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DEPARTMENT OF HEALTH RESEARCH

Closing Report on Health Technology Assessment

Cost effectiveness analysis of inducing therapeutic hypothermia using Phase Changing Material (MiraCradle) to reduce mortality and neurodevelopmental morbidity in moderate and severe Hypoxic-Ischaemic Encephalopathy (HIE)

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The Indian Institute of Public Health Shillong
In collaboration with
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Contents

1. Introduction

India contributes to one-fifth of the global live births and more than quarter of neonatal deaths (1). Nearly 0.75 million neonates die every year in India, the highest for any country in the world (2). The current neonatal mortality rate (NMR) for India is 28 deaths per1000 live births (3). The first 28 days of life, 'neonatal period' is the most vulnerable time for the child's survival with the highest risk of dying at an average of 17 deaths per 1000 live births (4) . Globally, infants dying in the first month of life in 2019 was estimated to be 2.4 million. Majority (75%) of the deaths among the neonates occur during the first week of life and one million newborns die within 24 hours of life. The main causes of neonatal deaths are preterm birth, intra-partum related complications-birth asphyxia, infection and birth defects (5).

Perinatal asphyxia is the condition indicating impaired gas exchange resulting in fetal hypoxemia and hypercarbia. Perinatal asphyxia occurs in 0.5% among live born newborns more than 36 week of gestational age and account for 20% of perinatal deaths. It contributes to 20-25% of neonatal deaths (Manual of Neonatal care) (6). Vople defines hypoxaemia as the "diminished amount of oxygen in the blood supply" and cerebral ischaemia as the "diminished amount perfusing the brain" in which the latter is more important of the two forms oxygen deprivation resulting to glucose deprivation (7).

Hypoxicischaemic encephalopathy (HIE) characterized as neonatal encephalopathy (NE) is the acquired syndrome of acute brain injury with evidence of intrapartum hypoxia (Neonatal care clinical guidelines) (6). Neonatal encephalopathy (NE) is the clinical syndrome of abnormal neonatal brain function, a serious and fatal clinical condition. The terminologies neonatal encephalopathy (NE) and hypoxic-ischaemic encephalopathy (HIE) are used synonymously. However, the latter attributes a cause (hypoxia-ischaemia) to the clinical condition (encephalopathy) having measured the cerebral oxygenation and blood flow (8). The term HIE should be used for the subset of cases of NE in which there is good evidence of a recent and usually intrapartum, hypoxic-ischemic cause of encephalopathy (9). \

It is estimated that about 30% of the cases of neonatal encephalopathy (NE) in developed countries and 60% of cases in developing counties are associated with the evidence of intrapartum hypoxia-ischaemia (9). In a study conducted by Futrakul (2006)concluded that inappropriate antenatal care, post- term gestation and vacuum extraction as the main risk factors for HIE (10). O ther factors found to be significantly associated with HIE were meconium stained amniotic fluid, prolonged –

second stage of labor and occurrence of obstetric sentinel events most likely to result in the death of the infants. Nearly a quarter of the HIE cases occur acutely, it is therefore imperative to recognize the intrapartum factors on managing labor (11).

Hypoxic ischemic encephalopathy (HIE) is one of the consequential birth complications affecting the term infants (12). In developed countries, the incidence of HIE is 1.5 per 100 live births while in developing countries the range varies between 2.3-26.5 per 1000 live births (13). By the age of two years, 60% of infants suffering from HIE will die or have severe disabilities such as mental retardation, epilepsy and cerebral palsy (14). Despite the advancing obstetrics care, the incidences of HIE has not declined (15), thus current neonatal research focusses on minimizing the extent of subsequent brain injury (16).

1.1 Rationale of the Study

The action Sustainable Developmental Goals aims to reduce neonatal mortality to 12 per 1000 and under-five mortality to 25 per 1000 by 2030 (17). The major contributors to neonatal mortality is birth asphyxia with prematurity, infections and low birth weight (5). About 2.8 % and 5.6% of all live births had moderate and severe asphyxia, respectively, in a multi-centric hospital based study in India; the case fatality rate was relatively low at ~8.7% (2). Many of these infants sustain brain injury which may develop to long-term sequelae like cerebral palsy, epilepsy and sensory deficits. minimizing the extent of brain injury leading to hypoxic-ischaemic encephalopathy (HIE) globally can significantly contribute to achieving the Sustainable Development Goals on neonatal mortality.

Therapeutic Hypothermia (TH) has proven to be effective in reducing morbidity associated with HIE and is a standard of care in developed countries (18). Long term outcomes related to neurological disability among birth asphyxiated infants and mortality were reported to be effective by inducing therapeutic hypothermia (19). Studies in India have also found therapeutic hypothermia if initiated within 6 hours and maintained for 72 hours after the asphyxial injury, reduce the combined outcome of mortality or major neuro-development disability at 18 months of age (RR 0.75; 95% CI 0.68-0.83) (20) (21). There are multiple methods to induce moderate hypothermia- selective head cooling, head cooling combined with body cooling and body cooling only (20) (22) (23)(20,22,23). Standard equipment like the advanced servo-controlled cooling device is expensive, feasible for developed countries. For low and middle income countries, a

cheaper alternative method with similar effectiveness is required. Studies demonstrating alternative use of cool gel and ice packs on infants for inducing therapeutic hypothermia have shown to be associated with adverse reactions like fluctuations in temperature, episodes of severe hypothermia, bradycardia and subcutaneous fat necrosis (24,25).

The **Mira cradle Neonate cooler** is a phase changing material (PCM) recently developed and used in India. Phase changing material is one of the alternative low cost technology used for cooling asphyxiated neonates. Studies have shown that inducing therapeutic hypothermia using PCM has a neuroprotective effect in newborns with moderate HIE in neonatal units (25–29).

1.2 The Severity of the problem

Globally 2.5 million newborn deaths occur annually contributing to ~47% of the under-5 child mortality (1, 2). Birth asphyxia (BA), assumed to be related to intrapartum hypoxia- ischemia, accounts anywhere from 30 to 35 percent of neonatal deaths (30)

In India, the reported incidence varies from 2 to 16.2% in community-based studies, with the reported case fatality rates ranging from 38.5 to 74%. Catastrophic deprivation of oxygen in the intrapartum period is thought to be directly responsible for 691,000 deaths and 1.02 million stillbirths each year, making it the fifth most common cause of childhood deaths under 5 years. For those infants that do survive, the multi-organ damage that can ensue means the risk of developing severe life-long morbidities is high. Intrapartum asphyxia results in a burden of 42 million disability years (DALYs). To put this figure in context, this is twice the DALYs imposed by diabetes (31)

HIE occurs in about 1 – 2 per 1000 livebirths in developed countries (32) and about 14 per 1000 live births in India(33)

1.3 Novelty of the Study

Mira cradle neonate cooling device is a low cost device that is made- in-India that replicate the working of high end devices used for cooling birth asphyxiated babies (34). Existing studies in the domain of HIE treatment mainly consists of effectiveness of the phase changing material based cooling device. The study aims to the perform cost-effectiveness analysis on Mira cradle device for cooling infants with HIE and the different costs related to the treatment of HIE. Considering that the incidence of birth asphyxia at the community range from 2 %– 16.2 % in the country (2),

an effective low cost phase changing material (PCM) for cooling infants can be an alternative for inducing therapeutic hypothermia in low resources setting.

1.4 Pathophysiology and available treatment of Hypoxic Ischemic Encephalopathy (HIE)

Hypoxic Ischemic Encephalopathy (HIE) is a complex condition resulting from a severe anoxic brain injury during the neonatal period The ultimate repercussion leading to premature mortality or various life-long morbidities comprising of both acute and chronic symptoms (35) (36) . Hypoxic Ischemic Encephalopathy (HIE) is a specific type of Neonatal encephalopathy (NE) and is important to note that not all NE cases are caused due to hypoxia- ischemia (37). The pathophysiology of HIE is well described by two episodes of primary and secondary energy failure based on the cerebral energy state in the newborn infant (16) . The first episode of the primary energy failure occurs during the HI event and is characterized by reductions in cerebral blood flow and oxygenation that can happen during the antepartum, peripartum or postnatal period (35) (37), followed by reduction in ATP and Phosphocreatine accompanied by tissue acidosis (16). Within a period of 6 and 15 hours after the HI insult, followed with a secondary energy failure associated with encephalopathy and increased seizure activity (35). The primary energy failure unlike secondary energy failure is not accompanied by decrease in the phosphocreatine, ATP and tissue acidosis (16), there is also release of excitatory neurotransmitters and free radicals that take place in the secondary energy failure (36).

The latent phase is the interval between primary and secondary energy failure which gives a window period for therapeutic treatment and initiation of treatment during the period of 6 hours has been proved successful in reducing brain damage (16). During the latent phase, biochemical processes such as oxidative metabolism, inflammation and continuation of apoptotic cascades take place (36).

The management of HIE affected infants has been limited to providing supportive intensive care (16) . Mild hypothermia treatment for infants with HIE was first discovered in 1950s and reported to be effective for asphyxiated infants by helping them to attain spontaneous respiration (38). Mild hypothermia can be described as body temperature in the range of (32-35degree Celsius) followed by moderate hypothermia (28-32 degree Celsius) and deep hypothermia (<28 degree Celsius) (37). Mild to moderate hypothermia are generally used and found to be clinically effective because of

its neuroprotective effect accompanied by reduced risks of medical complications, such as infection, arrhythmia, hypokalemia, coagulopathies, and bradycardia (37). Neuroprotection with hypothermia have been effective in the treatment for encephalopathy due to hypoxic ischemia as it effectively obstructs the cascade of events triggered by hypoxia and ischemia. The reduction in the brain temperature of neonates helps maintain the cerebral energy during or immediately after the ischemia followed by decrease in release of the excitatory neurotransmitters, caspace-3 activation and evidence of apoptosis (16). This reduction in temperature decreases the rate of cell death but also have an wide effect in the reduction of cerebral metabolism, storing the adenosine triphosphate, preventing the release of free radicals, survival pathways leading to inhibition of apoptosis and inflammation (37) (38). Therapeutic hypothermia is proven to be the current major treatment modality in the management of HIE with an aim to lower the temperature of the vulnerable deep brain structures (basal ganglia) to 32-34 degree Celsius (37).

The reduction in the temperature of the brain can be achieved by 2 methods- whole body cooling and selective head cooling. Selective head cooling or Cool cap method was discovered in the late 1990s as a possible intervention for brain injury or damage associated with HIE for asphyxiated infants (38). Rationale for performing the selective head cooling is that the newborn infant's brain produces 70% of total heat from the body and that systemic hypothermia may be harmful to the infant (37).

Erythropoietin (EPO), an effective neuro-protectant used in the treatment for HE injury based on the observation of the recombinant EPO (rEPO). (rEPO) administered to infants proved to be effective in terms of tissue protection, revascularization and neonatal injuries in neonatal brain injuries resulting in improved neurobehavioral outcomes (37).

As a result of brain ischemia, excessive release of excitatory amino acids and reduced neuronal inhibition also takes place and by using the anticonvulsant therapy may contribute in the neuroprotection. The major goal of using the pharmacological treatment through antiepileptic drugs is to counteract the abnormal brain excitement either by decreasing excitatory transmission or enhancing neuronal inhibition. The use of anticonvulsants that suppresses the synaptic activity in the brain is found to be associated with apoptotic neurodegeneration when administered during the brain growth (37).

A review by Allen A Kimberly et al (2011) discussed on the pathophysiology and experimental treatment for HIE. The authors brought to the attention that although moderate hypothermia improves neurological outcomes for some infants, a combination of treatments are should be explored to improve infant survival with normal developmental outcomes. The review inferred the need for further research on long term impacts of the experimental treatments and whether combination of treatments can improve the outcomes of infants with HIE (14).

2. Review of Literature:

2.1 Phase Changing Material (PCM):

Phase changing material (PCM) are the salt hydride, fatty acid and esters or paraffin material that can store 5–14 times more heat per unit volume in comparison to water. PCM functions in a way that it absorbs the heat from the baby till it melts. The PCM bed is made by using nylon outer covering, foam mattress and the PCM blocks (39). The baby has to the placed on the bed made of PCM where the heat from the baby gets transferred to the PCM and absorbs the heat. Thus, PCM has the potential to provide a mechanism whereby heat removal is made easier and safer than ice packs. It is important to keep the melting point of the PCM at the target temperature so as to ensure the baby's temperature will not fall below this temperature (24). When the human average temperature of 37^0 C comes in contact with the PCM, the PCM absorbs the body heat, thereby increasing the temperature of PCM. A great deal of additional energy is absorbed from the body in contact with the PCM, which remains at its specific set temperature until the phase change eventually occurs on reaching the PCM melting point. This natural property of PCMs of effectively cooling bodies in contact for extended periods of time acting like a heat sink and stabilizing the temperature of whatever it is in contact with (Tran, 2020) (40).

With the property of PCM to effectively cool down a body in contact can be an alternative, effective and low cost method of cooling babies in low-to-mid income countries (LMIC) and during transport (24) . PCM has an advantage over cool gel packs as there is no need for frequent changes, fewer temperature fluctuations and minimal risk of skin injury. PCM also has a potential to be used during transport even in high income countries where the use of cool gel has been associated with a high incidence of severe hypothermia. Babies with HIE can be cooled effectively using PCM and the target temperature can be achieved. Though PCM is not a servo controlled system, PCM is found to be easier to induce hypothermia (median 60 min), ability to maintain

target temperature (33.45 ± 0.26 ° C) and rewarm the babies in a slow and controlled manner (0.25 ° C/h) using PCM (24).

Frozen gel pack (FGP) and PCM are both effective and safe low-cost methods of cooling in asphyxiated neonates, with an efficacy comparable with the servo controlled equipment for maintaining the target temperature. PCM is found to have an edge in maintaining the target temperature with less nursing input in comparison with FGP (39). The use of phase changing material (PCM) for cooling is increasingly popular in India because of the availability of a relatively inexpensive device that can induce therapeutic hypothermia (18).

2.2 Mira Cradle Neonate Cooler:

MiraCradle-Neonate Cooler is a cradle made of a non-conducting material with phase changing material (PCM) blocks present in the hollowed-out area and a conducting mattress above the PCM blocks where the baby is placed. The PCM blocks stored in the refrigerator (2-8^{o} C) should be solid when used and disinfected with surgical spirit. Mira cradle consists of two types of PCM blocks namely FS-29 (FS, form stable) with melting point of 29^{o} C and FS-21 with melting point of 21^{o} C. During the induction phase, both FS-29 and FS-21 are used to decrease the baby's core temperature to the target range as swiftly as possible. When the temperature reaches 33.8^{o} C, the FS21 are removed and only FS-29 is used for the maintenance phase. The multi-parameter monitor sets the upper and lower alarm limits at 33.8^{o} C and 33.2^{o} C respectively. If the baby's temperature reach ≥33.8^{o} C, the cooling process is continued with the use FS-21 until the temperature come down to 33.5^{o} C. If the temperature reach ≤33.2^{o} C which is the lower alarm limit, steps are thereby taken to increase the core temperature by placing a sheet between the PCM bed and the baby and covering the baby with another sheet or switching on the radiant warmer. The radiant warmer when used in manual mode has an output of 10% and when adjusted, there are increments or decrements of 5% depending on the baby's temperature (24) (26). . PCM is an alternative, effective and low cost method of cooling babies in low middle income countries and during transport. However, as the PCM based cooling device is not a servo-controlled system, a careful monitoring and good nursing care are required especially in the induction and rewarming phases (24) .

Using PCM-based cooling device for inducing therapeutic hypothermia (TH) for neonates with HIE is a feasible and safe method when practiced in level 3 NICUs in India. PCM-based device is comparable to standard servo-controlled equipment in effectively maintaining the target

temperature (26).. Further studies, need to explore the environmental temperature influence on the performance of PCM mattress (40).Thomas N. et al concluded in the multi-centric study conducted across India that inducing therapeutic cooling using PCM based technology should become a standard of care in mild to moderate birth asphyxia cases (26) .

2.3 Hypothermia treatment for neonatal asphyxia using phase changing material (Mira Cradle)

A multi-centric uncontrolled clinical trial was done across 11 centers across India from November 2014 to December 2015 to measure the feasibility and safety measures using MiraCradle Neonate coolers for inducing therapeutic hypothermia among infants with perinatal asphyxia. The study enrolled 103 neonates from JIPMER, Puducherry (25), CMC Vellore (23), JMMC, Thrissur (15), SJMC, Bangalore (n=10), The Cradle, Gurgaon (10), KMC, Manipal (9), SRMC (3), Fernandez Hospital Hyderabad (3), Cloudnine Hospital Gurgaon (2), Neo Clinic Jaipur (2) and Shaiva Critical Care Ahmedabad (1). Infants ≥35 weeks of gestational and ≥1800gm (inborn and outborn babies) were included in the study. The mean (SD) gestational age and birth weight was found to be 38.5 (1.5) and 2925 (458), respectively. Among 103 neonates, three (2.9%) infants had mild, 81 (78.6%) had moderate and 19 (18.4%) infants had severe encephalopathy. The study concluded that using phase changing material (PCM) based cooling device as a standard protocol is a safe and feasible when practiced in level 3 NICUs for inducing therapeutic hypothermia. The study also found some common adverse effects inducing TH using Mira Cradle that were observed among the 103 neonates like shock/ hypotension (18%),coagulopathy (21.4%), sepsis/probable sepsis (20.4%) and thrombocytopenia (10.7%) (26)

Random control trial (RCT) studies carried across India (28) (27) to assess the effect of therapeutic hypothermia using Mira Cradle among neonates with moderate and severe HIE has shown that using phase changing material (PCM) is feasible, safe and can reduce mortality as well as neurological abnormalities.

Caroline Aker et al studied the evaluation of neuroprotective effect of therapeutic hypothermia (TH) induced by PCM among MRI biomarkers in infants diagnosed with HIE at Christian Medical College (CMC) Vellore in collaboration with the Norwegian University of Science and Technology (NTNU). The study included infants with >35 weeks gestational age, birth weight > 1800g with a history of perinatal asphyxia. Infants were either assigned to standard care or standard

care combined with 72 hours of hypothermia. Infants assigned to hypothermia (TH group) were placed on a PCM-based cooling device (MiraCradle Neonate Cooler, Pluss Advanced Technologies, India). The target core temperature was 33.5°C±0.5°C for 72 hours that is followed by controlled rewarming at 0.2°C–0.5°C per hour until the temperature above 36.5°C is achieved. Infants assigned to standard care were placed under radiant warmer with a target core temperature of 37.0°C±0.5°C. Fractional anisotropy (FA) and the diffusion tensor imaging (DTI) for 22 infants (44%, 11 in each group) showed significant higher FA in the cooled than among the non-cooled infants in left posterior limb of the internal capsule (PLIC) and several white matter tracts. After adjusting for gender, birth weight and gestational age, the mean difference in PLIC FA between groups was found to be 0.026 (95% CI 0.004 to 0.048, p=0.023). Conventional MRI conducted among 46 infants, demonstrated significantly less moderate and severe abnormalities in the cooled (n=2, 9%) than in the non-cooled (n=10, 43%) infants. No difference in adverse events between groups were found. This study confirmed that PCM demonstrated to be an alternative, effective and low cost method for inducing therapeutic hypothermia among infants with perinatal asphyxia in low-to-mid income countries. However, as Mira Cradle neonate cooler is not a servo-controlled system, recommendations for careful monitoring and good nursing care are needed especially in the induction and rewarming phases (28).

The RCT conducted in a level III NICU at a tertiary healthcare institute JIPMER situated in south India among term neonates with moderate and severe HIE to assess the effect of therapeutic hypothermia. A total of 162 term babies with moderate and severe encephalopathy according to Sarnat staging with pH ≤7, Apgar score at 10 minutes ≤6, clinical evidence of fetal distress and requiring assisted ventilation after delivery were included in the study. Around 78 infants in the hypothermia group had more normal survivors at discharge (38%) than the 84 infants in the normothermia group (30%), ratio 1.29 (95% confidence interval 0.84–1.99), and at 18 months of age (65% vs. 42%), ratio 1.54 (1.13–2.10). The study found significantly more normal survivors with hypothermia compared to normothermia at discharge, ratio 1.49 (1.18–1.88) and at 6–18 months of age, ratio 1.37 (1.17–1.60). Therapeutic hypothermia was achieved using PCM (MiraCradle Neonate Cooler) (27).

A prospective study conducted among 72 neonates with perinatal asphyxia in level 3 NICU at Bapuji Child Health Institute with the aim to report on the experience with whole body cooling.t The study had different inclusion criteria for inborn and out-born infants. Those inborn infants

with cord pH <7, Apgar score <5 at 5 minutes and need of resuscitation > 10 minutes while for out-born infants who did not cry at birth, presence of seizures, Apgar score <5 at 5 minutes nad Sarnat staging were applied for inclusion. The study reported on short term and long-term neurodevelopment assessment at one year of age on newborn group receiving hypothermia. Short term outcomes were measured in terms of requirement of anticonvulsants, cardiovascular instability, need of mechanical ventilation during stay which was found to be significantly reduced with therapeutic cooling. Long term outcome were measured in terms of neurodevelopment assessment at 1-year age were found to have significant improvement overall in all domains and recommended that inducing TH using Mira cradle for neonate with perinatal asphyxia is a treatment that should be made available in neonatal care centres (29).

A study using retrospective data was conducted by St. John's Medical College to assess the efficacy and safety of TH and a comparative clinical effectives using ice pack (IP) and phase changing material (PCM). Inborn infants with pH<7.0 or Apgar score ≤5.0 at 5 minutes or requiring positive pressure ventilation for 10 minutes at birth; criteria for out-born infants were those who did not cry at immediately at birth or requiring resustation or with an Apgar score <5 at 5 minutes were included in the study. Sixty-two cooled newborns- 29 in the ice pack arm and 33 in the phase changing material (PCM) with moderate to severe HIE were included in the study. The mean (SD) core temperature found during cooling was 33.47°C (0.33) for PCM while 33.44°C (0.34) for IP. The study demonstrated the use of low-cost methods – IP and PCM are equally effective in maintaining the target temperature of 33-34^{o} C for a total of 72 hours. However, adverse reactions like thrombocytopenia and coagulopathy (58% and 41%)and subcutaneous fat necrosis were significantly observed among the neonates intervened with ice packs. Neonates with PCM cooling method also experienced similar adverse reactions but the incidences were lower except for bradycardia. The incidence of bradycardia was found to be 29% with IP and 33% with PCM. The study concluded that the use of PCM (Mira cradle neonate cooler) is less labor intensive than use of ice packs with fewer serious adverse events (25).

Tran T T H et al conducted a study at Vietnam National Children's Hospital to evaluate the use phase changing material (PCM) for therapeutic hypothermia among asphyxiated newborns in a low-resource setting. A total 52 infants ≥36 weeks, Apgar score ≤5 at 10 minutes or infants showing signs of encephalopathy (altered consciousness, abnormal tone, abnormal primitive reflexes) were included. Infants diagnosed with HIE were treated under standard medical care and

cooled on a phase changing mattress with a continuous temperature monitoring. The target rectal temperature was maintained between the range 33.5^{o}C-34.5^{o}C for 72 hours. The author concluded that PCM based mattress can effectively cool infants with HIE and is a low-cost method of cooling infants in low-middle-income countries (40).

3. Aim

To conduct cost effective analysis of therapeutic hypothermia for moderate and severe hypoxic ischemic encephalopathy in newborns to reduce mortality and neurodevelopmental morbidity in asphyxiated neonates using the phase changing material (MiraCradle)

3.1 Policy Question

Is inducing therapeutic hypothermia in neonates that develop moderate to severe hypoxia ischemic encephalopathy with phasing changing material (MiraCradle) cost-effective in reducing mortality and neurodevelopmental morbidity in neonates?

PICO

Population	Inborn Neonates and out born Neonates	HIE will occur within the fist 6 hours of birth, beyond which cooling will be of no benefit to the neonate. Inborn neonates and out-born neonates brought within 6hrs of delivery will be included
Intervention	Therapeutic Hypothermia using phase changing materials	Therapeutic Hypothermia is shown to decrease mortality and improve long term neurodevelopmental outcome in neonates (41)
Comparator	Cooled by other means/ not cooled	Cooling methodology vary from low cost devices like frozen gel pack, water bottles, ice pack to much sophisticated and expensive equipment
Outcome	Mortality and neurodevelopmental morbidity due to HIE, (QALY gained/DALY lost)	Therapeutic hypothermia has been shown to reduce mortality and morbidity (41)

4. Methodology

A model-based estimation of incremental cost and DALYs averted due to Therapeutic hypothermia using phase changing materials in comparison to other forms of cooling will be adopted for the study. Decision tree model will be utilized and translated thereafter to a mathematical model using Excel.

The cost parameters for the model will be obtained through secondary literature review. The effectiveness of phase changing materials and quality of life (QoL) will be estimated from a systematic literature review. The information regarding the epidemiology of HIE and clinical and cost effectiveness of Therapeutic hypothermia in the reduction of neonatal mortality will be drawn out from secondary literature review.

4.1 Systematic review

A systematic review will be done to estimate the clinical and cost effectiveness of therapeutic hypothermia using phase changing material as compared to other forms of cooling.

a) Research Question
    1. Is therapeutic hypothermia amongst moderate and severe HIE with phasing changing materials a cost-effective measure to reduce neonatal mortality and neurodevelopmental morbidity?

P - Studies conducted within and outside India (Neonates who are ≥ 35 weeks and gestational age ≥ 1800 grams with one physiological and neurological criteria. Physiological criteria for Inborn babies (cord blood pH<7 or base deficit>12: 5 minutes APGAR<5; need to resuscitation for >10 minutes) and out-born babies (history of not having cried/breathed immediately after birth: given assistance for breathing soon after birth: 5-minutes APGAR < 5). The neurological criteria include moderate and severe encephalopathy as per modified Sarnat staging or seizures.

I - Therapeutic hypothermia using the phasing changing material in Moderate to severe HIE

C- Therapeutic hypothermia induced by other methods excluding phase changing material in Moderate to severe HIE

O- Difference in the mortality due to HIE/QALY gained/DALY lost to HIE

S- Following type of studies will be included in the systematic review:

1) Clinical effectiveness

   The studies including clinical effectiveness of Therapeutic hypothermia using the phasing changing material versus cooling by other methods intervention among inborn and out-born neonates <6hrs after birth developing moderate to severe HIE due to birth asphyxia will be used for the review. Randomized control trials if available and other hospital/community based studies addressing the issues birth asphyxia and HIE will be included

2) Economic Evaluation study

   The cost-effectiveness or cost-utility studies considering Therapeutic hypothermia using the phasing changing material as an intervention and cooling by other methods as a comparator will be used in the review.

b) Search Method

An electronic search will be done to identify the relevant studies. The studies conducted on humans and those published in English will be considered for the exercise. The following electronic database will be searched using appropriate MeSH terms

1. PubMed
2. Cochrane
3. Web of Science/Scopus
4. Google scholar

c) Selection of Study

The following inclusion and exclusion criteria will be used.

Inclusion Criteria:

1. Studies involving Therapeutic hypothermia in treatment of moderate to severe Hypoxia Ischemic Encephalopathy in clinical setting among inborn and out-born neonates within 6 hrs of birth and subsequent development of symptoms.
2. Randomized control trials on Therapeutic hypothermia conducted among neonates with moderate to severe Hypoxia Ischemic Encephalopathy

Exclusion Criteria:

1. Neonates beyond 6 hrs of birth with signs and symptoms HIE
2. Studies published in languages other than English.

d) Data Extraction

The information collected will be summarized into matrix created on MS-Excel. The matrix will include the author name, year of publication, objectives, population, methodology followed for the outcome and cost, sensitivity analysis method, etc.

4.2 Economic model overview

A decision tree/Markov-analytic/synthesis model will be used to calculate the Incremental cost-effectiveness ratio (ICER) for the intervention and comparator. The ICER will be calculated from the cost and QALY estimated by available secondary review.

5. Presentation in the Technical Appraisal Committee

The research proposal was presented to the Technical Appraisal Committee (TAC) in the 27th TAC meeting held on 22nd March 2022, where the experts evaluated the potential of the project. Following a thorough discussion, the TAC committee recommended the following:

- TAC recommended the research team to refer to – (i) the HELIX Trial, (ii) the NNF Position Paper authored by S. Ramji that recommended this technology for level III and IV NICUs and (iii) WHO Compendium that also included MiraCradle.
- TAC was of the opinion that at this point in time cost effectiveness study may not be conducted due to lack of data. However, a comprehensive systematic review of all studies and trials was suggested to look for more evidence.

6. Conclusion

Based on the recommendations of the 27th TAC meeting, wit was decided by the team to not to pursue the cost effectiveness analysis of Inducing therapeutic hypothermia using Phase Changing Material (MiraCradle) to reduce mortality and neurodevelopmental morbidity in moderate and severe Hypoxic-Ischaemic Encephalopathy (HIE). Rather, a Systematic Review is being conducted as a secondary research which will be completed and submitted to the TAC and the Secretariat soon.

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Annexure 1: Table: Summary of key published evidence

Sl. no	Title of the study	Study Area / Date	Objective of the Study	Authors	Study design	Population	Intervention-Technology	Comparison	Outcome	Conclusi
1	Phase changing Material for Therapeutic Hypothermia in Neonates with Hypoxic Ischemic Encephalopathy - Multi-centric Study	Multicentric study in India (2017)	To assess the feasibility and safety of cooling asphyxiated neonates using phase changing material based device across different neonatal intensive care units in India	Niranjan Thomas et al	Multi-centric uncontrolled clinical trial	* Inborn:≥ 35 weeks gestational age; ≥ 1800 grams. Outborn: A history of not having cried/ breathed immediately after birth, given assistance for breathing soon after birth, 5 minutes APGAR < 5	Inducing therapeutic hypothermia using Mira Cradle neonate cooler	None	The median (IQR) of time to reach target temperature is 90 miutes. The mean (SD) deviation of temperature during cooling phase is 33.5 (0.39 C). Common adverse effects are shock/ hypotension (18%), coagulation (21.4%), sepsis/ probable sepsis (20.4%) and thrombocytopenia (10.7%)	Therapeut hypotherm of neonate with HIE us PCM-based cooling de is feasible safe when practiced i level 3 NIC in India
2	Therapeutic hypothermia for neonatal hypoxic-ischaemic encephalopathy in India (THIN study): A randomised contollde trial	CMC Vellore (2019)	To evaluate the neuroprotective effect of therapeutic hypothermia (TH) induced by phase changing material (PCM) on MRI biomarkers lin infants with hypoxic -ischaeic encephalopathy in low resource setting	Karoline Aker et al	RCT	*Inborn: >35 weeks and birth weight > 1800 g admitted within 5 hours after birth with a history of perinatal asphyxia. Outborn: History of not having cried at birth.	Inducing therapeutic hypothermia using Mira Cradle neonate cooler	Standard care and placed under radiant warmer (37.0°C± 0.5°C). .	The target core temperature was 33.5°C±0.5°C for 72 hours that is followed by controlled rewarming at 0.2°C–0.5°C per hour until the temperature above 36.5°C is achieved. Fractional anisotropy (FA) and the diffusion tensor imaging (DTI) for 22 infants (44%, 11 in each group) showed significant higher FA in the cooled than among the non-cooled infants in left posterior limb of the internal capsule (PLIC) and several white matter tracts. After adjusting for gender, birth weight and gestational age,	The study confirmed that therapeuti hypotherm induced by PCM reduc brain injur which was detected o MRI in infa with moderate admitted i NICU in Ind The study suggested that optim supportive treatment should be focus for future reserach th finding the efficacy of therapeuti hypotherm in low-resource settings

									the mean difference in PLIC FA between groups was found to be 0.026 (95% CI 0.004 to 0.048, p=0.023). Conventional MRI conducted among 46 infants, demonstrated significantly less moderate and severe abnormalities in the cooled (n=2, 9%) than in the non-cooled (n=10, 43%) infants. No difference in adverse events between groups were found	
3	Effects of therapeutic hypothermia on the outcome in term neonates with hypoxic-ischemic encephalopathy - A randomised controlled trial (2020)	JIPMER, Puduch erry (2020)	To assess the effects of therapeutic hypothermia on the outcome inn term neonates with HIE	R.Christin a Catherine, et al	RCT	*Term babies with moderate and severe encephalopathy according to Sarnat staging	Inducing therapeutic hypothermi a using Mira Cradle neonate cooler	Normot hermia	Around 78 infants in the hypothermia group had more normal survivors at discharge (38%) than the 84 infants in the normothermia group (30%), ratio 1.29 (95% confidence interval 0.84–1.99), and at 18 months of age (65% vs. 42%), ratio 1.54 (1.13–2.10). The study found significantly more normal survivors with hypothermia compared to normothermia at discharge, ratio 1.49 (1.18–1.88) and at 6–18 months of age, ratio 1.37 (1.17–1.60)	Therapeut hypotherm reduced mortality a ,neurologi abnormali and result in more normal survivors among ter infants wit HIE

4	Therapeutic hypothermia for moderate and severe hypoxic ischaemic encephalopathy in newborns using low-cost cost devices - Ice-packs (IP) and phase changing material (PCM) (2018)	Bengaluru (2020)	To assess the efficacy and safety of therapeutic hypothermia (TH) and clinico-laboratory profile of neonates who underwent along with IP or PCM	Y N Prashantha et al	Retrospective analytical study	*≥35 weeks and 1.8 kg within 6 hr of life * National Institute of Child Health and Human Development (NICHD) criteria	Inducing therapeutic hypothermia using Mira Cradle neonate cooler	Conventional Ice-packs	The mean (SD) core temperature reported during cooling is 33.47°C (0.33) for PCM and 33.44°C (0.34); Adverse events observed were thrombocytopenia (54.8%), coagulopathy (30.6%), shock (30.6%), skin changes (12.9) and persistent pulmonary hypotension (8.1). Use of PCM is less labour-intensive than that of IP and is associated with fewer serious adverse effects	Low cost devices are safe and effective alternative for maintainin therapeuti hypotherm in low-resource settings wi adequate monitoring
5	Therapeutic hypothermia in asphyxiated neonates, using phase change material (Mira Cradle): Experience from neonatal intensive care unit of tertiary care centre South India (2019)	Karnataka (2019)	The aim of the study is to report our experience with whole body cooling in asphyxiated neonates admitted in level 3 NICU	Devina Sarawat,et al.	Prospective study	*≥36 weeks and ≥ 2.0 kgs (within six hours of age)	Inducing therapeutic hypothermia using Mira Cradle neonate cooler	None	Short term outcome: Average duration of hospitalisation was 12 days; almost all neonaytes tolerated the procedure well; 7 neonates died during the stay. Long-term outcomes: The study were followed up for a period of 12 months and repeated neurological examination revealed that 36 babies had normal neurological examination according to Hammersmith infant neurological examinaition and only 3 had psychomotor dely and 1 baby needed long term anticonvulsant.	The study suppoirt st beneficial effect in newborns with HIE a suggested availability the treatm in all centr invilved in neonatal c

6	Hypothermia treatment for neonatal asphyxia in low-resource settinhg using phase changing material - An easy to use and low-cost method (2020)	Vietnam (2020)	To evaluate whether phase changing material can be used for therapeutic hypothermia of asphyxiated newborns in low-resource setting	Hang T.T Tran et al.	Prospec tive study	≥36 weeks gestational and ≤6 hr after birth with encephalopathy and at least one perinatal factors	Inducing therapeutic hypothermi a using Medical cooling Sweden AB	None	The median time to reach target tempeurature is 2.5 (IQR 2-3); the mean temperature recorded during cooling phase is 33.95 ±0.2^{o}C. The mean temperature range recorded is 33.5-34.5^{o}C is maintained >80% of the time	Phase changing material based mattress c effectively cool infant with HIE a is a low-co method of cooling infants in l middle income countries