Institution: University of Bristol		
Unit of Assessment: 4) Psychology, Psychiatry and Neuroscience		
Title of case study: Post-hypoxic cooling reduces mortality and improves long-term outcomes in infants		
Period when the underpinning research was undertaken: 2000 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Marianne Thoresen	Professor of Neonatal Neuroscience	01/1998 – present
Sally Jary	Senior Research Associate	06/2012 – 10/2020
Elisa Smit	Clinical Research Fellow	12/2011 – 09/2014
Ela Chakkarapani	Senior Lecturer in Neonatology	10/2013 – present
Period when the claimed impact occurred: 1st August 2013 – 2020		
Is this case study continued from a case study submitted in 2014? Yes		

1. Summary of the impact

In 2010, University of Bristol research demonstrating the benefits of therapeutic hypothermia (cooling) following perinatal asphyxial injury, led to this becoming the standard of care across the developed world. This cooling protocol has had continued impact and remains recommended in updated 2015 international guidelines, which reduces mortality and severe disability from 66% to 51% at both 2 and 7 years of age, as well as reducing the risk of cerebral palsy by 15% and improving motor function scores. Post-2014, new research improvements to the protocol have been incorporated into national guidelines in the UK, Canada, Australia and New Zealand. In the UK alone, an estimated 165 infants per year have improved long-term outcomes due to these new protocol updates. Health economic analysis supports cost-effectiveness in both the UK and US, and significant savings to the NHS and UK families in care and compensation costs. Product development support resulted in a new mark stimulating device, now available in 50 countries which holds a leading market share globally.

2. Underpinning research

Severe lack of oxygen to the brain around the time of birth, hypoxic-ischaemic-encephalopathy (HIE), occurs in 1-6 per 1,000 term-born infants. HIE often causes permanent brain injury and leads to cerebral palsy and/or cognitive impairment. Prof Marianne Thoresen pioneered laboratory research revealing that post-hypoxic cooling reduced brain injury in newborn pigs and rat pups, and followed this with CoolCap, and TOBY (Total Body Hypothermia) [1] clinical trials, which demonstrated reduced incidence and severity of neurological abnormality in cooled groups. A subsequent meta-analysis co-authored by Prof Thoresen, incorporating CoolCap, TOBY and NICHD (National Institute of Child Health and Human Development) clinical trials, concluded that for infants with HIE, body and brain cooling to 33-34°C core temperature is associated with a consistent increase in healthy survival and reduction in death and neurological impairment at 18 months [2].

Based on this body of information in 2010, both the National Institute for Health and Clinical Excellence (NICE) and the International Liaison Committee on Resuscitation (ILCOR) recommended therapeutic hypothermia (TH) for 3 days as the standard of care. In 2014, the University of Bristol was presented with the Queen's Anniversary Prize for Higher Education and Research for work including Prof Thoresen's revolutionary research and treatment.

Following the TOBY trial, Prof Thoresen established a clinical protocol and maintained a true population-based cohort of cooling-treatment and long-term follow-up, encompassing 2.6 million people within 1.5 hours drive of Bristol. Subsequent studies and analyses of cooling therapy have focused on developing a detailed and highly consistent protocol to optimise long-term life chances. In 2013, analysis of cohort data showed that starting cooling early, between 0-3 hours after birth, compared with after 3-6 hours, improved motor outcomes for survivors [3]. The use of cooling for groups of infants who do not fulfil the standard criteria revealed no difference in complication rates or long-term outcomes [4]. This suggested cooling could be considered for infants with neonatal encephalopathy following postnatal collapse and those with underlying surgical or cardiac conditions, but not for infants with intracerebral bleeds following traumatic deliveries [4]. Follow-up of the 8-year cohort also revealed 70% lower rates of epilepsy than reported in the clinical cooling trials and suggested that the number of anti-convulsant drugs needed to stop the seizures was a good outcome predictor [5].

More recently, research from the group has focused on how cooled babies develop into children, adolescents and young adults in order to guide future therapy and ensure optimal initial therapy and subsequent support. A study of cooled children from the Bristol cohort without cerebral palsy investigated associations between perinatal factors, 18-month development scores and motor and cognitive outcomes at school age [6].

3. References to the research

1) Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, Kapellou O, Levene M, Marlow N, Porter E, **Thoresen M**, Whitelaw A, Brocklehurst P. (2009). Moderate Hypothermia to Treat Perinatal Asphyxial Encephalopathy. *New England Journal of Medicine*, 361, 1349–1358. DOI:10.1056/NEJMoa0900854

2) Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, Strohm B, **Thoresen M,** Whitelaw A, Azzopardi D. (2010). Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ,* 340:c363. DOI:10.1136/bmj.c363

3) **Thoresen M,** Tooley J, Liu X, **Jary S**, Fleming P, Luyt K, Jain A, Cairns P, Harding D, Sabir H. (2013). Time Is Brain: Starting Therapeutic Hypothermia within Three Hours after Birth Improves Motor Outcome in Asphyxiated Newborns. *Neonatology,* 104(3):228-233. DOI:10.1159/000353948

4) **Smit E**, Liu X, **Jary S, Cowan F**, **Thoresen M.** (2015). Cooling neonates who do not fulfil the standard cooling criteria – short- and long-term outcomes. *Acta Paediatrica* 104(2), pp.138–145. DOI:10.1111/apa.12784

5) Liu X, **Jary S, Cowan F**, **Thoresen M.** (2017). Reduced infancy and childhood epilepsy following hypothermia-treated neonatal encephalopathy. *Epilepsia*, 58, 1902–1911. DOI:10.1111/epi.13914

6) **Jary S,** Lee-Kelland R, Tonks J, **Cowan FM**, **Thoresen M,** Chakkarapani E. (2019). Motor performance and cognitive correlates in children cooled for neonatal encephalopathy without cerebral palsy at school age. *Acta Paediatr.* 108, 1773–1780. DOI:10.1111/apa.14780

4. Details of the impact

Hypoxic ischaemic encephalopathy (HIE) is associated with a high risk of death or early neurodevelopmental impairment. Among survivors, cerebral palsy, functional disability, cognitive impairment and epilepsy often presents with increasing severity later in childhood as the brain matures and integrated functions are expected to develop. The cost of these conditions to patients, their families and society is high.

As a result of pioneering work by Prof Thoresen [1, 2], in 2010 both the UK National Institute for Health and Clinical Excellence (NICE) and the International Liaison Committee on Resuscitation (ILCOR) recommended therapeutic hypothermia for 72 hours (3 days) to a core temperature of 33-34°C as the standard of care following perinatal brain injury. Since this intervention, detailed in a REF2014 impact case study, both initial [1, 2] and subsequent improvements to the protocol [3-5], have continued to inform guidance and practice, nationally and internationally.

Continued recommended international standard of care

Following the international recommendation in 2010, new clinical trial data has continued to uphold the benefit of therapeutic hypothermia for perinatal brain injury, and studies investigating cooling for longer (5 days) or at a lower temperature (32°C) have shown no additional benefit. The protocol, *commence with 6h of birth, cool to 33.5°C and continue for 72 hours after birth* (Class IIa, LOE A), demonstrated clinically [1], and corroborated by meta-analysis [2], remains internationally recognized as the only effective intervention in reducing death and disability. The recommendation remains unchanged in the updated 2015 European Resuscitation Council (*Section 7: Resuscitation and support of transition of babies at birth – Induced hypothermia)* [Aii], American Heart Association (*Part 13: Neonatal Resuscitation – Induced Therapeutic Hypothermia*) [Aiii], and Japan Resuscitation Council guidelines, endorsed by ILCOR [Ai].

Updates to UK and country specific guidance and practice

More recent updates to healthcare guidance continue to cite original studies [1, 2], while also reviewing and incorporating new studies [3-5] to inform safe and effective treatment. Updates to healthcare guidance in Canada (2018) [Ci], Queensland, Australia (2016) [Cii] and New Zealand (2019) [Ciii], cite evidence regarding infants who do not fulfil the standard criteria [4], and the Canadian Paediatric Society Position Statement [Ci], also incorporates evidence on rates of epilepsy [5], to recommend monitoring long-term motor, psycho-educational, auditory and cognitive outcomes is an important component of care. Prof Thoresen was also lead author of the first European-wide guidelines (2018), for term and near-term infants suffering HIE [B], endorsed by the European Foundation for the Care of Newborn Infants (EFCNI), which brings together 220 healthcare professionals, parent representatives and industry specialists from over 30 countries to harmonise treatment.

Prof Thoresen's research also continues to influence best practice across the UK. Following analysis revealing the benefit of earlier cooling (<3 hours of age) for motor outcomes [3], this protocol was implemented in Bristol and the South West Neonatal Network. The current Wales [Di], North West [Dii], and Yorkshire and Humber Neonatal Network guidelines for managing HIE and therapeutic hypothermia, also cite Prof Thoresen's evidence of improved motor outcomes [3] to recommend early cooling – within 3 postnatal hours or *'as soon as possible'.*

In November 2020, The British Association of Perinatal Medicine (BAPM) produced a new 'Framework for Practice' [E], to expand and update the 2010 BAPM Position Statement on Therapeutic Hypothermia. For case selection – eligibility: '*The framework suggests that TH treatment is instigated in babies who meet the criteria outlined in the TOBY study'* [E]. In addition, the framework cites Bristol cohort evidence [4] suggesting cooling may benefit infants following postnatal collapse [E]. Prior to use of therapeutic hypothermia 60% of infants with postnatal collapse experienced very poor outcomes.

Benefit to patient health and wellbeing

Therapeutic hypothermia reduces mortality and severe disability by 15% (66% without cooling; 51% with cooling). Since becoming the global standard of care in 2010, follow-up studies and meta-analyses, including a 2013 Cochrane review, continue to conclude cooling substantially reduces deaths and major disability. In the UK alone approximately 1,100 infants annually are estimated to be treated with therapeutic hypothermia (0.17% (occurrence of cooling in Bristol cohort) of 640,000 deliveries), which translates to 165 infants per year fewer experiencing poor outcomes.

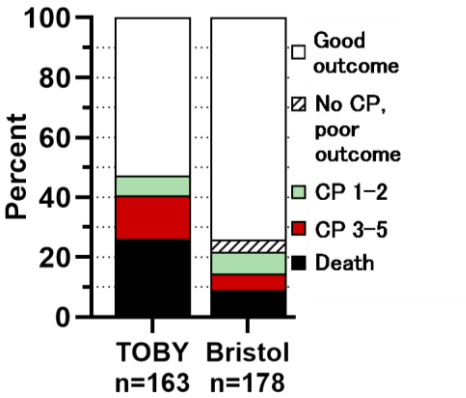

Fig 1 – Comparison of outcomes in cooled patients from the TOBY trial [2] and post-trial Bristol cohort.

In 2014, follow-up of participants in the TOBY trial showed the brain protection from therapeutic hypothermia continued until school age (6-7 years old), with 17% more children in the cooled group surviving with an IQ score of 85 or above (100 ± 15 (mean ± sd)) [F]. Survivors in the cooled group also had a 15% lower risk of cerebral palsy, a 15% lower risk of moderate or severe disability and better motor function scores compared with the control group [F]. Evidence from the Bristol population-based cohort shows further benefits of very early cooling with only 25% poor outcomes (Fig 1) including reduced cerebral palsy (CP) severity and epilepsy. 55% of CP children had grade 1 CP and were able to walk without support. Half of them had cognitive outcomes in the normal range [G].

A 2019 network meta-analysis, comparing efficacy and safety of neuroprotective therapies for neonates with HIE and using evidence from fifteen studies (including Cool Cap and TOBY trials), showed whole body cooling was the most effective in reducing risk of mortality [H].

Health economic benefit

A 2019 comparative assessment of the health care costs, using a follow-up of survivors in the TOBY trial at 6-7 years of age, showed the total mean NHS cost per child over a six-month period was GBP1,005 less in those who underwent cooling [Ii]. This translates to a cost saving for the NHS of approximately GBP330,000 per year (165 infants x GBP2,010 per year). The study also highlighted the progressively higher cost associated with greater disability, as well as noting that increased carer needs negatively impacted the ability of carers to undertake paid employment. A 2020 US cost-effectiveness analysis of a theoretical cohort also concluded that cooling is the most cost-effective intervention in neonates experiencing severe HIE [Iii].

The current average NHS financial reserve for claims for cerebral palsy related to birth injury is GBP10 million due to the life-long care needs and loss of income for carers. Therapeutic hypothermia reduces the risk of cerebral palsy by 15% [F] (an estimated 110 infants a year nationally). In the Bristol population-based cohort with very early cooling, the incidence and severity of cerebral palsy is further reduced (Fig 1). Therefore, a conservative estimate suggests therapeutic hypothermia saves the NHS over GBP500 million every year.

Development of specialist equipment

Long-term collaboration with Mennen Medical Ltd has enabled Prof Thoresen to be instrumental in the development and trialling of specialist equipment for cooling and brain assessment.

Selection of infants with HIE suitable for therapeutic hypothermia is best done using amplitude integrated EEG (aEEG) to diagnose depressed brain activity. Prof Thoresen undertook laboratory comparison of a new aEEG device developed by Mennen Medical with the 'gold standard' CFM monitor. These data supported the product to gain CE marking and FDA approval (Dec 2013) [J]. The VP Clinical Manager at Mennen Medical notes that '*Professor Thoresen's invaluable feedback resulted in a user friendly, robust and improved, 2 channel aEEG machine'.* Furthermore, when the device (CerebraLogik) launched (2014), the 2-channel approach was; *'unique, and stimulated development from competitors as well as driving down the market price. CerebraLogik is now available in 50 countries, has sold to hundreds of institutions and holds a leading market share in a competitive environment.'* [J].

5. Sources to corroborate the impact

A) ILCOR (2020). i) Publications: Guidelines 2015
ii) European Resuscitation Council Guidelines for Resuscitation 2015: Section 7. Resuscitation and support of transition of babies at birth. DOI:10.1016/j.resuscitation.2015.07.029 *[Induced hypothermia - cites: 1,2]*
iii) American Heart Association (2015). CPR & ECC Guidelines: Part 13: Neonatal Resuscitation. DOI:10.1161/CIR.0000000000000267 *[Induced Therapeutic Hypothermia - cites: 1,2]*

B) European Foundation for the Care of Newborn Infants (EFCNI) (2018). European Standards of Care for Newborn Health Postnatal management of newborn infants with hypoxic ischaemic encephalopathy (HIE)

C) i) Canadian Paediatric Society (2018). Position statement: Hypothermia for newborns with hypoxic-ischemic encephalopathy *[cites: 1,4,5]*
ii) Queensland Clinical Guidelines (2016). Hypoxic-ischaemic encephalopathy (HIE) *[cites: 4]*
iii) New Zealand Child and Youth Clinical Networks (2019). Neonatal Encephalopathy Consensus Statement from the Newborn Clinical Network

D) i) Wales Neonatal Network (2017). Guideline for the management of Infants with Moderate or Severe Perinatal Asphyxia requiring cooling *[cites: 1,3,4]*
ii) North West Neonatal ODN (2018). Hypoxic Ischaemic Encephalopathy (HIE) Guideline

E) British Association for Perinatal Medicine (BAPM) (2020). Therapeutic Hypothermia for Neonatal Encephalopathy - A Framework for Practice *[cites: 2,3,4,5]*

F) Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O, Goodwin J, Halliday HL, Juszczak E, Kapellou O, Levene M, Linsell L, Omar O, **Thoresen M**, Tusor N, Whitelaw A, Edwards AD. (2014). Effects of Hypothermia for Perinatal Asphyxia on Childhood Outcomes. *New England Journal of Medicine,* 371, 140–149. DOI:10.1056/NEJMoa1315788

G) **Jary S, Smit E,** Liu X, Cowan FM, **Thoresen M.** (2015). Less severe cerebral palsy outcomes in infants treated with therapeutic hypothermia. Acta Paediatr. 104, 1241–1247. DOI:10.1111/apa.13146

H) Lee *et al.* (2019). Comparative Efficacy and Safety of Neuroprotective Therapies for Neonates With Hypoxic Ischemic Encephalopathy: A Network Meta-Analysis. *Front. Pharmacol.* 10. DOI:10.3389/fphar.2019.01221

I) i) Rivero-Arias *et al.* (2019). Hypothermia for perinatal asphyxia: trial-based resource use and costs at 6–7 years. *Arch. Dis. Child. - Fetal Neonatal Ed.* 104, F285–F292. DOI:10.1136/archdischild-2017-314685
ii) Packer *et al.* (2020). Therapeutic hypothermia in severe hypoxic-ischemic encephalopathy: a cost-effectiveness analysis. *J. Matern. Fetal Neonatal Med.* 0, 1–8. DOI:10.1080/14767058.2020.1733519

J) i) Mennen Medical Ltd (2021). Supporting Letter – VP Clinical Manager
ii) FDA approval (Dec 2013) CerebraLogik