12 EVIDENCE STATEMENTS

I. RISK FACTORS

A. Patient risk factors

1. Age

There is acceptable evidence that age is not an important independent risk factor for the incidence of hypothermia, but older patients take longer to warm to 36°C postoperatively.

There is weak evidence to suggest that after three hours of general anaesthesia, patients 60 years and older have statistically significantly lower core temperatures than those younger than 60 years.

2. Gender

There is weak evidence to show that gender is not a significant independent risk factor for IPH.

3. ASA Grade

There is good evidence that an ASA grade greater than ASA I increases the incidence of perioperative hypothermia in PACU or ICU, and that the risk increases with ASA grade.

4. Body weight, fat, height

There is acceptable evidence that a lower body weight is a minor risk factor for perioperative hypothermia in ICU and inconsistent evidence for the effect of body weight and body fat on core temperature intraoperatively.

There is weak evidence to show no significant effect of height on the core temperature intraoperatively.

5. Diabetes

There is weak evidence that patients with diabetic neuropathy have lower temperatures after three hours of surgery.

6. Patient preoperative temperature

There is good evidence to show that a low patient preoperative core temperature is a significant independent risk factor for IPH.

B. Anaesthetic risk factors

1. Type of anaesthesia

There is inconsistent evidence to show if there is a significant effect of general anaesthesia compared with regional anaesthesia, on the incidence of hypothermia. The results appeared to depend on the definition of hypothermia.

There is weak evidence to show statistically significantly lower core patient temperatures at 30 minutes in patients undergoing general anaesthesia when compared with regional anaesthesia.

There is good evidence to show a significantly higher incidence of IPH in PACU or ICU in patients undergoing combined general and regional anaesthesia when compared with general or regional anaesthesia alone.

2. Duration of anaesthesia

In the studies that covered a wide range of durations of anaesthesia or surgery, there was weak evidence to show a significant effect of duration of surgery, above and below 2 hours, on the incidence of IPH in ICU. There may have been a dependence on the definition of hypothermia.

3. Height of spinal block

There is weak evidence to show a significant effect of the height of spinal block in regional anaesthesia, with a high level of block giving lower core temperatures.

4. Positive end expiratory pressure

There is insufficient evidence to determine if a positive end expiratory pressure has an effect on the incidence of hypothermia

C. Surgery risk factors

1. Magnitude of surgery

There is good evidence to show a significant effect of magnitude of surgery on the incidence of IPH intraoperatively or in ICU, with major surgery and intermediate surgery both increasing the incidence of IPH. Although there is heterogeneity between studies, each is significant separately.

2. Urgency of surgery

There is acceptable evidence to show no significant effect of urgency of surgery (elective/emergency) on the incidence of IPH in ICU.

3. Type of surgical procedure

There is acceptable evidence to show no significant difference in core temperatures intraoperatively between laparoscopic and open procedures.

4. Patient position intraoperatively

There is insufficient evidence to determine if there is an effect of patient position intraoperatively on the core temperature intraoperatively.

D. Other

1. Intravenous fluid infusion

There is weak evidence that a higher volume of intravenous fluid is a minor risk factor for perioperative hypothermia in ICU, but a lack of information on the warming of fluids was a limitation.

2. Irrigation fluids

There is acceptable evidence to show a large significant effect of room temperature irrigation fluid volume on the incidence of IPH in PACU. Lower volumes of fluids (below 20 litres) resulted in less hypothermia.

3. Blood transfusion

There is acceptable evidence to show that transfusion of unwarmed blood (4°C) as an independent risk factor increases the risk of IPH intraoperatively.

E. Environmental risk factors

1. Theatre temperature

There is good evidence that an increase in theatre temperature is protective of patients becoming hypothermic, both intraoperatively and in ICU.

There is weak evidence to show significantly higher core temperatures intraoperatively for patients undergoing surgery in a warmer theatre (21 to 24°C) compared with a cooler theatre (18 to 21°C).

There is acceptable evidence to show that the effect of theatre temperature has more effect for general anaesthesia when compared with regional anaesthesia.

2. Theatre humidity

There is weak evidence that theatre humidity is not an independent risk factor for IPH.

F. Pharmacological risk factors for IPH

1. Alpha$_2$-adrenergic antagonists

There is acceptable evidence comparing clonidine with placebo given in the preoperative phase, to show no significant effect on core temperature 30 minutes after induction of spinal anaesthesia and weak evidence to show a significantly lower temperature for clonidine after 180 minutes.

There is acceptable evidence comparing clonidine with placebo given at induction of anaesthesia, to show that there is no significant effect on core temperature at 60 minutes intraoperatively, or 15 or 60 minutes after extubation.

There is good evidence when comparing clonidine to placebo given at the end of surgery, to show that there is no significant effect of clonidine on core temperature at 15, 20, 60 or 120 minutes after extubation.

2. Benzodiazepines

There is weak evidence comparing a higher dose (50µg/kg IM) of midazolam with no premedication given in the preoperative phase, to show significantly lower patient core temperatures preoperatively. The evidence suggests a larger effect for increased doses.

There is acceptable evidence comparing midazolam with no premedication given in the preoperative phase, to show significantly higher patient core temperatures intraoperatively.

There is weak evidence comparing midazolam with no treatment given at the end of anaesthesia, to show no significant difference in patient core temperatures intraoperatively and up to 30 minutes postoperatively, but significantly lower temperatures at 60 minutes postoperatively.

3. Flumenazil

There is good evidence comparing flumenazil with no treatment given to patients as they start to awake, showing significantly lower patient core temperatures 20 to 60 minutes postoperatively.

4. Anti-muscarinic agents

There is weak evidence comparing atropine with placebo given preoperatively, to show a statistically significant increase in patient core temperature at the end of the preoperative period.

There is weak evidence comparing glycopyrronium to placebo given preoperatively, to show no significant difference in patient core temperature at the end of anaesthesia.

5. Physostigmine

There is weak evidence comparing IV physostigmine to placebo when given at the end of anaesthesia, to show no significant difference in patient core temperature 15 minutes postoperatively.

6. Drugs for induction of anaesthesia

There is weak evidence comparing ketamine to placebo given at induction of anaesthesia, to show statistically significantly higher patient core temperatures at 30 and 60 minutes intraoperatively and acceptable evidence for the end of surgery.

7. General anaesthesia drugs

There is insufficient evidence to determine if there is a difference in patient core temperature intraoperatively between isoflurane and propofol.

There is insufficient evidence to determine if there is a difference in patient core temperature intraoperatively between xenon or nitrous oxide in addition to isoflurane, compared with isoflurane alone.

There is insufficient evidence to determine if there is a difference in patient core temperature intraoperatively between 0.5% and 1.0% halothane.

8. Analgesia – opioids

There is acceptable evidence when comparing pethidine to placebo given just before spinal anaesthesia, to show there is no significant difference in patient core temperature intraoperatively.

There is good evidence comparing pethidine to placebo given at the end of surgery, to show there is no significant difference in patient core temperature postoperatively.

9. Analgesia – other centrally acting analgesics

There is weak evidence comparing tramadol to tramadol with glycopyrronium given preoperatively, to show there is no significant difference in patient core temperature at the end of anaesthesia.

There is acceptable evidence comparing tramadol to placebo given just before regional anaesthesia, to show there is no significant difference in patient core temperatures at 15 minutes intraoperatively, but significantly lower temperatures at 30 to 90 minutes.

There is acceptable evidence comparing nefopam with placebo given just before regional anaesthesia, to show there is no significant difference in patient core temperatures at 15, 30 and 60 minutes intraoperatively, but significantly lower temperatures at 90 minutes.

There is good evidence comparing tramadol to placebo given at the beginning of wound closure, to show there is no significant difference in the incidence of IPH.

There is good evidence comparing 0.05, 0.1 and 0.2 mg/kg doses of nefopam when given at the end of surgery, to show there is no significant difference in patient core temperatures at 15 and 60 minutes post extubation.

There is acceptable evidence comparing 1 or 2 mg/kg tramadol when given at the beginning of wound closure, to show there is no significant difference in the incidence of IPH.

There is acceptable evidence comparing tramadol with nefopam when given just before regional anaesthesia, to show there is no significant difference in patient core temperatures at 15 and 30 minutes intraoperatively, but significantly lower temperatures at 60 to 90 minutes.

10. Serotonin receptor antagonists

There is acceptable evidence comparing ondansetron with placebo given at the start of anaesthesia, to show no significant difference in patient core temperature intraoperatively.

There is weak evidence comparing dolasetron with placebo given at the start of anaesthesia, to show no significant difference in patient core temperature at the end of surgery or post extubation.

There is acceptable evidence comparing granisetron with placebo given in regional anaesthesia, to show significantly higher patient core temperatures at the end of surgery.

II. PREVENTION OF IPH

A. Warming mechanisms in the preoperative phase

1. Thermal insulation versus usual care

There is acceptable evidence comparing reflective hats with usual care in the preoperative phase to show no significant difference in patient core temperature at the end of prewarming.

There is acceptable evidence comparing reflective hats and jackets (thermal insulation) with usual care applied in the preoperative phase to show significantly higher patient core temperatures at 30 minutes intraoperatively and in PACU. All patients were re-randomised to reflective blanket (thermal insulation) or cloth blanket in the intraoperative phase.

2. Active warming versus usual care

There is insufficient evidence comparing either forced air warming or electric blanket versus usual care applied in the preoperative phase to determine if there is a difference in patient core temperature at 30 and 60 minutes intraoperatively.

There is insufficient evidence comparing forced air warming with usual care applied in the preoperative phase to determine the relative rates of cooling in patients in the intraoperative

period.

There is insufficient evidence comparing active warming (forced air warming or electric blanket) with usual care applied in the preoperative phase to demonstrate a reduction in the incidence of shivering postoperatively.

There is acceptable evidence comparing forced air warming with usual care applied in the preoperative phase to demonstrate a smaller incidence of surgical site infection, assessed at 2 and 6 weeks postoperatively, Number needed to treat is 13 (95%CI 7,100) for a control group rate of 14%.

There is good evidence comparing forced air warming with warmed cotton blankets applied in the preoperative phase to demonstrate a smaller incidence of hypothermia on arrival in PACU. Number needed to treat 4 (95%CI 3,12) for a control group rate of 72%.

B. Warming mechanisms in the intraoperative phase

1. Active versus usual care

1a. Electric blankets versus usual care (General anaesthesia)

There is insufficient evidence comparing electric blankets with usual care, applied in the intraoperative phase, to determine the effect on patient core temperature.

1b. Forced air warming versus usual care (General anaesthesia)

There is acceptable evidence comparing forced air warming with usual care, applied in the intraoperative phase, to demonstrate significantly higher patient core temperatures at 30, 60 and 120 minutes intraoperatively.

There is weak evidence comparing forced air warming with usual care, applied in the intraoperative phase, to demonstrate a significantly higher patient core temperature at 3 hours intraoperatively.

There is good evidence comparing forced air warming with usual care, applied in the intraoperative phase, to demonstrate significantly higher patient core temperature on admission to intensive care units.

1c. Water mattress versus usual care (General Anaesthesia)

There is acceptable evidence comparing water mattress with usual care, applied in the intraoperative phase, to determine there is no significant difference in core temperature at 60 minutes intraoperatively.

There is acceptable evidence comparing water mattress with usual care, applied in the

intraoperative phase, to determine there is a significantly higher patient core temperature at 2 hours and 3 hours intraoperatively.

There is weak evidence comparing water mattress with usual care to show no significant reduction in the incidence of hypothermia at the end of surgery.

1d. Circulating water vest and cap versus usual care (General Anaesthesia)

There is weak evidence comparing circulating water mattress with usual care, applied in the intraoperative phase, to determine there is a significant effect on patient core temperatures at 30 and 60 minutes intraoperatively.

1e. Forced air warming versus usual care (Regional Anaesthesia)

There is insufficient evidence comparing either upper or lower body forced air warming with usual care, applied in the intraoperative phase, to determine an effect on patient core temperature intraoperatively.

There is weak evidence compared upper body forced air warming with usual care, applied in the intraoperative phase, to demonstrate a significantly higher patient core temperature at the end of surgery.

1f. Forced air warming versus usual care (Combined General and Regional anaesthesia)

There is weak evidence comparing forced air warming with usual care, applied in the intraoperative phase, to demonstrate a significantly higher patient core temperature at 30, 60, 120 and 180 minutes intraoperatively and in PACU.

2. Thermal Insulation versus usual care

2a. Thermal insulation versus usual care (General anaesthesia)

There is weak evidence comparing reflective blankets (thermal insulation) with usual care, applied in the intraoperative phase, to demonstrate significantly higher patient core temperature at 30 minutes intraoperatively.

There is weak evidence comparing reflective blankets (thermal insulation) with usual care, applied in the intraoperative phase, to demonstrate no significant difference in temperature at 60 and 90 minutes intraoperatively.

2b. Thermal Insulation versus usual care (Regional anaesthesia)

There is weak evidence comparing reflective blankets (thermal insulation) with usual care, applied in the intraoperative phase, to show no significant difference in the change in patient core temperature relative to baseline at 30 and 60 minutes intraoperatively.

3. Active versus thermal insulation

3a. Active versus thermal insulation (General Anaesthesia)

There is weak evidence comparing forced air warming with reflective blankets, applied in the intraoperative phase, to demonstrate there is no significant difference at 30min and 60 minutes intraoperatively. In one study patients received warmed IV fluids.

There is weak evidence comparing forced air warming with reflective blankets, applied in the intraoperative phase, to demonstrate that there is a significantly higher patient core temperature at 2 hours intraoperatively. All patients received warmed IV fluids.

There is weak evidence comparing warmed cotton blankets compared with reflective blankets to show no significant difference in patient core temperature up to 60 minutes intraoperatively.

3b. Active versus thermal insulation (Combined Spinal-Epidural Anaesthesia)

There is weak evidence comparing forced air warming with reflective blankets, applied in the intraoperative phase to demonstrate no significant difference at 30 min and significantly higher patient core temperature at 60 and 120 minutes intraoperatively. All patients received warmed IV fluids.

There is acceptable evidence comparing forced air warming with reflective blankets, applied in the intraoperative phase to demonstrate a significantly higher patient core temperature at 2 hours intraoperatively. All patients received warmed IV fluids.

There is acceptable evidence comparing forced air warming with reflective blankets applied in the intraoperative phase, to show in patients warmed with forced air warming a smaller incidence of hypothermia on arrival into recovery room. All patients received warmed IV fluids.

3c. Active versus thermal insulation (Combined General and Regional Anaesthesia)

There is insufficient evidence when comparing forced air warming with reflective blankets applied in the intraoperative phase to determine if there is difference, in patient core temperature intraoperatively.

4. Active warming 1 versus Active warming 2

4a. Forced air warming versus warmed cotton blanket

There is weak evidence comparing forced air warming with warmed cotton blankets applied in the intraoperative phase to demonstrate there is no significant difference at 60 minutes intraoperatively.

There is acceptable evidence comparing forced air warming with warmed cotton blankets

applied in the intraoperative phase, to demonstrate there is a significantly higher patient core temperature at 2 hours intraoperatively and at entry into PACU.

There is acceptable evidence comparing forced air warming with warmed cotton blankets applied in the intraoperative phase, to show that for patients warmed with a forced air warmer, there is a smaller incidence of hypothermia at entry into PACU. Numbers needed to treat of 2 (95% CI 1, 3) for a control group rate of 66%.

4b. Forced air warming versus electric blanket (general anaesthesia)

There is insufficient evidence comparing forced air warming with electric blankets to determine if there is a difference in change in patient core temperature relative to the baseline intraoperatively. All patients received warmed IV fluids.

4c. Forced air warming versus electric blanket (combined general and regional anaesthesia)

There is insufficient evidence comparing forced air warming with electric blankets, applied in the intraoperative phase, to determine if there is a difference in patient core temperature intraoperatively. All patients received warmed IV fluids.

4d. Forced air warming versus electric under mattress*

*Majority General Anaesthesia; Some patients received regional in addition to general anaesthesia.

There is insufficient evidence comparing forced air warming with electric under mattress, applied in the intraoperative phase, to determine if there is a difference in patient core temperature intraoperatively. All patients received warmed IV fluids.

There is insufficient evidence comparing forced air warming with electric under mattress to determine if there is a difference in reduction in the incidence of hypothermia at entry into PACU. All patients received warmed IV fluids intraoperatively.

4e. Forced air warming versus electric heating pad (general anaesthesia)

There is acceptable evidence comparing forced air warming with electric heating pad, applied in the intraoperative phase, demonstrating no significant difference in patient core temperature at 30 and 60 minutes intraoperatively. All patients received warmed IV fluids.

There is acceptable evidence comparing forced air warming with electric heating pad, applied in the intraoperative phase, demonstrating significantly higher patient core temperature in patients given forced air warming at 2 hours intraoperatively. All patients received warmed IV fluids.

There is acceptable evidence comparing forced air warming with electric heating pad, to demonstrate no significant difference in the incidence of hypothermia. All patients received warmed IV fluids.

4f. Forced air warming versus electric heating pad (regional anaesthesia)

There is acceptable evidence comparing forced air warming with electric heating pads applied in the intraoperative phase to show no difference in the maintenance of patient core temperature intraoperatively. All patients received warmed IV fluids.

4g. Forced air warming versus circulating water mattress (general anaesthesia)

There is insufficient evidence comparing forced air warming with circulating water mattress, applied in the intraoperative phase, to show a change in patient core temperature relative to the baseline at 30, 120 and 180 minutes intraoperatively. All patients received warmed IV fluids.

There is weak evidence comparing forced air warming with circulating water mattress, applied in the intraoperative phase, to demonstrate significantly smaller change in core temperature relative to the baseline for patients warmed with forced air, at 60 minutes, intraoperatively. All patients received warmed IV fluids.

4h. Forced air warming versus circulating water mattress (combined regional and general anaesthesia)

There is insufficient evidence comparing forced air warming with circulating water mattress, applied in the intraoperative phase, to show a difference in patient core temperatures intraoperatively. All patients received warmed IV fluids.

4i. Forced air warming versus radiant heat (general anaesthesia)

There is insufficient evidence comparing forced air warming with radiant heat directed to the hand applied in the intraoperative phase, to determine if there is a difference in the incidence of hypothermia at end of surgery. All patients received warmed IV fluids.

There is acceptable evidence comparing forced air warming with radiant heat directed to the hand, applied in the intraoperative phase, to show no significant difference in patient core temperatures at 30 minutes, intraoperatively. All patients received warmed IV fluids.

There is acceptable evidence comparing forced air warming with radiant heat directed to the hand or the face, applied in the intraoperative phase, to show a significantly higher core temperature in patients given forced air warming from one to four hours intraoperatively. All patients received warmed IV fluids.

There is acceptable evidence comparing forced air warming with radiant heat directed to the palm or the face, applied in the intraoperative phase, to show a significantly higher core temperature in patients given forced air warming at end of surgery. All patients received warmed IV fluids.

There is weak evidence comparing forced air warming with radiant heat directed to the face, applied in the intraoperative phase, to determine if there is a difference in patient core temperatures at entry into PACU. All patients received warmed IV fluids.

4j. Forced air warming versus radiant heat (regional anaesthesia)

There is insufficient evidence comparing forced air warming with radiant heat directed to the palm, applied in the intraoperative phase, to demonstrate if there is a difference in the incidence of hypothermia upon arrival in PACU. All patients received warmed IV fluids.

There is acceptable evidence comparing forced air warming with radiant heat directed to the palm, applied in the intraoperative phase, to demonstrate there is no significant difference at 30 and 60 minutes intraoperatively.

There is acceptable evidence comparing forced air warming with radiant heat, applied in the intraoperative phase, to demonstrate there is significantly higher core temperature at the end of surgery (mean duration of anaesthesia 50 min vs 56 min).

4k. Electric blanket versus circulating water mattress (general anaesthesia)

There is insufficient evidence comparing electric blanket with circulating water mattress, applied in the intraoperative phase, to show a difference in change in patient core temperatures relative to the baseline intraoperatively. All patients received warmed IV fluids.

4l. Electric blanket versus circulating water mattress (regional anaesthesia)

There is insufficient evidence comparing electric blanket with circulating water mattress, applied in the intraoperative phase, to show a difference in the change in patient core temperatures relative to the baseline patient intraoperatively. All patients received warmed IV fluids.

5. Sites of forced air warming

5a. Forced air warming upper body versus forced air warming lower body (general anaesthesia)

There is weak evidence comparing forced air warming of the upper body with forced air warming of the lower body, applied in the intraoperative phase, to show no significant difference in patient core temperature at 30 minutes to 2 hours and at 4 hours intraoperatively.

All patients received warmed IV fluids.

There is weak evidence comparing forced air warming of the upper body with forced air warming of the lower body, applied in the intraoperative phase, to show significantly higher patient core temperature for the lower body forced air warmed group at 3 hours intraoperatively. All patients received warmed IV fluids.

5b. Forced air warming upper body versus forced air warming lower body (regional anaesthesia)

There is insufficient evidence comparing forced air warming of the upper body with forced air warming of the lower body applied in the intraoperative phase to demonstrate if there is a difference in patient core temperature intraoperatively.

6. Types of forced air warming

6a. Forced air warming insulated versus forced air warming regular (general anaesthesia)

There is weak evidence comparing insulated forced air warming with standard forced air warming, applied in the intraoperative phase, to demonstrate no significant difference at 60 min intraoperatively. All patients received warmed irrigation fluids.

There is weak evidence comparing insulated forced air warming with standard forced air warming, applied in the intraoperative phase, to demonstrate significantly higher patient core temperature when warmed with insulated forced air warming at 2 hours intraoperatively. All patients received warmed irrigation fluids.

7. Settings of forced air warming

7a. Forced air warming (40°C) versus forced air warming (ambient) (General anaesthesia)

GDG consensus was that patients should not receive forced air warming from devices set at ambient temperature.

7b. Forced air warming (aggressive) versus forced air warming (conventional) (regional anaesthesia)

There is acceptable evidence comparing aggressive forced air warming (to maintain core temperature at 36.5°C) with conventional forced air warming, applied in the intraoperative phase, to demonstrate significantly higher patient core temperature for patients receiving aggressive forced air warming at end of surgery (mean:1 hour 40 minutes) and after 3 hours PACU. All patients received warmed IV fluids.

There is acceptable evidence comparing aggressive forced air warming (to maintain core

temperature at 36.5°C) with conventional forced air warming, applied in the intraoperative phase, to demonstrate significantly lower volume of total blood loss for patients receiving aggressive forced air warming (to maintain core temperature at 36.5°C) intraoperatively and until the first postoperative morning.

8. Sites of thermal insulation

8b. Thermal (site 1+2) versus Thermal (site 1) (Combined General and Regional Anaesthesia)

There is weak evidence comparing reflective blankets covering the head/face, trunk and extremities with trunk and extremities alone, applied in the intraoperative phase, to demonstrate no significant difference at 30 minutes intraoperatively.

There is weak evidence comparing reflective blankets covering the head/face, trunk and extremities with trunk and extremities alone, applied in the intraoperative phase, to demonstrate significantly higher patient core temperature in patients insulated with reflective blankets at the head/face, trunk and extremities at 60 min and 2 hours intraoperatively.

C. Warming mechanisms in the pre and intraoperative phases

1. Thermal insulation versus usual care

There is acceptable evidence comparing reflective blankets with usual care, applied in both the preoperative and intraoperative phases, to show significantly higher patient core temperature at 30 and 45 min intraoperatively.

2. Active warming versus usual care

There is weak evidence comparing forced air warming with usual care, applied in both the preoperative and intraoperative phases, to show no significant difference in patient core temperature at 20, 40 and 60 minutes intraoperatively.

There is weak evidence comparing forced air warming with usual care, applied in both the preoperative and intraoperative phases, to show a significantly higher patient core temperature at 120 and 180 minutes intraoperatively, on arrival into PACU and at 40 min in PACU

There is weak evidence from an indirect study comparing forced air warming with usual care, given in both the preoperative and intraoperative phases, in patients receiving epidural anaesthesia for caesarean section to show significantly higher patient core temperature from 15 minutes to 2 hours intraoperatively.

There is good evidence comparing forced air warming and warmed fluids (1.1litre) with usual care (but some received warming at the discretion of the anaesthetist), applied in the pre and

the intraoperative phase, to demonstrate a smaller incidence of hypothermia. Number needed to treat 4 (95% CI 3,5) for a control group rate of 53%.

There is insufficient evidence to determine if there is an additional effect of an electric mattress to forced air warming and warmed IV fluids applied in the preoperative and intraoperative phases.

D. Fluid warming

1. Intravenous fluids (general anaesthesia)

There is good evidence comparing warmed IV fluids (1.8 to 1.3 litres) with room temperature fluids (1.8 to 1.4litre) to demonstrate a smaller incidence of hypothermia in patients receiving warmed IV fluids at end of surgery. Numbers needed to treat 3 (95% CI 2, 4) for a control group rate 35% to 64%.

There is good evidence comparing warmed IV fluids (0.9 to 3.3 litres) with room temperature fluids (0.9 to 3.6 litre) to demonstrate significantly higher patient core temperature up at 30 min and 1 hour intraoperatively.

There is acceptable evidence comparing warmed IV fluids (2.9 to 3.3 litres) with room temperature fluids (1.8 to 3.6 litre) to demonstrate significantly higher patient core temperature given warmed IV fluids at 2 hours.

There is insufficient evidence comparing warmed IV fluids (3.3 litres) with room temperature fluids (3.6 litres) to demonstrate a difference in patient core temperature 3 and 4 hours intraoperatively.

There is acceptable evidence comparing warmed IV fluids (1.3 to 3.3 litres) with room temperature fluids (1.8 to 3.6 litres) to demonstrate significantly higher patient core temperature given warmed IV fluids at 2 hours.

There is weak evidence comparing patients given warmed IV fluids (1.3 litres) with room temperature fluids (1.4 litre) to demonstrate significantly higher core temperature for patients given warmed IV fluids at entry into PACU.

2. Intravenous fluids and forced air warming (general anaesthesia)

There is acceptable evidence comparing warmed IV fluids and forced air warming (2.1 to 3.5 litres) with room temperature IV fluids (2.3 to 3.4 litres) to demonstrate a significant difference in patient core temperature up to 3 hours intraoperatively.

There is acceptable evidence comparing warmed IV fluids (3.5 litres) and forced air warming

with room temperature IV fluids (3.4 litres) to demonstrate a significantly higher patient core temperature up to 5 hours postoperatively.

3. Irrigation fluids (general anaesthesia)

There is weak evidence comparing warmed irrigation fluids (1.3 litres) compared with room temperature irrigation fluids (1.5 litres) to demonstrate no significant difference in the incidence of hypothermia. All patients rested on a heating blanket.

There is weak evidence comparing warmed irrigation fluids (1.3 litres) compared with room temperature irrigation fluids (1.5 litres) to demonstrate no significant difference in patient core temperature relative to baseline up to 1 hour intraoperatively. All patients rested on a heating blanket.

There is weak evidence comparing warmed irrigation fluids (17.6 litres) compared with room temperature irrigation fluids (17.3 litres) to demonstrate no significant difference in patient core temperature relative to baseline at end of surgery. All patients received a warmed blanket intraoperatively.

4. Irrigation fluids (regional anaesthesia)

There is weak evidence comparing passively warmed irrigation fluids (8.4 litres) compared with room temperature irrigation fluids (8.4 litres) to demonstrate no significant difference in the change in core temperature relative to baseline in patients up to 2 hours intraoperatively.

There is weak evidence comparing warmed irrigation fluids (volume not stated) compared with room temperature irrigation fluids to demonstrate significantly higher core temperature relative to baseline at the lowest intraoperative period, in patients given warmed irrigation fluids intraoperatively.

E. Warming of gases (general anaesthesia)

There is weak evidence comparing warmed insufflation gas (348 litres) unwarmed gases (267 litres) to show no significant difference in patient core temperature at 30 and 60 minutes intraoperatively.

There is weak evidence comparing warmed insufflation gas (348 litres) unwarmed gases (267 litres) to show a significantly higher patient core temperature at end of insufflation (approximately over 90 minutes intraoperatively).

There is weak evidence comparing warmed insufflation gas (131 to 348 litres) unwarmed gases (135 to 267 litres) to show a significantly higher patient core temperature at end of surgery.

There is acceptable evidence comparing warmed insufflation gas (67 to 348 litres) with unwarmed gases (63 to 267 litres) to show no significant difference in patient core temperatures at entry into PACU and duration of stay up to 4 hours in PACU.

There is weak evidence comparing heated-humidified gas with usual care to show a significantly lower the incidence of hypothermia at end of surgery.

There is acceptable evidence comparing heated-humidified gas with usual care to show a small statistically significant difference in patient core temperature at 30 minutes and 60 minutes intraoperatively.

There is inconsistent evidence comparing heated-humidified gas with usual care to demonstrate significantly higher patient core temperature at 120 minutes intraoperatively.

There is acceptable evidence comparing heated-humidified gas with usual care to demonstrate a significantly higher patient core temperature at 120 minutes intraoperatively.

F. Adverse Events of warming mechanisms

There is weak evidence to demonstrate a very low incidence of adverse effects related to the use of warming devices in patient care. There is very low reported incidence of burns of varying size and depth; possible tracheal tube displacement/ obstruction.

There is weak evidence related to the use of warming devices in patient care reports potential for increased bacterial contamination; disturbance to monitoring equipment and potentiation of transdermal drug delivery systems.

G. Pharmacological agents

1. Amino acids

There is insufficient evidence to determine an effect when giving infusions of amino acids in the preoperative phase only, on patient core temperature postoperatively.

There is inconsistent evidence comparing infusions of amino acids with placebo or no intervention, given in the intraoperative phase only, to show if there is a difference in patient core temperature intraoperatively

There is acceptable evidence comparing infusions of amino acids with placebo or usual care, given in both the pre- and intraoperative phases, to show significantly higher patient core temperature intraoperatively and postoperatively.

There is weak evidence to show a significantly reduced time in ICU and duration of hospital stay, for patients given an infusion of amino acids in both the pre and intraoperative phases, compared with placebo.

2. Phenylephrine

There is insufficient evidence to determine whether phenylephrine, given in the intraoperative phase increases patient core temperature intraoperatively compared with placebo.

3. Urapidil

There is moderate evidence to show that urapidil compared with placebo, given at the end of surgery, gives no significant difference in patient core temperature post-extubation, or time spent in PACU or the time to extubation.

4. Fructose

There is weak evidence to show significantly higher patient core temperature intraoperatively for an infusion of fructose, given in the pre and intraoperative phases, compared with placebo.

III. Treatment of perioperative hypothermia

A. Warming mechanisms in the preoperative phase

There is insufficient evidence to determine whether treating hypothermic patients with forced air warming preoperatively, in addition to intraoperative warming, has an effect on core temperatures intraoperatively.

B. Warming mechanisms in the pre and intraoperative phases

There is weak evidence comparing forced air warming with usual care, given in the pre and intraoperative phases for the treatment of IPH, to show significantly higher core temperatures from 30 minutes intraoperatively and a significantly lower incidence of IPH at the end of anaesthesia.

C. Warming mechanisms in the intraoperative phase

There is weak evidence comparing forced air warming with usual care, given in the intraoperative phase for the treatment of IPH, to show there is no significant difference in core temperature at 30 minutes intraoperatively, but significantly higher core temperatures at 60 and 120 minutes and a significantly lower incidence of IPH at the end of anaesthesia.

D. Warming mechanisms in the postoperative phase

There is weak evidence comparing forced air warming with usual care, given in ICU for the treatment of IPH, to show no significant difference in core temperatures at 30 and 45 minutes postoperatively and a borderline significance at 60 minutes, but significantly higher core temperatures at 120 and 180 minutes.

1. Active warming versus usual care

There is weak evidence comparing electric blanket with usual care, given in ICU for the treatment of IPH, to show no significant difference in the time to raise the temperature by 0.5°C.

There is weak evidence comparing radiant heat with usual care, given in ICU for the treatment of IPH, to show a significant decrease in the time to raise the temperature by 0.5°C.

2. Active warming 1 versus active warming 2

2a. Forced air warming versus warmed blankets

There is weak evidence comparing forced air warming with warmed blankets, given in PACU for the treatment of IPH, to show a significant increase in core temperature after 15 minutes postoperatively.

There is weak evidence comparing forced air warming with warmed blankets, given in PACU for the treatment of IPH, to show a significant decrease in the time to raise the temperature to 36.0°C, and a significant improvement in the rate of increase in temperature.

There is weak evidence comparing forced air warming with warmed blankets, given in PACU for the treatment of IPH, to show no significant difference in the time to discharge from PACU.

2b. Radiant heat versus warmed blankets

There is weak evidence comparing radiant heat with warmed blankets, given in PACU for the treatment of IPH, to show no significant difference in the time to raise the temperature to 36.0°C, and no significant difference in the time to discharge from PACU.

2c. Radiant heat versus electric blanket

There is weak evidence comparing radiant heat with electric blanket, given in ICU for the treatment of IPH, to show a significant decrease in the time to raise the temperature by 0.5°C.

3. Active warming versus thermal insulation

There is weak evidence comparing radiant heat with reflective blanket, given in PACU for the treatment of IPH, to show a significantly greater increase in median core temperature over two hours.

4. Thermal insulation versus usual care

There is acceptable evidence comparing reflective blankets plus reflective hats with usual care, given in PACU for the treatment of IPH, to show no significant difference in the time to raise the core temperature to 36.0°C.

5. Observational data

There is weak evidence from observational data in hypothermic patients given forced air warming in ICU or PACU, which indicates that the time taken to raise the core temperature is as follows: from 35.0°C to 35.5°C it is 15 to 37 minutes; from 35.5°C to 36.0°C it is 15 to 30 minutes; and from 36.0°C to 36.5°C it is around 60 minutes.

There is weak evidence from observational data in hypothermic patients given radiant heat in ICU or PACU, which indicates that the time taken to raise the core temperature by 0.5°C is about 25 minutes; including raising the temperature from 36.0°C to 36.5°C.

13 Cost effectiveness analysis

IPH is associated with adverse health consequences that could lead to the expenditure of NHS resources as well as adversely affecting patients' health status. As no published economic evidence had been identified by the literature review, it was necessary to carry out a new economic analysis to inform recommendations on the cost-effectiveness of interventions to prevent IPH.

Hypothermia is associated with an increased risk of surgical wound infection (SWI), morbid cardiac events (MCEs), blood transfusion, unplanned postoperative mechanical ventilation and pressure ulcers. It has also been shown to increase hospital length of stay and may increase PACU length of stay. The relationship between hypothermia and these adverse health consequences has been reviewed and discussed in section 8. Each of these adverse health consequences will result in increased resource use and some of them have the potential to result in long-term reductions in HRQoL. The economic model was designed to estimate the QALY gain and the reduction in resource use that can be achieved by reducing the incidence of IPH and therefore the incidence of these adverse consequences associated with IPH.

Model structure

A decision tree model has been used to estimate the impact of various clinical strategies to prevent hypothermia on the incidence of each of the adverse health consequences. These clinical strategies may involve one or more interventions in one or more phases of the perioperative pathway. In the economic model, hypothermia is defined a core temperature below 36.0˚C and normothermia is defined as a core temperature above 36.0˚C. The basic structure of the model is shown in Figure 1 and the adverse health consequences included are shown in Figure 2. We have assumed that the probability of a patient experiencing a particular adverse health consequence is independent of their probability of experiencing another health consequence. In addition to the binary outcomes shown in Figure 2 we also estimated the expected increase in hospital length of stay and PACU length of stay for hypothermic compared to normothermic patients. The decision tree model estimates the probability of each of the adverse consequences in the perioperative and post-operative period. The long-term impact of morbid cardiac events (MCEs) on expected life-time QALY gain has been estimated using a simple Markov survival model.

Figure 1: Decision tree showing the model structure

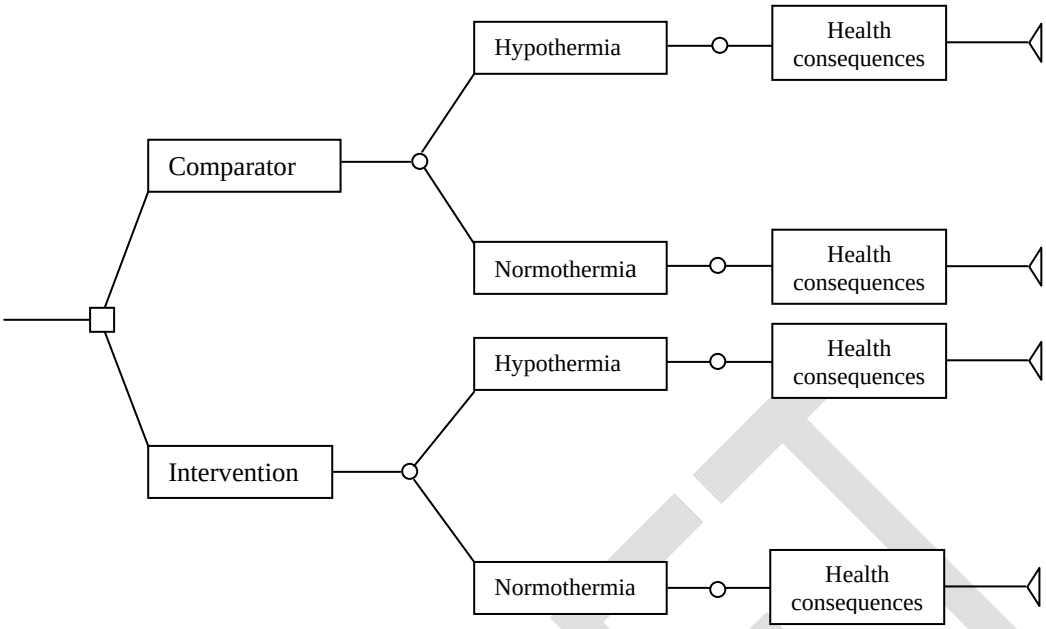
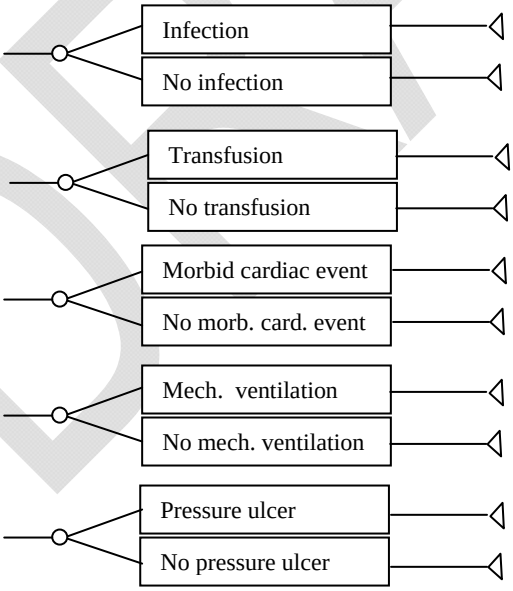


Figure 2: The health consequences of IPH described as binary outcomes in the model



Variation in cost-effectiveness across the population

The cost-effectiveness is dependent on the risk of hypothermia in patients receiving usual care, the effectiveness of each prevention strategy relative to usual care, the risk of each consequence and the cost and QALY impact of each consequence. It is also dependent on the cost of each prevention strategy compared to usual care. Some of these factors vary across the population covered by the guideline. For example the risk of IPH has been shown to be increased for patients having major surgery compared to those having minor surgery, for patients with higher ASA grades and for patients having combined general and regional anaesthesia. The risk of morbid cardiac events is expected to vary by age due to an increase in the population prevalence of ischaemic heart disease with age. The QALY loss due to morbid cardiac events is expected to vary by age due to differences in life-expectancy and variations in HRQoL prior to the morbid cardiac event. In the clinical effectiveness reviews the effectiveness of the various prevention strategies has been reviewed at various intraoperative time points. The GDG advised that it was necessary to consider whether the most cost-effective strategy varied depending on the duration of anaesthesia due to variation in the clinical effectiveness over different anaesthesia durations. Therefore, in order to capture the variation in cost-effectiveness across the population covered by the guideline we modelled several different clinical scenarios to allow the GDG to consider which subgroups of patients can be managed cost-effectively with each of the various strategies to prevent hypothermia. The factors varied across these clinical scenarios were:

- Magnitude of surgery (minor, intermediate or major);
- Anaesthesia type (general / regional or both combined);
- ASA grade (I, II or >II);
- Age (20, 50, 70);
- Duration of anaesthesia (30, 60, 120 minutes).

The GDG advised that the majority of surgery is minor surgery carried out under general or regional anaesthesia lasting around 60 minutes and that most patients are ASA I or II. The mean age for all patients having operations is 52 (HES Online 2005/2006). Based on this, we presented the full results for all clinical strategies for a patient aged 50, with ASA grade I having minor surgery under general anaesthesia lasting 60 minutes. We also presented full results for shorter and longer durations of anaesthesia as some prevention strategies did not have data at all time points. The results for longer durations were based on intermediate surgery as the GDG advised that most surgery lasting 120 minutes is likely to be intermediate or major rather than minor. The results for all prevention strategies at these three time points were used to determine which prevention strategies should be considered in the indirect comparison to determine the optimal strategy. The optimal strategy was then explored for various clinical scenarios to allow the GDG to determine whether separate recommendations were needed for any subgroup of the population covered by the guideline.

Baseline risk of consequences (including variation by surgery magnitude)

The baseline risk of each adverse health consequence is assumed to be the same across all patients covered by the guideline with the following exceptions:

- The incidence of morbid cardiac events is assumed to vary by age;
- The mix of MCEs is assumed to be different for hypothermic and normothermic patients based on the events observed in Frank (1997);
- The risk of blood transfusion and pressure ulcers is assumed to be zero in patients having minor surgery.

The baseline risk for each consequence used in the model should reflect the average risk in the population covered by the guideline as closely as possible. In general the baseline risks have been taken from cohort studies or UK national statistics. We have not been able to adjust the rates to allow for the fact that these cohorts will have included some patients who experienced IPH and were therefore at increased risk. The rates observed in these cohorts have been applied to normothermic patients in the model and may therefore overestimate the risk in normothermic patients.

Surgical wound infection: We used the baseline risk of surgical wound infection that was given in the Health Protection Agency (HPA) report on Surgical Site Infection Surveillance Service (Health Protection Agency, 2006). The surveillance service collects data on infections related to a surgical procedure that affect the surgical wound or deeper tissues handled during the procedure and which are identified prior to discharge from hospital.

Data was collected by 247 hospitals in England between October 1997 and September 2005. A total of 7,194 surgical wound infections were reported to have occurred in 239,953 operations across 11 surgical categories. This incidence of 3.00% has been applied in the model as the risk of a surgical wound infection in normothermic patients. It may underestimate the incidence of infections occurring post discharge, but the costs associated with infections identified after discharge are likely to be lower as they are less likely to result in excess hospital stay. The incidence of SWI was considered to be constant across different ages and magnitudes of surgery.

Pressure ulcer: The baseline risk of pressure ulcers was taken from a report on the incidence of pressure sores across a NHS Trust hospital (Clark, 1994). The number of patients that developed pressure sores was recorded during a period of 52 weeks (between 1990 and 1991) among patients admitted to the wards. It was reported that 1.8% of in-hospital surgical patients developed pressure sores. This did not include orthopaedic patients who were reported to develop pressure sores at a rate of 10.9%. We assumed in the model that the

incidence of pressure ulcers is zero in minor surgery as this is less likely to result in a period of prolonged immobility. We applied the reported rate for non-orthopaedic patients (1.8%) in the model for scenarios considering major or intermediate surgery. The rate in orthopaedic patients was used in a sensitivity analysis to determine whether the cost-effectiveness of strategies to prevent IPH is dependent on the risk of pressure ulcers.

Blood transfusion: The estimate of the baseline risk of blood transfusion in IPH is based on the number of red blood cell units transfused in England (Varney 2003), the proportion of all units that were used by surgery (Wells 2002) and the number of operations carried out (HES England, 2000/2001). The number of units of red blood cells issued to hospitals during 2000/2001 was 2,221,225 (98% of which were used). Wells (2002) reported that 40.70% of the 9,848 units issued by National Blood Service in Northern England during two 14 day periods in 1999/2000 (Newcastle centre serving a population 2.9million) were used for surgical indications. In the studies reporting blood transfusion as a consequence of hypothermia, the average number of units transfused was 1.95 units across all patients (hypothermic and normothermic). Using these figures we estimated that there were 454,500 transfusions in surgical patients. There were 6,509,400 finished hospital episodes for operations in 2000/01 (HES) and 49% of these were day case procedures. We assumed that no blood transfusions were given in day case surgery as the GDG advised that patients who are likely to require a transfusion would not be treated in a day case setting. We estimated from these figures that 14% of non day case patients received a blood transfusion. We applied this rate of blood transfusion to patients having intermediate or major surgery in the model and assumed a zero rate in patients having minor surgery which is more likely to occur in a day case setting. We carried out a sensitivity analysis using the transfusion rate (28%), taken from the studies reporting blood transfusion as a consequence of hypothermia, to see whether the cost-effectiveness is sensitive to a higher rate of transfusions.

Mechanical ventilation

The rate of unplanned postoperative mechanical ventilation was taken from a prospective cohort study conducted in Canada (Rose 1996) in which 41 of 15,059 patients having in-patient surgery (cardiac and neurosurgical procedures excluded) required admission to the ICU for ventilatory support. This rate of 0.27% was applied in the model to all patients regardless of the magnitude of surgery. An audit, also carried out in Canada (Swann 1993), which included day case surgery, had a similar rate of unplanned ICU admission (34/18,555=0.18%) although the rate was lower when day case surgical patients were considered separately (2/8,546=0.02%). The rate used in the model may be an overestimate for minor surgery in lower risk patients who are treated in a day case setting. However, as this adverse consequence is very rare, this limitation is unlikely to significantly bias the cost-effectiveness estimate.

Morbid cardiac events (MCEs)

The rate of cardiac complications was taken from a prospective cohort study conducted in the US (Polanczyk 2001) in which the incidence of cardiac complications in non-cardiac patients was measured in a cohort of 4,315 patients aged 50 years or older having nonemergent surgery with an expected length of stay of 2 days or more. We have defined morbid cardiac events as unstable angina/ischemia, cardiac arrest and myocardial infarction (MI). Polanczyk (2001) reported 8 cases of MI, 15 cases of unstable angina and 1 case of ventricular fibrillation or cardiac arrest in 1,015 patients aged 50 to 59 years giving an overall rate of 2.4% for MCE. In patients aged 70 to 79 years this rate was higher at 4.5%. These rates were applied in the model as the rate of MCEs in normothermic patients regardless of the magnitude of surgery. The GDG advised that the rate of events in patients aged less than 50 years should be calculated by considering the relative prevalence of ischaemic heart disease in the community. As the prevalence of ischaemic heart disease is very low in patients aged 20 (Health survey for England 2003, Table 1.2), we assumed in the model that there was no risk perioperative MCEs in this age group. In order to capture the variation in cost-effectiveness between these two ages, we also considered the rate of MCEs in patients aged 35 in a sensitivity analysis. We have assumed that the risk of morbid cardiac events at age 35 is one third of the risk at age 50 based on the relative prevalence of ischaemic heart disease in the general population (Health survey for England 2003, Table 1.2).

The mix of MCEs has been based on the incidence of events observed in Frank (1997), which differed for hypothermic and normothermic patients. For normothermic patients there were two events which were both unstable angina / ischaemia and for hypothermic patients there were 7 cases of unstable angina / ischaemia, 2 cases of cardiac arrest and 1 case of myocardial infarction.

Length of hospital stay

The GDG advised that the average length of stay in hospital varies by the magnitude of surgery and that typical average stay was around 1 day for intermediate surgery and 4 days for major surgery. They advised that the majority of minor surgery is now carried out in day case with an average duration of hospital stay of around 6 hours. These baseline durations were used in calculating the increased length of stay for hypothermic compared to normothermic patients based on a constant proportional increase of 23% indicated by the review on the consequences of hypothermia.

Table 1: Baseline risk of the consequences of IPH and average length of stay

Consequence	Point estimate
Surgical wound infection	3.00%
Blood transfusion (intermediate and major surgery)	14.00%
Blood transfusion (minor surgery)	0.00%
Morbid cardiac event (20 years)	0.00%
Morbid cardiac event (50 years)	2.40%
Morbid cardiac event (70 years)	4.50%
Mechanical ventilation	0.27%
Pressure ulcer (minor)	0.00%
Pressure ulcer (intermediate and major)	1.80%
Total hospital length of stay in days (minor surgery)	0.25
Total hospital length of stay in days (intermediate surgery)	1
Total hospital length of stay in days (major surgery)	4

Costs and QALY impact of each health consequence

The cost and QALY impact of each of the adverse health consequences is assumed to be the same regardless of whether the event occurs in a hypothermic or normothermic patient. They are also assumed to be the same across all patients covered by the guideline except in the following cases:

- The additional length of stay attributable to SWIs is assumed to be lower in minor surgery than in intermediate / major surgery;
- The QALY loss due to MCE is dependent on the age of the patient as this affects their pre-MCE HRQoL and their life-expectancy;
- Hypothermia is assumed to increase the hospital length of stay in proportion to the average length of stay which is assumed to increase according to the magnitude of surgery.

Surgical wound infection (SWI): The cost of SWI was based on data on the extra length of stay and the unit cost per bed day attributable to SWI. The extra length of hospital stay was derived from a surveillance of 12 categories of surgery in 140 English hospitals between October 1997 and June 2001 (Coello 2005) in which the average length of stay due to SWI was 11.37 days (range 9.43 to 13.66). The cost of a patient spending an extra day in hospital as a result of a SWI was based on the result of a cost study conducted in England between 1994 and 1995 (Plowman 2001). In that study, an average 7.1 days extra length of stay in hospital due to SWI was estimated to cost £1,594, giving a cost per day of £225 (1994/95 prices). We uplifted this using the Hospital and Community Health Services Pay and Prices Index (PSSRU 2006) to give a more accurate estimate of current costs resulting in an estimate of £339 (2006 prices) per additional day of hospital stay. The expected cost of SWI will vary with the different surgery magnitude (minor, intermediate and major). We assumed

the extra length of stay in intermediate and major surgery to be equal to the average amount reported across the 12 surgical categories considered by Coello (2005) which was 11.37 days. However, the mean duration of stay in non-infected patients varied across the 12 categories from 5.1 days for abdominal hysterectomy to 13.2 days for limb amputation. This suggests that these categories are not particularly representative for patients having minor surgery. For minor surgery we used the increased length of stay for patients with superficial SWI following an abdominal hysterectomy which was 2.8 days (95%CI 2.2-3.5) compared to patients without infection, as this was the lowest increase reported for the categories included by Coello (2005). The total average cost of a SWI was estimated at £3,858 and £950 for intermediate/major and minor surgery respectively. The cost for minor surgery may still be an overestimate and this potential bias was made clear to the GDG during their discussion of the cost-effectiveness results.

The impact of SWI on quality of life was derived from a case-control study of orthopaedic surgery patients (Whitehouse 2002). In that study, SWI patients and their matched controls were interviewed one year after the detection of SWI in the case patients and one year after the time of initial surgery in the control patients. The measurement of quality of life was done with a questionnaire containing 36 items (SF-36), and there was no composite measure of utility. Utility scores were obtained by converting the results of the SF-36 questionnaire using an algorithm developed by Shmueli (1999). Patients with SWI have a utility value of 0.57 (95% CI, 0.51, 0.64) and those without SWI, 0.64 (95% CI, 0.57, 0.71). This gave a mean difference of 0.07. We assumed that the utility was reduced for one year following infection as the HRQoL was measured at 1 year and it did not seem reasonable to extrapolate beyond this time frame.

Blood transfusion: The cost of a transfusion of one unit of red blood cells was obtained from a study on the annual cost of blood transfusions in the UK during 2000/2001 (Varney and Guest 2003). We considered red cell transfusions as there was evidence on the increased risk for this outcome but there was no evidence on the increased risk of requiring transfusion with other blood products such as platelets. The direct NHS costs considered by Varney (2003) were the NHS costs that relate to blood transfusion services (collecting, testing, processing and issuing blood products) and hospital resource use (transfusion committees, transfusion-related complications and hospital stay). In 2000/2001, the NHS spent £623.7 millions for 0.98 million transfusions of red blood cells (Varney and Guest 2003), with an average of 2.7 units per transfusion. Sixty-three percent of the overall cost was attributed to hospital stay. We excluded this cost from the cost of transfusion applied in the model as we did not expect blood transfusions given perioperatively to increase the overall length of hospital stay. A unit of red blood cells transfused in a patient with inadvertent perioperative hypothermia was estimated to cost £86.99 when excluding the cost of hospital stay. Uplifting this to 2006 prices gave a cost per unit of £106.88. The GDG advised that we use the mean amount of blood transfused

across normothermic and hypothermic patients from the studies reporting blood transfusion in the consequences review. We used the weighted average amount of blood transfused, which was 1.95 U. The cost of blood transfusion due to IPH applied in the model was therefore £208.55. We have not included any QALY loss for patients receiving a blood transfusion as we felt that any difference in HRQoL would occur only over a very short period and would therefore not result in significant QALY loss.

Mechanical ventilation: The cost of mechanical ventilation was estimated by multiplying the extra time spent in the hospital with the unit cost per day. Only one of the studies (Frank 1995) included in our review on the consequences of IPH reported the extra time required for mechanical ventilation. The mean duration of ventilatory support was 16 (SEM ± 6) hours (Frank 1995). We used the reported value in the economic model. On advice from the GDG, the unit cost for one day of mechanical ventilation was taken to be equivalent to one day of level 3 ICU care (£1,716 per occupied bed day [NHS Trust and PCT Reference Costs 2005/2006]). The cost associated with a hypothermic patient requiring mechanical ventilation was estimated to be £1,144. We have not included any QALY loss for patients requiring postoperative mechanical ventilation as we felt that any difference in HRQoL would occur only over a very short period and would therefore not result in significant QALY loss.

Length of stay: Any additional length of stay in PACU, ICU or in the hospital (extra total length of stay) due to IPH is associated with additional cost. The national average unit costs for one days stay on a hospital ward or in ICU were taken from the National Schedule of Reference Costs (Department of Health 2006).

For hospital length of stay, we used the "elective in patient excess bed day HRG data" database to estimate the cost of increasing total hospital length of stay by one day. We identified all surgery classes (23 classes), and estimated an average cost per day for each class of surgery and an average cost per day across all classes weighted by the total excess bed days for each class. The national average unit cost (per bed day) for surgery was estimated to be £275.

The National Schedule of Reference Costs does not provide a cost estimate for PACU. The intensity of care provided in PACU varies over the duration of stay as the patient's level of consciousness improves. We were advised by the GDG that the care provided in PACU varies between a level similar to that provided in ICU and a level similar to that provided in HDU. Therefore, the average costs for ICU and HDU care (level 2) was used for the duration of stay in PACU. The cost of an additional hour in PACU is estimated to be £44. In the basecase analysis, we assumed no additional stay in PACU. We did not estimate the cost of ICU stay because in the studies identified for the consequences of hypothermia review there was no significant difference in ICU stay between normothermic and hypothermic patients.

We did not estimate the QALY impact of extra length of stay because we felt that any difference in HRQoL would occur only over a very short period and would therefore not result in significant QALY loss.

Morbid cardiac event: The additional cost of morbid cardiac event due to hypothermia is determined by the increase in the length of stay and the cost per day for care of a patient after an MCE. We calculated the additional length of stay and cost per day for each of the three types of MCEs included in the model myocardial infarction, cardiac arrest, unstable angina/ ischeamia. We obtained data from the hospital episode statistics (HESonline 2005/06) on the mean length of stay associated with each type of event using events recorded as "other acute ischaemic heart diseases" (7.1 days), "cardiac arrest" (8.7 days) and "acute myocardial infarction" (9.0 bed days).

We obtained data on the national average unit cost per excess bed day for the three health conditions from National Schedule of Reference Costs (Department of Health 2006). Acute myocardial infarction (without comorbidity) costs £186 per day, ischaemic heart disease costs £285 per day and cardiac arrest costs £253 per day. Combining the cost per day with the mean length of stay gives an estimated cost of £2,023, £2,201 and £1,674 for ischeamic heart disease, cardiac arrest and MI respectively.

The expected lifetime QALY loss due to morbid cardiac event (MCE) was estimated under the assumption that the patient's health utility is reduced by a fixed percentage for every year after the event. This reduction is captured by using a utility multiplier. The utility multiplier for myocardial infarction was 0.76 (i.e. 24% reduction) based on the utility multiplier applied in an economic model used to estimate the cost-effectiveness of Statins (HTA 2007). This estimate was derived from a study by Goodacre (2004) which recorded HRQoL using the EQ-5D questionnaire in patients who presented at an emergency unit with chest pain and were subsequently diagnosed as having had an MI. (Goodacre 2004). Whilst the utility estimates in the Goodacre (2004) study were derived from a non surgical population, the GDG felt that the long-term morbidity would be the same regardless of the events leading up to an MI or cardiac arrest. We assumed that this utility reduction is the same for patients having a perioperative cardiac arrest. After discussion with the GDG, we assumed that there is no utility reduction for unstable angina / ischaemia as these are reversible conditions and may be clinically or sub-clinically present preoperatively.

The QALY due to MCE was estimated for each starting age considered by the model (20, 50 and 70 years). The impact of morbid cardiac events (MCE) on expected life-time QALY gain was estimated using a simple Markov survival model. The health states of this Markov model were "alive post-MCE" in which the HRQoL was reduced compared to patients in the "alive

without MCE event" state, and the absorbing state "dead". The annual risk of mortality was taken from UK interim life tables from 2003 to 2005, with no additional mortality risk attributed to patients in the "alive post-MCE" state. The "alive post-MCE" state consisted of three sub-states, one for each of the different MCEs that were considered and the utility multiplier of 0.76 was applied life-long to patients in the post-MI and post-cardiac arrest states but not to patients in the post-ischaemia state. The only transitions possible were to the dead state. The timeframe was until all patients were in the dead state. Males and females were modelled separately due to their different annual mortality rates and an average QALY loss was calculated across both sexes assuming that 44% of surgery occurs in males (HES Online 2005/2006). QALYs were discounted with a rate of 3.5%. The discounted QALY loss due to an MI or cardiac arrest occurring at ages 20, 50 and 70 were estimated as 5.41, 3.54 and 1.93 respectively. There was no QALY loss for ischaemia as we assumed no utility decrement for this health state.

Pressure ulcer: We took a conservative cost estimate of pressure ulcers by assuming that all pressure ulcers due to hypothermia are grade 1 pressure ulcers that are not associated with complications and that heal normally. Severe pressure sores are less common and are less than 5% of all cases (Clark 1994). We applied a cost of £1,064 (Range: £958 to £1,170) in the model for pressure ulcers based on a UK costing study (Bennett 2004).

We did not estimate the QALY impact of pressure ulcers. This health outcome may have long-term quality of life implications but we were unable to identify any literature on the utility loss associated with pressure ulcers.

Table 2: Summary of the cost and QALY impact of each adverse consequences of IPH

Consequence	Cost (£)	QALYs loss
Surgical wound infection (minor surgery)	9,50	0.07
Surgical wound infection (major surgery)	3,858	0.07
Transfusion	209	-
Morbid cardiac event (ischemia)	2,024	-
Morbid cardiac event (cardiac arrest)	2,021	5.41 at age 20 3.54 at age 50 1.93 at age 70
Morbid cardiac event (myocardial infarction)	1,674	
Mechanical ventilation	1,144	-
Pressure ulcer	1,064	-
PACU length of stay per hour	44	-
Hospital length of stay per day	275	-

Increased risk of adverse consequences in patients experiencing IPH

The relative risk of the consequences of IPH is taken from the review of those consequences (section 8). The risk estimates are summarised in Table 3 below.

In addition to these risks of adverse consequences, we have assumed a 23% proportional increase in the length of hospital stay. The GDG were concerned that the observed increase in mean hospital stay was as a result of the other consequences of hypothermia such as infection and morbid cardiac events and it should therefore not be considered separately in the model. However, as the adverse consequences are rare it was felt they would be unlikely to shift the mean length of stay significantly. The increase in mean length of stay was included in the basecase analysis, but to address this concern we have considered a sensitivity analysis in which the mean length of hospital stay is not increased to see if the cost-effectiveness is significantly impacted by this alternative assumption.

There was some evidence that the duration of PACU stay may be increased, but this evidence was not used in the basecase due to the considerable unexplained heterogeneity in the meta-analysis. Instead we considered a sensitivity analysis in which the mean PACU length of stay is increased by the amount estimated in the meta-analysis (3.26 minutes, 95% CI 0.01 to 6.51).

In the consequences of IPH review (section 8) we carried out a sensitivity analysis to see if our definition of hypothermia at 36.0˚C had a significant impact on the estimation of the consequences of hypothermia by considering an alternative definition of 36.5˚C. However, this did not significantly alter the risk estimates obtained so the alternative definition was not considered in the economic model.

Table 3: The relative risk of adverse consequences associated with hypothermia

Consequence	Relative risk (95% CI)
Surgical wound infection	4.58 (2.10 – 10.02)
Blood transfusion	1.30 (0.99 – 1.71)
Morbid cardiac event	2.20 (1.10 – 4.70)
Mechanical ventilation	1.58 (0.96 – 2.61)
Pressure ulcer	1.87 (0.86 – 4.06)

Factors affecting the risk of IPH

Based on the evidence identified in the risk factor review, the GDG identified three factors which could be used to distinguish between different risk groups: ASA grade, magnitude of surgery and anaesthesia type. These risk factors were included in the economic model and were used to generate cost-effectiveness results for different patient scenarios designed to

capture the variation in the cost-effectiveness across the population covered by the guideline due to variation in the risk of IPH across the population. The odds ratios associated with each of these risk factors are summarised in Table 4 below. The following risk factors were considered to be modifiable risk factors, rather than risk factors which are useful in distinguishing between high and low risk patients and were therefore not included in the model: the administration of unwarmed IV fluids and blood products, the use of unwarmed irrigation fluids, a low preoperative patient temperature and a low theatre temperature.

Table 4: Odds ratios for factors shown to increased the risk of IPH

Risk factor	Odds ratios		Source
	Mean	95%CI	
Intermediate vs minor surgery	4.31	2.03 – 9.13	Kongsayreepong 2003 and Abelha 2005
Major surgery vs minor surgery	3.20	1.68- 6.07	Abelha 2005 and Flores- Maldonado 1997
ASA II vs ASA I	1.97	1.19 – 3.24	Kongsayreepong 2003 and Lau 2001
ASA >II vs ASA I	2.68	1.40 – 5.12	Kongsayreepong 2003 and Lau 2001
Combined vs regional or general anaesthesia	2.86	1.81 – 4.51	Kongsayreepong 2003 and Lau 2001

Absolute risk of IPH in patients without risk factors

The absolute risk of hypothermia applied in the model was based on the cohort study (n=130) carried out in Mexico by Flores-Maldonado (1997). This study was identified from the studies included in the risk factor review as the most suitable on which to base an estimate of the risk of IPH as this study defined IPH as a core temperature of less than 36.0°C recorded intraoperatively. The surgery type was mixed with a mean duration of 83 minutes (SD 59 minutes) and included some emergency surgery (35%). Anaesthesia type was a mixture of general and regional anaesthesia and theatre temperature ranged from 22 to 24°C. Age, gender, theatre temperature, duration of surgery, magnitude of surgery, blood transfusion (unwarmed fluids) and type of anaesthesia, but not ASA grade, were included in the multivariate analysis and the ratio of events to covariates was 53/7 = 8. Potential disadvantages of the Flores-Maldonado (1997) study were that they did not state whether patients were warmed and the cohort included some children (age range 5 to 90 years), although the proportion of children is likely to be small (less than 12%) given the mean and SD of ages (Mean age 42 years, sd 20, normal distribution assumed).

Only two other cohort studies identified in the risk factor review (El-Gamal 2000; Kongsayreepong 2003) used an appropriate definition for hypothermia. El-Gamal (2000) was a small study (n=40) in which all patients had a similar procedure (lower extremity orthopaedic

surgery) and was therefore considered not to be particularly representative of the surgical population as a whole.

Kongsayreepong (2003) restricted the population to patients having non-cardiac surgery who were managed in ICU post-operatively and the mortality rate was 11/184 suggesting that this was a high-risk surgical population and was only partially representative of the surgical population as a whole. It also allowed some patients to receive warming and did not adjust for this factor in the multivariate analysis. Therefore, on balance the cohort study by Flores-Maldonado (1997) was considered to provide the most appropriate estimate of the incidence of hypothermia.

We took the incidence in the Flores-Maldonado (1997) cohort (40.7%, 95%CI 32.5% to 49.3%) and adjusted it using the prevalence and the midpoint ORs provided for transfusion of unwarmed fluids and magnitude of surgery by Flores-Maldonado (1997). The OR from Flores-Maldonado (1997) rather than the OR from Table 4 was used to adjust for magnitude of surgery as the Flores-Maldonado (1997) study separated the magnitude of surgery into minor and major rather than minor, intermediate and major. We also adjusted for the mix of ASA grade using the midpoint ORs from Table 4. It was not necessary to adjust for the prevalence of combined anaesthesia as patients had either general or regional anaesthesia in the Flores-Maldonado (1997) cohort.

This gave an estimated incidence of IPH of 23.6% (17.8% to 30.4%) for patients with ASA grade I, having general or regional anaesthesia, for minor surgery who do not receive transfusion of unwarmed fluids. This was used in the economic model as the baseline risk of IPH for a patient with no risk factors receiving usual care.

There was also some concern that the incidence of hypothermia was based on a cohort study with a mean surgical time of 83 minutes (SD59), and may therefore over estimate the incidence of IPH in shorter procedures. A sensitivity analysis was undertaken to consider the cost-effectiveness in shorter procedures (anaesthesia time of 30 minutes) under the assumption that the incidence of IPH is half that seen in longer procedures.

Clinical effectiveness of strategies to prevent IPH

The model estimates the incidence of IPH for various strategies to prevent IPH and compares these to the incidence expected under usual care. This requires an estimate of the RR of IPH for each strategy compared to usual care. However, the majority of the trials reported the mean temperature for each arm at various time points intraoperatively and at the end of surgery and very few of the clinical effectiveness trials provided data on the incidence of IPH. The GDG advised that it would be reasonable to use the mean temperatures from the clinical effectiveness trials at 30, 60 and 120 minutes intraoperatively to extrapolate the expected

mean temperatures at the end of anaesthesia in operations where the total anaesthesia time was 30, 60 or 120 minutes respectively.

We have assumed that the temperatures in each of the clinical trials are normally distributed and have used the mean and standard deviation reported in the trials to estimate the proportion of the participants with a temperature less than 36.0°C. This estimated incidence data was then used to estimate the relative risk of hypothermia for the intervention arm compared to the control arm for each trial.

This method of calculating the incidence, from the mean temperature and its standard deviation, is only exact if the temperature in each arm of the trial is normally distributed. This is likely to be true when there are a large number of patients in each arm. However, many of the RCTs have less than 25 patients in each arm. Under these conditions, the method we have used may not reflect the true incidence of IPH in each arm of the trial, but it is unlikely to be systematically biased.

We have compared the estimated incidence with the true incidence for several trials in which incidence data was provided to determine how closely our estimated incidence is to the true incidence. Smith (1998) reported the incidence of hypothermia as well as the final core temperature at the end of surgery. The final core temperature of patients in the warmed group was 36.3°C and no patient developed hypothermia. Seven patients in the control group developed hypothermia (defined as <35.5 in Smith 1998) and the final core temperature of the group was 35.6°C. Using the algorithm described above, we estimated that 0.53 (approximated to 1) patient developed hypothermia (defined as <35.5 for this example only) in the warmed group and 8.24 (approximated to 8) patients developed hypothermia in the control group. The Peto odds ratios were 0.10 (95% CI, 0.02, 0.52) and 0.16 (95% CI, 0.04, 0.69) for the reported and estimated incidence of hypothermia respectively.

Casati (1999) reported the incidence of hypothermia at recovery room entry. The mean duration of surgery was 100 and 105 minutes in the actively and passively warmed groups respectively. We compared the incidence reported at this time with the incidence we estimated at 120 minutes as this is the closest of the three time points we have considered in our model. Relative risks of 0.22 (95% CI, 0.07, 0.72) and 0.25 (95% CI, 0.08, 0.78) were calculated with the reported and estimated incidence respectively. These examples suggest that our approximate method for estimating incidence, and therefore the RR (or peto OR), of hypothermia from the mean temperatures gives a similar estimate of efficacy to using the measured incidence, even when the sample size is small (N less than or equal to 25)

This method could not be applied to studies in which the only outcomes reported were mean temperature changes from baseline or the mean temperature difference between intervention

and control. Therefore, some studies included in the clinical effectiveness review could not be used to inform the economic modelling.

Where there was evidence from more than one trial a meta-analysed RR of IPH was calculated unless there was reason to believe that this was inappropriate as the trials were not measuring the same effect in a similar enough population. In the clinical effectiveness analyses, it was assumed that the temperature change from each warming mechanism was independent, and the analyses supported this assumption. This allowed studies comparing warming mechanism 1 with usual care to be combined with studies comparing warming mechanisms 1 and 2 with warming mechanism 2. However, it was evident that when the temperature data were converted to risks of hypothermia, this assumption did not apply as the risks in both the control and intervention arms were lessened if a warming mechanism was already in place, but usually not to the same degree. The relative risk subsequently calculated appeared to depend on the proximity of the control group temperature to 36.0°C (the hypothermia threshold), the standard deviations for each group and the mean difference. Thus, the relative risk was not independent of the risk in the control group. Consequently, when estimating the effectiveness of each intervention compared to usual care, we excluded from the analysis studies that had a reliable method of warming in both arms (e.g. warmed fluids), and treated with caution other studies in which the control group temperature was close to, or above 36.0°C.

Only those interventions with an acceptable level of clinical effectiveness evidence have been included in the cost-effectiveness analysis. Interventions which did not statistically significantly increase mean temperature compared to usual care were excluded as they are not clinically effective. The comparisons modelled were:

- Forced air warming (intraoperatively) vs usual care;
- Warmed fluids vs unwarmed fluids;
- Forced air warming (intraoperatively) and warmed fluids vs forced air warming and unwarmed fluids (intraoperatively);
- Forced air warming (intraoperatively) vs electric heated pad (intraoperatively);
- Forced air warming (intraoperatively) vs warmed cotton blankets (intraoperatively);
- Forced air warming (intraoperatively) vs thermal insulation (intraoperatively);
- Circulating water mattress (intraoperatively) vs usual care;
- Forced air warming (pre and intraoperatively) and warmed fluids vs usual care;
- Thermal insulation (pre and intraoperatively) vs usual care;
- Amino acids (pre and intraoperatively) vs usual care;
- Forced air warming (preoperatively) vs warmed cotton blanket (preoperatively).

Not all of these comparisons had data at each of the time points. The majority of the data was in patients having general anaesthesia, with the exception of forced air warming vs thermal

insulation (Casati 1999) which had data in regional anaesthesia only. As the evidence base was more limited for combined anaesthesia we have applied the clinical effectiveness evidence from studies in which patients had either general or regional anaesthesia to patients having combined general and regional anaesthesia. We therefore present one set of results for regional / general anaesthesia for which the risk of hypothermia is not significantly different and consider whether the IPH prevention strategies are more cost-effective in combined anaesthesia due to the increased risk of IPH in patients undergoing both regional and general anaesthesia. The effectiveness data used in the model is summarised in Table 5. In order to determine which of the prevention strategies would result in the most cost-effective use of NHS resources, an indirect comparison was undertaken. In the indirect comparison it was necessary to assume that the usual care intervention was comparable across all studies. In doing so we defined usual care as including the administration of unwarmed IV fluids.

Table 5: Effectiveness estimates applied in the model*

Comparisons	Studies	Temperature difference (˚C)	Incidence of hypothermia in the comparator arm	Relative risk of IPH (95%CI)
Anaesthesia duration of 30 minutes				
FAW (intra) vs UC	Smith 1994, Ouellette 1993	0.28	13/33	0.39 (0.18, 0.88)
WF vs UC	Hasankhani 2005, Smith 1998	0.44	19/50	0.28 (0.11, 0.68)
FAW (intra) +WF vs FAW (intra)	Smith 1998b	0.43	23/30	0.63 (0.42 – 0.95)
FAW (intra) vs EHP (intra)	Leung 2007	-0.01	17/30	1.00 (0.64, 1.56)
TI (pre and intra) vs UC	Buggy 1994	0.15	2/34	0.14 (0.01, 2.01)
FAW (pre and intra) +WF vs UC	Smith 2007	0.90	135/180	0.21 (0.15, 0.31)
Anaesthesia duration of 60 minutes				
FAW (intra) vs UC	Camus 1993b2, Krenzischek 1995 Ouellette 1993	0.34	25/37	0.47 (0.28, 0.78)
WF vs UC	Hasankhani 2005, Smith 1998	0.42	32/59	0.43 (0.25, 0.75)
FAW (intra) +WF vs FAW (intra)	Smith 1998b	0.26	19/30	0.71 (0.44, 1.15)
FAW (intra) vs EHP (intra)	Leung 2007	0.17	27/30	0.85 (0.68, 1.07)
FAW (pre and intra) +WF vs UC	Smith 2007	0.60	114/180	0.33 (0.24, 0.46)
Amino acid (pre and intra) vs Placebo	Umenai 2006	0.33	44/68	0.89 (0.68, 1.17)
Anaesthesia duration of 120 mins				
FAW (intra) vs UC	Camus 1993b2, and Krenzischek 1995	0.86	25/25	0.37 (0.22, 0.61)
FAW (intra) vs WCB (intra)	Mason 1998	0.40	23/32	0.61 (0.39, 0.95)
FAW (intra) +WF vs FAW (intra)	Smith 1998b		15/30	0.52 (0.26, 1.04)
FAW (intra) vs EHP (intra)	Leung 2007	0.52	28/30	0.61 (0.44, 0.84)
CWM (intra) vs UC	Joachimsson 1987, Tollofsrud 1984a + 1984b	0.35	37/64	0.70 (0.51, 0.97)
FAW (intra) vs TI (intra)	Casati 1999	0.45	12/25	0.25 (0.08, 0.78)
Amino acid (pre and intra) vs Placebo	Umenai 2006	0.36	53/68	0.97 (0.81, 1.17)
FAW (pre) vs WCB (pre)	Fossum 2001	0.32	36/50	0.61 (0.43, 0.87)

*Abbreviations: FAW = forced air warming, WCB = warmed cotton blankets, TI = thermal insulation, CWM = circulating water mattress, UC = usual care (includes unwarmed fluids), WF = warmed fluids, EHP = electric heated pad, pre = preoperatively, intra = intraoperatively

Intervention costs

The cost per use is dependent on the cost of single use disposables, the power consumption per use, the number of uses per annum, the annual service and maintenance costs, and the annual costs for re-usable equipment, which in turn depends on the lease cost per annum, in the case of leased equipment, or the purchase cost and life-expectancy, in the case of purchased equipment.

We were able to obtain data on the costs of disposable FAW blankets, fluid warming inserts and passive warming blankets from the NHS Supply Chain catalogue. The cost of disposable FAW blankets ranged from £8.48 to £33.92. We were also able to obtain data from NHS Supply Chain on the distribution of usage for 336,700 blankets across 10 different blanket types, from which we estimated a weighted mean cost of £15.02. For fluid warming inserts the costs ranged from £4.16 to £21.48. This range excludes high flow sets which are more expensive and are likely only to be used in a minority of cases where it is necessary to give large volumes of fluids quickly. We did not have any data on the usage distribution so we assumed that the average cost would be lognormally distributed across the cost range, giving a mean cost of £9.38. There were some products in the NHS Supply Chain catalogue which were described as passive insulation but we were not able to confirm from the catalogue whether they were similar to the blankets used in the RCTs and whether they are suitable for intraoperative use. We decided to request further information from manufacturers to inform the cost estimate for thermal insulation.

The purchase / lease costs for FAW units, fluid warming units, circulating water mattresses, electric heating pads and blanket warming cabinets were not available from the NHS Supply Chain catalogue and we were unable to obtain list prices from the NHS Purchasing and Supply Agency (PASA). We identified eighteen companies as being potential manufacturers of patient or fluid warming devices or passive insulation products from three sources: the list of registered stakeholders, the companies listed on the websites of the two trade associations (ABHI and Barema), and the clinical effectiveness RCTs. These companies were contacted and invited to provide cost data on any products relevant to the guideline using a standardised data form. (The companies contacted and the data form used is given in Appendix H). The data provided by suppliers and manufactures has been treated as commercial in confidence and therefore the individual costs provided for specific products cannot be disclosed in the guideline. The annual cost for purchased equipment was calculated from the data provided as follows:

Cost per use =
(purchase cost / life expectancy of device in years) + annual cost for service or maintenance

The annual cost of leased products was calculated as the sum of the lease cost and the service / maintenance cost. We assumed that each device would be used 200 times per year in order to calculate a cost per use. Power costs were not considered in the analysis as these were not expected to be a large proportion of the total cost and we were unable to obtain estimates of the typical unit costs of electricity supplied to NHS Trusts. We were advised by the GDG that many FAW and fluid warming devices are leased free of charge to the NHS after purchase of a minimum number of associated disposable items. On this basis, we did not include equipment costs in the basecase analysis but carried out a sensitivity analysis to see if the cost-effectiveness was significantly different if equipment was purchased at the list price provided by manufacturers instead of being leased at zero cost.

The mean and range of costs for each of the warming mechanisms is summarised in Table 6. No costs estimates were obtained for circulating water mattresses, electric heated pads or warmed cotton blankets. We assumed that thermal insulation blankets and FAW blankets would not be transferred from the preoperative environment to the intraoperative environment as this may increase the infection risk and therefore that a second blanket is always used when FAW or thermal insulation is used in both phases.

The cost of amino acids has been based on the BNF (54th Ed) cost for Vamin 18 (£26.70 for 1000mL) using the amount given in the Umenai (2006) RCT. This was estimated as 732mL based on the infusion rate and the duration of infusion. The cost of 1000mL was applied in the model as it was assumed that vials could not be split across patients.

Table 6: Costs of patient and fluid warming mechanisms

Warming mechanism	Purchase or lease cost per annum for re-usable equipment*	Service / maintenance cost per annum for reusable equipment*	Unit cost for disposables per use*	Number of sources of data
Forced air warming	£1.57 (£1.39 – 1.79)	£0.61 (£0.50 – 0.75)	£15.02 (£8.47 – 33.92)	2
Fluid warming	£1.55 (£1.42 – 1.68)	£0.68 (£0.50 – 0.93)	£9.45 (£4.16 - 21.48)	3
Thermal insulation	N/A	N/A	£3.67 (£2.50 – 5.40)	5

*Mean cost (range)

Approach taken to sensitivity analysis

Univariate sensitivity analyses were carried out to determine the potential impact of model assumptions on the cost-effectiveness estimates. The net benefit per hypothermic case prevented is a key factor in determining the cost-effectiveness of strategies to prevent IPH and it is constant regardless of the strategy being evaluated. We decided to first consider whether the net benefit per hypothermic case prevented was sensitive to the assumptions used in the model. This was then used to determine which sensitivity analysis would be important in

describing the uncertainty in the cost-effectiveness of the various strategies to prevent hypothermia.

In the univariate sensitivity analysis we considered whether the model was sensitive to the assumptions used to extrapolate the QALY loss associated with MCEs by considering a scenario in which the HRQoL decrement was assumed to continued for 5 years rather than life-long and considering a second scenario in which there was no long-term reduction in HRQoL. We considered whether the model was sensitive to the QALY loss following surgical wound infection by considering a scenario in which there is no long-term HRQoL reduction following surgical wound infection. Many of the studies examining the relationship between IPH and its adverse consequences were carried out in higher risk populations. We carried out a sensitivity analysis using the higher rates observed in these studies to see whether the model is sensitive to the baseline risk of these consequences and to determine if it was necessary to consider these high risk groups as special cases in which the cost-effectiveness is likely to be significantly different. As the increased risk of pressure ulcers was not statistically significant, we carried out a sensitivity analysis in which the risk is not increased (relative risk of 1). We had assumed in the basecase that there is no significant increase in PACU stay for hypothermic patients as there was heterogeneity across the studies included in the consequences of hypothermia review (section 8). We therefore considered a sensitivity analysis using the weighted mean value reported across all studies. We had assumed that there was a significant increase in hospital length of stay for patients who are hypothermic, but there was concern that many of the other adverse consequences result in an increase in hospital length of stay. We therefore carried out a sensitivity analysis in which there was no increase in hospital length of stay. We also considered a sensitivity analysis in which we assumed that fluid warming devices were purchased rather than leased free of cost after purchasing a minimum number of associated disposables.

In addition to the univariate sensitivity analysis, a probabilistic sensitivity analysis was carried out. Probabilistic sensitivity analysis (PSA) is used to provide an estimate of the uncertainty in the cost per QALY estimate due to uncertainty in the model parameters used to estimate the cost-effectiveness. The most obvious example of parameter uncertainty in the model are the confidence intervals surrounding the clinical effectiveness estimates, but other parameters used in the model which were based on empirical measurement also had some uncertainty associated with them. We carried out a PSA which considered the parameter uncertainty around the clinical effectiveness estimates, the risk of IPH, the costs of adverse consequences, the utility estimates, and the costs of interventions to prevent IPH. The reference costs for pharmaceutical interventions and the population life-expectancy were assumed to be fixed in the model, as was the discounting rate which was fixed by the NICE "reference-case" for economic evaluations (NICE 2007). In the PSA we characterised the parameter uncertainty by using a probability distribution to describe each of the parameters,

details of which can be found in Appendix H. We then sampled from each distribution independently under the assumption that there was no correlation between the different input parameters. However, the same random number set was used to sample common parameters across the different cost-effectiveness comparisons to prevent sample bias being introduced when comparing the incremental cost-effectiveness of two interventions. We then calculated the model outcomes (incremental costs, incremental QALY gains) for each set of sampled parameters and used these to estimate the uncertainty surrounding the cost per QALY estimate.

We based our PSA on 1000 samples of the parameter distributions. The probabilistic sensitivity analysis was used to consider the likelihood that each prevention strategy is cost-effective compared to usual care and the likelihood that it is the optimal strategy. It should be noted that the PSA did not account for uncertainty around the model assumptions and these were explored separately using univariate sensitivity analysis as described earlier.

MODEL RESULTS

Net benefit per hypothermic case prevented

The net benefit per hypothermic case prevented is dependent on the risk of each adverse consequence in hypothermic and normothermic patients and the impact of each adverse consequence on costs and benefits (QALYs gained). The risk of morbid cardiac events applied in the model is dependent on age. The QALY impact of morbid cardiac events is also dependent on age due to variation in population HRQoL and life-expectancy with age. The risk of blood transfusions and pressure ulcers has been varied by the magnitude of surgery to reflect the low risk of these adverse consequences in minor surgery. The mean length of hospital stay and the increased duration of hospital stay associated with SWI has also been varied by magnitude of surgery.

Table 7 below shows the net benefit (NB) per hypothermic case avoided for each of the adverse consequences and the variance by age and magnitude of surgery where appropriate. At age 50 and above, MCEs contribute the greatest proportion of NB with the majority of the NB resulting from the QALY loss following MCE rather than the cost of treating MCEs. At younger ages where the risk of MCE is negligible, the most important contribution to NB is from infection. The QALY loss due to infection contributes £160 to the NB per hypothermic case prevented. The contribution to NB from the cost of treating an infection increases with the magnitude of surgery. Blood transfusion, postoperative mechanical ventilation and pressure ulcers all provide only a small contribution to the overall NB of preventing hypothermia.

Table 7: Contribution of each consequence to the net benefit per IPH case avoided

Consequence	Scenario (age or surgery magnitude)*	Cost saving	QALY gain	Net Benefit gain
Morbid cardiac events	50 years	£59	0.055	£1,165
	70 years	£111	0.057	£1,249
Hospital length of stay	minor surgery	£16	-	£16
	intermediate surgery	£63	-	£63
	major surgery	£252	-	£252
Surgical wound infection	minor surgery	£102	0.008	£252
	intermediate/major surgery	£414	0.008	£564
Pressure ulcer	intermediate/major surgery	£17	-	£17
	minor surgery	-	-	-
Blood transfusion	intermediate/major surgery	£9	-	£9
	minor surgery	-	-	-
Post-operative mechanical ventilations	All ages, and magnitudes of surgery	£2	-	£2

*For morbid cardiac events, the NB does not vary by magnitude of surgery and for all other outcomes the net benefit does not vary by age

Table 8 shows the resultant variation in the net benefit per hypothermic case prevented by age and magnitude of surgery. The values shown are the mean values across 1000 samples generated by the probabilistic sensitivity analysis and the range shown is that which includes 95% of the samples. The net benefit of preventing hypothermia determines the cost-effectiveness of any strategy to prevent hypothermia by fixing the minimum number needed to treat to prevent one case of hypothermia. For example if the net benefit per case prevented is £1000 and the cost per patient warmed is £20 then the minimum number needed to treat is 50 for the warming intervention to be cost-effective. Therefore a strategy with a high cost per patient may be cost-effective in older patients having major surgery, but the same strategy may not be cost-effective in younger patients having minor surgery, even if it is equally effective in both groups due to the difference in the NB per hypothermic case prevented.

Table 8: Net benefit (NB) per IPH case avoided by age and magnitude of surgery*

Age	Magnitude of surgery		
	Minor	Intermediate	Major
20	250 (87, 551)	727 (278, 1552)	925 (420, 1777)
50	1506 (455, 3687)	1983 (767, 4209)	2181 (926, 4396)
70	1606 (496, 3925)	2084 (811, 4507)	2282 (971, 4693)

*Mean and 95% confidence interval

As the net benefit per hypothermic case prevented is a significant factor in determining the cost-effectiveness of interventions to prevent hypothermia, we carried out sensitivity analysis

to determine the variation in this factor under alternative assumptions to those used in the base case. The variation in the net benefit per hypothermic case prevented for a patient aged 50 having intermediate surgery under various sensitivity analyses is shown in Table 9. Again it can be seen that the NB per hypothermic case prevented, and therefore the cost-effectiveness of strategies to prevent hypothermia, is most sensitive to changes in the incidence of infections and MCEs and also to the assumptions around the long-term impact of MCEs on QALYs. In younger patients where the incidence of MCEs is negligible, the cost-effectiveness is particularly sensitive to the infection rate and to the cost and QALY loss associated with infections.

From this analysis of the net benefit per hypothermic case prevented, it was clear that a sensitivity analysis should be carried out to determine whether the optimum strategy for prevention of IPH is sensitive to changes in the QALY loss due to MCEs, the QALY loss due to infection and the cost of infection. The cost-effectiveness is also dependent on the risk of each consequence of hypothermia. It was therefore also important to consider whether the optimum strategy differs for patients who are at a particularly high risk of IPH and its consequences or for patients with a lower risk of morbid cardiac events.

Table 9: Sensitivity analysis on the Net Benefit per IPH case avoided in patients aged 50, having intermediate surgery

Sensitivity description*	Parameter varied	Basecase value	Sensitivity value	Net Benefit per hypothermic case prevented, (£)(Mean (95%CI))	% change in mean Net Benefit from basecase
Basecase	N/A	N/A	N/A	1983 (767, 4209)	N/A
MCE no utility decrement after 5 years	QALY loss due to MI / CA	3.54 QALYs	0.93 QALYs	1110 (488 – 2169)	-44%
MCE no utility decrement	QALY loss due to MI / CA	3.54 QALYs	0 QALY	798 (315 – 1640)	-60%
SWI no utility decrement	QALY loss due to SWI	0.07 QALY	0 QALY	1816 (680 – 3980)	-8%
Pressure ulcer risk from orthopaedic surgery (high risk)	Baseline risk of pressure ulcer	1.80%	10.90%	2081 (821 – 4256)	5%
No increased risk of pressure ulcers	Baseline risk of pressure ulcer	1.80%	0%	1964 (754 – 4196)	-1%
Transfusion (high risk)	Baseline risk of blood transfusion	14%	28%	1993 (771 – 4218)	0%
MCE (high risk)	Baseline risk of morbid cardiac event	2.40%	4.5%	3109 (1093 – 7223)	57%
Ventilation (high risk)	Baseline risk of mechanical ventilation	0.27%	11.73%	2070 (821 – 4280)	4%
Infection risk (high risk)	Baseline risk of surgical wound infection	3%	9.2%	3289 (1358 – 6489)	66%
PACU stay increased	PACU length of stay	0.00 minute	3.26 minutes	1986 (770 – 4210)	0%
No increase in HLoS	Proportional increase in HLoS	23%	0%	1917 (716 – 4161)	-3%

*MCE is morbid cardiac event, SWI is surgical wound infection, PACU is postanaesthesia care unit, HLoS is hospital length of stay

The cost-effectiveness estimates are the same for patients having either regional or general anaesthesia as we have used the same effectiveness evidence in the economic model. Combined anaesthesia is associated with an increased risk of hypothermia and therefore the cost-effectiveness of interventions to prevent IPH will always be better in patients having

combined anaesthesia than in patients having either regional or general anaesthesia. The results presented below are applicable to either regional or general anaesthesia unless otherwise stated.

The tables below give the expected costs and benefits when using a particular strategy in a cohort of 1000 patients. For example, forced air warming costs on average £16.50 per patient, so the cost of warming for the forced air warming strategy is £16,500. Similarly, a reduction in hypothermic cases of 10 means a 1% reduction across all patients warmed. The tables show the mean estimates derived from the 1000 parameter samples undertaken for the probabilistic sensitivity analysis. In the tables showing the results of the direct comparison we also report the percentage of samples resulting in a cost per QALY under £20,000. In the tables showing the results of the indirect comparison we report the percentage of samples for which that particular prevention strategy was optimal (had the greatest net benefit) when applying a cost per QALY threshold of £20,000.

Direct comparisons between strategies to prevent hypothermia

The cost-effectiveness results for each of the direct comparisons considered in the model are shown in Table 10 below for a low risk patient (ASA I, minor surgery) aged 50 years having surgery with an anaesthesia time of 60 minutes. This scenario was determined by the GDG as the most representative for the majority of patients having surgery. This was supported by evidence from Hospital Episode statistics showing that the mean age for all patients having operations is 52 (HES Online 2005/2006). Tables 11 and 12 show the cost-effectiveness results for minor procedures with shorter anaesthesia durations and intermediate procedures with longer anaesthesia durations respectively.

Table 10: Cost-effectiveness of comparative interventions for 50 year old patients with ASA I, minor surgery and 60 minutes anaesthesia duration*

Comparison	Cases of IPH prevented	Cost saving from prevented consequences	QALY gain from prevented consequences	Incremental cost of warming	Incremental. Cost per QALY	Incremental. Net Benefit at £20K	% under £20K threshold
FAW (intra) vs UC	121	£18,500	8.15	£16,500	FAW dominates UC	£165,000	99.6%
WF (intra) vs UC	130	£20,000	8.77	£10,800	WF dominates UC	£184,700	99.9%
FAW (intra) +WF vs FAW (intra)	25	£3,900	1.71	£10,800	£4,000	£27,300	97.7%
FAW (intra) vs EHP (intra)	26	£4,100	1.77	Not available	Not estimable	Not estimable	Not estimable
FAW + WF (pre and intra) vs UC	157	£24,200	10.67	£43,900	£1,800	£193,800	99.5%
Amino Acids vs UC	23	£3,500	1.47	£26,700	£15,800	£6,100	51.9%

*Abbreviations: FAW is forced-air warming, UC is usual care, WF is warmed fluid, EHP is electric heating pad, intra is intraoperatively, pre is preoperatively

For a 50 year old patient (ASA I) having minor surgery with an anaesthesia time of 60 minutes, the cost-effectiveness model estimated that forced air warming (intraoperatively), warmed fluids, and forced air warming (pre and intraoperatively) plus warmed fluids were all cost-effective strategies compared to usual care, when applying a cost per QALY threshold of £20,000. Forced air warming (intraoperatively) plus warmed fluids was also cost-effective compared to forced air warming (intraoperatively) and unwarmed fluids. Whilst amino acids had a mean cost per QALY under £20,000, there was considerable uncertainty around the efficacy of amino acids at 60 minutes leading to usual care having a higher QALY gain and a lower cost in 20% of samples. Amino acids had a 52% likelihood of being cost-effective compared to usual care at a cost per QALY threshold of £20,000.

As we were unable to obtain a cost estimate for electric heating pads, it was difficult to say whether these are cost-effective compared to usual care. However, the results presented show that forced air warming resulted in a reduction in the incidence of hypothermia compared to electric heating pads and this was associated with an incremental net benefit of £39,500 before intervention costs are considered. Therefore, forced air warming is likely to dominate electric heating pad provided that it does not cost in excess of £39.50 more than electric heating pad. If we consider an extreme scenario in which electric heating pad has no additional cost relative to usual care, then forced air warming would still have a 63% likelihood of being cost-effective compared to electric heating pad at a threshold of £20K per QALY.

Shorter anaesthesia times

Table 11 shows the results for the same clinical scenario but when anaesthesia time is shorter at 30 minutes. Again forced air warming (intraoperatively), warmed fluid and forced air warming (pre and intraoperatively) plus warmed fluid are all cost-effective strategies compared to usual care at a cost per QALY threshold of £20,000. Forced air warming (intraoperatively) plus warmed fluids is also cost-effective compared to forced air warming (intraoperatively) with unwarmed fluids. Thermal insulation (pre and intraoperatively) is also cost-effective compared to usual care although usual care resulted in fewer cases of hypothermia than thermal insulation (pre and intraoperatively) on 6.1% of occasions due to large uncertainty in the clinical effectiveness.

The relative cost-effectiveness of forced air warming and electric heating pad is uncertain in this shorter anaesthesia scenario due to a lack of evidence on the relative cost of these interventions. However, the mean net benefit for forced air warming was £19,800 compared to electric heating pad before intervention costs are considered, suggesting that forced air warming would be cost-effective compared to electric heating pad provided that the additional cost of forced air warming is less than £19.80. Given that the mean cost for forced air warming compared to usual care was £16.50, it is likely that the mean cost per QALY for forced air

warming versus electric heating pad would be under £20,000 per QALY even if the electric heating pad is assumed to have no cost.

Table 11: Cost-effectiveness of comparative interventions for 50 year old patients with ASA I, minor surgery and 30 minutes anaesthesia duration*

Comparison	Cases of IPH prevented	Cost saving from prevented consequences	QALY gain from prevented consequences	Incremental cost of warming	Incremental Cost per QALY	Incremental Net Benefit at £20K	% under £20K threshold
FAW (intra) vs UC	136	£20,800	9.15	£16,500	FAW Dominates UC	£187,200	98.7%
WF (intra) vs UC	163	£24,900	10.95	£10,800	WF dominates UC	£233,000	99.7%
FAW (intra) +WF vs FAW (intra)	30	£4,700	2.07	£10,800	£3,000	£35,200	98.6%
FAW (intra) vs EHP (intra)	13	£2,100	0.88	Not available	Not available	Not available	Not available
FAW + WF (pre and intra) vs UC	186	£28,600	12.62	£43,900	£1210	£237,100	99.7%
TI (pre and intra) vs UC	159	£24,500	10.89	£7,500	TI (pre and intra) dominates UC	£234,800	99.7%

*Abbreviations: FAW is forced-air warming, UC is usual care, WF is warmed fluid, EHP is electric heating pad, TI is thermal insulation, intra is intraoperatively, pre is preoperatively

Longer anaesthesia times

Table 12 shows the cost-effectiveness results for the same clinical scenario but considering a patient having intermediate surgery lasting 120 minutes rather than minor surgery. Forced air warming (intraoperatively) is cost-effective compared to usual care at a threshold of £20K per QALY. Forced air warming (intraoperatively) plus warmed fluid is cost-effective compared to forced air warming (intraoperatively) and unwarmed fluids. Amino acids are not cost-effective compared to usual care for this duration of anaesthesia. As we were unable to obtain an estimate for the cost of warmed cotton blankets compared to usual care we have assumed that there is no additional cost compared to usual care. Under this assumption forced air warming (intraoperatively) is cost-effective compared to warmed cotton blanket (intraoperatively). As we have no evidence on the effectiveness of warmed cotton blankets compared to usual care, when used preoperatively, we have assumed that they do not affect the incidence of hypothermia when used preoperatively. This means that the forced air warming versus warmed cotton blanket comparison is essentially a forced air warming versus usual care comparison in the preoperative phase. Under these assumptions on the cost and effectiveness of warmed cotton blanket in the preoperative phase, forced air warming (preoperatively) is cost-effective compared to warmed cotton blanket (preoperatively). We were also unable to obtain a cost for circulating water mattress. However, the cost-effectiveness results show that the incremental net benefit excluding warming costs would be £319 per patient warmed. Therefore, circulating water mattress can cost up to £319 per

patient and it would still be cost-effective compared to usual care. For anaesthesia times of 120 minutes we also have data on the relative efficacy of forced-air warming (intraoperatively) and thermal insulation (intraoperatively) in patients undergoing regional anaesthesia. This direct comparison demonstrates with good certainty that forced air warming is cost-effective compared to thermal insulation when both are used intraoperatively.

Table 12: Cost-effectiveness of comparative interventions for 50 year old patients with ASA I, intermediate surgery and 120 minutes anaesthesia duration*

Comparison	Cases of IPH prevented	Cost saving from prevented consequences	QALY gain from prevented consequences	Incremental cost of warming	Incremental Cost per QALY	Incremental Net Benefit at £20K	% under £20K threshold
FAW (intra) vs UC	349	£220,300	23.49	£16,500	FAW Dominates UC	£673,500	100%
FAW (intra) +WF vs FAW (intra)	86	£54,400	5.81	£10,800	FAW (intra) +WF dominates FAW (intra)	£159,900	99.5%
FAW (intra) vs EHP (intra)	161	£104,300	10.97	Not available	Not available	Not available	Not available
FAW (intra) vs WCB	171	£109,700	11.59	£16,500 assuming WCB has no cost	FAW dominates WCB	£325,000	96.7%
CWM vs UC	162	£101,700	10.87	Not avail	Not avail	Not available	Not avail
FAW vs WCB (both pre only)	214	£134,800	14.47	£16539	FAW (pre) dominates UC	£407,800	99.6%
FAW vs TI (both intra)	992	£626,700	66.99	£12,800	FAW dominates TI	£1,953,800	99.3%
Amino acids vs UC	13	£8,100	0.68	£26,700	£27,300	-£5,000	47.1%

*Abbreviations: FAW is forced-air warming, UC is usual care, WF is warmed fluid, EHP is electric heating pad, WCB is warmed cotton blanket, CWM is circulating water mattress, intra is intraoperatively, pre is preoperatively

Indirect comparison of strategies

Having considered the cost-effectiveness of each of the direct comparisons for the three scenarios presented above, it was necessary to carry out an indirect comparison to determine which of the cost-effective strategies would result in the most efficient use of NHS resources when applying a willingness to pay threshold of £20,000 per QALY. The GDG decided that amino acids should not be included in the indirect comparison as they were unlikely to be cost-effective compared to usual care. Electric heating pad and warmed cotton blanket were not included in the indirect comparison due to uncertainty in the cost of these interventions and because it was considered unlikely that they would be cost-effective compared to forced air warming based on the direct comparison. Thermal insulation (intraoperatively) was also excluded as it was unlikely to be cost-effective compared to forced air warming (intraoperatively). The GDG decided that they were unlikely to recommend thermal insulation (pre and intraoperatively) as the mean temperature difference was small (0.15°C) and

therefore this intervention may not be clinically effective in practice despite being cost-effective. Circulating water mattress was initially included in the indirect comparison under the assumption that there was no intervention cost, however, even under this extremely favourable assumption, it was not cost-effective compared to forced air warming and it was therefore excluded as a possible strategy and is not reported in the results tables.

Therefore the strategies compared in the indirect comparison were:

- Forced-air warming (intraoperatively);
- Warmed fluids;
- Forced-air warming (intraoperatively) and warmed fluids;
- Forced-air warming (pre and intraoperatively) and warmed fluids;
- Forced-air warming (preoperatively).

The results of the indirect comparison are given in Table 13 for the example of a 50 year old (ASA I) having minor surgery with an anaesthesia time of 60 minutes. Whilst all of the strategies included in the indirect comparison are cost-effective compared to usual care, forced air warming (intraoperatively) and warmed IV fluids combined is the most cost-effective strategy based on the indirect comparison. This is because of the high net benefit associated with each prevented case of hypothermia even for minor surgery where there is a lower risk of blood transfusion and pressure ulcers, and a smaller cost associated with surgical wound infection (mean net benefit of £1,506, 95% CI £455 - £3687 for minor surgery). Given that the mean cost of forced air warming plus warmed fluids is £27.32 per patient, it is possible to treat approximately 55 patients to prevent one case of hypothermia and still achieve a positive net benefit. The majority of the net benefit associated with preventing hypothermia results from preventing morbid cardiac events (81%). The second most important contributor to the net benefit is the cost and QALY loss associated with surgical wound infections (18%). We carried out sensitivity analyses to test whether the optimum strategy is sensitive to our assumptions regarding the impact of these two adverse consequences of perioperative hypothermia for this clinical scenario. Firstly we considered the impact of assuming that perioperative myocardial infarction and cardiac arrest would result in a 24% reduction in HRQoL for only 5 years, instead of the lifetime impact assumed in the basecase analysis. Under this assumption forced air warming (intraoperatively), warmed fluid, forced air warming (intraoperatively) plus warmed fluid and forced air warming (pre and intraoperatively) plus warmed fluid were all cost-effective strategies compared to usual care, but warmed fluid was the optimal strategy for this clinical scenario. When we assumed that surgical wound infection does not result in any significant impact on costs or HRQoL in minor surgery, the most cost-effective strategy was forced air warming (intraoperatively) plus warmed fluid. When we considered a very conservative scenario in which MCEs were assumed to reduce HRQoL for only 5 years and infections were assumed to have no impact on costs or QALYs, then forced air warming (intraoperatively), warmed fluid, forced air warming (intraoperatively) plus warmed fluid and forced air warming

(pre and intraoperatively) plus warmed fluid were all still cost-effective compared to usual care, although warmed fluid alone was the most cost-effective option. The optimum strategy was unchanged when we assumed that fluid warming devices are purchased rather than leased at no cost as the purchase costs are small in comparison to the cost of disposables when divided over the lifetime usage. These sensitivity analyses suggest that the cost-effectiveness of these strategies compared to usual care is not sensitive to the most important assumptions in the cost-effectiveness model, but the optimum strategy is sensitive to changes in the HRQoL impact of morbid cardiac events.

Table 13: Indirect comparison of the cost-effectiveness of prevention strategies for 50 year old patients with ASA I, minor surgery and 60 minutes anaesthesia duration

Intervention*	Incidence	Cost of consequences	QALY loss of consequences	Cost of strategy	Cost per QALY compared to usual care	Net Benefit at £20K compared to usual care	% optimal strategy
UC	237	£106,400	227.42	£0	N/A	N/A	0%
FAW (intra)	116	£87,900	219.27	£16,500	Dominates usual care	£165,000	13%
WF (intra)	107	£86,400	218.65	£10,800	Dominates usual care	£184,700	27%
FAW+WF (intra)	91	£84,000	217.57	£27,300	£500	£192,100	44%
FAW + WF (pre and intra)	80	£82,200	216.75	£43,900	£1,800	£193,800	16%

*****Abbreviations: FAW is forced-air warming, UC is usual care, WF is warmed fluid, intra is intraoperatively, pre is preoperatively

In intermediate or major surgery, the results (see Tables 14 and 15) are more favourable towards the more effective prevention strategies as the risk of hypothermia is greater and the net benefit associated with preventing hypothermia is also increased. Forced air warming (intraoperatively) with warmed IV fluids is the most cost-effective strategy for patients aged 50 with an ASA grade of I having intermediate or major surgery with an anaesthesia time of 60 minutes or more.

Table 14: Indirect comparison of the cost-effectiveness of prevention strategies for 50 year old patients with ASA I, intermediate surgery and 60 minutes anaesthesia duration

Intervention*	Incidence	Cost of conseqqu ences	QALY loss of conseque nces	Cost of strategy	Cost per QALY compared to usual care	Net Benefit at £20K compared to usual care	% optimal strategy
UC	567	£576,600	249.64	£0	N/A	N/A	0%
FAW (intra)	277	£393,700	230.15	£16,500	Dominate s usual care	£556,100	8%
WF (intra)	256	£379,300	228.70	£10,800	Dominate s usual care	£605,300	15%
FAW+WF (intra)	218	£355,400	226.08	£27,300	Dominate s usual care	£665,000	47%
FAW + WF (pre and intra)	191	£338,200	224.19	£43,900	Dominate s usual care	£703,500	30%

***** Abbreviations: UC is usual care, FAW is forced-air warming, WF is warmed fluid, intra is intraoperatively, pre is preoperatively

Table 15: An indirect comparison of the cost-effectiveness of prevention strategies for 50 year old patients with ASA I, major surgery and 60 minutes anaesthesia duration

Intervention*	Incidence	Cost of consequences	QALY loss of consequences	Cost of strategy	Cost per QALY compared to usual care	NB at £20K compared to usual care	% optimal strategy
UC	497	£631,300	244.90	£0	N/A	N/A	0%
FAW (intra)	243	£420,500	227.83	£16,500	Dominates usual care	£535,700	8%
WF (intra)	224	£403,900	226.55	£10,800	Dominates usual care	£583,800	15%
FAW+WF (intra)	191	£376,809	224.26	£27,300	Dominates usual care	£640,000	47%
FAW + WF (pre and intra)	167	£356,700	222.60	£43,900	Dominates usual care	£676,900	30%

*****Abbreviations: UC is usual care, FAW is forced-air warming, WF is warmed fluid, intra is intraoperatively, pre is preoperatively

Patients with increased risk of the complications of IPH

In elderly patients (e.g. age 70) for whom the risk of morbid cardiac events is greatest, the net benefit per hypothermic case prevented is greater and forced air warming (intraoperatively) plus warmed fluid is still the optimum strategy (see Table 16). We carried out a sensitivity analysis to see whether forced air warming (pre and intraoperatively) with warmed fluid is the most cost-effective strategy for patients at very high risk of hypothermia and its consequences. For this we estimated the risk of hypothermia for an individual with ASA grade III, having major surgery under combined regional and general anaesthesia. We increased the risk of morbid cardiac events to reflect the expected rate in 70 year olds (but assumed that surgery and any perioperative morbid cardiac event occurred at age 50), increased the infection risk to that typical of large bowel surgery, increased the blood transfusion rate, pressure ulcer rate and risk of unplanned postoperative mechanical ventilation. We also assumed that IPH is associated with a marginally increased length of stay in PACU. Even under these conditions the optimal strategy was still forced air warming (intraoperatively) plus warmed fluid with a likelihood of 46%. Forced air warming (pre and intraoperatively) plus warmed fluids had a 37% likelihood of being optimal. Whilst the mean incidence of IPH is lower for forced air warming (pre and intraoperatively) with warmed fluids, the effectiveness of these two strategies overlap considerably and forced air warming (intraoperatively) with warmed fluids has a greater QALY gain on 49% on occasions. Therefore forced air warming (pre and intraoperatively) with warmed fluids provides only a marginal gain compared to forced air warming (intraoperatively) with fluids but is expected to have a higher cost. This indirect comparison may be subject to bias due to differences in the underlying risk of IPH between the two populations. The RCT used to estimate the efficacy of forced air warming (pre and intraoperatively) plus warmed fluid is likely to underestimate the efficacy of this

strategy compared to usual care, as some patients randomised to usual care received warming at the discretion of the anaesthetist (Smith 2007). The addition of forced air warming to the preoperative phase is unlikely to be the most cost-effective strategy even in those individuals at highest risk, given the evidence available at this time.

Table 16: An indirect comparison of the cost-effectiveness of prevention strategies for 70 year old patients with ASA I, minor surgery and 60 minutes anaesthesia duration

Intervention*	Incidence	Cost of consequences	QALY loss of consequences	Cost of strategy	Cost per QALY compared to usual care	NB at £20K compared to usual care	% optimal strategy
UC	237	£167,200	132.35	£0	N/A	N/A	N/A
FAW (intra)	116	£141,000	123.97	£16,500	Dominates usual care	£177,200	13%
WF (intra)	107	£138,900	123.34	£10,800	Dominates usual care	£197,800	25%
FAW+WF (intra)	91	£135,600	122.22	£27,300	Dominates usual care	£206,900	45%
FAW + WF (pre and intra)	80	£132,900	121.39	£43,900	£872	£209,700	17%

***Abbreviations: UC is usual care, FAW is forced-air warming, WF is warmed fluid, intra is intraoperatively, pre is preoperatively

Individual with lower or negligible risk of morbid cardiac events

As the cost-effectiveness results are heavily driven by the net benefit of preventing morbid cardiac events, we have carried out analyses to determine whether the optimum strategy is different for individuals at lower risk of morbid cardiac events. The prevalence of ischaemic heart disease increases with age in the general population and underlying ischaemic heart disease increases the risk of perioperative cardiac complications. We have illustrated two lower risk scenarios by considering an individual having surgery aged 35 and an individual having surgery aged 20. We have assumed that the risk of morbid cardiac events at age 35 is one third of the risk at age 50 based on the relative prevalence of ischaemic heart disease in the general population (Health Survey for England 2003). For the scenario at age 20, we have assumed that the risk of morbid cardiac events is negligible (zero).

In the population with negligible risk of MCE, (illustrated by age 20), the net benefit of preventing hypothermia in minor surgery is lower still at £250 (95%CI £78-551). For minor surgery with an anaesthesia time of 60 minutes, the most cost-effective strategy in lower risk patients (ASA I, minor surgery) who have a negligible risk of morbid cardiac events, is warmed fluids (see Table 17). FAW alone is cost-effective compared to usual care in these patients if fluids are not given.

When intermediate surgery with an anaesthetic time of 60 minutes was considered, the most cost-effective strategy in these patients was forced air warming (intraoperatively) plus warmed fluid (see Table 18) under the basecase assumptions. This reflects the higher net benefit

associated with preventing hypothermia in patients having intermediate rather than minor surgery.

In the population with lower cardiac risk (illustrated by age 35), the net benefit of preventing hypothermia in minor surgery is lower at £783 (95% CI £291-1736). When assuming that the risk of cardiac complications in this age group is one third of the risk in patients aged 50, WF and forced air warming plus warmed fluid have a similar likelihood of being the optimum strategy (40% and 37% respectively) and the mean incremental cost per QALY for the addition of forced air warming to warmed fluid lies in the £20,000 to £30,000 range (see Table 19).

Table 17: An indirect comparison of the cost-effectiveness of prevention strategies for 20 year old patients with ASA I, minor surgery and 60 minutes anaesthesia duration

Intervention*	Incidence	Cost of consequences	QALY loss of consequences	Cost of strategy	Cost per QALY compared to usual care	Net Benefit at £20K compared to usual care	% optimal strategy
UC	237	£38,600	323.49	£0	N/A	N/A	4%
FAW (intra)	116	£28,700	322.47	£16,500	£6,500	£13,800	21%
WF (intra)	107	£27,900	322.39	£10,800	£100	£21,900	63%
FAW+WF (intra)	91	£26,600	322.26	£27,300	£12,400	£9,300	12%
FAW + WF (pre and intra)	80	£25,700	322.16	£43,900	£23,300	-£4,400	0%

*****Abbreviations: UC is usual care, FAW is forced-air warming, WF is warmed fluid, intra is intraoperatively, pre is preoperatively

Table 18: An indirect comparison of the cost-effectiveness of prevention strategies for 20 year old patients with ASA I, intermediate surgery and 60 minutes anaesthesia duration

Intervention*	Incidence	Cost of consequences	QALY loss of consequences	Cost of strategy	Cost per QALY compared to usual care	NB at £20K compared to usual care	% optimal strategy
UC	567	£485,400	326.26	£0	N/A	N/A	0%
FAW (intra)	277	£323,000	323.82	£16,500	Dominates usual care	£194,700	11%
WF (intra)	256	£310,200	323.64	£10,800	£62,700	£216,900	24%
FAW+WF (intra)	218	£288,900	323.31	£27,300	Dominates usual care	£228,200	46%
FAW + WF (pre and intra)	191	£273,800	323.09	£43,900	Dominates usual care	£231,200	18%

*****Abbreviations: UC is usual care, FAW is forced-air warming, WF is warmed fluid, intra is intraoperatively, pre is preoperatively

Table 19: An indirect comparison of the cost-effectiveness of prevention strategies for 35 year old patients with ASA I, minor surgery and 60 minutes anaesthesia duration

Intervention*	Incidence	Cost of consequences	QALY loss of consequences	Cost of strategy	Cost per QALY compared to usual care	NB at £20K compared to usual care	% optimal strategy
UC	237	£61,200	280.18	£0	N/A	N/A	0%
FAW (intra)	116	£48,400	276.09	£16,500	£900	£78,000	15%
WF (intra)	107	£47,400	275.78	£10,800	Dominates usual care	£91,000	40%
FAW+WF (intra)	91	£45,800	275.24	£27,300	£2,400	£87,000	37%
FAW + WF (pre and intra)	80	£44,500	274.83	£43,900	£5,100	£79,800	9%

*****Abbreviations: UC is usual care, FAW is forced-air warming, WF is warmed fluid, intra is intraoperatively, pre is preoperatively

Short anaesthesia times

The results of the indirect comparison are given in Table 20 for various clinical scenarios. For the example of a 50 year old (ASA I), having minor surgery with an anaesthesia time of 30 minutes, all of the strategies are cost-effective compared to usual care, but the optimum strategy is warmed IV fluids. However, in patients with an ASA grade II or more the risk of hypothermia is increased and forced air warming plus warmed fluid has a similar likelihood of being cost-effective to WF alone (35% versus 35% respectively). In patients at a negligible risk of cardiovascular complications (illustrated in the model as a patient aged 20), the optimum strategy was warmed fluid for minor operations with a shorter anaesthesia duration. However, in patients with a higher ASA grade having intermediate surgery, forced air warming plus warmed fluid had a similar likelihood of being the optimal strategy as warmed fluid alone. These analyses suggest that forced air warming plus warmed fluid may be the optimal strategy in patients having shorter procedures who are at increased risk of IPH or its consequences, but warmed fluid alone is the optimal strategy in lower risk patients.

The GDG were concerned that the risk of hypothermia applied in the model may be overestimated for shorter anaesthesia durations. To examine this uncertainty a sensitivity analysis was carried out to determine whether each of the strategies is cost-effective compared to usual care when the baseline risk is halved. Warmed fluid had a high likelihood (80%) of being under £20K even in the lowest risk patients (Age 20, ASA I, minor surgery) when a lower incidence was considered. Forced air warming had a 47.7% likelihood of being under £20K compared to usual care and a 63.6% likelihood of being under £30K compared to usual care in the lowest risk patients when a lower incidence rate was considered.

Table 20: Optimal strategy for various clinical scenarios when the duration of anaesthesia is 30 minutes

Scenario	Likelihood of being the optimal strategy at a cost per QALY threshold of £20K*				
	UC	FAW (intra)	WF	FAW (intra) +WF	FAW (pre and intra) +WF
Age 50, ASA I, Minor	0%	10%	43%	32%	15%
Age 50, ASA II, Minor	0%	8%	35%	34%	23%
Age 20, ASA I, Minor	2%	17%	72%	8%	0%
Age 20, ASA I, intermediate	0%	10%	40%	33%	18%
Age 20 ASA II, intermediate	0%	8%	36%	34%	22%

*Abbreviations: UC is usual care, FAW is forced-air warming, WF is warmed fluid, intra is intraoperatively, pre is preoperatively

Summary of cost-effectiveness results and discussion

Warming IV fluids was cost-effective compared to giving unwarmed fluids even when the risk of IPH was low (minor surgery, ASA I, general or regional anaesthesia), the risk of cardiac complications was negligible (typical risk at age 20) and the anaesthesia duration was short (30 minutes). Despite uncertainty around the incidence of IPH in procedures with short

anaesthesia times, warmed fluids were still cost-effective when the incidence was assumed to be half the rate observed over longer anaesthesia times.

Forced air warming was cost-effective compared to usual care even when the risk of IPH was low (minor surgery, ASA I, general or regional anaesthesia), the risk of cardiac complications was negligible (typical risk at age 20) and the anaesthesia duration was short (30 minutes). However, when the risk of IPH at 30 minutes was assumed to be half the rate observed at longer anaesthesia times, the cost per QALY ratio was in the £20,000 to £30,000 range.

An indirect comparison was used to determine the optimal strategy for preventing IPH. For surgery with an anaesthesia time of 60 minutes, forced air warming plus warmed fluid was the optimal strategy for all patients having intermediate or major surgery. In minor surgery forced air warming plus warmed fluid was the optimal strategy for patients with a risk of cardiac complications that is typical for age 50. When the cardiac risk was reduced by two thirds, to reflect the typical risk at age 35, forced air warming plus warmed fluid had a similar likelihood of being the optimal strategy as WF alone and the incremental cost per QALY for forced air warming plus warmed fluid versus warmed fluid was in the £20 to £30K range. In patients with a negligible risk of cardiac complications, warmed fluid was the optimal strategy in patients having minor surgery but forced air warming plus warmed fluid was the optimal strategy in patients having intermediate surgery. In patients with the highest risk of IPH and its adverse consequences forced air warming plus warmed fluid was still the optimal strategy.

In procedures with a short duration of anaesthesia, the strategies forced air warming plus warmed fluid and warmed fluid alone had a similar likelihood of being the optimal strategy in patients at higher risk of IPH and its consequences. In patients at lower risk the optimum strategy was warmed fluid alone.

The cost-effectiveness analysis has several limitations which were considered by the GDG when interpreting the results of the analysis. The first important limitation resulted from a paucity of data on the incidence of hypothermia in the clinical effectiveness RCTs. In order to estimate the effectiveness in terms of the risk of IPH we assumed that the mean temperatures in each trial arm were normally distributed. This is likely to be true when there are a large number of patients in each arm, but many of the RCTs have less than 25 patients in each arm. However, when we compared the relative risks calculated using this approximation to those given in the few trials which reported the incidence of IPH, we found an agreement which suggests that this approximation was reasonable.

Our estimate of the baseline risk of hypothermia was based on a cohort study conducted in Mexico (Flores-Maldonado 1997) which included some children in the cohort. However, none of the alternative data sources identified were more suitable. The mean duration of surgery in the cohort study used to estimate the absolute risk of hypothermia was 83 minutes. There was

concern that the risk in shorter procedures may have been overestimated and this was considered in a sensitivity analysis and taken into account by the GDG when forming recommendations for shorter procedures.

For many of the adverse consequences considered in the economic model, the additional cost has been estimated by considering the additional inpatient costs due to increased length of hospital stay. This ignores any costs incurred in primary care and may also overestimate the costs in patients having day surgery who are not admitted to hospital. For several of the health outcomes, we were unable to obtain costs or baseline risks that were specific to patients having minor surgery so the cost-effectiveness in this group may be overestimated.

We were unable to obtain estimates of the reduction in HRQoL in patients experiencing morbid cardiac events perioperatively. We had to use indirect evidence from non-surgical patients and extrapolate the long-term QALY loss by making assumptions regarding the persistence of any HRQoL reduction. A sensitivity analysis was carried out which demonstrated that the optimum strategy is sensitive to these assumptions, but the cost-effectiveness of the individual interventions compared to usual care is not.

We had difficulty obtaining cost estimates for several warming mechanisms and were therefore unable to estimate the cost per QALY ratio for some comparisons. However, it was possible for the GDG to infer the likely cost-effectiveness by considering whether the incremental net benefit would be likely to outweigh the intervention costs.

As with any indirect comparison the results can be biased by differences in baseline risks or differences in the exact use of interventions between the individual trials. Given the range of interventions that were found to be cost-effective compared to usual care it was necessary to determine which was the most cost-effective strategy. It was not possible to do this analysis based solely on direct trial comparisons so an indirect comparison was necessary.

14 RECOMMENDATIONS FOR RESEARCH

1. Thermal insulation and forced air warming for short operations

Do thermal insulation methods (especially reflective blankets and reflective hats and jackets) and forced air warming prevent hypothermia in short operations with total anaesthesia time up to 1 hour (actual duration recorded)?

Why is this important?

There is insufficient evidence for short operations (total anaesthesia time less than 30 minutes). Review evidence (30 minutes) has been extrapolated from longer operative measurements. There is some evidence from poor quality/small studies demonstrating that reflective hats and jackets preoperatively and reflective blankets preoperatively and intraoperatively improve patient temperatures at 30 minutes. This needs investigation for comparative effects in different phases. A large five-armed randomised trial is proposed to compare the following: reflective blankets preoperatively and intraoperatively; reflective hats and jackets preoperatively only; reflective hats and jackets preoperatively and reflective blanket intraoperatively; reflective hats and jackets preoperatively plus forced air warming intraoperatively; forced air warming intraoperatively only. All intravenous fluids given should be warmed to 37°C. Participants should be adults undergoing surgery under general anaesthesia. Primary outcomes should be the incidence of hypothermia and patient temperatures at 15, 30, 45 and 60 minutes of anaesthesia and in recovery.

2. Forced air warming, electric heating mattress and electric heating pad

Are forced air warming devices, electric heating mattress and electric heating pad equally effective in preventing inadvertent perioperative hypothermia?

Why is this important?

One small trial (conference abstract 2007) suggests electric heating mattress and forced air warming are equally effective in preventing hypothermia. A larger trial (2007) reports similar efficacy comparing forced air warming and electric pad. Electric heating pad or mattress maybe more cost effective, determined by a large randomised trial comparing electric heating mattress, electric heating pad and forced air warming used intraoperatively. All intravenous fluids given should be warmed to 37°C. Participants should be adults undergoing surgery under general anaesthesia. Stratification should be total anaesthesia duration: short (less than 30 minutes), medium (30 minutes to 1 hour), moderate (1 to 2 hours) or long (more than 2 hours). Analysis should be intention to treat. Primary outcome should be incidence of hypothermia and patient temperatures recorded at 15, 30, 45, 60 and 120 minutes of anaesthesia and in recovery. Adverse effects and complications (e.g. morbid cardiac events) of hypothermia should be recorded.

3. Phenylephrine and other alpha adrenergic agonists

Are phenylephrine, metaraninol and other alpha adrenergic agonists, in combination with forced air warming and warmed fluids, effective in the prevention of IPH?

Why is this important?

Evidence is limited, but one small study suggested that phenylephrine (given as an infusion at the start of anaesthesia) had a large significant effect on core temperature intraoperatively. Clinicians on the GDG believe that vasoconstrictors like phenylephrine and metaranimol may prevent hypothermia, with these drugs given to augment other warming mechanisms (started at induction of anaesthesia). All intravenous fluids given should be warmed to 37°C. A large randomised trial is proposed, comparing phenylephrine, metaranimol and placebo. Participants should be adults undergoing surgery under general anaesthesia. Analysis should be intention to treat. Primary outcomes should be the incidence of hypothermia and patient temperatures at 15, 30, 45, 60 and 120 minutes of anaesthesia and in recovery. Adverse effects and numbers of patients with complications (e.g. morbid cardiac events) of hypothermia should be recorded.

4. Nutritional solutions

Are nutritional solutions such as amino acids and fructose, in combination with forced air warming and warmed fluids, effective in the prevention of IPH?

Why is this important?

Limited evidence suggests that amino acids or fructose in the preoperative and intraoperative phases may prevent hypothermia. The adjunctive effect of these solutions to other warming mechanisms should be investigated, together with other potential benefits such as healing from protein synthesis and general well being in fasted patients. These infusions should be commenced prior to induction of anaesthesia and continued throughout the intraoperative period. A large randomised trial is proposed, comparing infusions of amino acids, fructose and saline, given to augment forced air warming. All intravenous fluids given should be warmed to 37°C. Participants should be adults undergoing surgery under general anaesthesia. Analysis should be intention to treat. Primary outcomes should be the incidence of hypothermia and patient temperatures at 15, 30, 45, 60 and 120 minutes of anaesthesia and in recovery. Adverse effects and numbers of patients with complications (e.g. morbid cardiac events) of hypothermia should be recorded.

15 IMPLEMENTATION

The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health', issued in July 2004. Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/CGXXX). *[NICE to amend list as needed at time of publication]*

- Slides highlighting key messages for local discussion.
- Costing tools:
  - Costing report to estimate the national savings and costs associated with implementation
  - Costing template to estimate the local costs and savings involved.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- Audit criteria to monitor local practice.

16 RELATED NICE GUIDANCE

Published

Preoperative tests: the routine use of routine preoperative tests in elective surgery. NICE clinical guideline 3 (2003). Available from www.nice.org.uk/CG003

Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling. NICE public health intervention guidance 2 (2006). Available from www.nice.org.uk/PHI002

17 UPDATE OF THE GUIDELINE

NICE clinical guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence 2 and 4 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

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