis only 2 of the included studies used HumiGard. For open surgery only 1 of the 2 RCTs used HumiGard, while the other RCT used a different humidification device. Humidification systems other than HumiGard are outside scope for this assessment report.

Some studies reported the same outcome measure but at different or multiple time-points. The sponsor pooled these studies to estimate an overall effect size for the time period covering all the time-points. It is inappropriate to combine such studies for the different time-points to produce an overall effect size. Such an estimated overall effect size is not clinically useful in relation to the effect size at each individual time point. Some studies were counted more

than once as they reported the outcome at more than one time-point invalidating the analyses.

Summary of economic evidence submitted by the sponsor

The sponsor identified two existing cost-effectiveness studies and submitted a de novo analysis. Both existing studies were published as conference abstracts and assessed the HumiGard system compared with standard care in the UK. The sponsor provided unpublished manuscripts related to both abstracts.

The sponsor's de novo model compared HumiGard to standard care. The model was based on an analysis presented in one of the published abstracts. It models both laparoscopic and open surgery and presented combined results assuming a 70:30 split in usage of HumiGard. Both take the form of a simple decision tree, and incorporate the probability of complications associated with hypothermia and related NHS costs accrued. For open surgery, data on the proportions of patients experiencing hypothermia from a RCT of HumiGard were linked to data on the risk of complications associated with hypothermia from an observational study. In the basecase analysis for laparoscopic surgery, direct data on the proportions of patients experiencing complications with and without HumiGard were taken from a retrospective study. This study was only published in abstract form; however the sponsor also provided a draft unpublished manuscript relating to the study.

The basecase results of the sponsor's submission state that HumiGard costs £419 per patient compared to usual care of £724. The sponsor therefore estimates a cost saving of £305 per patient from HumiGard. The majority of the cost savings are derived from a reduction in SSIs (69%). The sponsor's basecase combines laparoscopic and open surgery, and the cost savings are largely driven by laparoscopic surgery.

Summary critique of economic evidence submitted by the sponsor

The search strategy for economic evidence was highly sensitive and well-constructed and the selection criteria reflected the final NICE scope. Both studies had only been published in abstract form. Although the sponsor provided copies of draft manuscripts for the studies, both were clearly still in development and not peer reviewed.

The sponsor's de novo model reflected the final NICE scope. The model was well presented and the EAC's model verification checks did not identify any coding errors. In the basecase analysis the results for laparoscopic and open surgery are combined. These different types of surgery are associated with different risks and resource consequences. The EAC considers that the

results for the two types of patients/surgeries should be considered as separate analyses.

The EAC accepts the sponsor's general approach to linking data on the complications associated with hypothermia with data on the proportions of patients experiencing hypothermia from the studies of clinical effectiveness. The EAC considers that it would have been preferable to use data on complications reported directly from the RCTs, but recognises that these were not generally available except for a subgroup of complications reported in a single conference abstract. The sponsor identified four alternative sources of data on complications. The EAC agrees with the sponsor's choice of data for the basecase analysis but noted that it is not free of limitations. In particular it included all surgeries and was not limited to abdominal surgery. The study also found no statistically significant association between SSIs and hypothermia, a key assumption in the sponsor's model. The EAC also notes that although detailed information on complication rates is not presented in the RCT of laparoscopic surgery, the authors report that complication rates and grades were equivalent between the HumiGard and standard care groups.

The EAC considers that some cost estimates included in the sponsors model to be outdated or based on inappropriate sources. The EAC identified recent cost estimates for the treatment of stroke based on a well conducted UK study, albeit based on data from a single region. The EAC considers the costs of myocardial infarction (MI) to have been incorrectly inflated given that these costs mainly consist of drug costs, the prices of which have decreased since the original paper was published. The EAC agrees with the sponsor that the uncertainty in the cost of treating SSIs is high, and sourced two alternative estimates based on reference costs and the published literature.

External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

The clinical evidence submitted by the sponsor for laparoscopic surgery was relatively robust in that it included 4 RCTs and 1 retrospective cohort study in appropriate patients, all of which compared HumiGard with standard unhumidified insufflant gas. The retrospective cohort study was submitted as academic in confidence at draft stage and has not yet been submitted for publication and undergone peer review. The clinical evidence submitted for open surgery was based on 2 small RCTs, one of which was a small pilot study published as abstract only.

The robustness of the economic analyses crucially rely on the robustness of data showing that HumiGard is effective in reducing the incidence of

hypothermia and complications, particularly stroke. As noted above the clinical evidence was based on one small RCT which showed no statistically significant in the reduction of hypothermia from the use of HumiGard in laparoscopic surgery and a retrospective cohort study. In addition to the uncertainties noted for the retrospective cohort study above, the multivariate analyses reported in the draft paper which adjusted for potential confounding effects on SSIs were not included in the sponsor's economic model. Neither the RCT, nor the retrospective cohort study, reported data on the incidence of stroke with and without HumiGard, which is a key driver of the economic model.

Summary of any additional work carried out by the External Assessment Centre

The EAC conducted literature searches on the effectiveness of HumiGard on MEDLINE, MEDLINE(R) In-Process & Other Non-Indexed Citations, EMBASE and Cochrane (CDSR; CENTRAL; DARE; HTA), from the inception of the databases to November 2015. Two reviewers independently screened through the citations and papers using the population, intervention, comparator and outcome measure defined in the final NICE scope as the study selection criteria. The EAC identified no relevant studies on HumiGard in addition to those identified by the sponsor.

The EAC extracted data on all outcomes of interest from relevant studies using HumiGard and produced meta-analyses based on only studies on HumiGard. The incidence of hypothermia was derived from one RCT which found no statistically significant differences between the groups [redacted] and one retrospective cohort study which found a statistically significant decrease in the HumiGard group compared with the control [redacted] Pooled estimate on this outcome appears to favour HumiGard [redacted] however, due to the difference between the studies in the designs and the effects observed, this pooled result should be interpreted with caution.

Three studies presented some outcomes using median (range) or median (interquartile range) which suggests that the data are not normally distributed. The EAC converted medians, ranges and interquartile ranges into means and standard deviations but advise that the additional meta-analyses using converted values should be interpreted with caution.

The EAC conducted searches for ongoing studies in ClinicalTrials.gov and WHO ICTRP databases, using the same search terms which were used in the

sponsor's submission and also using additional search terms. By expanding the searches the EAC identified 3 additional ongoing trials potentially relevant (2 from WHO ICTRP register and 1 from ClinicalTrials.gov).

The EAC conducted additional literature searches on the cost-effectiveness of HumiGard, checked all the literature included in the sponsor's report and the reference list of included studies. The EAC identified no additional studies.

The EAC reviewed the assumptions built into the sponsor's model in relation to available evidence and expert opinion and verified that there were no identifiable errors in the coding of the sponsor's model.

The EAC re-ran the sponsor's basecase and univariate sensitivity analyses for open and laparoscopic surgery separately. The EAC conducted additional analyses using its preferred estimates and for each type of surgery separately.

The key amendments included in the EAC re-analyses of the sponsor's model were:

- Inclusion of updated NHS reference costs of pneumonia, acute myocardial infarction and sepsis using NHS reference costs
- Annuitizing the capital cost of the HumiGard system
- Re-estimating the costs of post-MI to reflect current drug prices
- Use of alternative costs of treating stroke and SSIs
- Use of a five year time horizon
- Inclusion of the data on hypothermia from the RCT in laparoscopic surgery linked to data on complications from the retrospective cohort study (laparoscopic surgery only).

Additional sensitivity analyses conducted by the EAC included the use of a one-year time horizon, an alternative source for the costs of SSIs and (for laparoscopic surgery only) the direct data on complications reported in the abstract of the RCT in laparoscopic surgery. The EAC also reprogrammed the sponsor's model to allow a probabilistic sensitivity analysis to be conducted for the amended model.

For open surgery, the results of the EAC reanalysis suggest that HumiGard is cost saving compared to standard care with an average cost saving per patient of £209. This increase in cost saving compared to the sponsor's basecase was due to the longer time horizon. The probability that HumiGard

is cost saving was 98% in the probabilistic sensitivity analysis for the longer time horizon. The results for a one year time horizon were broadly similar to those reported by the sponsor (an average cost saving of £28 per patient).

The EACs reanalysis found lower cost savings for laparoscopic surgery than reported by the sponsor (an average cost saving of £77 per patient). This was largely due to the use of data from the RCT of HumiGard rather than the unpublished retrospective study. The probabilistic analysis found that HumiGard was cost saving in 67.5% of iterations. When a one year time horizon was used HumiGard was associated with a small additional cost of £11 per patient.

2 Background

2.1 Overview and critique of sponsor's description of clinical context

The HumiGard system is intended for use in heating and humidifying insufflant gas for laparoscopy and open surgery, specifically to minimise evaporative cooling and desiccation and prevent intra-operative hypothermia. Inadvertent perioperative hypothermia (defined as a patient core temperature of below 36.0°C) is a common but preventable complication of perioperative procedures, which is associated with poor outcomes for patients (NICE 2008).

The sponsor correctly states that the NICE CG65 recommend that each patient should be assessed for their risk of inadvertent perioperative hypothermia and potential adverse consequences before transfer to the theatre suite (NICE 2008).

This is in line with NICE guidance 65 which indicates that patients identified as being at higher risk of inadvertent perioperative hypothermia and who are having anaesthesia for less than 30 minutes should be warmed intraoperatively from induction of anaesthesia using a forced air warming device as should all patients who are having anaesthesia for longer than 30 minutes (NICE 2008).Patients should be managed as higher risk if any two of the following apply:

- ASA grade II to V (the higher the grade, the greater the risk)
- preoperative temperature below 36.0°C (and preoperative warming is not possible because of clinical urgency)
- undergoing combined general and regional anaesthesia
- undergoing major or intermediate surgery
- at risk of cardiovascular complications.

If the patient's temperature during the preoperative phase is below 36.0°C, forced air warming should be started preoperatively on the ward or in the emergency department and maintained throughout the intraoperative phase (NICE 2008). The patient's temperature should be measured and documented before induction of anaesthesia and then every 30 minutes until the end of surgery. During the postoperative phase if the patient's temperature is below 36.0°C, they should be actively warmed using forced air warming until they are discharged from the recovery room or until they are comfortably warm (NICE 2008). The current NICE guidance does not make specific recommendations on the usage of insufflation because it was observed that

warmed insufflation gases did not show a significant difference in mean core temperatures at 60 minutes. NICE MTG7 recommends that the Inditherm patient warming mattress should be considered for use in patients undergoing operations that carry a risk of inadvertent hypothermia (NICE 2011).

The sponsor claims that NICE CG65 failed to compare heated humidified gas (reduces evaporation) to heated dry gas (facilitates evaporation). The standard care arm in NICE CG65 comparison of warmed insufflation gas versus standard care although including cold-dry CO_2, also included unwarmed or room temperature CO_2 at with different ranges of humidity. Six of the 8 studies identified for this comparison were also identified by the sponsor and used in their meta-analyses (Champion 2006; Farley 2004; Hamza 2005; Mouton 1999; Ott 1998; Savel 2005). The sponsor correctly states that since publication of the guidance additional randomised controlled trials were published, including all that used HumiGard.

The sponsor states that even with current guidelines (NICE CG65), the incidence of perioperative hypothermia is in the order of 20%, citing Harper et al. (2008). This is not correct as that figure refers to an audit by one of the authors prior to publication of NICE CG65. In a study by Lavies et al. (2011), the effect of implementing NICE CG65 recommendations was compared with previous practice. The authors reported reductions in the number of patients with hypothermia (temperature below 36.0°C) at both the preoperative phase (39% (36/91) vs 17% (17/98)) and the postoperative phase (81% (74/91) vs 53% (52/98)).

The sponsor considered that the addition of the HumiGard system to deliver heated humidified insufflation could be easily implemented in the inadvertent perioperative hypothermia pathway, during the intraoperative care phase. For laparoscopic surgery standard insufflation tubing would be replaced by the HumiGard system. The system integrates between the existing insufflation equipment and the patient interface. For open surgical procedures the system easily connects to piped gas sources or alternatively if piped gas is unavailable a gas supply stand is available to deliver heated humidified CO_2 in any theatre environment.

2.2 Overview of sponsor's description of ongoing studies

The EAC replicated the sponsor's searches of ClinicalTrials.gov and the same 10 references were returned. The sponsor's searches are considered limited in that they only searched one trial database (Clinical Trials.gov) and further only used the search term "Surgical humidification". The EAC conducted a more sensitive search of ClinicalTrials.gov by adding further search terms (see section 3.9 Additional work carried out by the EAC for full details). The

EAC also suggest that a search of the WHO ICTRP (International Clinical Trials Registry Platform) would improve sensitivity as this covers some registers not included in ClinicalTrials.gov.

The sponsor identified 3 unpublished investigations that meet the scope (Frey et al., Weinberg et al. and Mason et al.), which were in the final stages of manuscript preparation. Copies of these manuscripts were provided as academic in confidence material. Frey et al. (2015) has now been published.

The EAC identified three additional ongoing trials using HumiGard (Table 1). The study ACTRN12606000287538 was registered in 2006 but the current status is “not yet recruiting”. The study ACTRN12615001231538 may not have been identified by the sponsor searches as it was only registered on 10th of November 2015, possibly after the sponsor conducted their searches. The study NCT02586974 was registered in May 2015 and is currently recruiting participants.

Table 1. Relevant ongoing studies

Study ID	Type of study	Comparison	Status	Completion date
The sponsor identified ongoing studies				
NCT01098175	Case control study	Humidified gas at 31-32 °C or exposure of the surgical wound to the air	Unknown	December 2011
NCT01887028	Crossover RCT	Warmed, humidified CO_2 or cool, dry CO_2	Unknown	September 2015
NCT02319902	Parallel RCT	Heated humidified CO_2 or cold CO_2	Currently recruiting participants	December 2015
Additional ongoing studies identified by the EAC				
ACTRN12606000287538	Parallel RCT	Humidified, heated CO_2 or use of cold, dry CO_2	Not yet recruiting	Unclear
ACTRN12615001231538	Crossover RCT	Heated humidified gas on or gas off (standard care) for 30 minute intervals	Not yet recruiting	Unclear
NCT02586974	Parallel RCT	Warmed, humidified CO_2 or standard CO_2 insufflation	Currently recruiting participants	August 2016

The sponsor excluded the study NCT01098175 on the basis that it was not investigating the correct outcome of temperature. However, the primary endpoint is decreased pain on day 1 and 2 after surgery and therefore it is

relevant to the decision problem. The recruitment status of this study when last verified in March 2010 was 'Not yet recruiting'. The EAC has not identified any publication associated with this study identifier.

The sponsor excluded the study NCT01344486 on the basis that it had been cancelled. There is nevertheless a full report of this study available (Koninckx et al., 2013). This report was not included by the EAC in the clinical evidence section because both the control group (standard humidification at 37°C using HumiGard) and intervention group (modified HumiGard was used in order to deliver fully humidified gas at 31°C) used humidified gas.

The sponsor considered that studies NCT01887028 and NCT02319902 are relevant to the decision problem. The estimated completion date for these studies was September 2015 and December 2015 respectively.

2.3 Critique of sponsor's definition of the decision problem

Population

The patient population in the NICE final scope is: people undergoing abdominal surgery, as an open or laparoscopic procedure. The subgroups to be considered are:

- 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)

The sponsor's definition of the population agreed with that of the final scope. The clinical evidence submitted by the sponsor includes analyses for the subgroups detailed in the final scope. The sponsor indicated that not all studies detailed ASA scores and therefore considered as a "high-risk" subgroup patients undergoing surgery with a pre-operative temperature below 36°C. It should be noted that a patient is considered "high-risk" if the patient meets 2 aspects of the criteria, which includes amongst others both ASA grade II to V and pre-operative temperature below 36°C (please see section 2.1). According to the EAC assessment of the studies meeting NICE CG65 criterion for "high-risk" subgroup patients (table 6), only Sammour et al. (2010) contained a "high-risk" subgroup of patients (pre-operative temperature below 36°C and major or intermediate surgery).

Intervention

The intervention in the NICE final scope is the HumiGard surgical humidification system for:

- Open abdominal surgery
- Laparoscopic abdominal surgery

The sponsor's definition of the intervention agreed with that of the final scope. The sponsor however refers to two versions of the HumiGard system, model MR860 and model SH870. The sponsor provided a table summarising the key specifications for both models and stated that they are equivalent in terms of therapeutic output but the SH870 offers a more simplified set up and a smaller device profile (Table 2). The EAC feels that the two models are comparable. There are no changes in the specifications between the consumable tubing kit used with model MR860 (ST310) and model SH870 (ST320). The model SH870 will be launched in the UK during the assessment report submission period.

Table 2. Comparison of MR860 and SH870 HumiGard systems

Humidifier	**MR860**	**SH870**
Dimensions (without chamber fitted)	140 mm x 173 mm x 135 mm	94 mm x 154 mm x 135 mm
Mass (without chamber fitted)	2.8 kg	1.7 kg
Supply voltage	230 V ~	No change
Supply frequency	50 Hz	No change
Supply current	1 A @ 230 V ~	<1 A @ 230 V~
Rated input	230 W	180 W
Heater-plate	150 W	No change
Heater-wire	22 V~, 60 W MAX	22 V ~, 30 W
93/42/EEC	Class IIa Medical Device	No Change
Recommended operating environment	18°C to 24°C, 20% RH to 60% RH	18°C to 26°C, 20% RH to 60% RH
IP rating	IPX1	No change
Humidity performance (0 to 10 L/min)	>33 mg/L	No change
Temperature and flow sensing	Via reusable 900ST100 probe	Built into SH870
Heated tubing connection	Via reusable 900ST100 probe	Built into SH870

The sponsor provided two Declarations of Conformity. Document REG-44 covered Surgical Humidification Systems and included MR860AEK Humidifier MR860 230v UK, MR860AFU Humidifier MR860 230v F/D/G EU, MR860AEU SH870AEK Surgical Humidifier 230v UK, SH870AFU Surgical Humidifier 230v F/D/G EU and SH870AEU Surgical Humidifier, all class IIa devices.

Document REG-46 covered Single use insufflation tube kits RT350 Humidified insufflation kite, ST310 Surgical humidification kit, ST300 Open surgery humidification kit, ST110 HumiGard insufflation tube, ST210 HumiGard chamber kit, ST010 HumiGard filter, 900ST600 Adaptor and ST320 Humidified insufflation kit, all class IIa devices.

A Full Quality Assurance System certificate valid from 2.3.2015 to 19.3.2020 was also provided.

Indications and contra-indications as given in the Instructions for use are given in Table 3.

Table 3. Indications and contra-indications as given in the Instructions for use

MR860 Laparoscopic Humidifier	Indication: For use in warming and humidifying surgical insufflation gas. Contra-indications: • Not for use in retroperitoneal surgery or endoscopic procedures other than intra peritoneal laparoscopy. • Not for use in patients that are contra-indication for laparoscopic surgery with carbon dioxide insufflation gas. • Not for use with gases other than carbon dioxide. • Not to be used with preconditioned carbon dioxide gas.
SH870 Surgical humidification system	Indication: For use in warming and humidifying surgical insufflation gas. Contra-indications: • Not for use in retroperitoneal surgery or endoscopic procedures other than intra peritoneal laparoscopy. • Not for use in patients that are contra-indication for laparoscopic surgery with carbon dioxide insufflation gas. • Not for use with gases other than carbon dioxide. • Not to be used with preconditioned carbon dioxide gas.
ST310 Surgical humidification kit	Intended use: For warming and humidifying surgical insufflation gas Laparoscopic procedures: Intended for patients of all ages undergoing laparoscopic procedures where carbon dioxide (CO_2) insufflation gas is used. Open surgery procedures: Intended for patients of all ages undergoing open abdominal or cardiothoracic surgical procedures where carbon dioxide (CO_2) insufflation gas is used.

Comparator(s)

The comparator in the NICE final scope for patients undergoing open abdominal surgery is: no insufflant; for patients undergoing laparoscopic abdominal surgery is: unheated, unhumidified insufflant gas. The sponsor's definition of the comparators agreed with that of the final scope although CO_2 was specified as the insufflant gas in patients undergoing laparoscopic abdominal surgery.

Outcomes

The outcome measures in the NICE final scope 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

The sponsor's definition differed from the NICE final scope in that the sponsor argued that in laparoscopic surgery, the incidence of hypothermia in the intra-operative and post-operative period was not documented. The sponsor considered that change in core temperature (between pre-operative and post-operative) is the standard reported temperature measure and this could be considered a marker of temperature maintenance. The EAC agrees with this argument but notes that the sponsor's economic model was based on the incidence of hypothermia. Data for post-operative hypothermia used by the EAC derived from an unpublished study (Mason et al.) and author's correspondence regarding the study by Sammour et al. (2010).

Cost analysis

The cost analysis in the NICE final scope stated that costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.

The sponsor's definition of the cost analysis agreed with that of the NICE final scope.

Special considerations, including issues related to equality

No special considerations including issues related to equality were identified in the scope or by the sponsor.

3 Clinical evidence

3.1 Critique of the sponsor's search strategy

Sponsors are recommended to search MEDLINE, EMBASE, Cochrane Library and MEDLINE In Process. In this case they have not done so but limited their searches to PubMed.

A PubMed search will include the content of MEDLINE but their searches will necessarily be limited by not searching EMBASE and the Cochrane Library's constituent databases. The searches (divided into 2 topics laparoscopic and open surgery) were conducted on 16 Aug 2015 followed by repeat search on 13 October 2015. No date limits were imposed on either search.

In section 10.1.4 the sponsors detail their PubMed strategy. The sponsors do not explain why the searches were divided into laparoscopic and open surgery rather than run one search overall. We also query why when both strategies were designed to locate randomised controlled trials one strategy used the term "randomised" where the other used "clinical".

Similarly both strategies searched on "humid* but the laparoscopy search also used "insuflo*". This would capture more than just using "humid*" alone. We also question whether a more sensitive search would have been achieved using "insuffl*" as well, since "insuflo*" would only capture the trade name whereas "insuffl*" would capture the medical term "insufflation".

For these various reasons the EAC felt a more sensitive strategy could have improved the yield of relevant references achieved by the sponsor's searches, as would the use of additional databases as recommended in the Procedures Manual.

The sponsors' open surgery search located 20 references and laparoscopic search located 48. The EAC search strategies themselves were more sensitively constructed, using a wider range of synonyms and use of adjacency to broaden their reach.

Section 10.1.5 of the sponsors' submission provides details of additional searches such as company or professional organisation databases. The sponsor searched in-house databases for all terms associated with risk or reports of harm. They searched the Product Surveillance database (new database) and The Product Complaints Database ("Old database"). Terms used (product numbers) are listed. The EAC is unable to comment in any depth on these searches as we are unfamiliar with the databases and their content but the process has been adequately reported by the sponsors.

Section 10.2 Appendix 2 of the sponsors' submission provides details of the search strategy for adverse events. The sponsors refer back to the PubMed search – they do not explain whether they screened the same results as for the effectiveness searches or whether they used a filter of adverse events terms, but given the small number of studies and the unreliable nature of adverse events filters the former is likely. Here we refer back to our concerns regarding the lack of sensitivity in the clinical effectiveness searches which apply also to the PubMed searches for adverse events. However, the wide range of incident databases which have been examined by the sponsors should make up for some of the deficiencies in the PubMed searching.

Additional searches conducted on the in house databases are already described on p143 section 10.1.5 – the information is repeated here as the searches largely focussed on risk/reports of harm. As previously stated the EAC does not have access to these databases so cannot comment in any detail beyond that search terms used were the relevant product numbers and this would seem a logical approach. However we are obviously unable to comment on the content of these databases and how they are maintained and updated.

The EAC considered that the adverse events searches conducted by the sponsor covered a good range of relevant resources. The information on adverse events searches could be more clearly presented to enable the reader to compare the terms and dates searched on each of the three adverse events databases. The EAC feels overall that what was done was adequate as it also included contact with collaborators to obtain information on unpublished adverse events information.

3.2 Critique of the sponsor's study selection

The sponsor's inclusion and exclusion criteria for published studies were:

Inclusion criteria	
Population (#1)	People undergoing open or laparoscopic abdominal surgery.
Interventions (#2)	Heated, humidified insufflation vs. no insufflation or unheated, unhumidified insufflation
Outcomes (#3)	Intra-operative core body temperature change (with and without an adjunctive warming device), patient reported pain measured by VAS and analgesic use, shoulder tip pain by VAS, total length of hospital stay, length of stay in post-operative recovery and any device related adverse events.
Study design (#4)	Randomised Control Trials or prior meta-analyses
Language restrictions	None
Search dates	No start limit – 31 October 2015
Exclusion criteria	
Population	Any non-human data: i.e. murine, fish, *in vitro*. Any non-abdominal surgeries.
Interventions	Any that did not contain the interventions above.
Outcomes	Any that did not contain temperature as an outcome
Study design	No reviews or comments.
Language restrictions	N/A
Search dates	N/A

The population in the sponsor's submission matched NICE's decision problem.

As to the intervention, the sponsor included studies on HumiGard as well as studies on other humidification systems in the clinical evidence review. A checklist was compiled to demonstrate that alternative insufflation interventions were comparable to HumiGard. The EAC considered that humidification systems other than HumiGard were out-of-scope and therefore studies on these systems should not be included.

The EAC noted that, the outcome inclusion criteria did not include hypothermia defined as a core body temperature of <36°C. As mentioned in section 2.3, the EAC considers that this omission from the inclusion criteria was due to no studies reporting this outcome. Pain was measured by a Visual Analogue Scale (VAS) only. Although other measures of pain are available, all of the studies assessing the use of HumiGard and measuring pain used a VAS. Studies which did not contain temperature as an outcome were excluded. This could have led to the exclusion of potentially relevant studies containing useful information on other outcomes (see section 2.2). However,

the EAC considers that all potentially relevant studies available using HumiGard were included by the sponsor.

Details of study screening and selection of the literature search results were reported in two QUORUM flow diagrams for laparoscopic and open surgery respectively, with reasons for exclusion of studies being given.

3.3 Included and excluded studies

The sponsor's clinical evidence included studies on HumiGard and other humidification systems.

In the sponsor's QUORUM diagrams illustrating study selection for laparoscopic and open surgery publications, 16 randomised controlled trials (RCTs) and 3 meta-analyses were included for laparoscopic surgery, and 2 RCTs were included for open surgery.

Of the 16 RCTs on laparoscopic surgery, 4 used HumiGard (Herrmann and De Wilde 2015; Manwaring et al. 2008; Sammour et al. 2010; Yu et al. 2013) and the rest used humidification devices other than HumiGard. Of the 3 meta-analyses on laparoscopic surgery, 2 included only studies that used devices other than HumiGard. In the third meta-analysis only 2 of the included studies used HumiGard (Manwaring et al. 2008; Sammour et al. 2010), which were however already in the list of included primary studies in the sponsor's clinical evidence review. See Table 4 below for details of the 3 meta-analyses.

Of the two RCTs on open surgery, 1 used HumiGard (Frey et al. 2012a) and the other used an alternative device (Frey et al. 2012b).

The sponsor also included the following 3 unpublished studies:

(1) Frey et al (in press): a retrospective analysis of two RCTs, both of which were already in the list of included primary studies of the sponsor's clinical evidence review, with one being on HumiGard (Frey et al. 2012a) and the other on another humidification device (Frey et al. 2012b);

(2) Mason et al. (in preparation for publication): a cost-effectiveness analysis based on a retrospective cohort study comparing patients undergoing laparoscopic colorectal resections with and without HumiGard;

(3) Weinberg et al. 2014: an abstract/poster reporting a pilot RCT comparing HumiGard with standard care and was already published.

A 5-year follow-up analysis (Sammour and Hill 2015) of a previously published RCT (Sammour et al. 2010, which was in the sponsor's list of included studies) was considered as a duplicate and thus excluded in the sponsor's review. As the 5-year follow-up study reported follow-up outcomes which were not previously reported, the EAC do not consider it as a duplicate. However, the EAC consider it irrelevant as the reported outcome measures were out-of-scope for the assessment report. One published abstract (Noor et al. 2015) reported the same study by Mason et al.. An author of the Mason et al. manuscript clarified that the Noor et al. (2015) abstract was a preliminary analysis of the study database covering the same timeframe as that in the Mason et al. manuscript. In the Mason et al. manuscript updated analyses were performed, with slightly different numbers of patients eligible. The author clarified that the Mason et al. manuscript supersedes the Noor et al. (2015) abstract.

Table 4. Outline of the 3 meta-analyses for laparoscopic surgery

Study ID	Studies included	Population	Comparison	Outcome measure	Comments
Birch et al. 2011	16 RCTs comparing heated (with or without humidification) CO_2 with standard cold CO_2.	Adult and paediatric patients undergoing laparoscopic abdominal Surgery.	Heated, with or without humidification, gas insufflation versus cold gas insufflation	Primary outcome: change in core temperature.	Device name was not reported. Checking the references of the included studies it shows that only 2 studies used HumiGard (Sammour et al. 2010; Manwaring et al. 2008), which were however already included in list of included primary studies of the sponsor's review.
Sajid et al. 2008	10 RCTs on laparoscopic procedures using standard dry CO_2 versus heated humidified CO_2 for pneumoperitoneum.	Patients of various surgical disciplines.	Heated humidified CO_2 compared with standard dry CO_2.	Postoperative pain, total analgesia usage, hospital stay, hypothermia, and lens fogging.	Device name was reported; none of the RCTs used HumiGard.
Sammour et al. 2008	7 RCTs comparing warmed and humidified insufflation with standard cold and dry CO_2 on adults undergoing elective laparoscopic abdominal surgery.	Adults undergoing elective laparoscopic abdominal surgery under general anaesthesia.	Humidified insufflation (WHI) compared with standard cold and dry carbon dioxide.	Pain by visual analogue score or morphine usage.	None of the included RCTs used HumiGard.

The EAC did not identify any additional relevant studies for the clinical evidence on HumiGard. The EAC considered that, in total, 7 studies were relevant, including 5 of the 21 RCTs included in the sponsor's flow charts that used HumiGard (Herrmann and De Wilde 2015; Manwaring et al. 2008; Sammour et al. 2010; Yu et al. 2013; Frey et al. 2012a), and 2 of the 3 unpublished studies stated by the sponsor that used HumiGard (Mason et al. and Noor et al. 2015; Weinberg et al. 2014).

Table 5 below outlines the characteristics of the 7 relevant studies on HumiGard, including 5 studies on laparoscopy and 2 on open surgery. Table 6 further presents the subgroup characteristics of these 7 studies in terms of adjunctive warming methods used, ASA grade, preoperative hypothermia (core body temperature <36^{o}C), combined general and regional anaesthesia, major or intermediate surgery, and whether at risk of cardiovascular complications.

Of the 5 studies on laparoscopic surgery, 4 were RCTs; the other was a retrospective cohort study reported by a published abstract (Noor et al. 2015) and an unpublished manuscript provided by the sponsor (Mason et al.). Of the 4 RCTs, 2 were conducted in New Zealand, 1 in Germany, and the other in Australia. Only the retrospective cohort study was based in the UK.

Of these 5 laparoscopic studies, 2 concerned gynaecological laparoscopic surgery, 2 elective laparoscopic colonic resection, and the other acute laparoscopic appendicectomy in children (aged 8–14 years). In the 4 RCTs HumiGard was compared with standard gas (defined as unheated, un-humidified carbon dioxide insufflation gas); while in the retrospective cohort study the control was without HumiGard. The mean operation time varied from 48.2 minutes to 213 minutes across the studies. The primary outcome measure was post-operative pain in 3 RCTs and total opiate analgesia use during the index inpatient stay in 1 RCT. In the retrospective cohort study it was stated that the primary outcome measure was the incidence of post-operative hypothermia.

Of the two studies on open surgery, one was a Sweden based RCT comparing HumiGard with no insufflation in adults undergoing elective colon surgery, and the other an Australia based pilot RCT comparing HumiGard plus standard care with standard care alone in adult patients undergoing primary orthotopic liver transplantation. The latter was published as an abstract only. Both measured intra-operative temperature as the primary outcome.

Table 5. Characteristics of the 7 relevant trials on HumiGard

Study ID	Study design	Setting	Population	Comparison [a]	Operating time (mean in minutes)	Outcome measure [b]
Laparoscopic Surgery						
Herrmann and De Wilde 2015	RCT	An university clinic for gynaecology in Germany	Patients aged 18 years or over with benign uterine diseases undergoing gynaecological laparoscopic surgery (N=104) Mean age 47 years	- HumiGard (n=52) - Standard gas (n=52)	84.1	- **Postoperative pain development at 2, 4, 6, 24, and 48 hours (all in VAS)** - Morphine consumption - Rejected boli - Temperature change during surgery - Length of time spent in the recovery room - Duration of inpatient stay
Manwaring et al. 2008	RCT	An university hospital in Australia	Women aged 18 to 55 years undergoing gynaecologic laparoscopy (N=60) Mean age 30 years	- HumiGard (n=30) - Standard gas (n=30)	48.2	- **Shoulder-tip pain at 4 hours post-surgery** - Time in recovery room - Nausea - Post-operative temperature - Pelvic pain
Sammour et al. 2010	RCT	Three public hospitals in New Zealand	Patients aged over 15 years or older undergoing elective laparoscopic colonic resection for any indication (N=82) Median age 70 years	- HumiGard (n=41) - Standard gas (n=41)	180.5	- **Total opiate analgesia use during the index inpatient stay** - Post-operative pain at 2 hours, 4 hours, 8 hours, 12 hours, day 1, day 2, day 3, day 7, day 14, day 30, and day 60 postoperatively (in VAS) - Intra-operative core temperature - Cytokine Response - Days of hospital stay
Yu et al. 2013	RCT	At a children's hospital in New Zealand	Children aged 8–14 years undergoing acute laparoscopic appendicectomy (N=195)	- HumiGard (n=97) - Standard gas (n=98)	65	- **Postoperative pain (analgesic use: recovery, day 1, day 2).** - Pain intensity scores

			Median age (IQR): 12 (3)			- Intra-operative core temperature - Postoperative recovery and return to normal activities
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Open Surgery						
Frey et al. 2012a	RCT	A university hospital in Sweden	Patient older than 18 years undergoing elective colon surgery (N=83) Mean age 63.5 years.	- HumiGard (n=42) - No insufflation (n=41)	- HumiGard: 181.5 - control: 217	- **Intra-operative temperature: core and wound (°C)** - Days of hospital stay
Weinberg et al. 2014 (abstract only)	RCT (pilot trial)	Australia	Adult patients undergoing primary orthotopic liver transplantation (N=22) Age not stated	- HumiGard plus standard care - Standard care alone (number of patients in each are not stated)	Not stated	**Intraoperative core temperature prior to reperfusion and at completion of surgery**

[a] Standard gas: unheated, un-humidified CO_2 insufflation gas. Number of patients reported in this table is that of patients randomised.

[b] Primary outcome measure in bold.

IQR, interquartile range.

Table 6. Subgroup characteristics of the 7 studies on HumiGard

Study ID	Adjunctive warming for both the comparison groups	ASA grade	Preoperative temperature below 36°C	Combined general and regional anaesthesia	Major or intermediate surgery *	At risk of cardiovascular complications
Laparoscopic Surgery						
Herrmann and De Wilde 2015	Upper body thermal blanket. Applied intraoperative fluids were preheated to 38◦C.	Not stated	Not stated	Not stated	YES (laparoscopy assisted vaginal hysterectomy)	Not stated
Manwaring et al. 2008	Upper body warming blanket	Not stated	Not stated	Not stated	NO (for endometriosis or adnexal pathology)	Not stated
Sammour et al. 2010	Forced air blanket. Choice, volume, and temperature of intravenous fluid given intra-operatively were discretion of anaesthetic team.	Patients with ASA>4 were excluded	YES The core temperature at the start of operation was 35.8 (0.7) in the intervention and 35.9 (0.8) in the control (median in °C, IQR)	Not stated	YES (elective laparoscopic colonic resection)	Not stated
Yu et al. 2013	Use of upper-body forced-air rewarming blankets and the choice, volume, and temperature of intravenous fluids given was discretion of anaesthetists.	Not stated	NO Baseline mean (SD) tympanic temperature (°C) was 37.1 (0.7) in the intervention and 37.0 (0.6) in the control group.	NO	NO (laparoscopic appendicectomy)	Not stated
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Open Surgery						
Frey et al. 2012a	Forced-air heating blankets over the upper part of the body, and whenever possible over the lower part of the body	Not stated	NO Core temperature before start of surgery was 36.7±0.5 in the intervention and 36.6±0.5 in the	NO All patients were given general anaesthesia and	UNCLEAR Stated as open colon surgery	Not stated

	and insulation of the limbs and head.		control group (in mean±SD, °C)	analgesia.		
Weinberg et al. 2014	Standard care involved intense measures to maintain temperature homeostasis including predetermined temperatures for infused fluid, ambient air and heating mattress temperatures.	Not stated	Not stated	Not stated	Not stated	Not stated
Abbreviations: ASA, American Society of Anaesthesiologists; IQR, interquartile range; SD, standard deviation. * The NICE guideline 65 did not define what 'major surgery' and 'intermediate surgery' are.						

3.4 Overview of methodologies of all included studies

Laparoscopic surgery

There were 4 RCTs and 1 retrospective cohort study on laparoscopic surgery.

In all the 4 RCTs, a power calculation was conducted in relation to the chosen primary outcome and an adequate sample size was recruited. Appropriate randomisation and adequate concealment were performed, and baseline comparability between the comparison groups was assessed and no statistically significant differences appeared. Blinding was adequate in only 2 of the 4 RCTs. Statistical approaches were stated and in general were appropriate. Drop-outs were reported in 3 of the 4 RCTs while it was unclear in the other. Intention-to-treat analysis was applied in 1 RCT only, while 2 RCTs used per protocol analysis only, and in the RCT in which drop-outs was unclear it was unknown whether intention-to-treat analysis was applied if drop-outs appeared. See Table 7 for details.

In the retrospective cohort study, the patients were recruited from a consecutive series; the control group were age and sex matched consecutive patients presenting over a different time frame. Baseline patient characteristics appeared to have no significant differences; however a greater proportion of patients in the control group underwent surgery for malignancy. See Table 8 for details.

Open surgery

There were 2 RCTs on open surgery, one of which was reported in abstract only. Details on methodology of the studies are shown in Table 7.

In the RCT reported in a full paper (Frey et al. 2012a), a power calculation was conducted in relation to the chosen primary outcome and an adequate sample size was recruited. Appropriate randomisation and adequate concealment were performed, and baseline comparability and intra-operative variables between the comparison groups were assessed and no statistically significant differences appeared. However, the operating team was not blinded to type of treatment, and it was unclear whether other personnel, patients and outcome assessors were blinded. Statistical approaches were stated and in general were appropriate. Drop-outs were reported but per protocol rather than intention-to-treat analysis was performed.

For the RCT reported in an abstract (Weinberg et al. 2014), there was insufficient information on the methodology of the study.

Table 7. Methodology and critical appraisal of RCTs

Study	Sample size	Appropriate randomisation and adequate concealment	Baseline comparable	Adequate blinding	Statistical analyses	Drop out reported	Intention-to-treat analysis	Selective reporting
Laparoscopic surgery								
Herrmann and De Wilde 2015	N=104. Adequate sample size which was based a statistical power analysis.	YES Computer generated randomisation. Independent, externally prepared sequentially numbered, opaque, sealed envelopes, opened before operation	YES No significant differences between groups in all recorded baseline or operative characteristics.	NO Surgeon was not blinded to the group assignment. Participants, personnel and outcome assessors were blinded to treatment allocation	ANOVA with Greenhouse-Geiser's epsilon correction, Mann–Whitney U test	YES 7 (4 from the intervention and 3 from the control group).	NO Per protocol analysis	NO No evidence of selective outcome reporting.
Manwaring *et al.* 2008 (10)	N=60 (as 'eligible for inclusion', with 30 in each arm). Adequate sample size which was based a statistical power analysis.	YES A random number generator was used. Allocation was sealed in sequential opaque envelop.	YES No significant differences in baseline or operative characteristics.	NO Operating staff were not blind to the group assignment. All nursing staff were blinded to the nature of insufflation gas used. Unclear whether patients and outcome assessors were blinded.	X^2 test, paired/unpaired t-test	UNCLEAR If the operation continued for more than 90 minutes or an exclusion factor was identified through the procedure the patient was excluded from the study. However, the number excluded was not reported.	UNCLEAR It is unclear whether the 60 participants were the number of randomised or the number finally included for analyses.	NO No evidence of selective outcome reporting.
Sammour *et al.* 2010 (11)	N=82. Adequate sample size which was based a statistical power analysis.	YES Computerised, stratified by hospital. Allocations were concealed in opaque numbered envelopes until interventions were assigned on the day of surgery	YES No significant differences in age, sex, BMI, ASA, Cr Possum, previous abdominal surgery, operation performed, diagnosis, or histologic stage.	YES Patient, investigators, surgeon, and medical staff responsible for patient care were all blinded to patient allocation. Data collection and data analysis were also blinded.	Shapiro-Wilk test, Fisher's exact test or X^2 test, Mann-Whitney U test	YES 8 (6 from the intervention and 2 from the control group).	YES Intraoperative conversions to open surgery were recorded and analysed in the allocated group on an intention to treat basis.	YES Intra-operative core temperature was measured at 15 minutes intervals but only the change in temperature between the start and end of the procedure, as well as the minimum, maximum, and mean/median

								temperatures were reported. Data on morphine equivalent usage per kilogram of patient weight and data on the core body temperature at all-time points were not shown.
Yu *et al.* 2013 (12)	N=195. Adequate sample size which was based a statistical power analysis.	YES Computerised randomisation with numbers sealed in opaque envelopes till the start of each study procedure.	YES No significant differences were found between the groups.	YES Patient, investigators, surgeon, anaesthetist, theatre personnel, and the ward nursing staff responsible for intra- and postoperative care of participants all blinded to group allocations.	Mann-Whitney U tests, t-tests, X^2 test	YES 5 (2 from the intervention and 3 from the control group) were subsequently excluded from data analysis because of major protocol violation, and the study's exclusion criteria.	NO Per protocol analysis	YES Data on patient self-evaluated postoperative recovery were not shown. Data on temperature were recorded at 10 minute intervals but only report on change in temperature from the start of the procedure to the end and temperatures between the comparison arms.
Open surgery								
Frey et al. 2012a	N=83 Adequate sample size which was based a statistical power analysis.	YES Three nurses from an independent hospital department generated the random allocation sequence and they were kept uninformed of all other parts of the study.	YES No significant differences between the groups regarding clinical variables (age, gender, weight, height, and body mass index), patients' diagnoses, operation codes, and intraoperative variables.	NO Operating team including nurse measuring patients' temperature was not blinded to type of treatment. Unclear whether other personnel, patients and outcome assessors were blinded.	Student t test, X^2 test or Fisher's exact test, Mann–Whitney U test or Wilcoxon test	YES 4 (2 from each arm).	NO Per protocol analysis.	NO No evidence of selective outcome reporting.
Weinberg et al. 2014 (abstract)	N=22 (no further details)	Described as randomised; no details were stated	Stated that both groups were evenly matched for age, body mass index, MELD,	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Not applicable

			SOFA and APACHE II scores, baseline temperature, and duration of surgery. No details were provided.					

Table 8. Methodology and critical appraisal of observational studies*

Studies	Acceptable recruitment of cohort	Accurate measurement of exposure to minimise bias?	Accurate measurement of outcome to minimise bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis?	Was the follow-up of patients complete?	Statistical analyses	How precise are the results?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

						■		

* Largely adopted from the sponsor's report

3.5 Overview and critique of the sponsor's critical appraisal

The sponsor's review summarised the study design and methodology of each of their included trials, including the 7 studies on HumiGard that the EAC considered as relevant, using the suggested table in the NICE template. For all these 7 studies on HumiGard, the sponsor stated that the primary outcome was intro-operative core temperature (in Table B 5 on page 33-35 of the sponsor's submission). However, in only 2 of these 7 studies (Frey et al. 2012a; Weinberg et al. 2014) was the primary outcome intra-operative core temperature (see details in Table 5 for characteristics of relevant trials). In the retrospective cohort study although the authors stated that the primary outcome measure was post-operative hypothermia, the primary objective of the study was to evaluate the effect of HumiGard on the incidence of surgical site infections, and it was stated that no power calculation of sample size was conducted due to the lack of literature regarding the impact of CO_2 conditioning on hypothermia and surgical site infections in elective colorectal surgery.

Critical appraisal was presented for all the 7 relevant studies. RCTs and observational studies were appraised separately using appropriate sets of quality checking questions. In general the critical appraisal for the 7 relevant studies is accurate.

3.6 Results

The sponsor completed a results table for each relevant study. However, results for each comparison arm were not stated in the tables; instead, the sponsor calculated the results on differences between the comparisons and reported in the tables.

The following errors in the data extracted/calculated were identified in the sponsor's report:

- For all the 7 relevant studies on HumiGard the sponsor stated that the primary outcome measures was core temperature, while actually it was the case in only the two open surgery studies.

- For the study by Herrmann and De Wilde (2015) the sponsor's submission reported morphine dose consumption as per kg. The sponsor clarified later through communication with the EAC that this unit is mg/day per patient. There are errors in the sponsor's calculation of the difference in morphine dose consumption between the comparison groups in recovery and day 1.

- For the Yu et al. (2013) study a p value of 0.201 was reported in the sponsor's table as for the mean difference between the comparison groups on absolute difference between start and end on core temperature change, while actually the p value was for the mean difference between the two groups at start of procedure in the paper. For this study, the data on post-operative opiate analgesia use (morphine equivalent daily dose) extracted by the sponsor for recovery, day 1 and day 2 respectively as per kg, were actually mean dose rather than dose per kg.

- For the Sammour et al. (2010) study, the core temperature change reported in the paper was median (IQR) rather than mean; the sponsor calculated the mean difference by treating the median data as mean data. For this study, the sponsor extracted the data on analgesia usage as dose per kilogram of patient weight, while in the study paper the data were reported as absolute dose rather than dose per kilogram.

- For the Frey et al (2012a) study, the sponsor presented calculations for the mean differences between the comparison groups on "core temperature change" and on "wound area temperature change". However, according to the calculations, these derived results should be the differences between the comparison groups on 'mean core temperature during the surgery' and 'mean wound area temperature during the surgery'. The sponsor later clarified through communication with the EAC that the calculations were in fact for mean differences between groups on core temperature during surgery and on wound area temperature during surgery.

As the sponsor's results tables contained findings from all studies, including studies on HumiGard and those on other devices, the EAC tabulated the outcomes from the 7 relevant studies on HumiGard only. The total number of patients in each of the 7 studies and the number of patients in each treatment arm are shown in Table 5.

Table 9 illustrates what key outcomes listed in the NICE final scope were measured in each of the studies, and Table 10 to Table 14 summarise the key outcomes from the studies.

Table 9. Outcomes measured in the 7 relevant studies on HumiGard

Study ID	Temperature (core, wound area or edge)	Surgical site infections	Length of stay in post-operative recovery	Length of hospital stay	Device-related adverse events	Patient-reported pain
Laparoscopic Surgery						
Herrmann and De Wilde 2015	√		√	√	√	√
Manwaring et al. 2008	√		√			√
Sammour et al. 2010	√ (Hypothermia)*			√	√	√
Yu et al. 2013	√					√
Mason et al.	√ (Hypothermia)	√	√	√		
Open surgery						
Frey, JM et al. 2012	√ (Hypothermia)			√		
Weinberg et al. 2014	√					

* Hypothermia rates provided by the sponsor (author's correspondence)

Table 10. Key outcomes — hypothermia; temperature (core, wound area/edge)

Study ID	Outcomes [a]	Intervention	Control	Difference	Comments
Laparoscopic Surgery					

Study ID	Outcomes [a]	Intervention	Control	Difference	Comments
Herrmann and De Wilde 2015	Core temperature change during surgery (°C), median (range), ANOVA.	−0.1 (−0.7 to 0.7)	−0.1 (−0.7 to 0.5)	p=0.768	
Manwaring et al. 2008	Core temperature in theatre (°C), mean (SD) Core temperature in recovery (°C), mean (SD) Change in core temperature from theatre to recovery (°C), mean (SD)	36.4 (0.47) 36.3 (0.63) -0.20 (0.52)	36.3 (0.38) 36.2 (0.57) -0.13 (0.61)	p=0.289 p=0.686 p=0.027	
Sammour et al. 2010	[redacted] [redacted] Change in core temperature between start and end of procedure (°C), median (IQR) Median of mean temperatures during surgery (°C), (IQR)	[redacted] [redacted] 0.4 (0.7) 36.0 (0.6)	[redacted] [redacted] 0.6 (0.9) 35.9 (0.6)	 p=0.324 p=0.981	More data reported on core temperatures. Intraoperative core temperature was measured at 15 minutes intervals using an oesophageal probe.
Yu et al. 2013	Core temperature (°C), mean (SD): • Absolute difference between start and end of procedure • Difference between maximum and minimum • Mean during procedure • End of procedure	 0.34 (0.34) 0.46 (0.32) 36.9 (0.7) 37.0 (0.7)	 0.38 (0.34) 0.48 (0.32) 36.8 (0.6) 36.9 (0.7)	 p=0.463 p=0.637 p=0.623 P=0.378	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study ID	Outcomes [a]	Intervention	Control	Difference	Comments
Open surgery					
Frey et al. 2012a	**Proportion of patients with core temperature <36.0°C at end of surgery (n)**	0	18% (7/39), 95% CI 5% to 31%	Mean difference 18%, 95% CI 6% to 30%, p=0.005	
	Proportion of patients with core temperature <36.5°C at end of surgery (n)	20% (8/40), 95% CI 7% to 33%	62% (24/39), 95% CI 46% to 78%	p=0.001	
	Core temperature (°C) before start of surgery (mean (SD))	36.7 (0.5)	36.6 (0.5)	p=0.179	
	Core temperature (°C) at end of surgery (mean (SD))	36.9 (0.5)	36.3 (0.5)	p<0.001	
	Core temperature (°C) during surgery, mean AUC (SD)	36.5 (0.5)	36.1 (0.5)	p=0.001. Sponsor calculated mean difference: -0.40, 95% CI -0.62 to -0.18, p=0.001	
	Wound area temperature (°C) during surgery, mean AUC (SD)	31.3 (1.2)	29.6 (1.3)	95% CI 1.2 to 2.3, p<0.001. Sponsor calculated mean difference: -1.70, 95% CI -2.25 to -1.15, p<0.001	
	Wound edge temperature (°C) during surgery, mean AUC (SD)	30.3 (1.1)	28.5 (1.1)	95% CI 1.3 to 2.3, p<0.001	
Weinberg et al. 2014	**Core temperature immediately prior to reperfusion (°C, via nasopharyngeal probe), mean (SD)**	36.0 (0.41)	35.4 (0.74)	p=0.02	
	Core temperature on wound closure (°C, via nasopharyngeal probe), mean	36.7	36.1	p=0.041	
	Core temperature immediately prior to reperfusion (°C, via pulmonary artery catheter), mean (SD):	35.9 (0.51)	35.5 (0.79)	p=0.14	
	Core temperature on wound closure (°C, via pulmonary artery catheter), mean	36.8	36.3	p=0.09	
	Core temperature immediately prior to reperfusion (°C, via bladder probe), mean (SD):	36.2 (0.63)	35.5 (1.03)	p=0.09	
	Core temperature on wound closure (°C, via bladder probe), mean	36.8	36.5	p=0.27	

[a] Primary outcome in bold.

Study ID	Outcomes [a]	Intervention	Control	Difference	Comments
[b] Hypothermia rates provided by the sponsor (author's correspondence)					

Table 11. Key outcomes — surgical site infection (laparoscopic surgery)

Study ID	Outcomes	Intervention	Control	Difference
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Table 12. Key outcomes — length of hospital stay or stay in post-operative recovery

Study ID	Outcomes	Intervention	Control	Difference	Comments
Laparoscopic surgery					
Herrmann and De Wilde 2015	Length (days) of hospital stay, median (range) Recovery room time (minutes), median (range)	6 (3–9) 130 (7 to 1440)	6 (5–9) 135 (60 to 135)	Difference between medians 0.00; 95% CI 0 to 0; p=0.392 Difference between medians 0, 95% CI -20 to 20, p=0.994	There appears to be an error for the difference between medians.
Sammour et al. 2010	Length (days) of hospital stay, median (IQR)	7 (7)	5 (7)	p=0.873	
Yu et al. 2013	Length (days) of hospital stay, median (IQR)	2 (2)	2 (3)	p=0.683	
Mason et al.; Noor et al. 2015	[redacted]	[redacted]	[redacted]	[redacted]	
	Length (minutes) of stay in post-operative recovery, mean*	186	190	p=0.86	
Manwaring et al. 2008	Recovery room time (minutes), mean (SD)	62.0 (19.87)	62.6 (17.65)	p=0.892	
Open surgery					

Frey et al. 2012a	Hospital stay	Not reported	Not reported	No significant differences between the groups (no data were reported)	
* Data from Noor et al. 2015					

Table 13. Key outcomes — patient-reported pain (laparoscopic surgery)

Study ID	Outcomes	Intervention	Control	Difference	Comments
Herrmann and De Wilde 2015	**Post-operative pain (VAS 0-10)**, median (range):			Difference between medians:	Data were also reported for 2, 4, 6, 24, 46 hours respectively. It is unclear why some of the reported median and range values appeared to be over 10 while the VAS scale was 0-10.
	• Total rest pain	10.2 (0-31.7)	11.1 (1.4 to 28.0)	0.05; 95% CI -2.8 to -3.1, p=0.977.	
	• Total movement pain	14.2 (0.5–28.3)	13.65 (0.4–33.7)	0.7; 95% CI -3.1 to 4.2, p=0.719.	
	• Total shoulder tip pain	0.35 (0–11.2)	1.6 (0–24.4)	1.25; 95% CI 0-2.1, p=0.037	
	• Total cough pain	16 (1.9–29.8)	14.65 (1.2–35.1)	-0.2; 95% CI -4 to 3.1, p=0.880.	
Manwaring et al. 2008	**Post-operative pain (VAS), mean (SD):**				
	• Recovery	6.4 (3.16)	7.1 (2.73)	p=0.582	
	• 24 hours - overall	4.2 (2.0)	4.2 (2.4)	p=0.948	
	• 24 hours – **shoulder**	3.0 (2.6)	2.1 (2.9)	p=0.243	
	• 24 hours – pelvic	4.1 (2.5)	3.5 (2.4)	p=0.407	
Sammour et al. 2010	Post-operative pain at rest (VAS), median (IQR):				Data were also reported for baseline, 2, 4, 8 and 12 hours, and day 3, 7, 14, 30 and 60.
	• Day 1	4 (3)	2 (2)	p=0.01	
	• Day 2	3 (2)	2 (3)	0.743	
	Post-operative pain on moving (VAS), median (IQR):				
	• Day 1	6 (3)	4 (2)	p= 0.018	
	• Day 2	5 (3)	5 (3)	p=0.509	
	Post-operative pain on coughing (VAS), median (IQR):				
	• Day 1	5 (4)	5 (4)	p= 0.222	

	• Day 2	5 (3)	6 (4)	p=0.873	
Yu et al. 2013	Pain perceived at rest and on moving measured by the VAS (0-10)	See comments	See comments	No differences at the time points (0, 2, 4, 6, 8, 10, 12, 24 and 48 hours) between the two groups.	Data were reported in graphs only.
[a] Primary outcome in bold.					

Table 14. Key outcomes — Analgesic use (laparoscopic surgery)

Study ID	Outcome [a]	Intervention	Control	Difference	Comments
Herrmann and De Wilde 2015	Morphine consumption (mg)				Data on mean morphine consumption were also reported (without SD). Differences between medians with 95% CIs were reported.
	• Intra-operative, mean (SD)	0.3 (1.5)	0.3 (1.1)	No significant differences (data not reported)	
	• Operation day, median (range)	10.5 (3.0–45.0)	13.5 (0–37.5)	p=0.054	
	• Recovery, mean (SD)	5.2 (5.2)	4.5 (3.9)	No significant differences (data not reported)	
	• Day 1, median (range)	7.5 (0–46.5)	9 (0–36.0)	p=0.061	
	• Day 2, median (range)	0 (0–12.0)	0 (0–7.5)	p=0.896	
Manwaring et al. 2008	Post-operative morphine (mg) given at recovery, mean (SD)	9.2 (6.26)	10.1 (6.45)	p=0.567	
Sammour et al. 2010	**Post-operative analgesic use (Morphine equivalent daily dose), median (IQR):**				More data on analgesia usage were available in the paper.
	• **Recovery**	10.0 (16.0)	8.0 (18.0)	p=0.783	
	• **Day 1**	22.0 (28.5)	36.0 (41.0)	p=0.344	
	• **Day 2**	16.0 (21.5)	20.0 (32.0)	p=0.156	
Yu et al. 2013	**Post-operative opiate analgesia morphine equivalent daily dose (mg/kg), mean (SD)**				More data on analgesia usage were available in the paper.
	• **Recovery**	0.9 (2.1)	0.7 (1.6)	p=0.524	
	• **Day 1**	6.6 (14.0)	7.2 (11.1)	p=0.737	
	• **Day 2**	2.2 (5.8)	2.2 (5.8) 2.8	p=0.557	

			(8.9) 0.557*		
[a] Primary outcome in bold.					

3.7 Description of the adverse events reported by the sponsor

The sponsor reviewed the studies retrieved using their search strategy for description of adverse events associated with heated, humidified insufflation. The MAUDE database, ECRI database, MHRA database, and the Fisher & Paykel Healthcare Internal product complaint database were also searched for device related events. The sponsor concluded that no published studies reported any adverse events associated directly with heated, humidified insufflation. From the EAC review, 2 of the 7 relevant studies mentioned adverse events (Herrmann and De Wilde 2015; Sammour et al. 2010); both found no adverse events specific to the intervention device.

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

The sponsor analysed the clinical evidence and conducted meta-analyses based on studies on HumiGard as well as studies on alternative devices. A random effects model was used for the meta-analyses.

Table 15 below presents the meta-analyses that were conducted by the sponsor for laparoscopic surgery, where studies on HumiGard were included.

For open surgery, the sponsor conducted a meta-analysis on core temperature change and a meta-analysis on wound area temperature change respectively, each combined two studies, one of which was on HumiGard.

In the following meta-analyses submitted by the sponsor, studies were pooled whereby the same outcome measure was reported but the outcome was measured at different follow-up time-points:

- Post-operative core temperature analysis after laparoscopic surgery (ICU admission; ICU 1 hour; ICU 4 hours);
- Pain VAS scores from recovery to 48 hours after laparoscopic surgery (recovery; 4-6 hours; 3-12 hours; 24 hours; 48 hours);
- Analgesic usage from recovery to 72 hours after laparoscopic surgery (recovery; 1 day; 2 days; 3 days);
- Patients reported pain (VAS) for “high-risk” laparoscopic patients (4-6 hours; 3-12 hours; 24 hours; 48 hours);
- Patients reported pain (analgesic use) for “high-risk” laparoscopic patients (recovery; 1 day; 2 days; 3 days).

As each of the time points represents a different outcome, it is inappropriate to combine such studies for the different time-points to produce an overall effect size. Such an estimated overall effect size is not clinically useful in relation to the effect size of each individual time point. Furthermore, in some of the above mentioned meta-analyses, some studies reported the outcome for more than one time-point; therefore the same study, and the same patients, contributed more than once to the summary.

Table 15. Sponsor's meta-analyses that included studies on HumiGard

Meta-analysis that included studies on HumiGard	Total number of studies	Number of studies on HumiGard	Overall effect size (mean difference)
Core temperature changes during laparoscopic surgery (with adjunctive warming)	10	4	-0.47; 95% CI -0.78 to -0.16; p=0.003
Pain VAS scores from recovery to 48 hours after laparoscopic surgery			-0.16; 95% CI -0.31 to -0.02; p=0.03
• Recovery	3	1	
• 4-6 hours	5	1	
• 3-12 hours	5	1	
• 24 hours	10	2	
• 48 hours	6	1	
Shoulder tip pain from 12 to 24 hours after laparoscopic surgery	6	2	-0.41; 95% CI -0.75 to -0.06; p=0.02
Analgesic usage from recovery to 72 hours after laparoscopic surgery			-0.15; 95% CI -0.25 to -0.05; p=0.003
• Recovery	8	4	
• 1 day	9	3	
• 2 days	7	3	
• 3 days	2	1	
Total length of hospital stay after laparoscopic surgery	10	3	-0.07; 95% CI -0.24 to 0.10; p=0.42
Total length of stay in postoperative recovery after laparoscopic surgery	6	1	0.58; 95% CI -1.20 to 0.04; p=0.07
Core temperature change for high-risk laparoscopic patients	5	1	-1.12, 95% CI -1.95 to -0.30; p=0.008
Patient reported pain (VAS) for high risk laparoscopic patients			-0.17; 95% CI -0.32 to -0.02; p=0.03
• 4-6 hours	3	1	
• 3-12 hours	3	1	
• 24 hours	5	1	
• 48 hours	3	1	
Patient reported pain (analgesic use) for high risk laparoscopic patients			-0.24; 95% CI -0.45 to -0.02; p=0.0
• Recovery	2	1	
• 1 day	4	1	
• 2 days	3	1	
• 3 days	1	1	
Total length of hospital stay for high risk laparoscopic patients	3	1	-0.43; 95% CI -0.98 to 0.12; p=0.12

As NICE is interested in the effectiveness of HumiGard rather than the overall estimate of effectiveness of heated and humidified insufflation by any devices,

and the effectiveness of HumiGard cannot be discerned from the pooled effect sizes including studies on HumiGard and studies on alternative devices, the EAC thus summarised the clinical evidence, and where appropriate conducted meta-analyses using random effects model, based on studies that used HumiGard only. Although no statistically significant differences were observed for some of the outcomes, the EAC considered that it would be useful to produce, where appropriate, forest plots with only studies using HumiGard.

Incidence of hypothermia in the intra- and post-operative period

Laparoscopic surgery

Two studies measured the hypothermia incidence (Sammour et al 2010; Mason et al.).

[redacted]

The pooled results should be interpreted with caution and the methodological heterogeneity as well as clinical diversity between the two studies should be noted (see table 5-8 for details). The two studies are very different in terms of study design; one being a RCT (Sammour et al. 2010) and the other a retrospective cohort study (Mason et al.). There are also differences between the studies in terms of the clinical settings, the study participants, the care that patients received and the outcome measures.

[redacted]

Hypothermia was defined as core temperature below 36°C in the Mason et al. study. Compared with patients receiving peritoneal insufflation with room temperature, dry CO_2, patients in the HumiGard group had a statistically lower incidence of hypothermia both perioperatively and postoperatively

[redacted]

[redacted] 10 [redacted] There were no statistically significant differences between intervention and control group in the RCT (Sammour et al. 2010).

Four RCTs reported outcomes on core or wound area/edge temperature rather than hypothermia (Herrmann and De Wilde 2015; Manwaring et al. 2008; Sammour et al. 2010; Yu et al. 2013). No statistically significant differences were shown between the HumiGard and the control groups (see Table 10 for details).

The EAC pooled the 2 studies that reported mean and standard deviation for the mean difference on core temperature changes during laparoscopy (Figure 2) and for the mean difference on core temperature during and after laparoscopy using a random effects model (Figure 3). No statistically significant differences were found.

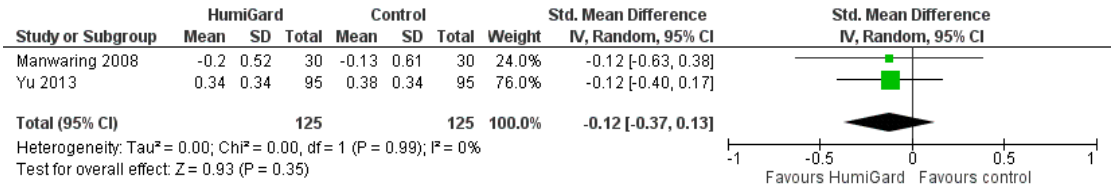


Figure 2. Core temperature changes during laparoscopic surgery

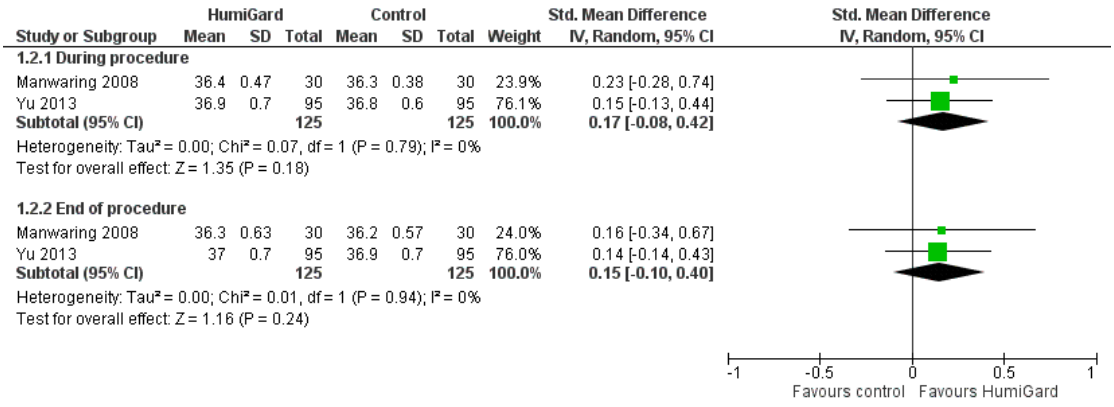


Figure 3. Core temperature during and at end of laparoscopic surgery

Open surgery

Only one RCT reported outcomes on hypothermia (Frey et al. 2012a). At the end of surgery no patients had hypothermia in the HumiGard group, while the incidence of hypothermia in the control was 18% (7/39), and the difference between the two groups was statistically significant (p=0.005).

Incidence of surgical site infections

Only one retrospective cohort study on laparoscopic surgery reported outcomes on surgical site infection (SSI) (Mason et al.).

[redacted]

The EAC notes however that the draft manuscript does not specify the form of model used (assumed to be logistic regression), give univariate data for the variables considered for the model, or report the rationale or method for model selection. The multivariate analyses must therefore be regarded as provisional.

[redacted]

It should be noted that this study is a retrospective cohort study currently at a draft stage and has not yet been submitted and undergone peer review.

No studies on open surgery reported outcomes on incidence of surgical site infections.

Length of hospital stay or length of stay in post-operative recovery

Four RCTs (Herrmann and De Wilde 2015; Sammour et al. 2010; Yu et al. 2013; Manwaring et al. 2008) and 1 observational study (Mason et al.; Noor et al. 2015) on laparoscopic surgery reported length of hospital stay or stay in post-operative recovery. None found statistically significant differences between the HumiGard group and the control (see Table 12 for details).

One RCT on open surgery reported on length of hospital stay (Frey et al. 2012a). It stated that there were no statistically significant differences between the comparison groups; however data were not provided.

Device-related adverse events

Two RCTs on laparoscopic surgery mentioned adverse events (Herrmann and De Wilde 2015; Sammour et al. 2010); both found no adverse events specific to the intervention device.

No studies on open surgery reported outcomes on device-related adverse events.

Patient-reported pain

Four RCTs on laparoscopic surgery (Herrmann and De Wilde 2015; Manwaring et al. 2008; Sammour et al. 2010; Yu et al. 2013) reported post-operative pain (see Table 13).

In the Herrmann and De Wilde (2015) study there was no statistically significant difference between the comparison groups in total rest pain, total movement pain, and total cough pain. Patients in the HumiGard group had a significantly lower score of should tip pain compared with those in the control group (difference between medians 1.25, p=0.037). In this study the VAS scale used was 0-10; it was unclear why some of the reported median and range values appeared over 10.

In the Manwaring et al. (2008) study no statistically significant differences on post-operative pain score were found between the comparison groups in either recovery or 24 hours.

In the Sammour et al. (2010) study, the HumiGard group had significantly lower median pain score at rest or on moving when compared with the control in day 1, but the scores were not significantly different between the two groups in day two. There were no significant differences between the two groups on pain on coughing either in day 1 or in day 2.

The Yu et al. (2013) study found that there were no differences at any of the elected time points (0, 2, 4, 6, 8, 10, 12, 24 and 48 hours) between the intervention and control.

Analgesic use

Four of the RCTs on laparoscopic surgery (Herrmann and De Wilde 2015; Manwaring et al. 2008; Sammour et al. 2010; Yu et al. 2013) reported analgesic use (see Table 14). No statistically significant differences in analgesic use were observed in the studies between patients in which HumiGard was used and those that did not use HumiGard. The EAC pooled estimates of mean difference for analgesic use at recovery room of the 3

studies that reported analgesic use as mean and standard deviation and found no statistically significant differences (Figure 4).

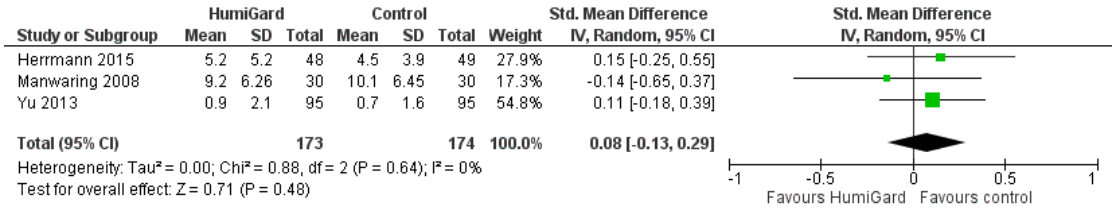


Figure 4. Analgesic usage after laparoscopic surgery (recovery room)

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

The EAC conducted literature searches on the effectiveness of HumiGard on MEDLINE, MEDLINE(R) In-Process & Other Non-Indexed Citations, EMBASE and Cochrane (CDSR; CENTRAL; DARE; HTA), from the inception of the databases to November 2015 (see search strategy in appendix 1). The EAC checked all the literature included in the sponsor's report, and also checked the reference list of included studies. For the effectiveness, a total of 1207 hits from the database searches were obtained. Eighteen records from other sources were also identified. Two reviewers independently screened through the citations and papers using the population, intervention, comparator and outcome measure defined in the NICE final scope as the study selection criteria. The study screen and selection process is shown in Figure 12 (Appendix 1). The EAC identified no additional studies.

The meta-analyses included in the sponsor's submission comprised studies using humidification devices other than HumiGard and not commercially available in the UK. The EAC extracted data on all outcomes of interest from relevant studies using HumiGard and produced meta-analyses based on HumiGard studies only. It should be noted that 3 studies (Herrmann and De Wilde 2015; Sammour et al. 2010; Yu et al. 2013) presented the outcomes using median (range) or median (interquartile range) which suggests that the data are not normally distributed. The EAC considers that it is inappropriate to rely on conversions of the median (range) into mean and standard deviation for the purposes of using the data in the meta-analyses where data are skewed. However, for information purposes the EAC has converted median (range) into mean and standard deviation as suggested by Hozo et al. (2005). If median (interquartile range) were presented, the EAC used the median as mean and considered the width of the IQR as 1.35 standard deviations

(Higgins and Green, 2011). The additional meta-analysis (appendix 3) should be interpreted with caution as the conversion of medians into means assumes that the data is normally distributed, which does not seem to be the case.

Only one study (Sammour et al. 2010), contained a “high-risk” subgroup of patients (pre-operative temperature below 36°C and major or intermediate surgery), therefore the EAC did not conduct a sub-group analysis for this patient group.

The EAC repeated sponsor’s searches of “surgical humidification” in ClinicalTrials.gov database and same 10 references were returned as were originally located. In addition we applied the following search terms: humigard, insuflow, insufflation and heated, perioperative and humidification, surgical AND humidification. We also searched in the database WHO ICTRP using the term “surgical humidification” and same 10 references were returned as were originally located by the sponsors in ClinicalTrials.gov (i.e. all duplicates). The EAC then tested the additional search terms used to expand the ClinicalTrials.gov searches on the WHO ICTRP databases, also with the intention of creating a more sensitive search. By expanding the searches the EAC identified 3 additional ongoing trials potentially relevant (2 from WHO ICTRP register and 1 from ClinicalTrials.gov) (see section 2.2).

3.10 Conclusions on the clinical evidence

All relevant studies on HumiGard were identified in the sponsor’s report, and relevant data from these studies were included. However, the sponsor’s conclusions were drawn from meta-analyses which included studies on both HumiGard and other humidification systems. The sponsor submitted a statement of equivalence between HumiGard and additional humidification systems available. The EAC considers that the mechanism between the systems may be similar; however, for the purposes of this assessment report, humidification systems other than HumiGard were out-of-scope and therefore should not be considered.

For laparoscopic surgery, as studies did not generally include hypothermia as an outcome, the sponsor included changes in core temperature as an outcome. The sponsor’s meta-analysis of RCTs using all humidification devices favoured humidification, although studies had a high degree of heterogeneity. The sponsor’s meta-analyses also showed statistically significant differences favouring humidification systems for pain VAS scores from recovery to 48 hours after laparoscopic surgery, shoulder tip pain from 12 to 24 hours after laparoscopic surgery, analgesic usage from recovery to 72 hours after laparoscopic surgery, core temperature change for high-risk laparoscopic patients, patient reported pain VAS for high risk laparoscopic

patients, and patient reported pain (analgesic use) for high risk laparoscopic patients.

For open surgery, the sponsor's meta-analyses showed statistically significant differences favouring humidification systems for core temperature change and wound area temperature change.

As the sponsor presented no analyses and no conclusions specifically for HumiGard, the EAC summarised the clinical evidence for HumiGard only.

One RCT and one retrospective cohort study reported on the incidence of hypothermia after laparoscopic surgery. The RCT did not observe any statistically significant differences while the retrospective cohort study found statistically significant reduction by using HumiGard in abdominal laparoscopic surgery. The pooled estimate for this outcome appears to favour HumiGard; however, there were differences between the studies in the designs and the effects observed in that the RCT produced results less favourable to HumiGard than the observational study. The pooled result should be interpreted with caution as it may incorporate bias resulting from study design.

Four RCTs assessing the use of HumiGard during abdominal laparoscopic surgery did not observe statistically significant differences between HumiGard and the control for temperature during perioperative or postoperative phases, or temperature changes between these phases.

Incidence of surgical site infection was only reported in one observational study on laparoscopic surgery. A multivariate analysis showed a statistically significant decrease in the risk of SSI with the use of HumiGard. In those patients who had hypothermia there was a statistically higher incidence of SSI compared with those without hypothermia. It was not clear from the report whether SSI only occurred in those patients with hypothermia.

The use of HumiGard was not associated with differences in length of hospital stay.

Two RCTs on laparoscopic surgery mentioned adverse events. No device-related adverse events were reported.

Four RCTs on laparoscopic surgery reported post-operative pain scores at different time points. Two of the RCTs did not observe statistically significant differences in pain scores between the groups while 1 RCT found that HumiGard led to statistically significant lower pain score for shoulder tip pain and 1 RCT observed similar significance for pain score at rest or on moving in day 1.

Four RCTs on laparoscopic surgery reported analgesic use. No statistically significant differences in analgesic use were observed in the studies between patients in which HumiGard was used and those that did not use HumiGard.

Two RCTs on laparoscopic surgery mentioned adverse events. No device-related adverse events were reported.

Four RCTs on laparoscopic surgery reported post-operative pain scores at different time points. Two of the RCTs did not observe statistically significant differences in pain scores between the groups while 1 RCT found that HumiGard led to statistically significant lower pain score for shoulder tip pain and 1 RCT observed similar significance for pain score at rest or on moving in day 1.

Four RCTs on laparoscopic surgery reported analgesic use. No statistically significant differences in analgesic use were observed in the studies between patients in which HumiGard was used and those that did not use HumiGard.

Only 1 RCT reported on hypothermia for open surgery. It observed a statistically significant difference in incidence of hypothermia between patients using HumiGard and those in the control group. Data on length of hospital stay was not reported, although the authors state that no significant differences were observed between the groups. No additional outcomes relevant to the decision problem were reported by studies assessing the use of HumiGard for open abdominal surgery.

In summary, the sponsor's submission evidence in favour of humidification was based on synthesis of studies and consideration of different humidification systems to be equivalent. If, in line with the assessment report scope, HumiGard alone is considered, the evidence base is reduced.

4 Economic evidence

4.1 Published economic evidence

Critique of the sponsor's search strategy

Sources

As suggested by the NICE MTEP Sponsor Submission template, the sponsor searched: MEDLINE (Ovid), MEDLINE In Process (Ovid), EMBASE (Ovid), EconLit (Ovid), NHS EED (Cochrane/Wiley) Issue 2 of 4 2015. Additionally the sponsor extended their searches to the HTA database (Cochrane/Wiley Issue 4 of 4 2015, Web of Science Conference Proceedings Citation Index and ISPOR Scientific Presentations database). Most of the searches were run on 17 November 2015.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) meeting selected for searching was the 18th Annual European Congress. The returned results were screened and assessed online. It was only possible to search this database by simple single term searches.

The reference lists from the clinical evidence review were assessed to locate any further suitable studies, although none were identified. The research team also discussed any known studies assessing the cost-effectiveness of HumiGard. It was hoped that the research team would identify further studies on the cost effectiveness aspects of HumiGard. Nothing which had not already been identified by the database searches was retrieved.

The searches were limited from 2007 to the present, given that 2007 was identified by experts as the earliest date studies on the HumiGard system would be found.

Prior to searching, the sponsor checked the strategy by testing its ability to retrieve a sample of known relevant economic studies (taken from the MTEP clinical evidence submission and a Cochrane review). This draft strategy retrieved all studies successfully. The one known economic study was among those papers retrieved.

Section 8.1 of the submission explains in some detail how the strategy was constructed. The four concepts the strategy was broken into were: economic evaluation and cost terms; terms for CO_2; humidification and heating. The sponsor combined them using Boolean operators as below:

Economic filter AND CO_2 AND (humidification OR heating).

The CO_2 set of terms also included terms relating to insufflation and pneumoperitoneum in case the CO_2 concept was not explicit in the database records. Likewise the strategy included terms aimed at identifying studies referring to humidification, warming or heating of non-specific gases and another set aimed specifically at identifying the HumiGard systems and related device manufacturer names.

The final combination would look something like:

((CO2 OR insufflation OR pneumoperitoneum) AND (humidification OR heating))
OR
(humidification of non-specific gases)
OR (HumiGard)
AND
Economic filter
NOT
(animal) or (editorial OR letter)
AND
2007- current
AND
English language

The strategy used a combination of subject index terms and free text. The search terms were arrived at by a combination of methods – discussion with the team, scanning background literature, consulting thesauri and using the PubReMiner tool.

The economic filter is based on the algorithm used to capture economic evaluations to populate the NHS EED database of the Cochrane Library http://www.crd.york.ac.uk/crdweb/PDFs/NHS%20EED%20MEDLINE%20021220 13.pdf. The EconLit search did not require the use of a filter as it is a specialist economic database.

We note that in the EconLit and Conference Proceedings Citation Index strategies the terms for surgery are more extensive (lines 16-22 in EconLit and lines 26-31 in CPCI) than in the other databases, and it was unclear why this approach was taken. However, overall the search strategies were sensitive and well-constructed and were likely to have captured most of the few relevant studies.

Clinical parameters and variables

The sponsor conducted a pragmatic review to identify studies reporting on clinical outcomes on patients with hypothermia and normothermia post-

surgery (SS: Section 9.2, page 25). A search was undertaken to identify suitable studies published since 2007, when searches were conducted to inform the development of NICE CG65 (NICE, 2008). A targeted search combining Surgery AND infections AND hypothermia was conducted, including a highly focused set of terms aimed at identifying a sample of those studies which report on infections but do not explicitly refer to infections in the database record. The search terms were arrived at by a combination of methods as before, including discussion with the team, scanning background literature, consulting thesauri and using the PubReMiner tool.

Resource identification, measurement and valuation studies

The sponsor did not conduct a separate search for resource identification, measurement and valuation studies (SS: Section 9.3.3) as the required information was taken from studies identified in section B of the submission. In addition to this, costs of clinical events were derived from NHS Reference Costs 2013/14 and previous NICE guidance rather than literature searching.

Summary

The searches in section C of the submission for existing economic evaluations are highly sensitive and well-constructed. There does not appear to be much consistency between the searches in part B and part C. The former were much less sensitive and restricted to fewer databases, although the searches for adverse events were well conducted and comprehensive.

The search strategies for economic evidence in section C were consistent with the requirements of the MTEP Sponsor Submission Template, searching all the recommended databases and three supplementary ones. The strategy itself was tested on a known set of studies on the topic and retrieved 100% of the relevant references. The database searches were supplemented by reference searching and consultation with experts - overall a highly sensitive strategy (although with some detriment to precision) and likely to have located most relevant studies.

Critique of the sponsors study selection

The inclusion/exclusion criteria in the study selection process are presented in Table 16. The selection criteria used by the sponsor is inclusive of the NICE final scope.

Table 16. Selection criteria used for health economic studies

Category	Inclusion criteria	Exclusion criteria
Population	People undergoing open or laparoscopic abdominal surgery	People undergoing surgery that is not abdominal

Interventions	HumiGard surgical humidification system	Any non-HumiGard System
Comparator	None specified (either no comparator or standard care)	-
Outcomes	Any	None
Study design	All types of economic evaluations and cost studies including cost analyses and cost-effectiveness and budget-impact analyses	Animal studies
Language restrictions	English	Non-English
Search dates	2007 onwards	Prior to 2007

Source: Sponsor Submission (SS), Table C1

Included and excluded studies

A total of 1007 records were identified from the literature and, after screening, 3 potentially relevant articles were retrieved. Only two studies met the inclusion criteria. Both are conference abstracts and assessed the HumiGard system compared with standard care in the UK (see Table 17). The EAC conducted additional literature searches. No new studies reporting cost effectiveness of HumiGard was identified. The sponsor provided unpublished manuscripts (Jenks et al., Mason et al.) related to both abstracts.

Table 17. Summary list of all evaluations involving costs

Study (year) Country	Design	Population	Costs	Outcomes	Results
Jenks *et al.* (2015) **UK**	Cost-utility analysis using decision analytic model of the HumiGard system compared with standard care	Patients undergoing open or laparoscopic colorectal surgery	Not reported in abstract, but included: Device costs; Complication costs	QALYs	The HumiGard system dominated over standard care in both open and laparoscopic surgery patients.
Mason *et al.* (2015) **UK**	Trial based cost-benefit analysis of the HumiGard system compared with standard care	Patients undergoing laparoscopic colorectal surgery	Treatment costs of surgical site infection (SSI)	SSI	The HumiGard system dominated over standard care: Cost savings = £1,226 per SSI avoided. This cost saving already includes the offset costs of the avoided SSI.

Source: SS, Table C2

Overview of methodologies of all included economic studies

Jenks et al. (2015); Jenks et al. (unpublished)

The abstract by Jenks (Jenks et al., 2015) reported cost utility of local insufflation of warmed humidified air in patient undergoing colorectal surgery and laparoscopic colorectal surgery. Compared to usual practice, use of HumiGard yielded cost savings of £33 per open surgery and £438 per laparoscopic surgery; and avoided QALY loss of 0.013 and 0.0006 per open and laparoscopic patients respectively. The authors estimated net monetary benefit per patient of £296 for open surgery and £450 per laparoscopic (given NICE CE threshold of £20,000 per QALY).

The unpublished manuscript by Jenks et al provided further detail on the study.

[redacted]The model presented in the sponsor's submission is based on the analysis presented in Jenks et al (Jenks et al, unpublished) and further details are reported in Section **Error! Reference source not found.** describing the sponsor's economic model.

Mason et al. (2015); Mason et al. (unpublished)

The abstract by Mason et al. (2015) reported a cost effectiveness analysis of HumiGard in patients undergoing laparoscopic colorectal surgery. The analysis included SSI, peri-operative hypothermia and costs per patient receiving warmed and humidified carbon dioxide compared to usual practice. Treatment costs including SSI costs for patients in the control group were approximately £31,000 compared to £21,500 in the intervention group. It was reported that it costs on average £1226 less to generate each additional

infection-free patient using HumiGard. The EAC has been unable to replicate the ICER calculation of £1226.

Two versions of a full manuscript corresponding to the abstract were provided to the EAC during the course of the review. These were not complete and the EAC considers them to be 'work in progress'. The analysis was based on a retrospective cohort study conducted in the UK (Noor et al., 2015). There were several differences between the unpublished manuscript and the published abstract. These data are used in the economic model and discussed further in the Section on 'Clinical effectiveness parameters' and 'Sensitivity analyses' below.

[redacted]

Overview and critique of the sponsor's critical appraisal for each study

The sponsor has not provided a critical appraisal of the studies included.

Does the sponsor's review of economic evidence draw conclusions from the data available?

The economic model submitted by the sponsor was adapted from the model reported in Jenks et al (Jenks et al, unpublished).

4.2 De novo cost analysis

The sponsor submitted a de novo economic model adapted from an existing model reported in a currently unpublished paper (Jenks et al, unpublished). The model estimates the resource-consequences of the use of the HumiGard system in abdominal surgery. The model includes the use of HumiGard in open and laparoscopic surgery.

In open surgery, cost savings are determined by differences in the proportions of patients with hypothermia at the end of surgery with and without HumiGard, linked to data on complications associated with hypothermia from secondary sources. In the basecase for laparoscopic surgery, cost savings are

determined by differences in the proportions of patients experiencing SSIs and pneumonia with and without HumiGard. A scenario analysis is also presented for laparoscopic surgery which uses the same approach as for open surgery (combining baseline risk of complications with the proportions of patients with hypothermia).

The EAC received replies from two of the three NICE clinical experts contacted for advice regarding various assumptions included in the sponsor's submission. Specific details are reported below and in the Correspondence log.

Patients

The analysis includes patients undergoing open or laparoscopic abdominal surgery as defined in the NICE final scope.

In the basecase the ratio of patients undergoing laparoscopic vs open surgery is 70:30. The two clinical experts consulted by the sponsor stated that HumiGard is currently only used during laparoscopic surgery in their centres. Of the two NICE clinical experts who responded to the EAC, one reported that HumiGard is only used in a laparoscopic setting in their centre and the other noted a general low uptake in an open setting and attributed this to a lack of knowledge, experience and staff training.

In the basecase analysis the results for laparoscopic and open surgery are combined. These different types of surgery are associated with different risks and resource consequences. The EAC considers that the results for the two types of patients/surgeries should be considered as separate analyses.

Technology

The technology is the HumiGard system to provide local insufflation of warmed humidified CO_2 during surgery.

Comparators

The comparators are consistent with the NICE final scope. The comparator for open surgery is no insufflant. The comparator for laparoscopic surgery is unheated and unhumidified insufflant gas.

The EAC notes that whilst other devices are commercially available internationally, these are not currently available in the UK and therefore considers the comparators to be appropriate and in accordance with the NICE final scope.

Model structure

In the base case two models were presented to estimate mean cost savings per patient associated with use of the HumiGard system compared with no HumiGard use. The models were constructed to reflect savings in open repair and laparoscopic colorectal surgery respectively. Both take the form of a simple decision tree, and incorporate the probability of complications associated with hypothermia and related NHS costs accrued.

Open surgery:

In the open surgery model, data on the risk of hypothermia (<36^{o}C) (Frey et al, 2012) and consequent associated risk of 6 complications (MI, stroke, sepsis, pneumonia, SSI and mortality) (Billeter et al., 2014) were utilised to estimate the expected cost per patient when using HumiGard and without its use. A diagrammatical representation is shown in **Error! Reference source not found.**.

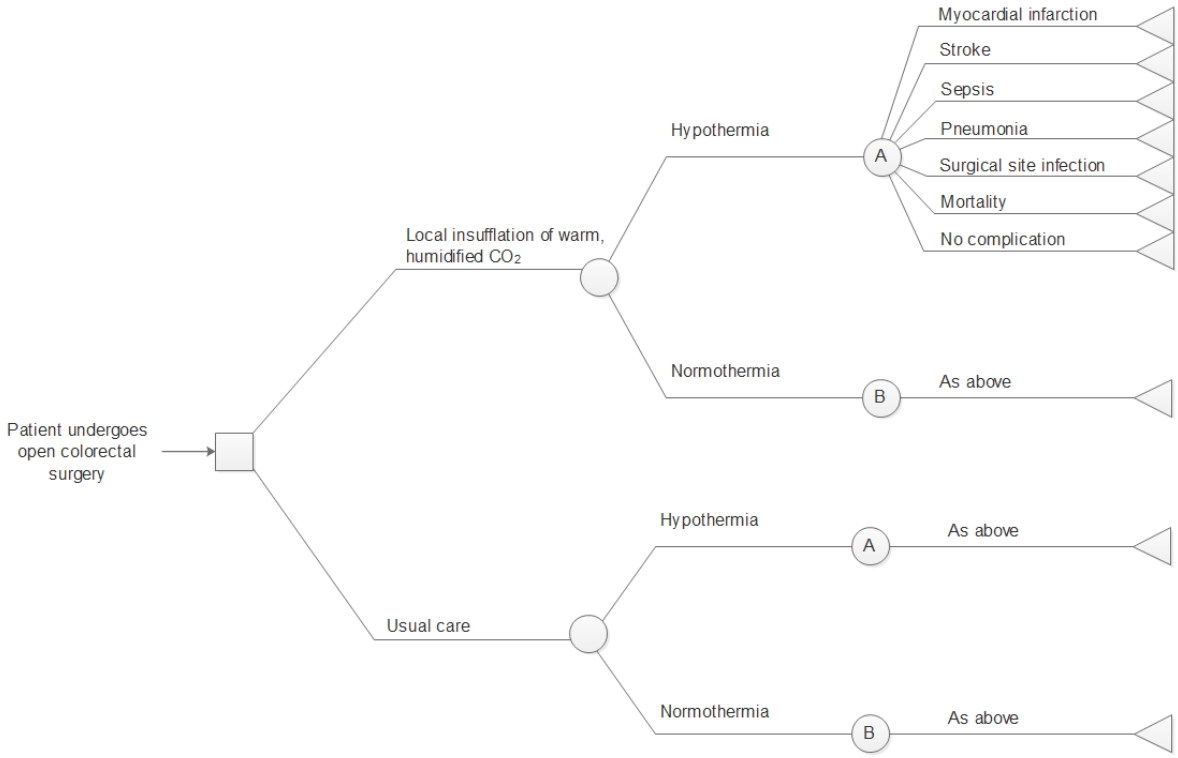


Figure 5. Open surgery model structure

Laparoscopic surgery:

In the laparoscopic surgery model, direct comparative data on two associated complications (Noor et al., 2015), SSIs and pneumonia, was used to reflect the probability of a patient experiencing either. The associated costs of each event were applied to estimate the expected cost per patient in the two arms. A diagrammatical representation is shown in **Error! Reference source not found.**.

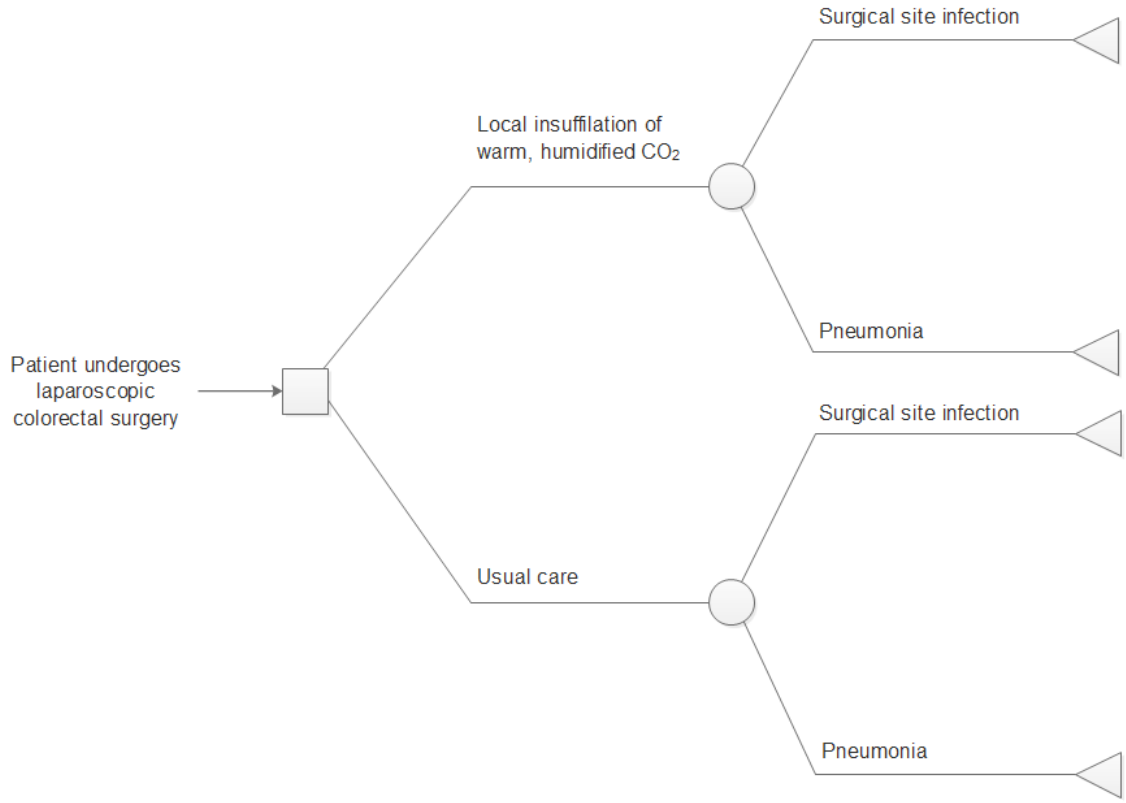


Figure 6. Laparoscopic surgery model structure

Clinical parameters and variables

Clinical effectiveness - Open surgery

In the analysis for open surgery, effectiveness is determined by combining two data sources: the proportion of patients with hypothermia at the end of surgery and the proportions of patients with and without hypothermia who experience complications.

The proportion of patients with hypothermia at the end of surgery is obtained from the study by Frey et al. (2012a). In brief, this was a RCT in patients undergoing elective open colon surgery conducted in Sweden. Patients were randomised to receive local wound insufflation of warmed humidified CO_2 during surgery using the HumiGard system (n=40) compared to standard care alone (n=39). Both groups received standard care which included forced-air warming, warm fluids and insulation of the limbs and head. The primary outcome in the study was change in core temperature. The study also reported the proportion of patients who were hypothermic at the end of surgery, defined as <36^{o}C: 0 in the HumiGard group; 18% (95% CI: 5% to 31%) in the control group; p=0.005. Further details and quality assessment are reported earlier in this report.

The risk of complications is obtained from a retrospective observational study conducted in the USA (Billeter et al., 2014). A large database of information from multiple hospitals was interrogated to examine the impact on complications of hypothermia, defined as core body temperature of less than 35^{o}C. Patients identified as having hypothermia during elective operative procedures (n=707) were matched with controls (n=698). Patients were matched for type of procedure, Diagnosis Related Group, demographics, severity of illness at admission, pre-existing co-morbidities and blood transfusions. The pre-defined level at which statistical significance is determined is not reported in the paper. However, patients with unintentional hypothermia had significantly worse outcomes including mortality ($p<0.001$), sepsis ($p<0.001$), pneumonia ($p<0.001$), stroke ($p=0.001$) and myocardical infarction ($p=0.01$). There appeared to be no statistical difference in wound infection between patients with and without unintentional hypothermia (5% vs 3.3%; $p=0.14$).

The BBC EAC notes that the study by Billeter et al. (2014) was a large study (N=707) and designed to match cases and controls for a range of characteristics. One of NICE clinical experts considered the data from USA would be generalisable to a UK population. The study has, however, several limitations. Firstly, it was not limited to patients undergoing abdominal surgery; it included a large proportion of patients undergoing general surgery (25%) in addition to patients undergoing surgery for a variety of other reasons. One of the NICE clinical experts noted that the impact and cost of SSI is greater in patients undergoing colorectal surgery; however no information was provided by the experts as to whether the rates of complication associated with hypothermia would be expected to differ between the different types of surgery. The study also excluded patients with mild hypothermia (35 to 36^{o}C) from their definition of hypothermia (the definition of normothermia was not explicitly stated), whereas the other studies of clinical effectiveness included patients with mild hypothermia within their definitions. It is not possible to directly estimate the impact of this on the results; however, if the rates of compilations are expected to be lower in patients with mild hypothermia compared to moderate/severe hypothermia, the use of these data would underestimate the cost savings associated with reducing rates of hypothermia. The EAC further notes that the difference in the proportions of patients experiencing SSI was not statistically significant.

Three alternative sources of evidence for the proportions of patients experiencing complications with and without hypothermia are presented in scenario analyses. These are discussed further in the section describing Sensitivity Analyses.

Clinical effectiveness – Laparoscopic surgery

In the basecase for laparoscopic surgery, effectiveness was based on the proportions of patients experiencing a SSI or pneumonia with and without HumiGard reported in a published abstract (Noor et al., 2015). The study was a retrospective 'before and after' cohort study. The first cohort included patients undergoing laparoscopic colorectal resections before the HumiGard system was introduced to the centre (Sept 2012 to July 2013) and the second cohort included patients after the introduction of HumiGard (July 2013 to [month not stated] 2014). The authors reported that the incidence of SSI reduced from 12% to 4.7% with HumiGard (p=0.047) and a non-statistically significant reduction in pneumonia (n=4 vs 1; p=0.21). Limited details are available from the abstract to assess the study design and quality.

As noted above, the sponsor also provided draft manuscripts reporting a cost-effectiveness study (Mason et al., unpublished) and noted that this is the same study as reported in Noor et al. (2015).

The EAC notes discrepancies between the published abstract and unpublished manuscript.

[redacted]

[redacted]

The current manuscript and correspondence with sponsor/authors highlighted that the manuscript is work in progress and emphasises the importance of the peer review process for journal articles before the study and findings can be considered robust.

The sponsor also provided two alternative scenario analyses, which use the same approach of combining data on proportions of patients experiencing hypothermia and complications as used for open surgery. One of these used data from the unpublished paper by Mason et al. described above and another used data from a RCT of HumiGard (Sammour et al., 2010). The scenario analyses are discussed further in the section on sensitivity analyses below.

Time horizon

The time horizon in the basecase is one year. The sponsor notes that in the clinical studies complications were usually reported in the first month following surgery. The sponsor also notes that as mortality and other complications within the model are not mutually exclusive, and using a one-year time horizon aims to reduce the consequences of long term stroke or myocardial infarction costs being accrued for people who have died.

Longer time horizons of up to 5 years are reported in scenario analyses; these simply extend the period of which post MI and stroke costs are incurred and therefore only affect the basecase for open surgery.

Overall the EAC considers that the use of a one year time frame is conservative. A five year time frame is used in the EAC additional analyses.

Resource identification, measurement and valuation

With the exception of long term costs of MI and stroke, and the cost of SSIs, the clinical management of patients undergoing abdominal surgery was costed using NHS reference costs.

Cost of SSIs

The sponsor included the cost of an SSI based on a NICE Quality Standard 45 for the management of SSIs (NICE, 2013). This reports that the cost of SSI ranges from £2,100 to £10,500 depending on the nature of surgery. The EAC verified that the range of costs referred to in the sponsor's submission reflect those reported in the NICE QS45. However, the source of data and methods of calculation are not reported for these estimates. Information provided by NICE suggested that the range reported in QS45 is derived from a report on the financial burden of SSIs (Frampton, 2010). While the lower estimate of £2,100 was stated in the report (albeit without reference), the upper estimate was not found. The report does note the cost of SSI for two types of surgeries at 2007 prices: £1,403 for breast surgery patients (N=16) and £10,366 for colorectal surgery patients (N=29) (Frampton, 2010). A cost of £6,300, which is the mid-point of the range specified by NICE, is used in the sponsor's economic model.

The EAC notes that an earlier NICE clinical guideline (65) on 'Hypothermia: prevention and management in adults having surgery' includes a much lower estimate of £2,391 (2008 prices) for an SSI (NICE, 2008) based on a study by Plowman et al.; however this study was conducted in 1994/95 (Plowman et al., 2000).

A more recent study by Jenks et al. (2014) used data on SSIs in a single NHS Hospital Trust between April 2010 and 2012 and the Patient Level Information and Costing System to estimate the additional cost of an SSI, in 2011/12 prices. Analysis of 14,300 SSIs and patient follow-up resulted in a median additional hospital length of stay of 10 days. Individual patient costs were calculated based on HRGs and NHS references costs to estimate a median additional cost of £5,239 (95% CI: 4,622–6,719) per SSI. The EAC considers that this methodology is likely to have produced robust estimates and represents one of the most up-to-date attempts to estimate SSI costs in

England, but cautions that it only represents the experience of one trust. The presentation of mean rather than median costs and confidence intervals would be preferable and based on data presented on mean costs per surgery and surgery associated with an SSI, the EAC was able to estimate the mean cost per SSI to be £9,340 across all surgery types. For an SSI of the large bowel the mean cost was £5,004 and £4,887 for an SSI of the small bowel. A weighted average was calculated based on the two types of bowel surgeries and inflated to current prices for further analysis by EAC, giving an estimate of £5164.

The EAC also notes that the NHS reference costs include codes for 'Infections or other complications of procedures' (DH, 2015). The EAC considers that these would be expected to include SSIs, albeit in addition to other procedures. The EAC attempted to clarify the use of the codes from a range of sources including the NICE clinical experts; however was unable to obtain additional information. The average cost of an SSI based on the weighted average of these codes is £1858. Further details are provided inTable 18: Calculation of SSI costTable 18.

Table 18: Calculation of SSI cost

Code	Description	Activity	Unit cost
WH07A	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+	1222	£9,141.60
WH07B	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1	2726	£5,166.15
WH07C	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+	1305	£5,299.45
WH07D	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1	5539	£3,037.69
WH07E	Infections or Other Complications of Procedures, without Interventions, with CC Score 4+	697	£3,455.15
WH07F	Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3	4937	£2,103.57
WH07G	Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1	40234	£1,080.69
	Weighted average		**£1,857.92**

The EAC considers the Reference Cost data to be the most appropriate source and has used this in its additional analyses. A further analysis is conducted using the data reported in the paper by Jenks et al. (2014).

Post-MI and post-stroke costs

The long term cost of myocardial infarction and stroke are not available from the NHS reference cost database. The sponsor used the 2004 NICE clinical guideline on managing hypertension to estimate the cost of myocardial

infarction (NICE, 2004) and inflated these to 2013/14 prices using the Hospital & Community Health Services pay and Prices Index. The cost after inflating to 2013/14 prices was £646.

The EAC notes that these costs differ substantially from the cost used in a recent TA355 on edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation (NICE, 2015). The EAC considers that the approach to inflating the costs is inappropriate. The post-MI costs comprise mainly of drug costs: in TA355 this comprised a weighted average of the cost of treatment with beta-blocker (bisoprolol), ACE inhibitor (ramipril) and statin (atorvastatin). The prices of these drugs have reduced substantially in the past ten years, and therefore the 2004 post-MI cost should be reduced rather than inflated. The EAC has estimated an updated annual cost of myocardial infarction after the acute phase, based on current drug prices (BNF 2016), to be £43.25. The number of scripts sourced from prescription cost analysis 2013 and the prices of drugs in 2004 and 2016 (BNF 2004, BNF 2016) are presented in Table 19.

Table 19: Calculation of Post-MI costs

Monthly post MI costs	**Cost per 28-tab pack**			**SPM ***	**Weighted cost**		
	2004	2013	2016	2013	2004	2013	2016
Bisoprolol 5mg tabs	£8.56	£0.91	£0.86	199			
Bisoprolol 10mg tabs	£9.61	£0.99	£0.84	105			
					£8.92	£0.94	£0.85
Ramipril 1.25mg caps	£13.00 **	£1.00	£0.94	188			
Ramipril 1.25mg tabs	£5.30	£1.10	£1.07	5			
Ramipril 10mg caps	£13.00 **	£1.21	£1.13	811			
Ramipril 10mg tabs	£14.24	£1.31	£1.20	19			
Ramipril 2.5mg caps	£13.00 *	£1.07	£1.01	480			
Ramipril 2.5mg tabs	£7.51	£1.10	£1.04	10			
Ramipril 5mg caps	£13.00 **	£1.14	£1.07	550			
Ramipril 5mg tabs	£10.46	£1.14	£1.00	11			
					£12.95	£1.14	£1.07
Atorvastatin 10mg tabs	£18.03	£1.09	£1.03	119			
Atorvastatin 20mg tabs	£29.69	£1.31	£1.21	145			
Atorvastatin 40mg tabs	£29.69	£1.53	£1.39	167			
Atorvastatin 80mg tabs	£29.69	£2.50	£2.41	268			
					£1.68	£27.70	£1.78
Total monthly cost					**£49.58**	**£3.86**	**£3.60**
Annual cost					**£594.97**	**£46.30**	**£43.25**

*Scripts per month; **Cost per 35 capsule pack

The longer term cost of stroke was derived by the sponsor from the NICE costing template for dabigatran etexilate (NICE, 2012) which used a study by Youman et al. (2003) to estimate the cost of stroke over five years. The sponsor inflated this cost to £21,532 using the Hospital & Community Health services (HCHS) Index, Unit costs of health and social care 2014, PSSRU. In the costing study the cost of stroke in first year (£12,228) was estimated from another NHS commissioning report which focused on Atrial Fibrillation (NHS Improvement, 2009). The sponsor subtracted the cost of stroke sourced from NHS reference cost for the acute phase (£2,788) from the total (£21,532), and the remaining (£18,744) was divided across five years to provide an annual cost of £3,749. The model estimated the cost of stroke in first year as £6,537 (acute costs plus annual longer term cost).

The sponsor has noted that it is likely that a greater proportion of the costs will be accrued in the first year post stroke. The EAC agrees and have identified a more recent study by Luengo-Fernandez et al. (2012) to estimate the costs of stroke. This was a UK (Oxfordshire) population based cohort study (Oxford Vascular Study) to assess hospital care costs during five years after stroke. A total of 729 stroke patients were recruited in the study between 2002 and 2007, and followed up until 2010. Resource use was obtained from patient hospital records from the date of first stroke and all resources consumed were valued using 2008/09 unit costs. Of the 729 patients experiencing stroke, 239 were alive at 5 years, 333 had died and 157 had not reached complete five year follow up. The study estimated five year hospital costs after stroke as $24,376 (of those surviving to 5 years). The EAC considers the Luengo et al. study to have more robust, complete and up-to-date results. This study collected resource use data over five year follow up while Youman et al. had data only for one year and a Markov model was used to extrapolate costs across the five year period. All costs were presented in US Dollars in the paper by Luengo et al. The EAC converted the costs to pound sterling and inflated to 2014/15 prices using the HCHS index (Curtis, 2015). The annual average cost after stroke are presented in **Table 20**.

Table 20: Annual average costs after stroke based on the Oxford Vascular Study

(n=239)	**Year1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
2008/09, US Dollar	12,972	2,303	3,486	2,527	3,088	24,376
2008/09, UK Pound	8,302	1,474	2,231	1,617	1,976	15,601
2014/15, UK Pound	9,114	1,618	2,449	1,775	2,170	17,126
Note: PPP in 2009 of USD $1.00 = £0.64 pound						

Source: Luengo-Fernandes, 2012.

Acute costs of other complications

Acute costs of pneumonia, MI, stroke, septicaemia and sepsis were costed using NHS reference costs for the year 2013-14 (DH, 2014). The sponsor used total HRG costs which include both elective and non-elective costs; it also noted that the reference costs refer to all patients and not just those going abdominal surgery.

The NHS reference costs for 2014-15 were published in November 2015 (DH, 2015) and the EAC has updated the HRG codes and costs to reflect most recent practice. The data used to derive the costs are presented in Table 21 to Table 24. The cost of pneumonia, myocardial infarction, stroke (acute) and sepsis for 2014/15 were estimated as £1798.59, £1468.51, £2833.76 and £2149.02 respectively.

Table 21: Cost of an inpatient stay for pneumonia

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	3080	£6,781.02
DZ11M	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 0-8	2334	£4,527.96
DZ11N	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 13+	3194	£5,940.28
DZ11P	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 8-12	10661	£4,088.00
DZ11Q	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-7	9890	£2,835.76
DZ11R	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 14+	11399	£3,727.66
DZ11S	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10-13	66256	£2,657.37
DZ11T	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9	97309	£1,888.36
DZ11U	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-6	123592	£1,478.31
DZ11V	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3	89245	£1,054.85
DZ22K	Unspecified Acute Lower Respiratory Infection, with Interventions, with CC Score 9+	1244	£5,194.09
DZ22L	Unspecified Acute Lower Respiratory Infection, with Interventions, with CC Score 0-8	2063	£3,305.00
DZ22M	Unspecified Acute Lower Respiratory Infection, without Interventions, with CC Score 13+	2655	£3,134.90
DZ22N	Unspecified Acute Lower Respiratory Infection, without Interventions, with CC Score 9-12	16158	£2,110.49
DZ22P	Unspecified Acute Lower Respiratory Infection, without Interventions, with CC Score 5-8	45592	£1,416.85

DZ22Q	Unspecified Acute Lower Respiratory Infection, without Interventions, with CC Score 0-4	64635	£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+	2949	£2,881.35
DZ23M	Bronchopneumonia without Interventions, with CC Score 6-10	7019	£1,985.04
DZ23N	Bronchopneumonia without Interventions, with CC Score 0-5	5634	£1,254.23
	Weighted average cost		**£1,798.59**

Table 22: Cost of an inpatient stay for myocardial infarction

Code	Description	Activity	Unit cost
EB10A	Actual or Suspected Myocardial Infarction, with CC Score 13+	6805	£3,152.74
EB10B	Actual or Suspected Myocardial Infarction, with CC Score 10-12	16111	£2,206.96
EB10C	Actual or Suspected Myocardial Infarction, with CC Score 7-9	26483	£1,572.56
EB10D	Actual or Suspected Myocardial Infarction, with CC Score 4-6	36255	£1,202.47
EB10E	Actual or Suspected Myocardial Infarction, with CC Score 0-3	31118	£939.29
	Weighted average cost		**£1,468.51**

Table 23: Cost of an inpatient stay for stoke

Code	Description	Activity	Unit cost
AA35A	Stroke with CC Score 16+	4967	£8,762.40
AA35B	Stroke with CC Score 13-15	10392	£6,331.42
AA35C	Stroke with CC Score 10-12	18426	£4,677.43
AA35D	Stroke with CC Score 7-9	31069	£3,313.96
AA35E	Stroke with CC Score 4-6	43479	£2,434.74
AA35F	Stroke with CC Score 0-3	36402	£1,772.81
AA29C	Transient Ischaemic Attack with CC Score 11+	2396	£2,284.90
AA29D	Transient Ischaemic Attack with CC Score 8-10	4193	£1,366.22
AA29E	Transient Ischaemic Attack with CC Score 5-7	9081	£950.43
AA29F	Transient Ischaemic Attack with CC Score 0-4	15816	£674.81
	Weighted average cost		**£2,833.76**

Table 24: Cost of an inpatient stay for sepsis

Code	Description	Activity	Unit cost
WJ05A	Septic Shock with CC Score 5+	266	£2,106.63
WJ05B	Septic Shock with CC Score 0-4	246	£1,415.23
WJ06A	Sepsis with Multiple Interventions, with CC Score 9+	425	£9,673.21
WJ06B	Sepsis with Multiple Interventions, with CC Score 5-8	922	£7,886.38
WJ06C	Sepsis with Multiple Interventions, with CC Score 0-4	502	£6,423.83
WJ06D	Sepsis with Single Intervention, with CC Score 9+	766	£5,708.14

WJ06E	Sepsis with Single Intervention, with CC Score 5-8	2502	£5,019.67
WJ06F	Sepsis with Single Intervention, with CC Score 0-4	2027	£3,686.18
WJ06G	Sepsis without Interventions, with CC Score 9+	5578	£3,003.26
WJ06H	Sepsis without Interventions, with CC Score 5-8	31286	£2,078.12
WJ06J	Sepsis without Interventions, with CC Score 0-4	42249	£1,533.32
	Weighted average cost		**£2,149.02**

Costs were discounted at 3.5% in accordance with NICE recommendations in the scenario analyses with time horizons beyond one year.

In summary, the EAC considers that the updated NHS reference costs, the re-estimated costs for post-MI and the costs of stroke from the study by Luengo et al. (2012) to be more appropriate estimates for the analysis and the impact of these is explored further in the following section reporting EAC amendments to the model.

Technology and comparators' costs

The costs of the HumiGard technology are shown in Table 25. The costs include the cost of purchasing the equipment, tubing kits for each patient and the costs of training nurse staff.

Table 25: Costs per treatment associated with the HumiGard system

Items	Value	Source
Price of the technology per treatment	£1,600 (per humidifier with 5 year life span)	Fisher and Paykel Healthcare Ltd
Consumables Laparoscopic surgery: ST310 Humidified and Heated Tubing Kit Open surgery: ST310 Humidified and Heated Tubing Kit and VITA-diffuser (ST300 DF)	£75 per patient £99 per patient	Fisher and Paykel Healthcare Ltd
Maintenance cost Provided annually	£0	Fisher and Paykel Healthcare Ltd
Training cost 10 hours of nurse team manager time	£510	Training resource = Fisher and Paykel Healthcare Ltd Nurse team manager time = £51 per hour of non-patient contact
Other costs (staff) None	£0	Fisher and Paykel Healthcare Ltd
Total cost per treatment	Laparoscopic: £75+£5.63 = £80.63 Open: £99+£5.63 = £104.63	£1,600 cost of device and £510 of training spread among 75 patients per year for 5 years plus the cost of consumables.

Source: SS Table C6

The sponsor estimates the cost of the comparators to be:

- For laparoscopic surgery: £5 per patient (dry line tubing kit)
- For open surgery: no additional cost

The EAC queried the estimates of training time with the NICE clinical experts. One considered that the amount of time was broadly correct, but considered that pairs of team leaders would be trained. The other expert considered that the training time for nurses may have been overestimated. The EAC concludes that the estimates of training time to be broadly correct and unlikely to have a significant impact on the overall estimates of total costs.

The EAC also considers it necessary to annuitize the capital cost of the humidifier, taking into account the opportunity cost of purchasing equipment and its lifespan, applying a discount rate of 3.5% over 5 years. Given the cost per patient was already low; this adjustment had only a small effect, increasing the humidifier cost per patient from £4.27 to £4.57.

Sensitivity analysis

The sponsor conducted a range of sensitivity analyses. These include scenario analysis to explore the use of alternative sources of clinical effectiveness, univariate deterministic sensitivity analysis and a probabilistic analysis of the basecase results. Scenario analyses using alternative time horizons (up to 5 years) are also presented.

Data on complications associated with hypothermia

For the analysis of open surgery, three alternative sources for the proportions of patients experiencing complications were used (Kurz et al., 1996; Flores-Maldonado et al., 2001; Anannamcharoen et al., 2012).

The study by Kurz et al. (1996) was a US-based randomised trial of perioperative hypothermia in adult patients undergoing elective colorectal resection for cancer or inflammatory bowel disease. Patients were randomized to one of two temperature management groups: a normothermia group whose temperature was maintained near 36.5^{o}C (n=104) and a hypothermia group whose temperature was allowed to decrease to 34.5^{o}C (n=96). The sponsor used the incidence of SSI from the study in the sensitivity analysis: normothermia group n=6 (6%); hypothermia group n=18 (19%); p=0.009. No other complications were included in the sensitivity analysis.

The study by Flores-Maldonado et al. was a prospective cohort study, conducted in Mexico, of patients who had undergone an elective cholecystectomy (n=290). The majority of patients were women (84.7%), had an ASA risk of 1 (77%) and an average age of 40 years. The sponsor used the incidence of SSI for patients with and without mild perioperative hypothermia (less than 36^{o}C) from the study in the sensitivity analysis. In the hypothermic group 18 (1.9%) patients experienced SSI compared to 2 (11.5%) patients in the normothermia group (p=0.004). No other complications were included in the sensitivity analysis.

The study by Anannamcharoen et al. was a prospective cohort study of open colon and rectal resections performed in an army hospital in Thailand (n=229). The majority of surgeries were performed as elective cases (83%), 58% of the sample were male and the average age was 63 years. The authors calculated the incidence of SSIs and explored risk factors associate with SSIs. The authors found that, in addition to postoperative hypothermia (defined as < 36^{o}C), BMI, preoperative albumin levels, Hartmann's procedure and post-operative hypotension were risk factors associated with incisional SSI. A total of 17.6% of those with normothermia experienced an SSI, whereas 30.8% of hypothermic patients experienced and SSI.

All of the sources of data on complications associated with hypothermia are limited. It is unclear if the studies set in single sites in Thailand or Mexico would be generalisable to a UK NHS setting. In addition the population included in the Mexican study were younger, more likely to be female and had lower ASA risk scores than on average in the UK. The studies by Flore-Maldonado et al and Kurz et al are both over 15 years old. All of the studies report only SSI complications. The study used in the basecase is not without limitations; specifically that it is not limited to abdominal surgery and excludes mild hypothermia from the definition of hypothermia. However, it is a large study matching cases to controls, is set in the USA which may be more generalisable to the UK than Mexico and Thailand, and reports a wider range of complications.

Data on the effectiveness of laparoscopic surgery

The sponsor presented two scenario analyses for laparoscopic surgery. Both of these analyses use data on the proportions of patients experiencing hypothermia and linking these with complications using data included in the basecase for open surgery (Billeter et al., 2014). The first sensitivity analysis uses data from the unpublished study by Mason et al. which has been described previously.

[redacted]

A second scenario analysis uses data from a double-blinded RCT of HumiGard compared to standard dry carbon dioxide for insufflation from a published study conducted in New Zealand (Sammour et al., 2010). This study has been discussed earlier in the report. Briefly, patients undergoing elective laparoscopic colonic resection were randomised to the study group (n=35) or control (n=39). No statistically significant differences were found in the primary endpoint of MEDD usage. The authors noted that a marginal but statistically significant benefit was found in intraoperative core temperature maintenance in the study group. The authors also reported that complication rates and grades were equivalent between the study groups. The proportions of patients experiencing hypothermia are not directly reported in the publication; however the sponsor obtained this information direct from the study authors[redacted]

[redacted]

Although the study by Sammour et al. (2010) is not based in the UK and is relatively small, it is a well-designed prospective double blinded RCT. The proportions of complications between the HumiGard and control arms are not reported directly; however the authors note that the rates were similar between the study groups. The laparoscopic surgery structure used in the sponsor base case would be preferable as it utilises head to head comparative data on complications with and without the use of HumiGard, however the data used to inform the model was Mason et al. manuscript. Whilst promising, the study by Mason is still work in progress and not yet submitted for consideration for publication. There are also discrepancies between the unpublished manuscript and published abstract, the sources of which have not been resolved. The EAC therefore considers the evidence from Sammour et al to be the highest quality evidence currently available and has focused on this our re-analyses. As such the EAC later presents the alternative model structure combining (Sammour et al., 2010) and complications modelled according to Billeter et al. (2014) as the preferred analysis for laparoscopic surgery.

4.3 Results of de novo cost analysis

Base-case analysis results

The basecase results of the sponsor's submission state that HumiGard costs £419 per patient compared to usual care of £724. The sponsor therefore estimates a cost saving of £305 per patient from HumiGard. The majority of the cost savings are derived from a reduction in SSIs (69%). The sponsor's basecase combines laparoscopic and open surgery, and the cost savings are largely driven by laparoscopic surgery. The results of the sponsor's analysis, separating open and laparoscopic surgeries are presented in Table 26.

Table 26: Sponsor basecase results for open, laparoscopic and combined surgeries

Type of surgery	HumiGard	Usual Care	Increment
Open	£483	£503	-£20
Laparoscopic	£391	£819	-£428
Combined (sponsor basecase)	£419	£724	-£305

4.4 Sensitivity analysis results

The sponsor presented a Tornado diagram showing the impact of varying specific parameters in univariate sensitivity analyses (Figure 7). The results were sensitive to the probability of SSI in the control group. When the absolute difference in risk of SSI reduces to around 0.3% (e.g. 4.7% versus 5%) the HumiGard system becomes cost increasing.

The sponsor also presented the results of the scenario analyses for laparoscopic and open surgery separately. HumiGard remained cost saving for open surgery for all analyses using alternative clinical effectiveness data. For open surgery, the use of the data from the RCT (Sammour et al, 2010) substantially reduced the cost savings, and HumiGard was associated with a modest additional cost when these data were combined with data on complications from the studies by Billeter et al. (2014) or Flores-Maldonado et al. (2001).

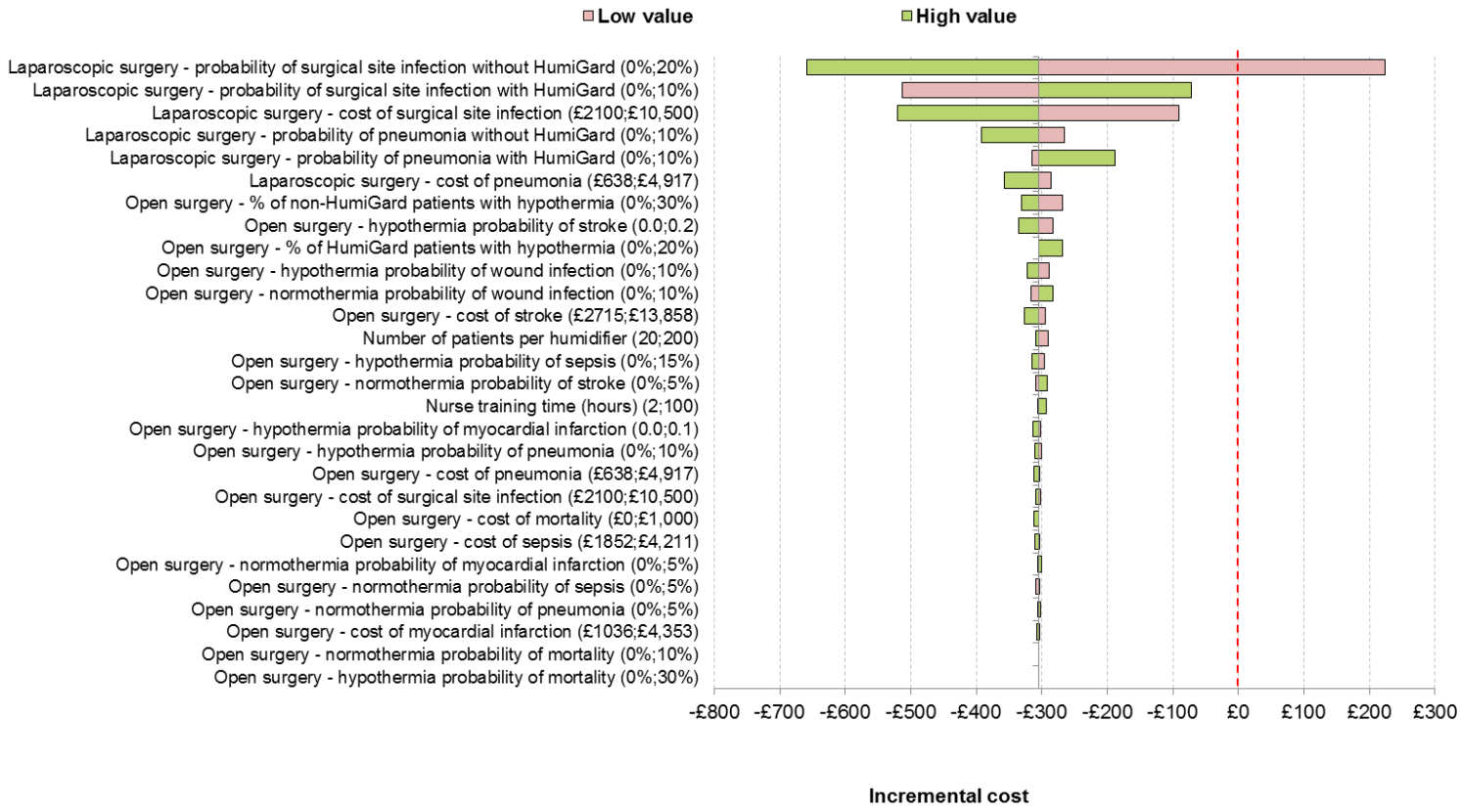
The EAC re-ran the sponsor's univariate sensitivity analyses for open and laparoscopic surgery separately (see Figure 8 and Figure 9).

For open surgery, the results were sensitive to several parameters. HumiGard was not cost saving when the lower ranges of values were used for the percent of control group patients experiencing hypothermia, the probability of stroke, sepsis and wound infection associated with hypothermia, and the cost of stroke. It was not cost saving when the upper ranges were used for the proportion of patients experiencing hypothermia with HumiGard, and the probabilities of wound infection and stroke associate with normothermia.

For laparoscopic surgery, HumiGard remained cost saving for all amendments except for using the lower value for the probability of SSI without HumiGard.

The sponsor's probabilistic sensitivity analysis found that HumiGard was cost saving in 97.4% of iterations and the average probabilistic cost savings were £302 per patient. The sponsor noted that the results of the PSA have a skewed distribution (see SS Figure C7) and state that this is due to the distribution of costs of complications within the model which have a gamma distribution bounded by 0, but no upper limit.

Figure 7: Sponsors univariate sensitivity analysis on basecase (laparoscopic surgery and open surgery)



Source: SS Figure C5

Figure 8: Tornado diagram for univariate sensitivity analysis (open surgery)

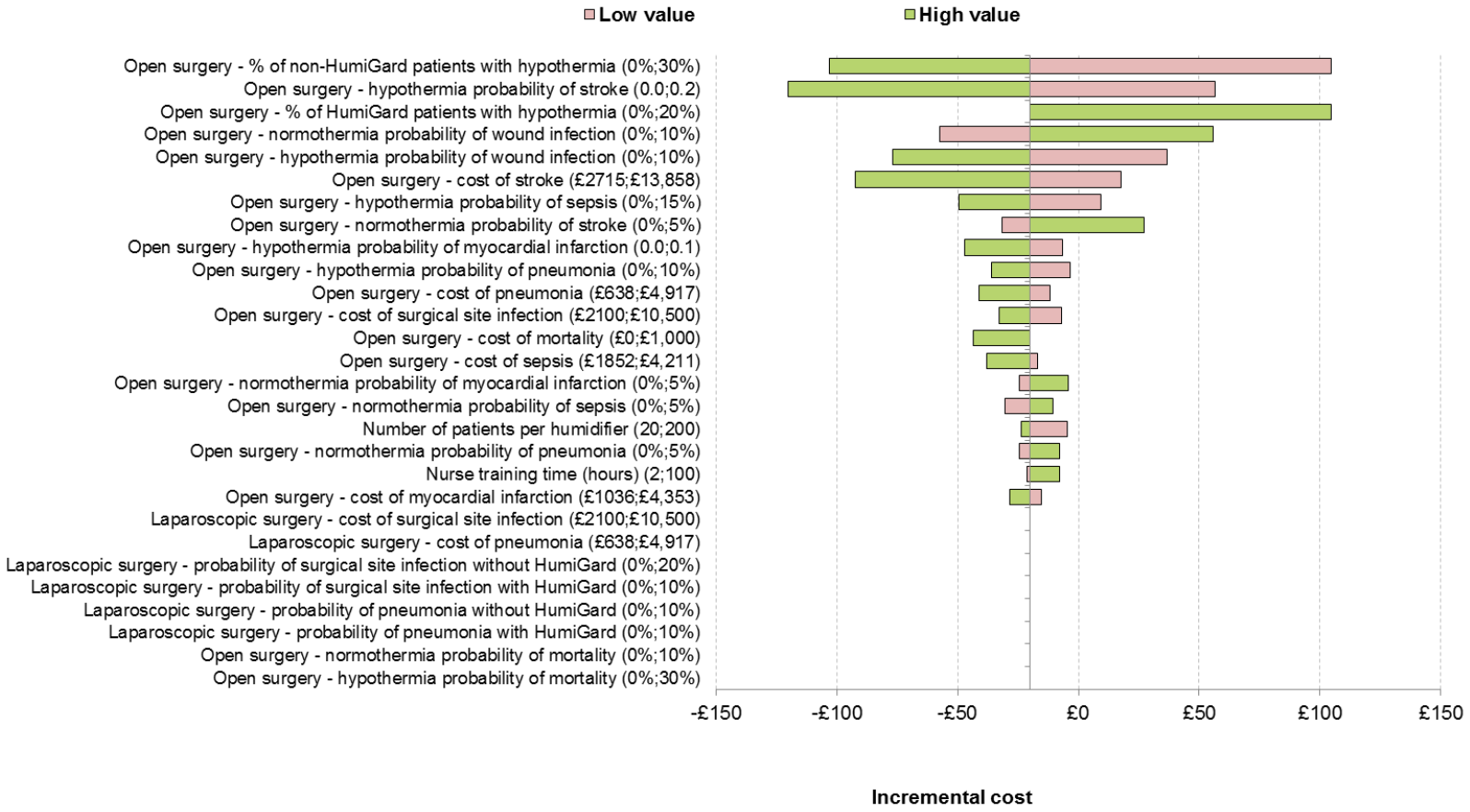
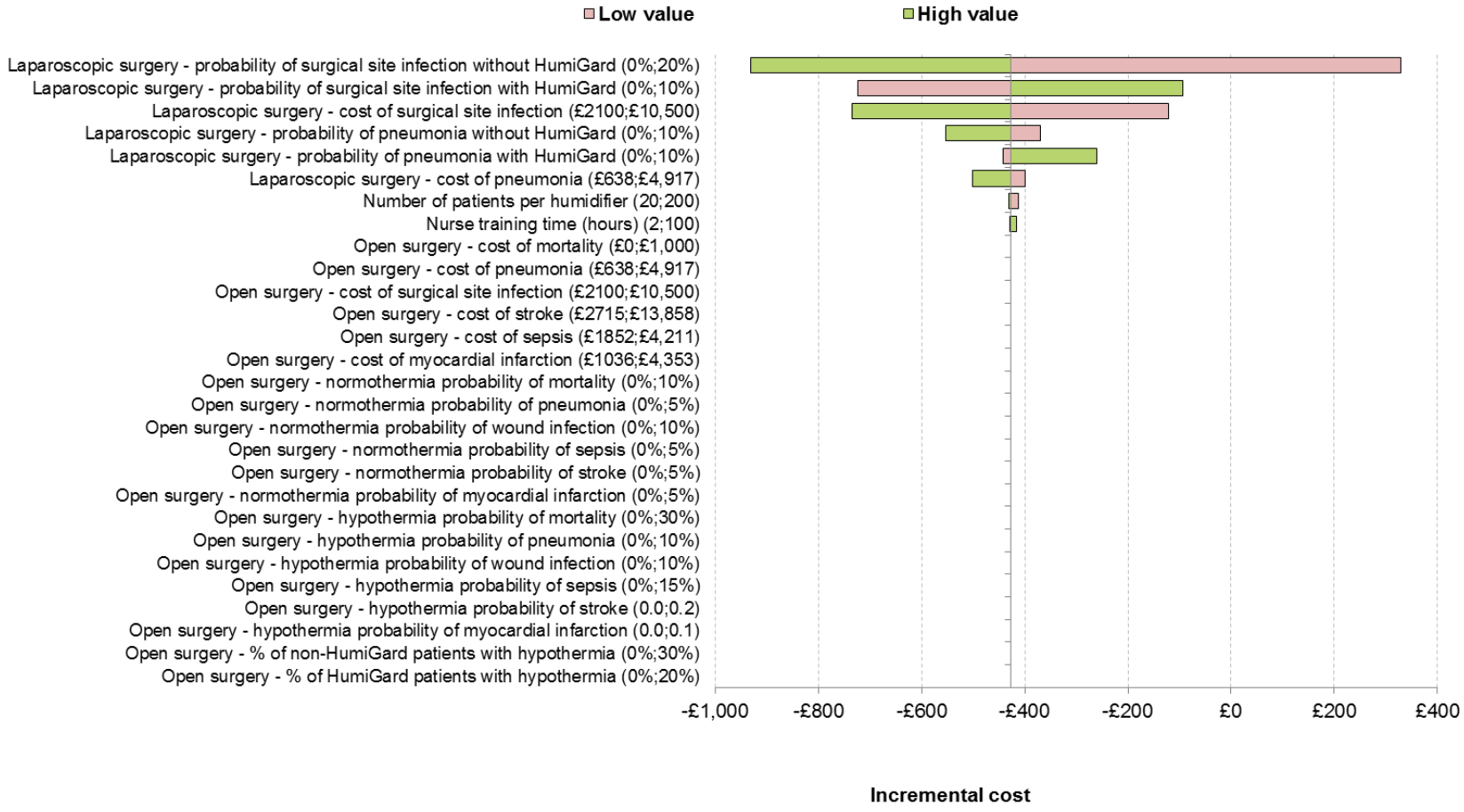


Figure 9: Tornado diagram for univariate sensitivity analysis (laparoscopic surgery)



4.5 Subgroup analysis

The NICE final scope specified two subgroup analyses:

- 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)

The sponsor noted that the studies of clinical effectiveness used in the basecase analysis included only patients who used forced-air warming blankets; therefore the basecase analysis reflects this subgroup.

The sponsor also noted that insufficient detail was provided in the papers on clinical effectiveness to enable a subgroup analysis for high risk groups to be conducted.

4.6 Model validation

The sponsor stated that the Microsoft Excel based modelling had been built by one health economist with an additional health economist involved in the development. The model was independently checked by a third. A member of the EAC team undertook a thorough, systematic coding check of all worksheets in the excel spreadsheet, including all formulae, and tracing precedent and dependent cells.

Model verification was also completed by the EAC, with key input parameters changed to extreme values to ensure the model behaved as expected. This included manipulation of effectiveness values and costs. In open surgery the risk of hypothermia for both HumiGard and no HumiGard use was set to 0% and cost differences were observed to be only a product of additional device costs. Similarly in the both the open and laparoscopic surgery models, the probability of complications was set to zero and, as expected, the mean cost per patient reflected only increased device costs from the use of HumiGard.

Device costs (HumiGard unit, nurse training and consumables) were all set to £0 and this was accurately reflected in per patient cost only being a reflection of associated complication costs. Similarly, complication costs were set to £0 and cost per patient was only a reflection of device costs.

Other parameters were manipulated, including the number of patients undergoing surgery (higher, greater cost savings), the lifespan of the device

(longer, greater cost savings) and the model behaved consistent with expectations.

The sponsor stated that the results of the model were cross validated against published cost-effectiveness studies (Jenks, 2015; Mason, 2015) and that they were congruent in terms of cost savings.

4.7 Interpretation of economic evidence

The sponsor concluded that HumiGard system generates cost savings compared to usual care whilst generating greater benefits, and that this is in line with the evidence from the two published abstracts (Noor et al., 2015; Mason et al., 2015). The sponsor notes that conducting a RCT in open and laparoscopic surgery patients which reported on both clinical events and the resource implications of these clinical events would increase the robustness of the findings, but considers that the value of gaining further information should first be assessed given that they consider the uncertainty in the current base case results to be relatively low.

The EAC agrees that the results from the sponsor's analysis generally concord with those from the published abstracts, but considers this unsurprising given the similarities in models and data sources used. It considers that the analyses for open and laparoscopic surgery should be conducted and presented separately given the differences in comparators, outcomes and costs for these types of surgery. The EAC notes that the sponsor's analysis shows that the cost savings are less, and more uncertain, for HumiGard in an open surgery setting. The EAC also considers that some of the evidence underpinning the clinical effectiveness in the model for laparoscopic surgery to be uncertain as it is currently only published in abstract form (Noor et al, 2015) and the draft manuscript is incomplete and has not been peer reviewed (Mason et al., unpublished). The EAC agrees that a RCT would increase the robustness of the results.

4.8 Additional work undertaken by the External Assessment Centre in relation to economic evidence

The EAC conducted literature searches on the cost-effectiveness of HumiGard on MEDLINE, MEDLINE(R) In-Process & Other Non-Indexed Citations, EMBASE, HTA and EED, from the inception of the databases to November 2015 (see search strategy in appendix 2). The EAC checked all the literature included in the sponsor's report, and also checked the reference list of included studies. For the cost-effectiveness, a total of 320 citations were obtained from the searches and 2 records obtained through other sources. Two reviewers independently screened through the citations and papers using the same criteria used for the clinical effectiveness. The screen and selection

process is shown in **Error! Reference source not found.** (Appendix 2). The EAC identified no additional studies.

The EAC verified the sponsor's search strategies for economic studies by conducting independent searches and reviewed studies evaluating the cost effectiveness of Humigard. The two abstracts identified from the search, were Mason et al. (2015) and Jenks et al. (2015) which described cost utility and cost effectiveness analyses. Both found that the HumiGard system dominated over standard care. The model used by the sponsor is based on study reported in Jenks et al. (2015).

The EAC reviewed the assumptions built into the sponsor's model in relation to available evidence and expert opinion. The EAC verified the coding of the sponsor's model and found no errors. The sponsor's basecase combined results for laparoscopic and open surgery based on a ratio of 70:30. Two NICE clinical experts were contacted by EAC to confirm the 70:30 split of abdominal surgery and the proportions did not reflect current practice in their centres. The two types of surgery are associated with different risks and resource consequences and therefore the EAC separated the results of open and laparoscopic surgeries. The EAC re-ran the sponsor's univariate sensitivity analyses for open and laparoscopic surgery separately, presented as tornado diagrams earlier in the report. The other additional analyses conducted by the EAC are presented for each type of surgery separately.

The key amendments included in the EAC re-analyses of the sponsor's model are:

- Inclusion of updated costs of pneumonia, acute myocardial infarction and sepsis using NHS reference costs for the year 2014-15 (DH, 2015)
- Use of an annuitized capital cost of HumiGard by applying a discount rate of 3.5% over 5 years
- Updated post-MI cost based on updated drug costs (BNF, 2016) and quantities (NICE TA355, 2015)
- Updated costs of stroke based on the Oxford Vascular Study inflated to current prices (Luengo et al, 2012)
- Use of reference costs for SSI (DH, 2015)
- A five year time horizon in the basecase.

In addition, for the analysis of laparoscopic surgery:

- Data on the proportions of patients experiencing hypothermia were based on the RCT by Sammour et al (2010) and the risk of complications from the study by Billeter (2014).

The parameters included in the EAC's re-analysis are presented in Table 27.

Table 27: Model parameters used by EAC

Item	Sponsor estimate	EAC estimate	EAC source/rationale
Proportion of patients with hypothermia			EAC estimate from Sammour et al (2010) Sponsor estimate from Mason et al (2015)
HumiGard	[redacted]	[redacted]	
No HumiGard	[redacted]	[redacted]	
Time horizon	1 year	5 years	1 year considered conservative
Myocardial infarction (Acute)	£1607.84	£1468.51	NHS Reference Costs 2014-15 (DH, 2015)
Sepsis	£2181.79	£2149.02	NHS Reference Costs 2014-15 (DH, 2015)
Pneumonia	£1824.61	£1798.59	NHS Reference Costs 2014-15 (DH, 2015)
Surgical site infection	£6300.00	£1857.92	NHS Reference Costs 2014-15 (DH, 2015)
		£5131.07	Jenks et al (Jenks 2014) (average of bowel surgeries, inflated)
Stroke cost			
Year 1	£6,536.67	£9113.63	Luengo et al (Luengo, 2012)
Year 2	£3,622.10	£1563.28	Luengo estimate (discounted)
Year 3	£3,499.61	£2286.29	Luengo estimate (discounted)
Year 4	£3,381.27	£1601.29	Luengo estimate (discounted)
Year 5	£3,266.93	£1890.60	Luengo estimate (discounted)
Device cost	£4.57	£4.27	Sponsor cost (discounted)
Post MI cost	£646.13	£46.30	Edoxaban TA355 and BNF 2016

The EAC considers that as stroke and MI have long term resource implications a longer time horizon is preferable; however the model incorporates this by simply adding in additional costs to later years. Therefore the EAC also conducted analyses using a one year time horizon.

Additional sensitivity analyses conducted by the EAC include:

- The use of a one year time horizon
- An alternative estimate for the cost of SSI of £5164 based on a recent study by Jenks et al (2014).

For the analysis of laparoscopic surgery:

- Use of the direct data on complications reported in the abstract by Noor et al (2015).

The EAC also reprogrammed the sponsor's model to allow a probabilistic sensitivity analysis to be conducted for the amended model.

4.9 Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The results generated by the EAC after implementing preferred alternative parameter values over a five year time horizon are presented in **Error! Reference source not found.**.

Table 28: EAC basecase results for open and laparoscopic and combined surgeries

Type of surgery	HumiGard	Usual Care	Increment (per patient)
Open	£537	£746	-£209
Laparoscopic	£763	£840	-£77

For open surgery, the results suggest that HumiGard is cost saving compared to standard care with an average cost saving per patient of £209. This cost saving is greater than that estimated by the sponsor's model (which estimated an average cost saving per patient of £20) and is driven by the use of a longer time horizon of 5 years (instead on one). When a one year time horizon is used in the EAC analysis, the average cost saving (£28) is broadly similar to that included in the sponsor's analysis. The use of lower cost estimates for post-MI and SSI included in the EAC analysis were offset by the inclusion of higher stroke costs in the analysis. Sensitivity analysis using the alternative estimate of SSI costs resulted in a cost saving of £219 (5 year time horizon).

The estimated cost savings in laparoscopic surgery is lower in the EAC analysis compare to the sponsor's analysis (average cost saving of £77 per patient in the EAC analysis compared to £428 in the sponsor's analysis). This

is mainly a result of using the data from the RCT of HumiGard (Sammour, 2010) rather than the unpublished retrospective study. When the time horizon was projected as one year only, HumiGard was no longer cost saving with a modest additional cost of £11 per patient. Sensitivity analysis using the alternative estimate of SSI costs gave a cost saving of £82 per patient (5 year time horizon).

The EAC conducted probabilistic sensitivity analyses using the new basecase inputs for open surgery and laparoscopic separately. The HumiGard system was cost saving in 98.2% of iterations and the average probabilistic cost savings were £209 per patient in open surgery. In laparoscopic surgery, HumiGard was cost saving at 67.5% with average cost saving of £80 per patient. The PSA distributions for the two types of surgery are presented in **Error! Reference source not found.** and **Error! Reference source not found.**.

Figure 10: Probabilistic sensitivity analysis distribution in open surgery

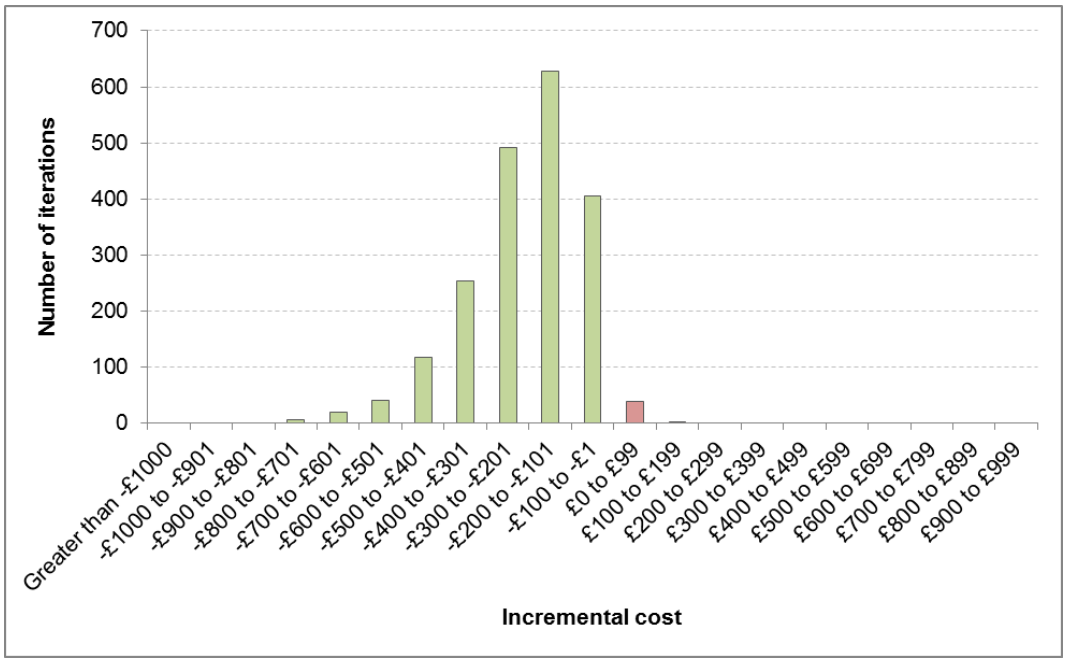
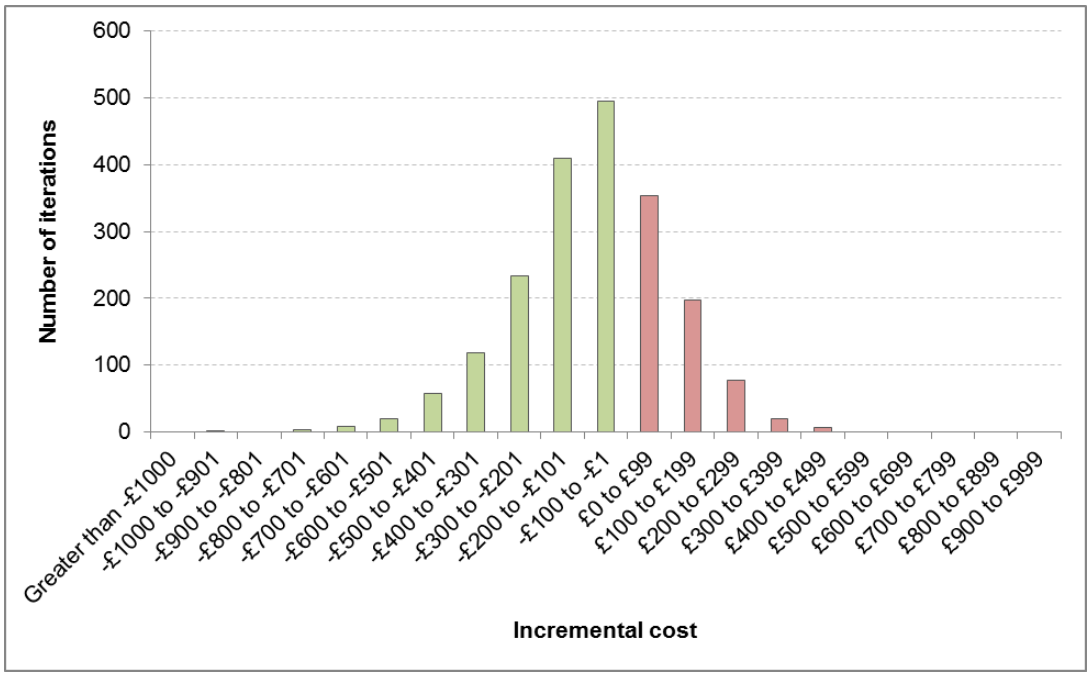


Figure 11: Probabilistic sensitivity analysis distribution in laparoscopic surgery



4.10 Conclusions on the economic evidence

The economic evidence submitted by the sponsor reflected the NICE final scope with the exception of the inclusion of specified subgroup analyses: patients with adjunct warming and high risk patients. The EAC agrees with the sponsor's justification for not providing subgroup analyses and that data were not available to model the use of HumiGard for high risk patients, and that the basecase results apply only to patients with adjunct warming.

The results of the economic analyses suggest that HumiGard is likely to be cost saving or cost neutral; however the robustness of these results rely on the robustness of the clinical evidence. The EAC considers the data on clinical effectiveness to be associated with considerable uncertainty.

For laparoscopic surgery, the data on clinical effectiveness in the sponsor's submission are from a study published in abstract form only. The sponsor provided the EAC with an unpublished draft manuscript relating to the study; this was incomplete and still in development. Whilst the draft manuscript provided some further information on the study, the EAC noted several discrepancies in the numbers of patients between the reports. Upon clarification, this was found to be due to different numbers of patients included in the two study reports and for different outcomes. The authors were not able to provide data on number of SSIs amongst those who had hypothermia in the

HumiGard and control groups within the timeframe of the analyses. In addition, following a request for clarification, the authors noted that the analysis of proportions of patients experiencing hypothermia was based on a substantially reduced sample size due to problems in the measurement of temperature

[redacted]

[redacted]It is unclear if the baseline characteristics of patients differ between the groups used for this analysis. The EAC noted that the authors had conducted multivariate analyses of the risk of hypothermia and SSI and that these suggested it is important to adjust for some factors; however these results were not used in the economic model. The EAC notes that the conclusions of the authors of the abstract and draft manuscript state that a RCT to further assess the role of warming and humidifying insufflation gases in reducing the SSI and length of hospital stay is warranted.

Given the uncertainties surrounding the study by Mason et al., the EAC considers that the data from the double-blinded RCT by Sammour et al (2010). to be a more appropriate source of data for clinical effectiveness. As for the analysis of open surgery, this requires data on complications to be indirectly included in the analysis by linking the risk of complications from external source to data on the probability of hypothermia from the RCTs. The sponsor included four alternative sources for data on complications. The EAC agreed with the sponsor that the most appropriate source for the basecase analysis was the study by Billeter et al. (2014); however considered to not be free of limitations. In particular it included all surgeries and was not limited to abdominal surgery. The study also found no statistically significant association between SSIs and hypothermia, which is a key assumption in the sponsor's base case deterministic analysis of open surgery. The EAC also notes that although detailed information on complication rates is not presented in the study by Sammour et al. (2010), the authors report that complication rates and grades were equivalent between the HumiGard and standard care groups.

5 Conclusions

The sponsor's clinical evidence was based on studies on HumiGard as well as studies on other humidification systems. The EAC considers that for the purposes of this assessment report, humidification systems other than HumiGard were out-of-scope. The EAC thus summarised the clinical evidence based on studies on HumiGard only.

For laparoscopic surgery 4 RCTs and 1 retrospective cohort study that compared HumiGard with unheated, unhumidified carbon dioxide insufflation gas were considered relevant to the decision problem.

The incidence of hypothermia was derived from one RCT which found no statistically significant differences between the groups, and one retrospective cohort study which found a statistically significant decrease in the HumiGard group compared with the control. Pooled estimate on this outcome appears to favour HumiGard; however, due to the difference between the studies in the designs and the effects observed, this pooled result should be interpreted with caution.

Data on surgical site infections following laparoscopic surgery derived from only one retrospective cohort study which is currently at draft stage and has not yet undergone peer review.

Only 1 RCT reported on hypothermia for open surgery. It observed a statistically significant difference in incidence of hypothermia between patients using HumiGard and those in the control group. SSI was not reported in open surgery studies using HumiGard.

The economic analyses suggest that HumiGard is likely to be cost saving or cost neutral; however the robustness of these results rely on the robustness of the clinical evidence. The EAC considers the data on clinical effectiveness to be associated with considerable uncertainty.

For laparoscopic surgery no statistically significant differences were found for the incidence of hypothermia. Rates of complications were not reported directly in this study, but noted by the authors to be equivalent. As noted above, although the retrospective study reported statistically significant differences, this is currently only a draft. Furthermore the economic analysis did not include results of the multivariate analyses included in the draft manuscript.

For open surgery the RCT found statistically significant differences in the incidence of hypothermia, but as rates of complications were not directly reported in this study, the sponsor had to indirectly include these in the model

using data from a retrospective observational study. This study did not find a statistically significant association between SSI and hypothermia, despite SSI being a key outcome in the sponsor's economic model.

6 Implications for research

The EAC recommends that further research includes prospective RCTs of HumiGard compared to standard care in patients undergoing laparoscopic and open surgery. The EAC recommends that these studies report information on rates of complications in addition to temperature change.

The EAC also recommends further research to obtain more robust estimates of the costs of treating SSIs.

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Appendix

Appendix 1. Effectiveness search strategies

Laparoscopic surgery

Database: Ovid MEDLINE(R) <1946 to November Week 3 2015>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 exp Carbon Dioxide/

6 exp Nitrous Oxide/

7 5 or 6

8 (heated or warm).mp. or temperature.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9 7 and 8

10 1 or 2 or 3 or 4 or 9

11 exp Laparoscopy/

12 exp Endoscopy/

13 exp Minimally Invasive Surgical Procedures/

14 (laparoscop$ or endoscop$).mp. or pneumoperitoneum.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

15 or/11-14

16 10 and 15

17 limit 16 to "reviews (maximizes specificity)"

18 limit 16 to "therapy (maximizes specificity)"

19 17 or 18

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 25, 2015>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide or nitrous oxide)).ti,ab.

5 or/1-4

6 (laparoscop$ or endoscop$).mp. or pneumoperitoneum.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7 (minimally invasive adj2 surg$).ti,ab.

8 or/6-7

9 5 and 8

10 limit 9 to "reviews (maximizes specificity)"

11 limit 9 to "therapy (maximizes specificity)"

12 10 or 11

Database: Embase <1974 to 2015 November 25>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 exp carbon dioxide/

6 exp nitrous oxide/

7 5 or 6

8 (heated or warm or temperature).ti,ab.

9 7 and 8

10 1 or 2 or 4 or 9

11 exp laparoscopy/

12 exp endoscopy/

13 exp minimally invasive surgery/

14 (laparoscop$ or endoscop$).mp. or pneumoperitoneum.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

15 11 or 12 or 13 or 14

16 10 and 15

17 limit 16 to (human and "reviews (maximizes specificity)")

18 limit 16 to (human and "therapy (maximizes specificity)")

19 17 or 18

Open surgery

Database: Ovid MEDLINE(R) <1946 to November Week 3 2015>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 exp Carbon Dioxide/

6 exp Nitrous Oxide/

7 5 or 6

8 (heated or warm).mp. or temperature.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9 7 and 8

10 1 or 2 or 3 or 4 or 9

11 (open adj3 (surgery or procedure$)).ti,ab.

12 10 and 11

13 limit 12 to "therapy (best balance of sensitivity and specificity)"

14 limit 12 to "reviews (maximizes specificity)"

15 13 or 14

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 25, 2015>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 (open adj3 (surgery or procedure$)).ti,ab.

6 1 or 2 or 3 or 4

7 5 and 6

Database: Embase <1974 to 2015 November 25>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 exp carbon dioxide/

6 exp nitrous oxide/

7 5 or 6

8 (heated or warm or temperature).ti,ab.

9 7 and 8

10 1 or 2 or 4 or 9

11 (open adj3 (surgery or procedure$)).ti,ab.

12 10 and 11

13 limit 12 to "therapy (best balance of sensitivity and specificity)"

14 limit 12 to "reviews (maximizes specificity)"

15 13 or 14

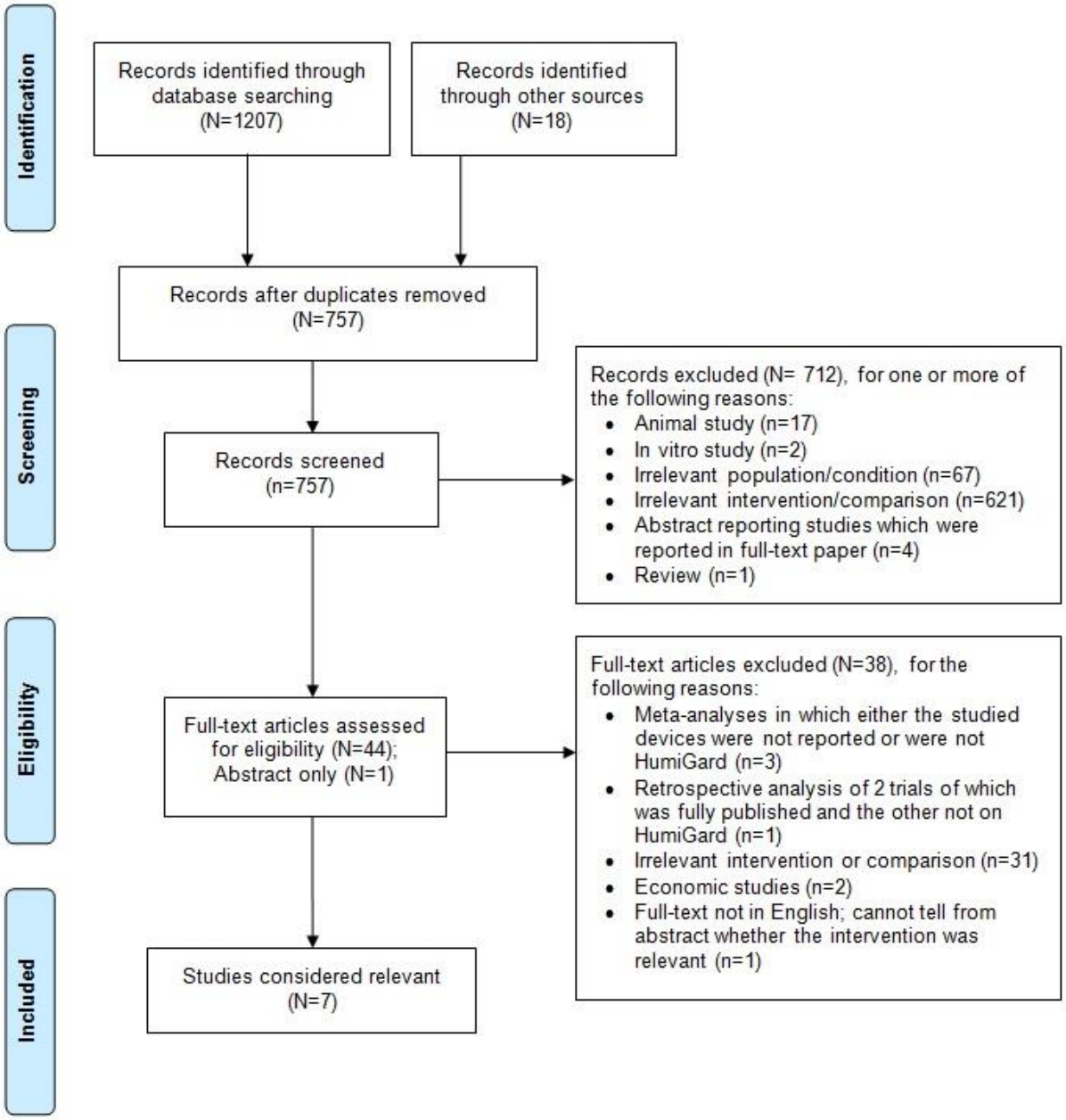

Figure 12. Flow diagram for the selection of studies on effectiveness

Appendix 2. Cost-effectiveness search strategies

Laparoscopic surgery

Database: Ovid MEDLINE(R) <1946 to November Week 3 2015>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 exp Carbon Dioxide/

6 exp Nitrous Oxide/

7 5 or 6

8 (heated or warm).mp. or temperature.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9 7 and 8

10 1 or 2 or 3 or 4 or 9

11 exp Laparoscopy/

12 exp Endoscopy/

13 exp Minimally Invasive Surgical Procedures/

14 (laparoscop$ or endoscop$).mp. or pneumoperitoneum.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

15 or/11-14

16 10 and 15

17 limit 16 to "costs (maximizes sensitivity)"

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 25, 2015>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide or nitrous oxide)).ti,ab.

5 or/1-4

6 (laparoscop$ or endoscop$).mp. or pneumoperitoneum.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7 (minimally invasive adj2 surg$).ti,ab.

8 or/6-7

9 5 and 8

10 limit 9 to "costs (maximizes sensitivity)

Database: Embase <1974 to 2015 November 25>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 exp carbon dioxide/

6 exp nitrous oxide/

7 5 or 6

8 (heated or warm or temperature).ti,ab.

9 7 and 8

10 1 or 2 or 4 or 9

11 exp laparoscopy/

12 exp endoscopy/

13 exp minimally invasive surgery/

14 (laparoscop$ or endoscop$).mp. or pneumoperitoneum.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

15 11 or 12 or 13 or 14

16 10 and 15

17 limit 16 to "economics (best balance of sensitivity and specificity)"

Open surgery

Database: Ovid MEDLINE(R) <1946 to November Week 3 2015>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol

supplementary concept word, rare disease supplementary concept word, unique identifier]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 exp Carbon Dioxide/

6 exp Nitrous Oxide/

7 5 or 6

8 (heated or warm).mp. or temperature.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9 7 and 8

10 1 or 2 or 3 or 4 or 9

11 (open adj3 (surgery or procedure$)).ti,ab.

12 10 and 11

13 limit 12 to "costs (maximizes sensitivity)"

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 25, 2015>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 (open adj3 (surgery or procedure$)).ti,ab.

6 1 or 2 or 3 or 4

7 5 and 6

8 limit 7 to "costs (maximizes sensitivity)"

Database: Embase <1974 to 2015 November 25>

Search Strategy:

1 humidif$.ti,ab.

2 insuffl$.ti,ab.

3 humigard.mp. or insuflow.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

4 ((heated or warm or temperature) adj2 (CO2 or carbon dioxide)).ti,ab.

5 exp carbon dioxide/

6 exp nitrous oxide/

7 5 or 6

8 (heated or warm or temperature).ti,ab.

9 7 and 8

10 1 or 2 or 4 or 9

11 (open adj3 (surgery or procedure$)).ti,ab.

12 10 and 11

13 limit 12 to "economics (maximizes sensitivity)"

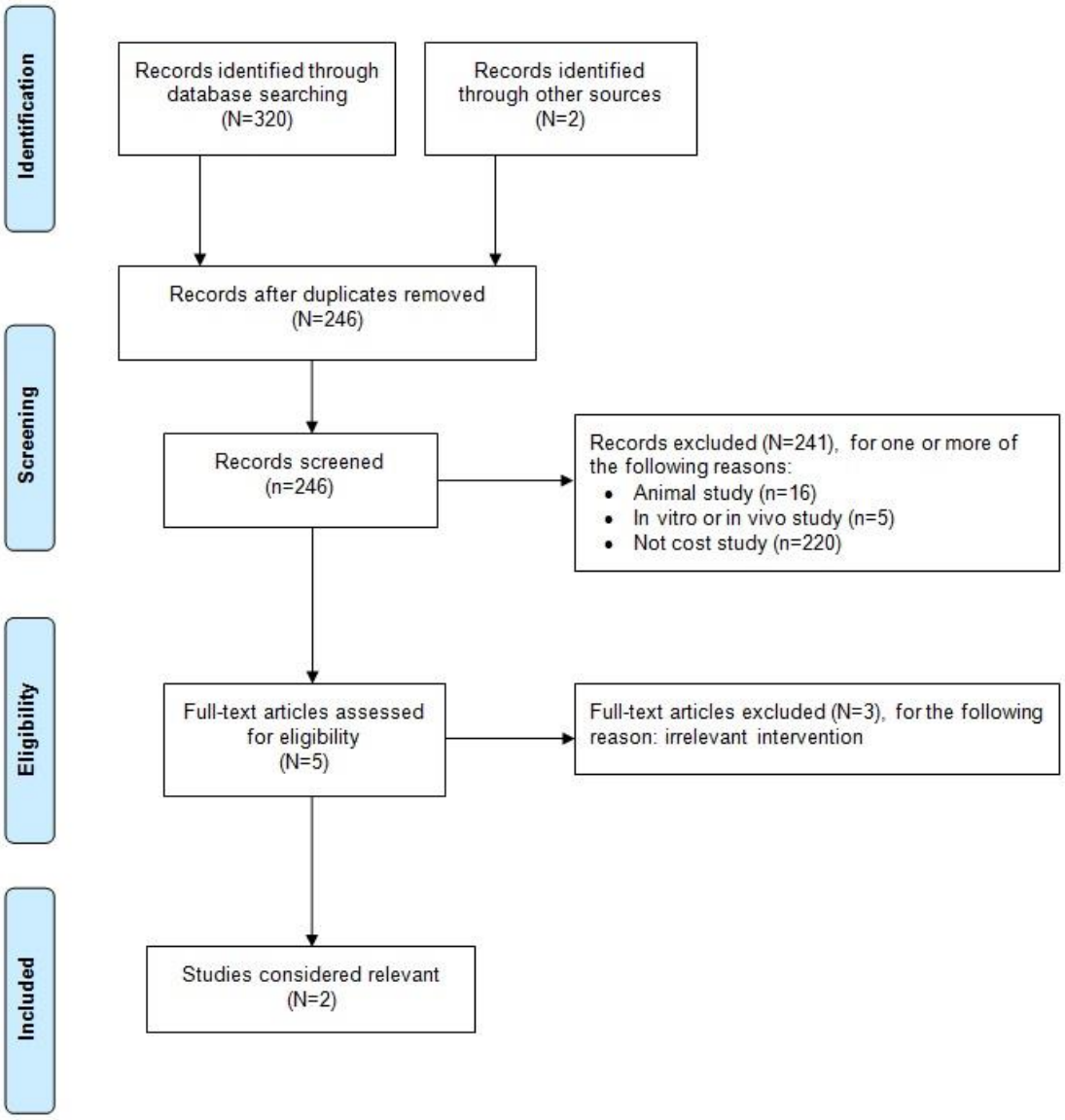

Figure 13. Flow diagram for the selection of studies on cost

Appendix 3. Additional meta-analyses using converted values (laparoscopic surgery)

Core temperature

In total, 4 studies reported on core temperature changes. Three of the studies reported core temperature change between start and end of procedure (Herrmann et al. 2015; Sammour et al. 2010; Yu et al. 2013). The study by Manwaring et al. (2008) reported changes in core temperature from theatre to recovery. Data from Herrmann et al. (2015) for temperature-related outcomes were converted to mean ± SD using the formula developed by Hozo et al. (2005). Sammour et al. (2010) presented the results for temperature-related outcomes as median (IQR). The EAC used the median as mean and considered the width of the IQR as 1.35 standard deviations. The pooled effect size for core temperature changes from start to end of laparoscopic surgery using converted values was -0.13 (95% CI -0.33 to 0.08, p=0.22) (Figure 14).

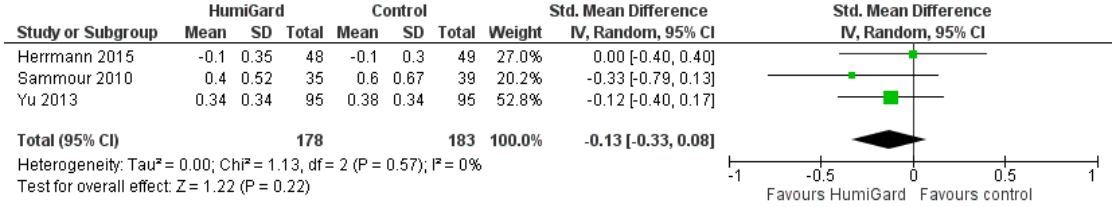

Figure 14. Core temperature changes from start to end of laparoscopic surgery (all HumiGard studies reporting this outcome)

Core temperature during and at end of laparoscopic surgery was reported by 3 studies (Figure 15).

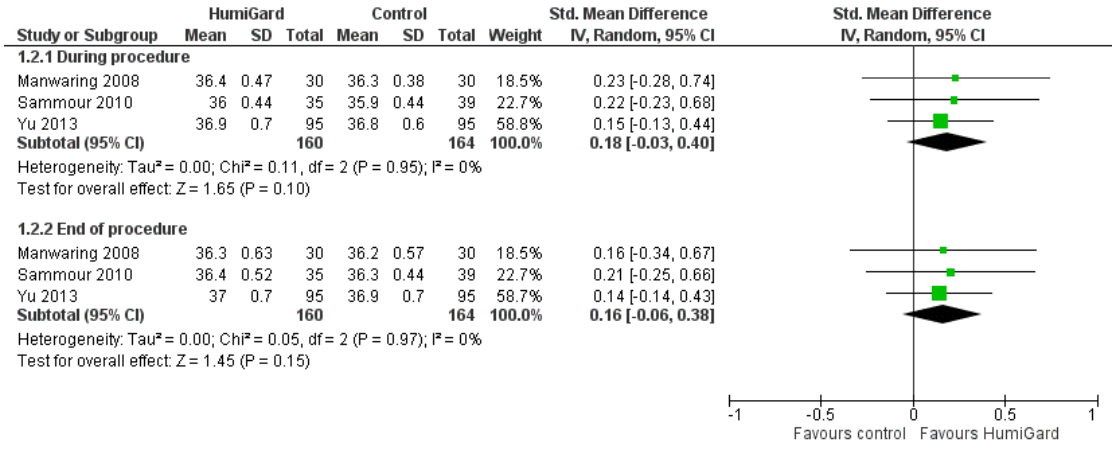

Figure 15. Core temperature during and at end of laparoscopic surgery (all HumiGard studies reporting this outcome).

Length of hospital stay or length of stay in post-operative recovery

In total 2 studies reported length of stay in postoperative recovery and 3 reported total length of hospital stay. The data from Herrmann et al. (2015) and Yu et al. (2013) for length of stay-related outcomes, were converted from median (range) to mean ± SD. Sammour et al. (2010) presented the results for temperature-related outcomes as median (IQR). The EAC used the median as mean and considered the width of the IQR as 1.35 standard deviations. The meta-analysis conducted by the EAC using converted values showed a pooled effect size of 0.66 (95% CI -0.68 to 2.01, p=0.34) (Figure 16).

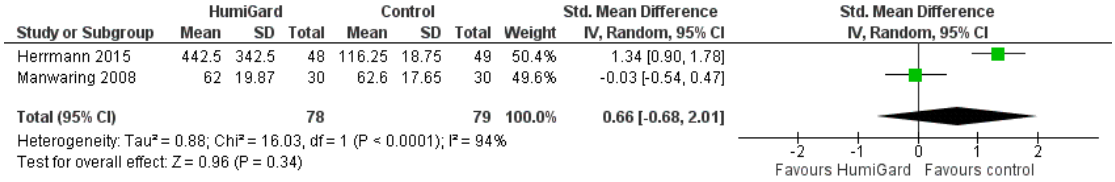

Figure 16. Total length of stay in postoperative recovery after laparoscopic surgery (all HumiGard studies reporting this outcome)

The meta-analysis conducted by the EAC using converted values for total length of hospital stay after laparoscopic surgery showed a pooled effect size of 0.08 (95% CI -0.13 to 0.29, p=0.47) (Figure 17).

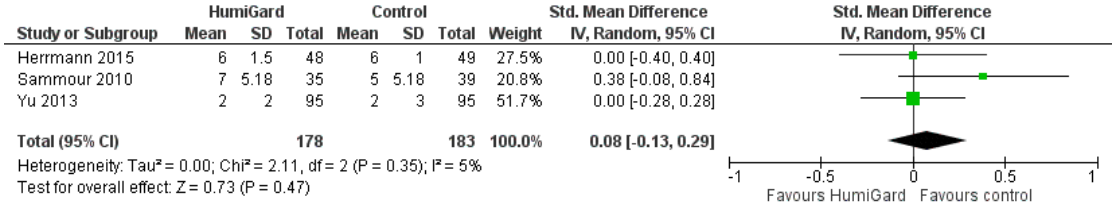

Figure 17. Total length of hospital stay after laparoscopic surgery (all HumiGard studies reporting this outcome)

Patient-reported pain

Two studies reported on shoulder-tip pain. The data from Herrmann et al. (2015) were reported as median (range) and mean without SD. The EAC used the mean provided in the paper and calculated the SD based on median (range) (Figure 18).

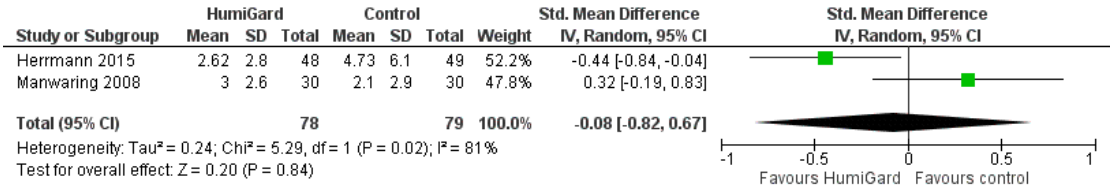

Figure 18. Shoulder tip pain 24hrs after laparoscopy (all HumiGard studies reporting this outcome)

Three studies reported pain using the VAS. The EAC used the outcome pain at rest from Herrmann et al. (2015) and Sammour et al. (2010). The data from Herrmann et al. (2015) were converted from median (range) to mean ± SD. Sammour et al. (2010) presented the results for pain-related outcomes as median (IQR). The EAC used the median as mean and considered the width of the IQR as 1.35 standard deviations (Figure 19).

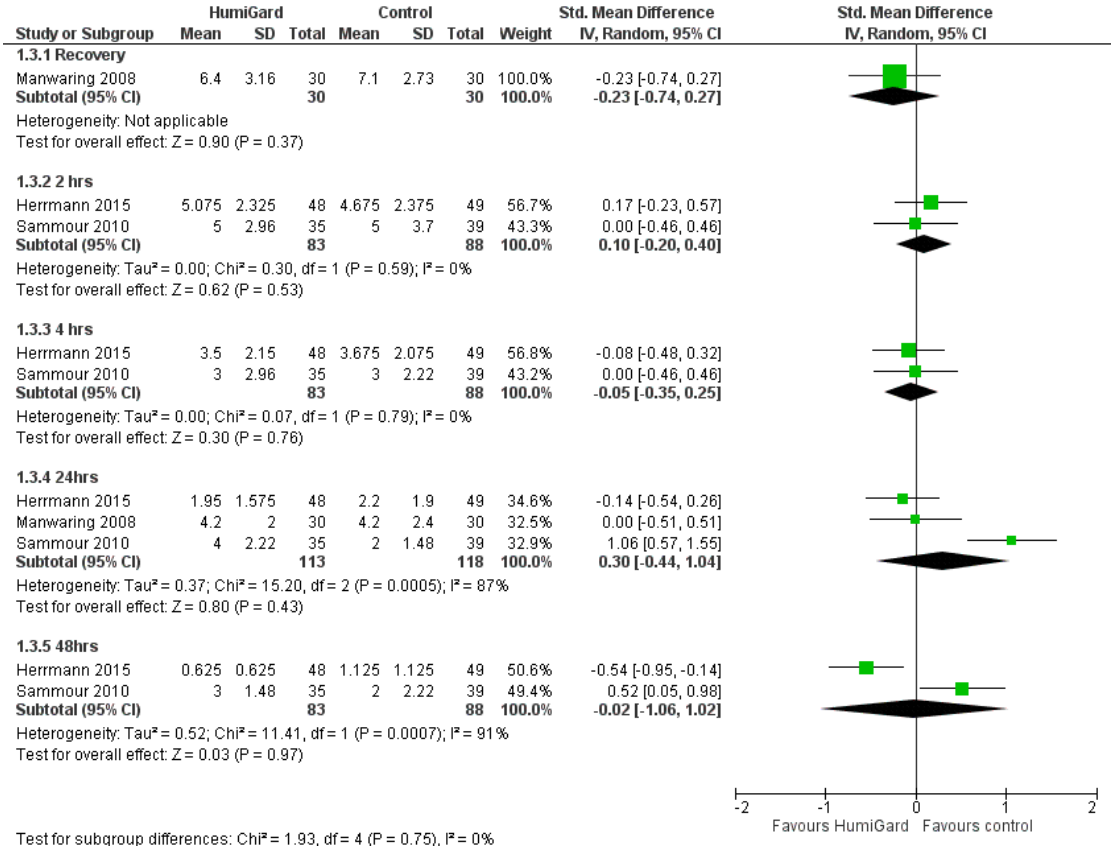

Figure 19. Pain VAS scores from recovery to 48hrs after laparoscopic surgery (all HumiGard studies reporting this outcome)

Analgesic use

Four studies reported on analgesic use at different time points. Herrmann et al. (2015) reported analgesic use as mean ± SD at recovery but as median (range) and mean (without SD) at day 1 and day 2. The EAC used the mean provided in the paper and calculated the SD based on median (range). Sammour et al. (2010) presented the results for analgesic use as median (IQR). The EAC used the median as mean and considered the width of the IQR as 1.35 standard deviations (Figure 20).

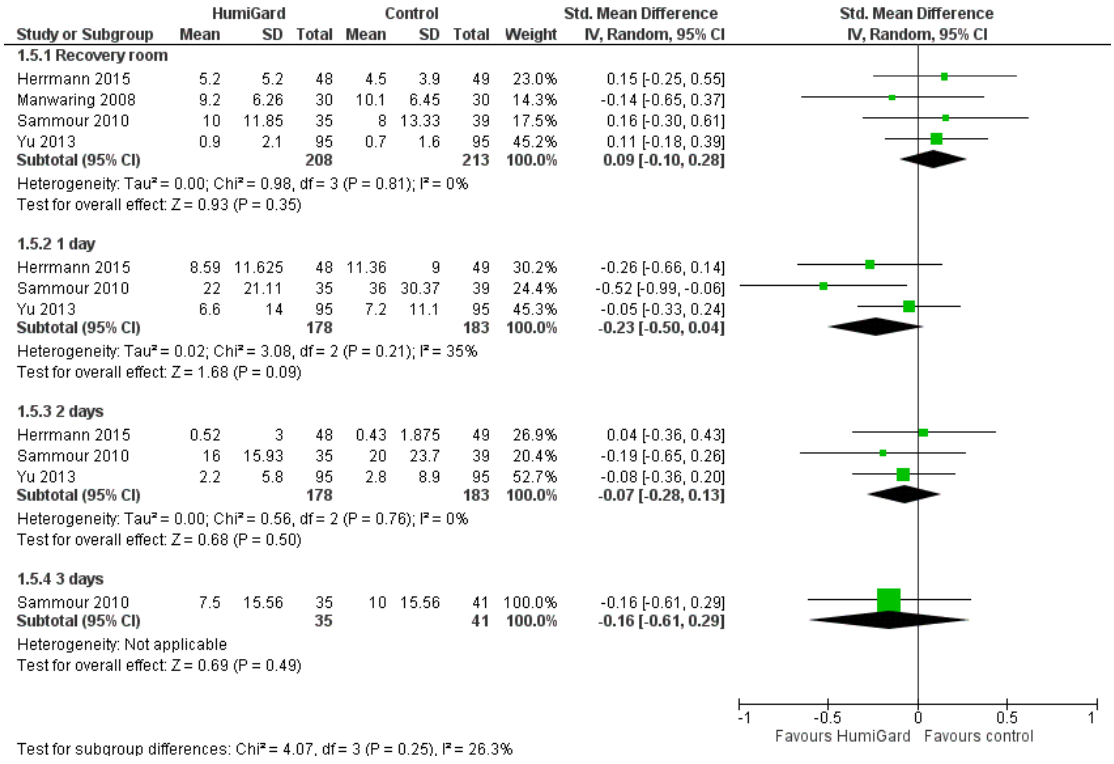

Figure 20. Analgesic usage from recovery to 72hrs after laparoscopic surgery (all HumiGard studies reporting this outcome)

In the meta-analyses presented in this appendix none of the summary mean differences showed statistically significant differences. It should be noted that how far the distributions of the data included depart from the normal distribution will affect the validity of the analyses and results should be viewed with caution.