

Cost-Effectiveness of Therapeutic Hypothermia to Treat Neonatal Encephalopathy

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ABSTRACT

Objective: To estimate the cost-effectiveness (CE) of total body hypothermia plus intensive care versus intensive care alone to treat neonatal encephalopathy.

Methods: Decision analytic modeling was used to synthesize mortality and morbidity data from three randomized controlled trials, the Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY), National Institute of Child Health and Human Development (NICHD), and CoolCap trials. Cost data inputs were informed by TOBY, the sole source of prospectively collected resource utilization data for encephalopathic infants. CE was expressed in terms of incremental cost per disability-free life year (DFLY) gained. Probabilistic sensitivity analysis was performed to generate CE acceptability curves (CEACs).

Results: Cooling led to a cost increase of £3787 (95% confidence interval [CI]: -2516, 12,360) (€5115; 95% CI: -3398–16,694; US\$5344; 95% CI: -3598, 26,356; using 2006 Organisation for Economic Co-operation and

Development (OECD) purchasing power parities) and a DFLY gain of 0.19 (95% CI: 0.07–0.31) over the first 18 months after birth. The incremental cost per DFLY gained was £19,931 (€26,920; US\$28,124). The baseline CEAC showed that if decision-makers are willing to pay £30,000 for an additional DFLY, there is a 69% probability that cooling is cost-effective. The probability of CE exceeded 99% at this threshold when the throughput of infants was increased to reflect the national incidence of neonatal encephalopathy or when the time horizon of the economic evaluation was extended to 18 years after birth.

Conclusions: The probability that cooling is a cost-effective treatment for neonatal encephalopathy is finely balanced over the first 18 months after birth but increases substantially when national incidence data or an extended time horizon are considered.

Keywords: cost-effectiveness, neonatal encephalopathy, pediatrics.

Introduction

The incidence of neonatal encephalopathy has been estimated at between one and four per 1000 term live births in the developed world, with adverse outcomes ranging from death to severe cerebral palsy and neurodevelopmental impairment [1,2]. New interventions are urgently needed to improve the outcome of infants with neonatal encephalopathy, but it is important to understand the cost-effectiveness (CE) of these interventions before widespread implementation. Recent studies and systematic reviews have suggested that reducing body temperatures 3–5°C below normal is safe and improves neurological function [3–12]; a recent meta-analysis found that therapeutic hypothermia resulted in a clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability at 18 months of age (typical relative risk [RR] 0.76; 95% confidence interval [CI] 0.65–0.89) [8]. Nevertheless, none of the studies included in these reviews or the meta-analysis incorporated CE outcomes. We now report a health-care CE study that used outcomes data from three randomized controlled trials, the Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY) [13], and the National Institute of Child Health and Human Development (NICHD), and CoolCap trials [14,15]; health service cost data were obtained from TOBY, the sole

source of prospectively collected resource utilization data for encephalopathic infants.

Methods

Economic Model

A decision analytic model was constructed to estimate the incremental CE of intensive care plus cooling versus intensive care alone for the treatment of moderate to severe neonatal encephalopathy. The time horizon of the baseline model was the first 18 months after birth. In the first 12 months after birth, each infant could transition to either survival with unconfirmed neurological function or death; in the period 12 months to at least 18 months, surviving infants could transition to one of three mutually exclusive health states: survival without neurological abnormality, survival with neurological abnormality, or death. Incremental costs (ΔC) were measured from the British National Health Service (NHS) health care and personal social services perspective [16], and incremental effectiveness (ΔE) was measured in terms of disability-free life years (DFLYs) gained [17]. The primary outcome of the economic evaluation was the incremental CE ratio (ICER; $\Delta C/\Delta E$). Costs and effects were discounted at a rate of 3.5% per year as recommended by the National Institute for Health and Clinical Excellence [16].

Transition Probabilities to the Health States

The proportion of children in each health state during each time period was obtained from the three randomized controlled trials of therapeutic hypothermia for the treatment of neonatal

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encephalopathy, namely our own recently completed TOBY trial [13], and the NICHD and CoolCap trials [14,15]. Data synthesis for the transition probabilities was used because the sample size calculation for the TOBY trial was not based on the requirements of the economic evaluation; *ex post* sample size calculations suggested that TOBY did not have sufficient power for the ICER. We therefore elected to incorporate all available evidence appropriate for informing costs and the DFLY.

In brief, the TOBY trial randomized 325 infants less than 6 hours of age and a gestational age of at least 36 weeks with neonatal encephalopathy and abnormal amplitude integrated electroencephalography (aEEG) to intensive care plus total body cooling for 72 hours ($n = 163$) or intensive care alone ($n = 162$). The primary outcome for TOBY was the combined 18-month outcome of mortality or severe neurodevelopmental disability defined as Bayley Mental Developmental Index [18] (MDI) < 70 , Gross Motor Function Classification Score [19] (GMFCS) 3 to 5, or bilateral cortical visual impairment with no useful vision. NICHD randomized 208 infants with neonatal encephalopathy to intensive care plus total body cooling (for 72 hours; $n = 102$) or intensive care without cooling ($n = 106$); the primary outcome was death or moderate or severe disability (moderated disability defined as having one of: MDI 70–84, GMFCS of 2, hearing deficit with amplification, or a seizure disorder; severe disability was defined as: < 70 on the Bayley MDI, GMFCS 3–5, or bilateral blindness or deafness) at 18 months of age. The CoolCap trial randomized 234 encephalopathic infants to intensive care plus head cooling (for 72 hours; $n = 116$) or intensive care without cooling ($n = 118$) and used a primary outcome of combined frequency of mortality and severe neurodevelopmental disability (defined using GMFCS 3–5, Bayley MDI < 70 , or bilateral cortical visual impairment) at 18 months of age. We synthesized the data from these three trials using a Bayesian approach to meta-analysis where the outcomes data from the NICHD and CoolCap trials were treated as prior information to the TOBY trial likelihood data for each period in the model (10–12 months; 12–18 months). If the required data could not be obtained directly from the NICHD or CoolCap trial publications [14,15], the investigators from both trials provided the required information.

Measurement and Valuation of Resource Utilization and Costs

The TOBY trial had been designed to incorporate a prospective economic evaluation and to our knowledge, provided the sole source of prospectively collected and validated resource utilization data for total body cooling for encephalopathic infants. The data on resources used, including personnel, were collected during transport to/from a cooling hospital and throughout the hospital stay. Each infant's clinical course was classified by four mutually exclusive levels of neonatal care as defined by the British Association of Perinatal Medicine [20].

Data on hospital readmissions, outpatient hospital visits, and the use of other health-care services after discharge were obtained from information gathered at the TOBY 18-month clinical follow-up assessment and was supplemented by questionnaires completed by parents at 6, 12, and 18 months. Any missing data on resource utilization were imputed using the ICE multiple imputation program in Stata version 10 (StataCorp, College Station, TX).

Unit costs were attached to each resource utilization item to obtain a cost per child for each health state. The cost per level of neonatal care was obtained from the NHS Reference Costs database [21], and drug costs were from the British National Formulary [22]. The cost associated with infant death was derived from

previously published observational research conducted at our research unit [17].

In TOBY, costs that were specific to total body cooling included the capital costs of the aEEG machine and the Tecotherm total body cooling system (Tecotherm, TS Medical 200M, Tec-Com, Halle, Germany). Noncapital costs associated with these machines were obtained via telephone interviews with the UK suppliers of the cooling equipment (Inspiration Health Care UK) or from UK TOBY centers. The cost of each machine was annuitized over 5 years using equivalent annual costing and a discount rate of 3.5%. The cost of aEEG and total body cooling was calculated by dividing the equivalent annual cost of the machines by the number of infants per year who received total body cooling in each TOBY participating center. The baseline model therefore distributed the cost of the intervention across the 163 infants cooled in 42 participating TOBY centers (an average of 1.7 infants per center per year was cooled in TOBY centers). All costs are in pound sterling valued at 2006 to 2007 prices.

Measurement of Effectiveness

The effectiveness measure was the DFLY metric [17]. This endpoint is similar to a clinical endpoint of survival without neurological abnormality except that it accounts for the duration spent in the health state. We defined survival without neurological abnormality as Bayley MDI > 84 , Bayley psychomotor development index (PDI) > 84 , no neuromotor impairment, normal vision, and normal hearing [13]. Children without a neurological abnormality were assigned a health state value of 1 for each disability-free year of survival. Children with neurodevelopmental abnormalities or who died were assigned a health state value of 0.

Statistical Analysis

The decision model was analyzed using TreeAge Pro (TreeAge Pro Inc, 2008; TreeAge Software, Williamstown, MA). A number of sensitivity analyses informing different scenarios important to decision-makers and hospital planners were conducted to assess their effect on the ICER. The number of infants treated in each neonatal unit under controlled conditions during the TOBY trial may differ from current or future practice. The cost per infant per center per year for aEEG and total body cooling was therefore varied assuming: 1) patient throughput reflected current practice in the UK Cooling Register (mean (SD) of 7.1 (4.5) infants per center per year across 28 centers) and 2) patient throughput reflected the national incidence of neonatal encephalopathy distributed across the current configuration of neonatal services (calculated at 15 infants per tertiary level neonatal unit per year). One major trial has conducted cooling without the use of aEEG [15]; alternatively, some units already provide this service. The cost per infant for the cooling equipment was therefore calculated excluding the cost of the aEEG machine. The time horizon of the baseline model was extended to 18 years of age using gestation and disability status-specific data generated from a study by Mangham et al. [23].

Probabilistic sensitivity analysis was conducted for each of these analyses. A beta distribution was assigned to the prior and likelihood data for transition probabilities based on binomial data; the Dirichlet distribution was assigned to the prior and likelihood data for transition probabilities based on multinomial data [24]. For costs, the gamma distribution was assumed for all variables except the cost per infant of aEEG and total body cooling. These costs were bootstrapped because they did not follow a convenient distribution [25]. Nonparametric bootstrapping was also used for the uncertainty surrounding the time spent

Table 1 Resource use values and unit costs of resource items (£ sterling 2006–2007 prices)

Resource use variable	Cooling group mean resource use (SE)	Standard care group mean resource use (SE)	Unit cost (£)*
Resource use of inpatient stay [§] (days)			
Intensive care (level 1)	5.45 (0.41)	4.76 (0.35)	938 [†]
High dependency care (level 2)	2.67 (0.73)	3.19 (0.91)	671 [†]
Special care (level 3)	7.14 (0.87)	9.13 (1.04)	405 [†]
Ordinary care (level 4)	2.87 (0.63)	3.00 (0.80)	267 [†]
Readmission after initial discharge**	0.84 (0.13)	0.95 (0.17)	480 or 1833 ^{†‡}
Resource use of additional investigations			
X-rays	2.12 (0.21)	1.92 (0.20)	31 [†]
Ultrasound scans	3.20 (0.10)	3.83 (0.14)	56 [†]
ECGs	0.38 (0.05)	0.46 (0.66)	35 [†]
MRIs	0.72 (0.035)	0.76 (0.397)	239 [†]
Resource use associated with transfer [¶]			
Transfer	0.94 (0.06)	0.94 (0.06)	257 [†]
Consultant	0.21 (0.05)	0.26 (0.05)	103 [‡]
Registrar	0.48 (0.06)	0.54 (0.07)	57 [‡]
Nurse grade D & E	0.14 (0.04)	0.10 (0.08)	42 [‡]
Nurse grade F	0.16 (0.04)	0.32 (0.08)	62 [‡]
Nurse grade G & I	0.23 (0.05)	0.14 (0.04)	72 [‡]
Community resource use** (visits)			
General practitioner visit	7.25 (0.99)	7.34 (1.27)	34 [‡]
Health visitor visit	10.72 (1.31)	11.87 (2.14)	36 [‡]
Practice nurse visit	2.68 (0.38)	2.58 (0.69)	30 [‡]
Community nurse visit	3.52 (1.29)	5.81 (1.96)	63 [‡]
Community pediatrician visit	2.25 (0.51)	2.43 (0.62)	58 [‡]
Physiotherapist visit	8.17 (2.08)	13.76 (2.23)	40 [‡]
Social worker visit	0.95 (0.38)	1.24 (0.37)	39 [‡]

*Source:

[†]National Schedule of Reference Costs.[‡]Personal Social Services Research Unit.[§]Measured in days of care until initial discharge, where <9.5% of values were missing.^{||}Resource use until initial discharge where <30% of values were missing.[¶]Resource use until discharge where <4% of values were missing.^{‡‡}£480 for standard bed day and £1833 if ventilation was required.^{***}Resource use over 18 months.

ECG, electrocardiogram; MRI, magnetic resonance imaging.

in the final health state because TOBY follow-up varied between children. To propagate the uncertainty throughout the model, Monte Carlo simulation was used and 10,000 draws from the input distributions was specified. The joint uncertainty of cost and effectiveness was represented using the CE plane and CE acceptability curves (CEACs) [26]. Statements about CE are based on notional willingness to pay thresholds held by decision-makers of £20,000 per DFLY gained and £30,000 per DFLY gained [16].

Results

Model Inputs

Mean resource use inputs and their unit costs are summarized in Table 1. The costs and transition probabilities associated with the health states in the decision model are shown in Table 2. The estimated mean cost of cooling was £5918 (95% CI 1347–14,304). The mean hospital cost to initial discharge for survivors was £12,441 (95% CI 10,331–14,772) in the cooled group and £12,728 (95% CI 10,553–15,108) in the noncooled group. For those infants who died before discharge, the mean cost per infant was £5315 (95% CI 4445–6233) in the cooled group and £7637 (95% CI: 5707–9765) in the noncooled group. The probability of an infant surviving to 12 months was 0.74 (95% CI 0.70–0.79) in the cooling group and 0.70 (95% CI 0.65–0.74) for the noncooled group.

Also in Table 2 are the model inputs for the 12- to 18-month period. The probability of surviving without neurological abnormality was 0.47 (95% CI 0.41–0.52) and 0.32 (95% CI 0.27–0.38) in the cooled and noncooled groups, respectively. The probability of survival from 12 to 18 months with neurological

abnormality or death was 0.52 (95% CI 0.46–0.58) and 0.01 (95% CI 0.00–0.03), respectively, in the cooling group. For the noncooled group, the probability of survival with neurological abnormality or death over this period was 0.64 (95% CI 0.59–0.70) and 0.03 (95% CI 0.01–0.05), respectively.

Health service costs over the 12- to 18-month period differed depending on the neurological status of the child. For those children categorized as having no neurological abnormality, mean hospital inpatient costs were £124 (95% CI 42–254) for the cooled group and £129 (95% CI 29–306) for the noncooled group. For those children categorized as having a neurological abnormality, the mean inpatient costs for those in the cooled versus not cooled groups were estimated at £1578 (95% CI 606–2995) and £1105 (95% CI 372–2248), respectively.

CE of Therapeutic Hypothermia

The costs and effects of intensive care plus cooling and intensive care without cooling are presented in Table 3. Over the first 18 months after birth, the mean health service cost was £22,324 (95% CI 16,782–30,738) in the cooled group and £18,537 (95% CI 16,062–21,224) in the noncooled group. The mean incremental cost associated with cooling was £3787 (95% CI –2516–12,360). As depicted on the CE plane in Figure 1, a number of bootstrap replicates predicted that cooling would result in cost savings (15% of the incremental cost draws were negative). The mean number of DFLYs was estimated at 0.54 (95% CI 0.49–0.64) and 0.35 (95% CI 0.28–0.42) for the cooled and noncooled groups, respectively. Cooling resulted in an additional 0.19 (95% CI 0.07–0.31) DFLYs over the first 18 months after birth.

Table 2 Estimated model parameter inputs

Parameter	Mean (95% CI) cooling group	Mean (95% CI) standard care group	Distribution [†]
First 12 months: transition probabilities and costs			
Survival with unconfirmed neurological function	0.74 (0.70–0.79)	0.70 (0.65–0.74)	Beta(281,98) [‡] Beta(270,116) [§] Beta(98,281) [‡] Beta(116,270) [§]
Death	0.26 (0.21–0.30)	0.30 (0.25–0.35)	Uniform (nonparametric bootstrap) Gamma(122.35,0.829) [‡] Gamma(111.08,0.769) [§]
Cost of cooling equipment and aEEG* in £	5,918 (1,347–14,304)	N/A	
Cost of transfer in £	147 (123–175)	144 (119–172)	Gamma(123.48,0.009) [‡] Gamma(118.98,0.009) [§]
Hospital costs to discharge for survivors in £	12,441 (10,331–14,772)	12,728 (10,553–15,108)	Gamma(132.09,0.025) [‡] Gamma(54.87,0.007) [§]
Hospital costs for nonsurvivors in £	5,315 (4,445–6,233)	7,637 (5,707–9,765)	Gamma(16.25,0.015) [‡] Gamma(2404.65,0.004) [§]
Inpatient costs post discharge in £	1,086 (628–1,661)	2,397 (1,140–4,013)	Gamma(102.01,0.15) [‡] Gamma(63.46,0.089) [§]
Community care costs post discharge to 6 months in £	681 (556–816)	713 (552–897)	Gamma(33.58,0.676) [‡] Gamma(23.42,0.034) [§]
Community care costs 6 to 12 months	440 (304–1,601)	684 (436–994)	
12 to 18 months: transition probabilities and costs			
Age assessed	1.54 (1.41–1.72)	1.64 (1.51–1.86)	Uniform (nonparametric bootstrap)
Survival without neurological abnormality	0.47 (0.41–0.52)	0.32 (0.27–0.38)	Dirichlet($\alpha_1 = 132$) [‡] Dirichlet($\alpha_1 = 87$) [§]
Survival with neurological abnormality	0.52 (0.46–0.58)	0.64 (0.59–0.70)	Dirichlet($\alpha_2 = 147$) [‡] Dirichlet($\alpha_2 = 175$) [§]
Death	0.01 (0–0.03)	0.03 (0.01–0.05)	Dirichlet($\alpha_3 = 4$) [‡] Dirichlet($\alpha_3 = 8$) [§]
Inpatient costs, children without neurological abnormality in £	124 (42–254)	129 (29–306)	Gamma(5.20,0.011) [‡] Gamma(5.32,0.024) [§]
Inpatient costs, children with neurological abnormality in £	1,578 (606–2,995)	1,105 (372–2,248)	Gamma(5.32,0.005) [‡] Gamma(6.55,0.004) [§]
Community care costs, children without neurological abnormality in £	217 (119–342)	214 (113–348)	Gamma(14.48,0.067) [‡] Gamma(12.98,0.061) [§]
Community care costs, children with neurological abnormality in £	338 (178–553)	459 (260–709)	Gamma(12.63,0.038) [‡] Gamma(15.98,0.035) [§]
Death in £	1,623 (1,308–1,941)	1,623 (1,308–1,941)	Gamma(93.78,0.0578) ^{‡§}

*Expected cost per cooled infant per year in each trial center ($n = 163$); inclusive of fixed costs for aEEG and cooling machines amortized over 5 years, the cost of maintaining the cooling equipment, and variable costs.

[†]All distributions follow the parameterization documented by TreeAge Pro (2008) software, except that of the beta distribution which was parameterized in terms of Beta(α, β), where α = number of events, r , and $\beta = n - r$ when n is the sample size.

[‡]Distribution parameters for the cooling group.

[§]Distribution parameters for the standard care group. All costs are reported in 2006–2007 £ sterling.
aEEG, amplified EEG; N/A, not applicable.

The ICER was calculated at £19,931 per DFLY gained in the baseline analysis. The uncertainty surrounding the ICER is summarized on the CE plane (Fig. 1) and by using the CEAC (Fig. 2), which plots the probability that cooling is cost-effective at different willingness to pay thresholds (λ) for a DFLY gain. Figure 1 shows there is substantial uncertainty surrounding the ICER, and by extension, it is uncertain if cooling is cost-effective. The CEAC in Figure 2 (top left panel) shows the exact probabilities of CE for cooling at alternative values of λ . If λ is £30,000, there is a 69% probability that total body cooling is cost-effective; if $\lambda = £20,000$, the probability of CE is 52%.

Sensitivity Analyses

The sensitivity analyses are presented in Table 3. Sensitivity analyses 1 and 2 varied the number of infants undergoing cooling at each hospital. When the number of infants per center per year reflected current data from the UK Cooling Register, cooling was, on average, cost-saving (£–295; 95% CI –4555–5414), cooling dominated standard care (on average, less costly and more effective), and there was a 92% probability that cooling is cost-effective at $\lambda = £20,000$ (upper right panel, Fig. 2). If 15 infants were cooled per center per year, cooling was again cost-saving (£–1708; 95% CI –5251–1730). The CEAC demonstrated when $\lambda = £7,100$, there was a 95% probability that cooling is cost-

effective under this scenario (Fig. 2, middle left panel). The third scenario excluded the cost of the aEEG machine. The incremental cost of cooling was £601 (95% CI –3811–5584) and the ICER was £3163 per DFLY gained. If $\lambda = £30,000$, there was a 95% probability that cooling is cost-effective under this scenario (Fig. 2, middle right panel). Sensitivity analysis 4 extended the baseline model to a time horizon of 18 years; the estimated model inputs (transition probabilities and costs) are presented in online Appendix 1 at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i6_Regier.asp. The incremental effectiveness of cooling over 18 years was 1.30 DFLYs gained (95% CI 0.51–2.15), and the incremental cost was £1847 (95% CI –4494–10,303). The ICER was £1421 per DFLY gained and there was a 99% probability that cooling is cost-effective if $\lambda = £20,000$ (Fig. 2, lower left panel). Therapeutic hypothermia had a 95% probability of being cost-effective if $\lambda = £8300$.

Conclusion

This study used decision modeling to synthesize clinical outcomes from three randomized controlled trials that examined therapeutic hypothermia for infants with moderate or severe neonatal encephalopathy; the health service costs associated with hypothermia or normothermia were obtained from TOBY, which

Table 3 Cost-effectiveness results and sensitivity analyses

Parameter	Mean (95% CI) cooling group	Mean (95% CI) standard care group	Mean difference* (95% CI)
Baseline analysis			
Cost in £	22,324 (16,782–30,738)	18,537 (16,062–21,224)	3,787 (–2,516–12,360)
Effectiveness	0.54 (0.49–0.64)	0.35 (0.28–0.42)	0.19 (0.07–0.31)
ICER	£19,931 per DFLY gained		
λ = 20,000	52% probability that cooling is cost-effective		
λ = 30,000	69% probability that cooling is cost-effective		
Sensitivity analysis 1: number of infants per center per year cooled informed using the UK Cooling Register			
Cost in £	18,242 (15,214–23,559)	18,537 (16,062–21,224)	–295 (–4,555–5,414)
Effectiveness	0.54 (0.49–0.64)	0.35 (0.28–0.42)	0.19 (0.07–0.31)
ICER	On average, cooling dominates standard care		
λ = 20,000	92% probability that cooling is cost-effective		
λ = 30,000	96% probability that cooling is cost-effective		
Sensitivity analysis 2: 15 infants per center per year require cooling			
Cost in £	16,829 (14,578–19,224)	18,537 (16,062–21,224)	–1,708 (–5,251–1,730)
Effectiveness	0.54 (0.49–0.64)	0.35 (0.28–0.42)	0.19 (0.07–0.31)
ICER	On average, cooling dominates standard care		
λ = 7,100	95% probability that cooling is cost-effective		
λ = 20,000	99% probability that cooling is cost-effective		
Sensitivity analysis 3: aEEG cost excluded			
Cost in £	19,419 (16,228–23,736)	18,537 (16,062–21,224)	601 (–3,811–5,584)
Effectiveness	0.54 (0.49–0.64)	0.35 (0.28–0.42)	0.19 (0.07–0.31)
ICER	£3,163 per DFLY gained		
λ = 20,000	88% probability that cooling is cost-effective		
λ = 30,000	95% probability that cooling is cost-effective		
Sensitivity analysis 4: baseline analysis extended to 18 years			
Cost in £	30,719 (24,460–39,048)	28,872 (25,224–32,747)	1,847 (–4,944–10,303)
Effectiveness	7.75 (5.84–9.50)	6.45 (4.58–8.15)	1.30 (0.51–2.15)
ICER	£1,421 per DFLY gained		
λ = 8,300	95% probability that cooling is cost-effective		
λ = 20,000	99% probability that cooling is cost-effective		

*The mean of the standard care group is subtracted from the mean of the cooling group. The probability of cost-effectiveness at λ = £20,000 and λ = £30,000 was reported unless there was a 95% probability of cost-effectiveness at a λ ≤ £20,000. All costs are reported in 2006–2007 £ sterling.

aEEG, amplified EEG; DFLY, disability-free life year; ICER, incremental cost-effectiveness ratio; λ, willingness to pay threshold held by decision-makers for an additional DFLY.

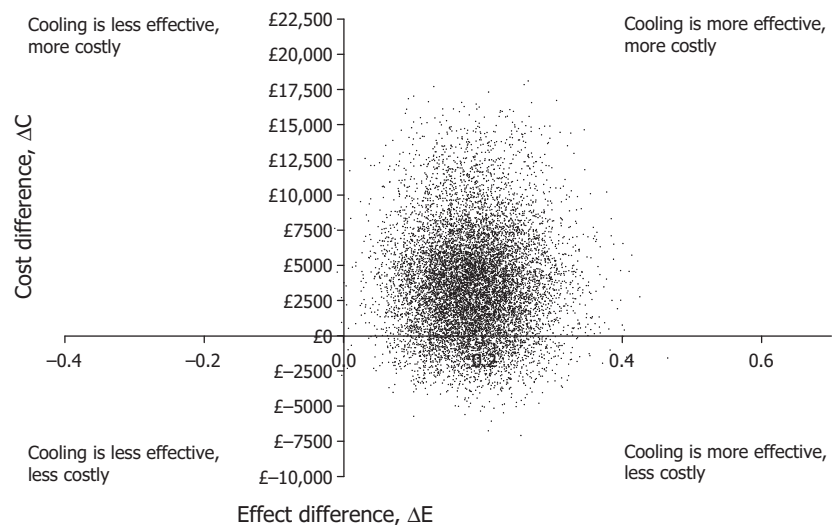


Figure 1 Cost-effectiveness plane plotting the joint density of the incremental costs and effectiveness of each of the 10,000 simulated cost-effectiveness ratios (baseline analysis).

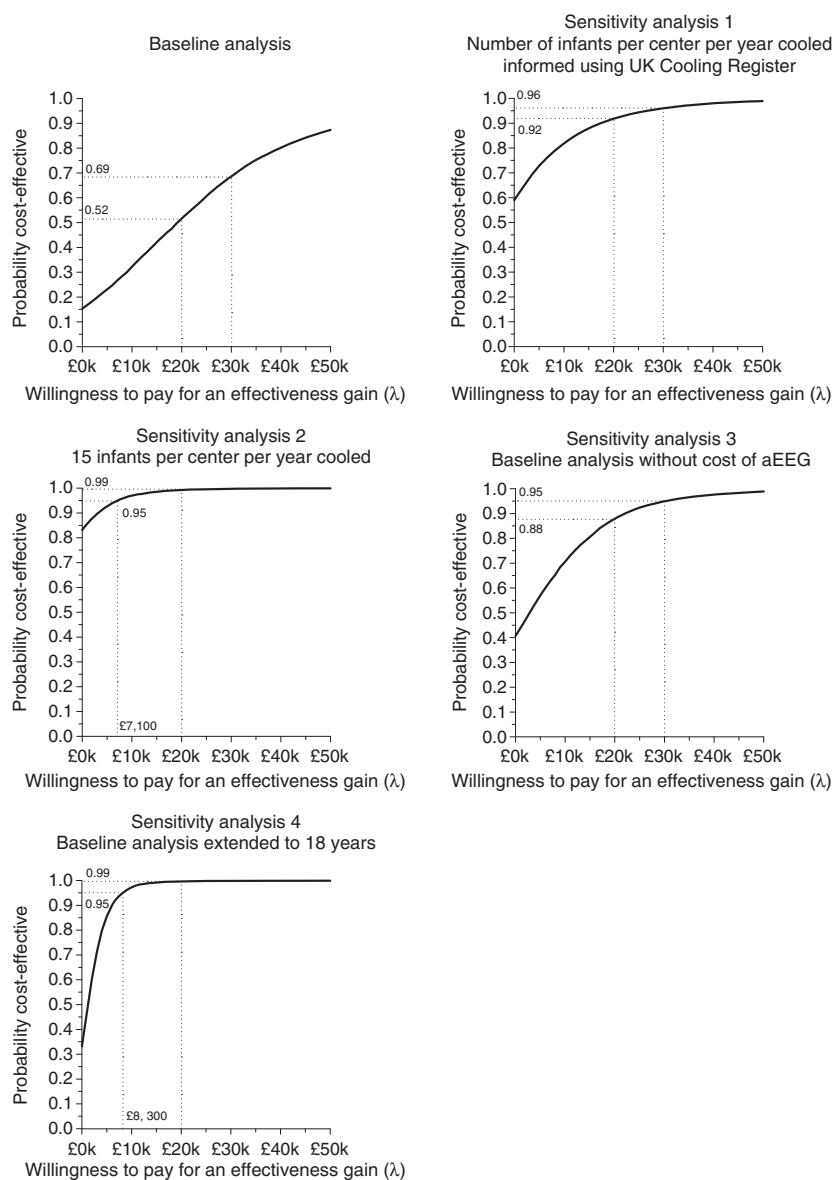


Figure 2 Cost-effectiveness acceptability curve (expressed in '000s (k) 2006–2007 £ sterling).

to our knowledge is the sole source of prospectively collected resource use data for encephalopathic infants. Although the TOBY trial could inform a prospective economic evaluation, we used decision modeling to facilitate data synthesis because none of the published randomized controlled trials have provided conclusive proof of efficacy. Further, TOBY was not powered to detect statistically significant differences in our effectiveness outcome: the DFLY. We therefore sought to incorporate all available evidence with a view to inform decision-makers as to the CE of therapeutic hypothermia [27].

We found that therapeutic hypothermia resulted in increased costs and effectiveness over the first 18 months after birth. Within the current decision-making context of the British NHS (ICER \leq £30,000), and considering the commonly cited willingness to pay a threshold of US\$50,000 and €30,000 for an effectiveness gain, the baseline ICER of £19,931 (US\$28,124; €26,290; using 2006 Organisation for Economic Co-operation and Development (OECD) purchasing power parities) per DFLY

gained suggested that cooling may offer good value for money [16,28]. Nevertheless, the probabilistic sensitivity analysis revealed that there is sufficient uncertainty surrounding the baseline ICER. This is evident when examining the CEAC, which demonstrated that there is a 69% probability that cooling is cost-effective when decision-makers' willingness to pay threshold was £30,000 for a DFLY gain. The probability that cooling was cost-effective fell to 52% when $\lambda = £20,000$. The CE of cooling is therefore finely balanced over the first 18 months after birth.

The sensitivity analyses examined how the ICER differed across critical assumptions important to decision-makers and hospital planners. When the number of infants cooled per year reflected current data from the UK Cooling Register, cooling, on average, dominated standard care, and there was a 92% probability that cooling is cost-effective if $\lambda = £20,000$ and a 96% probability of CE when $\lambda = £30,000$. Future analyses should assess the efficiency balances between the numbers of centers offering cooling, the throughput of infants in each center, and the

numbers of transfers required if smaller or larger cooling centers are adopted as policy.

Therapeutic hypothermia was also cost-effective when the baseline model was extended to a time horizon of 18 years because the ICER was £1421, and there was a 95% probability that cooling was cost-effective if $\lambda = £8300$. Consequently, the totality of evidence seems to favor the adoption of cooling into routine clinical practice. Nevertheless, local configurations of neonatal services and future levels of demand for cooling should be considered when interpreting the study findings.

Although this economic evaluation was conducted according to current methodological guidelines [16,29], there are a number of caveats. First, the effectiveness of cooling was not measured in terms of the quality adjusted life years (QALY) metric currently recommended to inform resource allocation decisions [16]. The QALY metric was not used because of methodological concerns surrounding the use of preference-based measurement in early childhood [30]. The DFLY metric was used instead of the QALY approach [17]. The limitation of the DFLY metric is that it does not distinguish between varying levels of disability likely to have different utilities attached to them. The DFLY assumption can be considered conservative in this context because those in the non-cooled group of TOBY were shown to have a higher incidence of moderate to severe neurodevelopmental disability [13]. Nevertheless, there is a need for further research developing preference-based instruments in early childhood.

Second, we excluded the costs borne by other sectors of the economy, for example, costs borne by parents or informal caregivers, the cost of education services, or medical-legal costs. Incorporation of these wider societal costs may reduce the ICER given the additional clinical burden of neurological abnormality (and by extension, economic burden) in the noncooled group. Finally, our sensitivity analysis extending the time horizon to 18 years was informed by cohort data. Future research will use data from the TOBY 7-year follow-up study to validate these data inputs.

In conclusion, we show that the CE of therapeutic hypothermia for treating moderate to severe neonatal encephalopathy is finely balanced over the first 18 months after birth because there was a 69% probability that cooling is cost-effective when $\lambda = £20,000$. The probability of CE increases substantially over an extended time horizon because the probability of CE reached 95% at a willingness to pay threshold of £8300 for a DFLY gain. These data should aid local decisions on the likely economic impact of implementation of this intervention.

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