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3M – Medical & Clinical Affairs – Technical Report



Review of *Optimized management of patient normothermia* health economics tool

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Executive Summary

Some of the evidence used to develop this HE tool derives from the NICE systematic review, which is now 11 years old. Much of the evidence used by the NICE systematic review is relatively weak, over 20 years old, and not relevant to clinical practices of today. I believe that you will encounter resistance from customers if you try to base economic estimates on this old data.

One major difference between older and newer trials relates to the practice of dichotomizing core temperature to identify hypothermic from normothermic patients. While the hypothermia threshold is typically established at 36 °C, the mean core temperature of patients in the < 36 °C group tends to be substantially lower in older studies than that seen today.

Due to the age and study conditions, the effect sizes reported by many of these older trials are unjustifiably large and could lead to unreasonable estimates of economic benefits from patient warming interventions in a modern clinical environment. I would not use this tool as the basis of a risk sharing agreement.

Additionally, several review papers are cited as primary evidence for various effect sizes. Review papers are not acceptable sources of primary data for health economic analysis tools. Please cite and use the original papers for these tools. Also, while the evidentiary quality of newer trials may be lower than some older trials, please use the more modern estimates of effect sizes for this tool.

Thermal discomfort is difficult, but not impossible, to monetize. Please review some willingness-to-pay and welfare economics papers that describe how to monetize this outcome.

If this is a customer-facing document, please pick a uniform format for citations. There are a few misspelled words in the presentation.

Review of major topics

Risk of Surgical Site Infection and morbid cardiac events

Although the meta-analyses used to compute much of the economic burden of complications from hypothermia are relatively new, the underlying data is quite old and was collected during a time when very large differences existed between normothermic and hypothermic patients. This large difference has the effect of accentuating the effect size associated with the intervention. In fact, the authors (Kurz and Frank) of the two most important randomized control trials have concluded that the estimates of benefit they computed originally are likely too great now that surgical patients are not permitted to become as cold, regardless of what the warming intervention is. There are now at least 10 retrospective studies that have detected no significant differences in surgical infection rates between normothermic and hypothermic patients.¹⁻¹⁰

Although Frank did not know it at the time, the rate of morbid cardiac events he detected was far too low, and many investigators no longer cite this study for that reason.¹¹ For example, a recent very large retrospective study by Frank and colleagues showed no significant difference in wound infection or

myocardial infarction between groups of patients who were normothermic and those who were hypothermic.⁶

Need for mechanical ventilation

The two studies used to provide a relative risk assessment for this variable had large mean core temperature differences (1.4 and 1.3 °C, respectively) between normothermic and hypothermic patients.¹² ¹³ In neither study was the need for mechanical ventilation significantly different (0.55 and 0.07, respectively) between groups and in the meta-analysis, the confidence interval was 0.96 to 2.61, which is also nonsignificant.

Need for blood transfusion

The NICE analysis for blood transfusion included six studies conducted in 1994, 1996, 1997, 1999, 2000, and 2002.¹⁴⁻¹⁷ Transfusion thresholds were substantially different in the era during which these studies were conducted, moreover, in the two subsequent analyses in which cell saver and overlap studies were excluded, there were no significant differences between groups.

Extra length of stay in the recovery room (PACU)

Except for the study by Smith, all the studies included in the meta-analysis were conducted in the 1990s, so the core temperature differences tend to be substantially larger than those seen today. In the study by Lenhardt, et al, for example, the mean intraoperative core temperatures in the control groups was 34.8 °C, and the core temperature difference was purposefully maintained at 2.0 °C between the warmed and unwarmed patients.¹⁸ In the trial by Smith, et al, patients in the control group received about 1400 mL of 21 °C saline and the patients in the treatment group received 1300 mL of 43 °C saline.¹⁹ No patient was warmed intra- or postoperatively. Interestingly, the most recent study included in the meta-analysis found no difference in ICU time between the groups, although there was a substantial increase in cost in the treatment group.²⁰

The weighted mean difference (WMD) found by the NICE meta-analysis (p.194) is a nonsignificant three minutes, not three times increase in ICU time.

Increase in mortality

The risk adjusted OR is 0.41 with a 95% CI of 0.29 to 0.58.⁶ This is a big deal and confirms the large effect size seen by at least one other previous meta-analysis.²¹

Postoperative Shiver

Is this really an important outcome today given the wide availability of Meperidine? The citations are from 1992 and 1997 when practices were quite different.^{22, 23} Also, only one of the papers cited is a trial; the other is a review. Review papers should not be used as a primary reference for health economic tools. Please cite the original work, not a derivative.

Thermal discomfort

While it is true that patients dislike thermal discomfort, the paper cited in the tool is a review and does not describe a method to monetize this outcome. Please review some willingness-to-pay and welfare economics papers that describe how to monetize this outcome.²⁴⁻²⁸

Why 3M Technology?

Please include this citation in your presentation.²⁹

References

1. Barone JE, Tucker JB, Cecere J, Yoon MY, Reinhard E, Blabey RG, Jr., Lowenfels AB. Hypothermia does not result in more complications after colon surgery. *Am Surg.* Apr 1999;65(4):356-359.
2. Linam WM, Margolis PA, Staat MA, Britto MT, Hornung R, Cassedy A, Connelly BL. Risk factors associated with surgical site infection after pediatric posterior spinal fusion procedure. *Inf Cont Hosp Epi.* 2009;30(2):109-116.
3. Melton GB, Vogel JD, Swenson BR, Remzi FH, Rothenberger DA, Wick EC. Continuous intraoperative temperature measurement and surgical site infection risk: analysis of anesthesia information system data in 1008 colorectal procedures. *Ann Surg.* 2013;258(4):606-613.
4. Tillman M, Wehbe-Janek H, Hodges B, Smythe WR, Papaconstantinou HT. Surgical care improvement project and surgical site infections: can integration in the surgical safety checklist improve quality performance and clinical outcomes? *J Surg Res.* 2013;184(1):150-156.
5. Constantine RS, Kenkel M, Hein RE, Cortez R, Anigian K, Davis KE, Kenkel JM. The impact of perioperative hypothermia on plastic surgery outcomes: a multivariate logistic regression of 1062 cases. *Aesth Surg.* 2015;35(1):81-88.
6. Scott AV, Stonemetz JL, Wasey JO, Johnson DJ, Rivers RJ, Koch CG, Frank SM. Compliance with Surgical Care Improvement Project for Body Temperature Management (SCIP Inf-10) Is Associated with Improved Clinical Outcomes. *Anesthesiology.* 2015;123(1):116-125.
7. Baucom RB, Phillips SE, Ehrenfeld JM, Muldoon RL, Poulouse BK, Herline AJ, Wise PE, Geiger TM. Association of perioperative hypothermia during colectomy with surgical site infection. *JAMA Surg.* 2015;150(6):570-575.
8. Brown MJ, Curry TB, Hyder JA, Berbari EF, Truty MJ, Schroeder DR, Hanson AC, Kor DJ. Intraoperative Hypothermia and Surgical Site Infections in Patients with Class 1/Clean Wounds: A Case-Control Study. *J Am Coll Surg.* 2017;224(2):160-171.
9. Frisch NB, Pepper AM, Rooney E, Silverton C. Intraoperative Hypothermia in Total Hip and Knee Arthroplasty. *Orthopedics.* 2017;40(1):56-63.
10. Lehtinen SJ, Onicescu G, Kuhn KM, Cole DJ, Esnaola NF. Normothermia to prevent surgical site infections after gastrointestinal surgery: holy grail or false idol? *Annals of Surgery.* Oct 2010;252(4):696-704.
11. Devereaux PJ. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. *JAMA.* Apr 25 2017;317(16):1642-1651.
12. Frank SM, Higgins MS, Breslow MJ, Fleisher LA, Gorman RB, Sitzmann JV, Raff H, Beattie C. The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. A randomized clinical trial. *Anesthesiology.* Jan 1995;82(1):83-93.
13. Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S, Beattie C. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. *JAMA.* Apr 9 1997;277(14):1127-1134.

14. Bennett J, Ramachandra V, Webster J, Carli F. Prevention of hypothermia during hip surgery: effect of passive compared with active skin surface warming. *Br J Anaesth*. Aug 1994;73(2):180-183.
15. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med*. 1996;334(19):1209-1215.
16. Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. *Lancet*. Feb 3 1996;347(8997):289-292.
17. Johansson T, Lisander B, Ivarsson I. Mild hypothermia does not increase blood loss during total hip arthroplasty. *Acta Anaesthesiol Scand*. Nov 1999;43(10):1005-1010.
18. Lenhardt R, Marker E, Goll V, Tschernich H, Kurz A, Sessler DI, Narzt E, Lackner F. Mild intraoperative hypothermia prolongs postanesthetic recovery. *Anesthesiology*. 1997;87(6):1318-1323.
19. Smith CE, Gerdes E, Sweda S, Myles C, Punjabi A, Pinchak AC, Hagen JF. Warming intravenous fluids reduces perioperative hypothermia in women undergoing ambulatory gynecological surgery. *Anesthesia & Analgesia*. 1998;87(1):37-41.
20. Smith C, Sidhu R, Lucas L, Mehta D, Pinchak A. Should patients undergoing ambulatory surgery be actively warmed? *Internet Journal of Anesthesia*. 2007;12(1).
21. Mahoney CB, Odom J. Maintaining intraoperative normothermia: a meta-analysis of outcomes with costs. *Aana J*. 1999;67(2):155-163.
22. Just B, Delva E, Camus Y, Lienhart A. Oxygen Uptake during Recovery Following Naloxone Relationship with Intraoperative Heat Loss. *Anesthesiology*. 1992;76(1):60-64.
23. Sessler DI. Mild Perioperative Hypothermia. *N Engl J Med*. 1997;336(24):1730-1737.
24. van den Bosch JE, Bonsel GJ, Moons KG, Kalkman CJ. Effect of Postoperative Experiences on Willingness to Pay to Avoid Postoperative Pain, Nausea, and Vomiting. *Anesthesiology*. 2006;104(5):1033-1039.
25. Look X, Mok MUS, Tay YS, Abdullah HR. How do Singapore patients view post-anaesthesia adverse outcomes? A single-centre willingness-to-pay study. *Singapore medical journal*. 2018;59(5):264-270.
26. Carvalho B, Cohen SE, Lipman SS, Fuller A, Mathusamy AD, Macario A. Patient preferences for anesthesia outcomes associated with cesarean delivery. *Anesth Analg*. Oct 2005;101(4):1182-1187.
27. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg*. Sep 1999;89(3):652-658.
28. Macario A, Fleisher LA. Is There Value in Obtaining a Patient's Willingness to Pay for a Particular Anesthetic Intervention? *Anesthesiology*. 2006;104(5):906-909.
29. Bräuer A, Bovenschulte H, Perl T, Zink W, English MJ, Quintel M. What determines the efficacy of forced-air warming systems? A manikin evaluation with upper body blankets. *Anesth Analg*. 2009;108(1):192-198.

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