Institution: Imperial College London

Unit of Assessment: 04 Psychology, Psychiatry and Neuroscience

Title of case study: Cooling Babies Limits Brain Injury

1. Summary of the impact (indicative maximum 100 words)

Imperial College researchers have pioneered the implementation of therapeutic hypothermia to improve survival of neonates following perinatal asphyxia.

Following their programme of clinical research to prove feasibility, Professors Azzopardi and Edwards led the Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY), a multicentre, randomised trial investigating the effects of total-body cooling for 72 hours in babies with asphyxial encephalopathy from a lack of oxygen at birth. This work demonstrated that infants in the cooled group had an increased rate of survival without neurologic abnormality. This work has influenced public policy and healthcare provision, through the implementation and audit of therapeutic hypothermia nationally and internationally. In the UK, cooling therapy is now carried out in 1000-1500 cases annually (Data reported to the UK National Register of Cooling). Cooling following perinatal asphyxia is now standard of care in most resource rich and intermediate countries.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College Researchers:
Professor Denis Azzopardi, Professor of Neonatal Medicine (1993-present)
Professor A David Edwards, Weston Professor of Neonatal Medicine (1992-2012) now Visiting Professor

Following his appointment at Imperial College in 1993, Professor Azzopardi focused on developing clinical trials of neuroprotective intervention in newborns. In 1999, Professor Azzopardi developed a simple classification for the cot side analysis of amplitude integrated EEG to assess objectively the severity of neonatal encephalopathy. The classification facilitated the first clinical trials of hypothermia in encephalopathic newborns and has since been adopted widely, including by major international trials. The report of this work has been cited more than 170 times to date [1].

In 2005, Professor Azzopardi and Professor Edwards published results of the first pilot study of intervention with total body hypothermia in newborns. The study provided evidence that neural rescue is possible after birth asphyxia, with hypothermia providing a simple, cost effective treatment [2]. To date this work has been cited over 732 times since publication in 2005, and has been the subject of position statements by the NIH, Royal College of Paediatrics and Child Health, and the American Paediatric Association.

To pursue this work Professors Azzopardi and Edwards obtained funding from the Medical Research Council (MRC) to carry out the largest international trial of this therapy, the TOBY study, which recruited in excess of target, and confirmed the preliminary findings of their previous studies [3-4]. The TOBY trial (325 infants enrolled) demonstrated that following induction of moderate hypothermia for 72 hours in infants who had perinatal asphyxia Infants in the cooled group had an increased rate of survival without neurologic abnormality. Among survivors, Cooling resulted in significantly reduced risks of cerebral palsy and improved scores on the Mental Developmental Index [3].

The trials [2-4] and synthesis of the trial data [5] confirm in larger populations that 72 hours of cooling to a core temperature of 33-34^{o}C, started within six hours of birth, reduces death and disability at 18 months of age and improves a range of neurodevelopmental outcomes in survivors. The studies carried out by Professors Azzopardi and Edwards showed that therapeutic hypothermia increases the rate of survival with a normal outcome by about 50%. This Imperial programme and clinical trials has demonstrated that therapeutic hypothermia improved the rate of intact survival

following perinatal asphyxia. An economic evaluation showed that the treatment is cost effective [6].

3. References to the research (indicative maximum of six references)

(1) al Naqeeb, N., Edwards, A.D., Cowan, F.M., Azzopardi, D. (1999). Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. *Pediatrics,* 103 (6), 1263-71. DOI. Times cited: 170 (as at 23rd September 2013 on ISI Web of Science). Journal Impact Factor: 5.43

(2) Gluckman, P.D., Wyatt, J.S., Azzopardi, D., Ballard, R., Edwards, A.D., Ferriero, D.M., Polin, R.A., Robertson, C.M., Thoresen, M., Whitelaw, A., Gunn, A.J. (2005). Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet,* 365 (9460), 663-670. DOI. Times cited: 732 (as at 23rd September 2013 on ISI Web of Science). Journal Impact Factor: 38.27

(3) Azzopardi, D.V., Strohm, B., Edwards, A.D., Dyet, L., Halliday, H.L., Juszczak, E., et al. TOBY Study Group. (2009). Moderate hypothermia to treat perinatal asphyxial encephalopathy. *New England Journal of Medicine*, *361*(14), 1349-1358. DOI. Times cited: 322 (as at 23rd September 2013 on ISI Web of Science). Journal Impact Factor: 53.29

(4) Rutherford, M., Ramenghi, L.A., Edwards, A.D., Brocklehurst, P., Halliday, H., Levene, M., Strohm, B., Thoresen, M., Whitelaw, A., & Azzopardi, D. (2010). Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *Lancet Neurology*, *9* (1), 39-45. DOI. Times cited: 85 (as at 23rd September 2013 on ISI Web of Science). Journal Impact Factor: 23.46

(5) Edwards, A.D., Brocklehurst, P., Gunn, A.J., 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. *British Medical Journal*, *340*, c363. DOI. Times cited: 140 (as at 23rd September 2013 on ISI Web of Science). Journal Impact Factor: 14.09

(6) Regier, D.A., Petrou, S., Henderson, J., Eddama, O., Patel, N., Strohm, B., Brocklehurst, P., Edwards, A.D., & Azzopardi, D. (2010). Cost-effectiveness of therapeutic hypothermia to treat neonatal encephalopathy. *Value in Health*, *13* (6), 695-702. DOI. Times cited: 3 (as at 23rd September 2013 on ISI Web of Science). Journal Impact Factor: 2.19

Key funding:

- MRC (2002-2008; £676,497), Principal Investigator (PI) D. Azzopardi, Whole body hypothermia for perinatal asphyxial encephalopathy.
- MRC (2010-2014; £1,045,270), PI D. Azzopardi, Outcomes at school age following therapeutic hypothermia for perinatal asphyxial encephalopathy.

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, commerce, public policy and services, practitioners and services
Main beneficiaries include: patients, NHS, NICE, industry, international guideline bodies

Severe perinatal asphyxia is a serious complication occurring in about 1-3 infants in every 1000 births (approximately 1500-2000 infants in the UK) with a 60% risk of death or disability in survivors. Following the studies carried out by Professors Azzopardi and Edwards, therapeutic hypothermia is now recognised as a significant advance in clinical medicine by the National Institute of Health and Clinical Excellence (NICE) and the British Association of Perinatal Medicine (BAPM) in 2010 for general introduction into the NHS [1-2].

Professor Azzopardi set up a National Registry, known as the TOBY register, of treatment with

hypothermia which provides guidance for clinicians and has led to co-ordinated implementation of this therapy nationally [3]. The Register, coordinated by the National Perinatal Epidemiology Unit, Oxford, also undertakes surveillance and audit and provides feedback to participants and publishes regular newsletters and reports. Professor Azzopardi developed guidelines and protocols on therapeutic hypothermia that are used widely in neonatal networks throughout the UK. Both NICE and the BAPM recommend that the details of neonates who receive the cooling treatment be entered into the TOBY register [1-2]. The latest analysis of Register data published by Professor Azzopardi in PLOS in 2012 showed that this therapy is now standard care in the UK [3]. For example, the TOBY register clinician's handbook provides practical guidelines to the selection of infants and their clinical management and is widely used [3]. Data from the clinical trials of hypothermia and the National Register indicate that as a result of therapeutic hypothermia 100 fewer infants annually develop cerebral palsy due to birth asphyxia. Since inception of the Register it is estimated that there has been a cost saving to the health economy of about £150M. Nationwide surveys modelled on the UK Register have been carried out in Switzerland and Japan [4].

This work has also impacted international guidelines and clinical protocols [5]. For example; the American Heart Association (AHA) & American Academy of Paediatrics (2010) recommends "Therapeutic hypothermia (whole body or selective head cooling) recommended for infants ≥ 36 weeks with moderate to severe hypoxic ischemic encephalopathy as per the protocol used in major cooling trials with provision for monitoring for side effects and long term follow up". In 2010 this guidance was updated and changed to reflect the findings of the Imperial lead TOBY study published in 2009 [5].

Professor Azzopardi's classification of the amplitude integrated EEG for assessing the severity of neonatal encephalopathy and its use for infant selection into neuroprotective trials using a British designed monitor first developed in the 1960s, led to the further development of modern digital portable cot-side brain function monitors that now are used routinely in neonatal intensive care units (eg The CFM Olympic Brain Monitor, Natus Ltd USA).

To carry out the MRC-funded international TOBY trial of cooling therapy for neonatal encephalopathy Professor Azzopardi successfully used a simple, modified cooling mattress originally designed for topical cooling in adults and this subsequently was developed into a CE marked servo controlled neonatal cooling system that is used widely (Tecotherm Neo, Inspiration Healthcare Ltd Leicester UK). The positive results of the clinical trials led by Professor Azzopardi drove the development of other specific cooling equipment (eg Criticool, MTRE Ltd, Israel). This work has led to the international sale and distribution of neonatal cooling equipment [6].

Patients and patient advocacy groups have played an important role in Imperial's clinical research. A representative from SCOPE participated in the Trial Management Group for the TOBY cooling trial and helped develop the patient information literature. BLISS, the UK charity supporting newborn care, hosted an internet forum for parents of infants participating in the TOBY trial. A parent of a child who participated in the TOBY trial is a member of the Children's Study Trial Steering Committee, led by Professor Azzopardi, and now lay members participate in the Management Group for neonatal neuroimaging research at Imperial College.

A Neonatal Taskforce (Department of Health) has developed a toolkit to facilitate the delivery of equitable, transparent and auditable neonatal care. The aim of the toolkit is to ensure that premature and sick newborn babies receive the care necessary to produce the best long-term outcomes. The toolkit provides a set of principles for quality neonatal services. These standards of care provision reflect the findings of the Imperial lead TOBY study [7].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] NICE clinical guidelines reflecting TOBY findings:
National Institute for Health and Clinical Excellence. Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. 2010. http://guidance.nice.org.uk/IPG347

[2] Position statement and national treatment guidelines:

- British Association of Perinatal Medicine. Position statement on therapeutic cooling for neonatal encephalopathy (2010). Archived on 8th November 2013
- The East of England Perinatal Networks: Guidelines for Management of Infants with Suspected Hypoxic Ischaemic Encephalopathy (HIE) http://www.neonatal.org.uk/documents/5456.pdf. Archived on 8th November 2013
- Techniques developed are now standard protocols within the NHS – For example South Central NHS.http://www.networks.nhs.uk/nhs-networks/south-central-neonatal-network/documents/guidelines/South%20Centralneonatal%20Network%20Initiation%20of%20cooling%20guideline.pdf Archived on 8th November 2013

[3] The TOBY Cooling Register:

- Azzopardi, D., Strohm, B., Linsell, L., Hobson, A., Juszczak, E., Kurinczuk, J.J., Brocklehurst, P., Edwards, A.D.; UK TOBY Cooling Register (2012). Implementation and conduct of therapeutic hypothermia for perinatal asphyxial encephalopathy in the UK--analysis of national data. *PLoS One*, 7(6):e38504. DOI.
- Professor Azzopardi developed guidelines and protocols on therapeutic hypothermia that are used widely in neonatal networks throughout the UK (see www.npeu.ox.ac.uk/tobyregister – archived on 8th November 2013).
- TOBY register clinician's handbook https://www.npeu.ox.ac.uk/tobyregister/docs (archived on 8th November 2013)

[4] Iwata, O., Nabetani, M., Takenouchi, T., Iwaibara, T., Iwata, S., Tamura, M. (2012). Working Group on Therapeutic Hypothermia for Neonatal Encephalopathy, Ministry of Health, Labor and Welfare, Japan; Japan Society for Perinatal and Neonatal Medicine. Hypothermia for neonatal encephalopathy: Nationwide Survey of Clinical Practice in Japan as of August 2010. *Acta Paediatr*, 101(5), e197-202. DOI.

[5] International standards/guidance:

- American Heart Association (AHA) & American Academy of Paediatrics (AAP) http://www.newbornwhocc.org/pdf/NRP2010-Changes.pdf (archived on 8th November 2013)
- Canadian Paediatric Society Hypothermia for newborns with hypoxic ischemic encephalopathy Published: Jan 1 2012: http://www.cps.ca/en/documents/position/hypothermia-for-newborns-with-hypoxic-ischemic-encephalopathy (archived on 8th November 2013)

[6] Neonatal cooling equipment is sold and distributed internationally.

- Within Europe neonatal cooling equipment is distributed by: Eurocare (France), AdQUIPMENT MEDICAL BV (Netherland), Heinen & Lowenstein GmbH & Co.KG (Germany), Medical Market INT. AB (Sweden). In addition the equipment is distributed in Russia (MODUS Closed Joint Stock Company) China (Beijing Oumike Science and Technology Co Ltd) and Chile (Mediplex S.A)

http://www.inspiration-healthcare.com/ukIreland/GetInTouch/DistributerMap.asp (archived on 8th November 2013)

[7] Toolkit For High Quality Neonatal Services (Department of Health)