THE PERCEIVED BARRIERS TO TIMELY THERAPEUTIC HYPOTHERMIA TREATMENT FOR NEONATES DIAGNOSED WITH HYPOXIC-ISCHAEMIC ENCEPHALOPATHY WHEN BORN OUTSIDE THE COOLING FACILITY WITHIN THE PRIVATE HEALTHCARE SETTING

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Abbreviations

AEA:	Ambulance Emergency Assistant
BA:	Birth Asphyxia
BAA:	Basic Ambulance Assistance
BBB:	Blood-Brain Barrier
BLS:	Basic Life Support
CCRS:	Critical Care Retrieval Service
CNRI:	Continuous Neurological Rollover injury
EEG:	Electroencephalogram
EMC:	Emergency Medical Care
EMS:	Emergency Medical Services
ESSN:	Essential Steps in Managing Obstetric Emergencies
HBB:	Helping Babies Breath
HIC:	High Income Country
HIE:	Hypoxia Ischemic Encephalopathy
ILS:	Intermediate Life Support
IHT:	Inter-hospital transfer
IP:	Ice Pack
KBTH:	Korle Bu University Teaching Hospital
LMIC:	Low-middle Income Country
MDG:	Millennium Developing Goals
PCM:	Phase Changing Material
SEFP:	Secondary Energy Failure Phase
TH:	Therapeutic Hypothermia
TOBY:	Total Body Hypothermia
WHO:	World Health Organization

Contents

Background

Epidemiology of under-five mortality in the world, LMIC (Low-middle Income Country) and South Africa.

One of the Millennial Development Goals (MDG) was to reduce the global mortality rate for children under five. Previously, this goal was known as the fourth MDG but is currently referred to as the third goal under the Sustainable Development Goals (SDG). In essence, the primary aim is to reduce the global mortality rate for the population under five years to less than 25 deaths for every 1000 live births. Furthermore, the objective is to achieve this by no later than 2030 (1, 2).

Unfortunately, 5.2 million global paediatric deaths were recorded in 2019. Most of these patients died from preventable and treatable causes. Of the 5.2 million deaths recorded, 2.4 million deaths were registered under the neonatal patient population (0 to 28 days old). Furthermore, the mortality recorded for patients between 1 and 11 months was 1.5 million. The remaining deaths were recorded in the 1-to 4-year age range (3, 4). The majority (99%) of the neonatal deaths recorded were within the Low-to-Middle-Income Countries (LMIC), especially in South Asia and sub-Saharan Africa (5).

The World Health Organization (WHO) also stated that birth asphyxia (BA), trauma, and congenital abnormalities were some of the leading causes of death. In addition, malaria and diarrhoea were also contributing factors (3, 4). Thus, due to the global combined effort to address these issues, a significant impact on the mortalities was seen in some countries. Globally, there was a 59% reduction in under-five mortality from 1990 to 2019. The number of deaths recorded for the under-five patient population declined from 93/1000 to 38/1000 live births (3, 4).

Despite the progress to reduce global neonatal and paediatric mortality, the poorer countries represent the highest under-five mortalities. For example, sub-Saharan Africa recorded a neonatal mortality rate of 28/1000 live births in 2018 (5). However, there are some concerns that discrepancies may exist between reported mortality rates and actual mortality within the LMIC. This discrepancy may be due to underreporting of neonatal and paediatric deaths (5). South Africa also had a poor

under-five mortality rate between 2000-2008 and was not on track to meet the proposed 2015 Millennial Development Goals. The leading cause for this upward trend during this period was a result of HIV/AIDS (6). The prevalence of HIV/AIDS in the under-five age group declined due to the roll-out of preventative measures to reduce mother-to-child transmission and the availability and accessibility to antiretroviral drugs (6).

Neonatal challenges

Unfortunately, neonatal mortality is still a global health concern and represents a significant portion of under-five mortality. This age group represents 2.4 million of the estimated 5.2 million deaths (4). Factors like maternal age, accessibility to modern healthcare, lower maternal educational levels, nutrient deficiency, and environmental contamination may significantly influence mortality (1).

Rhoda et al. reported that the leading causes of neonatal mortality in South Africa are prematurity complications (47.9%), and 24.3% are intrapartum complications like intrauterine hypoxia. Postpartum infections like pneumonia accounted for 11.6% of neonatal mortality. Neonates with a birth weight of less than 1000g had a premature mortality rate of 60%, primarily due to organ immaturity (7).

Interestingly Rhoda et al. stated that 25.46% of neonatal death could have been avoided. Some of these mortalities are healthcare-system-related, like the lack of neonatal equipment, inadequate neonatal facilities, and inability to detect fetal distress. Accessibility to a bed within a neonatal ICU with a ventilator and monitoring equipment was also mentioned. Staff shortages, referral delays, and transport complications between medical facilities and ambulatory transport from home to hospital were highlighted as potential areas contributing to neonatal mortality (7).

One should also note that traditionally, within the rural areas in sub-Saharan Africa, the older women within the community perform midwife duties, often with no medical training. The lack of basic neonatal training may increase the risk of missing the signs of birthing complications that may lead to BA. Furthermore, ambulatory care is non-

existent in rural Africa, with poor road infrastructure and a lack of readily available transport that may further delay adequate medical care (8).

Considering Rhoda's findings, from an HIE perspective and understanding the neonatal challenges within the South African context, it is not difficult to see that a BA neonate might miss the recommended treatment window. Early advanced medical treatment with trained personnel during labour may reduce the incidence of HIE by providing timely medical care. Early recognition of BA, followed by the early mitigation of airway and circulatory complications, may prevent a catastrophic neurological injury by restoring brain perfusion. Unfortunately, readily available advanced pre-hospital and in-hospital care is primarily available in mature, well-developed healthcare systems (9).

The medical treatment provided in the pre-hospital and rural clinic setting within well-developed healthcare is far removed from the level of care in rural Sub-Saharan Africa, with a doctor-to-patient ratio of 1:50,000 (8). These limitations will adversely affect neonatal patients born in rural areas, especially neonates who suffer BA with an increased risk of developing HIE. Despite South Africa's ambulatory care and primary healthcare infrastructure that is better defined than in other Sub-Saharan countries, there is still unequal distribution of advanced medical resources between rural and metropolitan areas. This adds to the challenges of providing adequate neonatal care to all (10).

South Africa strategised by addressing neonatal mortality related to prematurity and intrapartum events. These strategies are training-orientated to manage antenatal as well as postnatal care. The Helping Babies Breathe (HBB), including the Essential Steps in Managing Obstetric Emergencies (ESSN), are some of the better-known examples. Due to financial constraints, South Africa cannot expand its healthcare workforce rapidly. Still, it may be able to upskill and train the current workforce to deliver better quality of care and redistribute to higher-risk areas (7).

The potential added benefit of well-trained neonatal staff is the better quality of care during the delivery and care advances made during the perinatal period. The upstream approach to maternal health and scheduled clinic visits may identify high-risk

pregnancies. Some strategies to mitigate risks are more readily available scheduled ultrasound visits to monitor fetal development and fetal monitoring equipment at a clinic level. Hypothesising that early identification and recognition of birthing complications may lead to early escalation to higher-tier medical interventions. A prolonged second stage during labour and poor five and ten-minute APGAR score in the presence of a well-trained nurse may lead to early activation for an HIE consultation if BA is suspected.

The downstream treatment for BA, especially for those that developed HIE, is complex, expensive and needs specialised oversight. Often treatment is only available in dedicated facilities within the bigger metropole. The lack of adequate equipment, specialist skills, and logistical issues makes dedicated treatment difficult or even impossible. Therefore, providing appropriately trained staff within the primary healthcare system trained in perinatal care and obstetrics emergencies may reduce the incidence of BA.

Hypoxic-Ischemic Encephalopathy

Hypoxic Ischemic Encephalopathy (HIE) is a neurological injury with potentially debilitating long-term consequences resulting from birth asphyxia. The incidence of HIE ranges from 1-8/1000 live births in high-income countries (HIC) with a well-developed healthcare system compared with LMIC, which may have incidence rates of up to 26/1000 live births (11-13).

Birth asphyxia (BA) is one of the contributing factors to paediatric and neonatal mortality and morbidity. Asphyxia or ischemia, a period of inadequate blood supply to the brain or imperfect oxygenation during delivery or shortly thereafter, is responsible for the severe neurological injury that follows (12). There is a 60% chance that children diagnosed with birth asphyxia, which leads to Hypoxic Ischemic Encephalopathy, might die before age two (11).

A prospective study in India analysed 58 neonates that met the inclusion requirements for birth asphyxia over six months (March 2016 - August 2016). During this period, 540 admissions were recorded. This study had a frequency of birth asphyxia of 10.7%,

consistent with other studies that reported 9% to 13% incident rates. The study acknowledged that birth asphyxia is more significant than in HICs which reported 0.37-0.9% of live deliveries. India also has the highest neonatal mortality globally, with 0.75 million reported deaths (14).

In sub-Saharan countries, 15-20% of asphyxia neonates will die annually within the neonatal period, while a quarter of surviving neonates will have permanent neurological complications (15, 16). Furthermore, an estimated 280,000 neonatal deaths are recorded annually within the first 24-hours of life, all are related to birth asphyxia (16).

A retrospective, descriptive study that was done in South Africa (2011) investigated the incidence and predictors of HIE. The study was conducted over 12 months with a sample size of 21,086 patients. This study found that the incidence of asphyxia was as high as 0.87- 1.52 % for live births recorded. Furthermore, the study concluded that 60% of asphyxia cases developed moderate to severe HIE. The overall mortality rate for HIE patients within this study was 7.8%. The mortality for moderate HIE was 7.1%, and those diagnosed with severe HIE had a mortality rate of 62.5%. This study also concluded that HIE and birth asphyxia are higher than HIC (17).

This study was a retrospective study based on the written data from the patient hospital files. This could potentially lead to an overestimation of HIE cases that may have skewed the study data. Reasons for potential overestimation were the inexperience of the person conducting the examination and completing the documentation, like mislabelling birth asphyxia as HIE by junior doctors. However, the study highlighted the burden of asphyxia and encephalopathy within South African public healthcare (17).

Progressive stages of HIE

HIE is a complex injury and should not be viewed as a single lone-standing event that follows shortly after birth asphyxia. Instead, HIE is more of a cascade of events at a molecular level, put in motion by a specific incident (18). Therefore, this evolving injury is better described as a continuous neurological rollover injury (CNRI) that could span

over 3-4 days (19). If left untreated, the severity of the injury can increase in the following hours, with potentially irreversible debilitating damage like cerebral palsy and seizures (20).

The long-term outcome of an HIE case that followed a hypoxic event is that approximately 26.4% of infants have survived with moderate to severe neurological impairment, with a further 14% that have reported mild impairments in the era before Therapeutic Hypothermia (TH) treatment (21).

Initial or Primary injury phase

The hypoxic or ischemic event sets in motion a cascade of events that is divided into distinct phases (12). The first phase, the acute phase or primary energy failure, encompasses the initial neurological insult caused by reduced serum oxygen and glucose. The immediate response to the primary energy failure is an uncontrolled release of excitatory neurotransmitters within the brain, responsible for neuronal cell damage (12).

The neuronal cell damages occur at cytoplasmic and mitochondrion levels. Furthermore, the blood-brain barrier (BBB) becomes compromised, including the activation of an inflammatory response. As a result of normal oxidative metabolism failure, increased anaerobic activities occur. Furthermore, there is a reduction in adenosine triphosphate observed (12, 22).

Due to the anaerobic metabolism, lactic acid formation increases. As a result of reducing adenosine triphosphate, the cell wall fails to prevent the influx of sodium and calcium into the cell. Water will follow the sodium leading to increased intracellular pressures causing failure of the cell wall integrity (12). Following the initial insult, there might be some neurological recovery, depending on the timing of the injury and the initiation of medical treatment. This partial recovery is observed between 30-60 minutes from the time of injury (12).

Latent Phase

After 60 minutes from the initial insult is the start of the latent phase. The latent phase is theoretically 1-6 hours after the injury (12). This phase also marks the ideal window period for therapeutic hypothermia. Therapeutic hypothermia treatment should begin before the secondary energy failure phase (SEFP) (18, 20, 23, 24). This SEFP is the theoretical period between 6-15 hours after the initial injury (12, 22).

The depth of injury increases during the latent phase as the activated apoptotic cascade continues, even though cerebral oxygenation and circulation are restored. (12, 22). The early onset of seizures following the neurologic injury might indicate the severity of HIE as seizures are more typical of the SEFP (12).

The secondary energy failure

The theoretical start of the secondary energy failure is 6 hours after the initial injury and end about 15 hours after birth (12, 22). For best neurological preservation and therapeutic outcome, cooling should have been initiated by now.

It is important to note that the intensity and duration of the initial injury are proportional to the severity and outcome (25). Therefore, following an intense neurological insult in severe cases may have a shorter transition time between the latent and SEFP, leading to a shorter therapeutic window for optimal treatment than in mild HIE cases (11, 25).

This implies that for severe HIE cases, the onset of the secondary energy failure might occur before the theoretical 6 hours, which significantly reduces the optimal treatment window of HIE. It is important to note that the therapeutic window of 6 hours must not be viewed as a sudden cut-off time limit that shuts down with guillotine-like precision. For mild HIE, this window may potentially be extended to a timeframe beyond the 6-hour limit with a favourable outcome (25, 26).

As mentioned previously, seizures are more common within the SEFP as more excitotoxins are released. In addition, inflammatory responses and oxidative stresses continue to add further depth to the injury. Finally, an almost complete mitochondrial failure characterises the SEFP leading to cellular death. At this stage, the neonate will

show clinical deterioration in those with moderate to severe neurological injuries (12, 22).

Tertiary phase

Theoretically, the 15 hours following the initial hypoxic and Ischemic injury marks the transition from the SEFP to the tertiary phase. The tertiary phase is characterised by late cellular death, brain remodelling, and astrogliosis. The tertiary phase can continue for months after the initial injury (12, 22).

Before implementing TH, 10-13% of the surviving patients had cerebral palsy, although these numbers varied in mild to moderate cases. If seizures were reported, the risk would further increase threefold. Other complications include dyskinetic cerebral palsy, and spastic quadriplegia are the most common subtype, representing 80% of perinatal-ischemic patients. Sensory disruption was also noted in patients following a hypoxic event at birth. Hearing loss was reported in 17.1% of neonates with persistent neuro-deficits. Visual dysfunctions were also reported in 41% of patients within the first year of life (21).

However, TH show an improvement in the outcome in patients with moderate to severe HIE. The increased likelihood of survival with an average reported IQ (RR=1.31) and survival without neurological abnormalities (RR=1.6) at 6-7 years of age (21).

Literature review

Literature review objectives

The literature review aimed to find and evaluate the latest evidence regarding neonatal HIE and perceived barriers to timely treatment, documented in peer-reviewed and respectful medical journals. Because the barriers to care are multifactorial and not defined by a single event, a literature search included different fields within Emergency Medical Care (EMC) and in-hospital treatment.

The literature review aims to:

A. Describe therapeutic hypothermia treatment for HIE.

B. Describe pre-cooling of birth asphyxiated neonates and TH and transport.

C. Describe the barriers to timely interhospital transfer

Search strategy

The literature search was done using PubMed. All non-human studies and studies irrelevant to birth asphyxia (BA) and HIE and treatment were excluded. The process of elimination was conducted by reading the study titles. Articles that could potentially be relevant were evaluated by reading the study's abstract and objectives. The articles that provided background information, including articles directly related to HIE and associated barriers to care, were selected.

Keywords included in the literature search are Neonatal, birth asphyxia, Hypoxic Ischemic Encephalopathy, transport, Low- and Middle-income Countries, Under-five mortality Literature was selected based on the date of first publication.

- **Search one**
  "Neonatal" AND "mortality" AND "global" AND "asphyxia" AND under five
- **Search two**
  “Birth asphyxia” AND “therapeutic hypothermia”
- **Search three**
  "Hypoxic-ischemic encephalopathy" AND "cooling" AND "low-middle income countries"
- **Search four**
  "Hypoxic-ischemic encephalopathy" AND "Africa."
- **Search five**
  "Birth asphyxia" AND "transport"
- **Search six**
  "Hypoxic-ischemic encephalopathy" AND "transport"
- **Search seven** "Therapeutic hypothermia" AND "outborn vs inborn patients.

Therapeutic Hypothermia Trials

Before Therapeutic Hypothermia (TH) became the standard treatment for HIE, supported by ongoing research, HIE neonates were treated with supportive management (27). Therapeutic hypothermia is preferably done within a designated cooling facility capable of dealing with the neurologic injury and the potential complications associated with induced hypothermia. (27).

The Total Body Hypothermia trial (TOBY) was a multicentre, prospective, randomised controlled trial. The TOBY trial hypothesised that whole-body cooling for patients with neonatal asphyxial encephalopathy would reduce mortality and neurodevelopmental disabilities. (28). The TOBY trial randomly allocated neonates in ICU with asphyxial encephalopathy to cooling and non-cooling groups. The control group was not subjected to cooling, and 37 +/- 0.2°C temperatures were strictly maintained. The treatment group was subjected to temperatures of 33-34 degrees centigrade for the entire treatment duration of 72 hours. Rectal temperature monitoring was used in both the control and treatment groups (28).

The TOBY study enrolled 325 term neonates diagnosed with asphyxia encephalopathy. The primary outcome focused on survival frequency and IQ score of 85 or above in patients now between 6-7 years of age. In the treatment arm, 52% (75/145) survived with IQ above 85 compared to the 39% (52/139) in the control arm (Relative risk 1.31; P=0.04) (29).

Mortality was almost identical between the treatment group 29% (47/163) and the control 30% (49/162). The study reported that 90% (86/96) of mortalities were documented before the 18 months follow-up assessment. The study also showed that the treatment group reported fewer neurological abnormalities, 45% (65/145) compared to the control of 28% (37/132) (Relative risk 1.60; 95% CI 1.15 to 2.22). Furthermore, the study concluded a significant reduction in cerebral palsy in the treatment arm compared to the control (21% vs 36%, P=003), with a reported risk reduction of moderate and severe disability of 22% vs 37% (29).

In the 6-year follow-up, the TOBY study concluded that TH had outcomes favouring the treatment group. However, no significant differences could be found for many secondary outcomes. Some of the pre-set tests used in the study to assess IQ as the primary outcome were determined by the assessor's evaluation of whether or not the child maintained adequate performance during the IQ test due to physical impairment. The study also mentioned that 30% of the children did not complete the psychometric tests. Although the study hypothesised that TH could reduce mortality, no significant differences were seen at the 6-year follow-up (29).

In another randomised controlled trial conducted by Gluckman and Wyatt, neonates diagnosed with an asphyxia injury were randomly assigned to either the control group or treatment group. This study had a sample of 234 neonates ($\geq$36 weeks gestation). Those neonates that were randomly selected for cooling received TH within 6-hours for the total duration of treatment (72-hours) (30).

This study differs from the TOBY trial in two ways. Head cooling was used in this trial vs whole-body cooling used in the TOBY study. The target temperature for this study was 34-35°C range compared to the TOBY, which targeted treatment at 33-34°C. This study also utilised rectal core temperature measurements. A total of 112 neonates were assigned for cooling and 118 to the control arm. Both groups had eight patients lost to follow-up at 18 months (30).

The primary outcome of this study was mortality or severe disability recorded at 18 months following TH treatment with the intention to treat. This study concluded that the treatment arm had a more favourable outcome than the control group (odds ratio 0.47; 95% CI 0.26-0.87 and p=0.021; NNT 6 (95% CI 3-27)). However, the study found no difference in outcome in the most severe cases (n=46) (OR 1.8, 95% CI 0.49-6.4, p=0.51). (30).

The authors speculate that some factors could have contributed to the ineffectiveness of cooling in this study. The treatment group had more neonates with severe injury based on electroencephalogram (EEG) tracings and APGAR scores than the control group. Although cases were randomly selected, the authors said the incidence was

likely due to a change effect of randomisation. The authors further suggested that the timing of treatment could have played a role as only 12% of the treatment group were cooled before 4-hours after birth. The authors further hypothesised that the severity could have led to shorter time intervals from "time of injury" to secondary deterioration in some individual cases. (30).

The authors concluded that head cooling could be an effective treatment option for mild to moderate encephalopathic neonates due to birth asphyxia. Those neonates that received TH showed a reduction in severe neuromotor disability of 50% (30). Although the authors indicated a difference in the severity profile between the treatment group and control, the study did see a benefit in the treatment group. All the enrolled cases for both studies were born at the cooling facility and received cooling within the 6-hour window.

A 2013 Cochrane study investigated the long-term neurodevelopment and mortality of TH of neonates that suffered birth asphyxia. This study only investigated randomised controlled and quasi-randomised studies. This study focused on studies that investigated TH treatment compared to standard care treatment in encephalopathic or later pre-term neonates. The study concluded that TH resulted in a clinically meaningful and statistically significant reduction in mortality or neurodevelopmental outcome at 18 months of age. (RR 0.75 (95% CI 0.68 to 0.83); RD -0.15, 95% CI -0.20 to -0.10), NNT 7 (95% CI 5 to 10)). This result encompasses eight studies that looked at a combined total of 1344 infants (31).

This study also found a statistically significant mortality reduction in 11 other studies that looked at 1468 infants (RR 0.75 (CI 95% -0.13 to -0.04); NNT 11 (95% CI 8-25)); for neurodevelopmental disability reduction in eight studies with a total of 917 patients)RR 0.77 (95% CI 0.63 to 0.94), RD -0.13 (95% CI -0.19 to -0.07); NNTB 8 (95% CI 5 to 14)) (31).

Some critics acknowledge that TH in HIE is a revolutionary treatment option but feel that more effective therapeutic interventions should be investigated. TH, combined with other therapies like xenon, magnesium and erythropoietin, could yield better

results. They argue that clinical trials showed a 40% mortality and morbidity in patients who received only cooling as treatment (32).

Therapeutic hypothermia in low and middle-income countries

TH treatment is implemented as standard practice within HICs with promising outcomes and a good safety profile. In LMICs, the safety of TH should be further investigated as it is challenging to compare TH treatment results of those of High-income countries. The differences in available resources in HICs compared to LMICs will make comparison difficult. Furthermore, the patient co-morbidity profiles between HICs and LMICs are different. LMICs have a higher incidence of foetal growth restriction compared to HIC peers. The incidence of meconium aspiration is higher, as well as that of perinatal sepsis. Neonatal sepsis and other congenital conditions might compromise the TH treatment safety profile and compromise the overall neuroprotective effect (33).

Furthermore, TH in the HICs is primarily done within a designated cooling facility with high care. These neonatal care units provide optimal care with multidisciplinary input and high nurse-to-patient ratios. This contrasts with neonatal care within LMICs that cannot provide one-on-one care, nor do they have access to the same equipment availability. HICs use servo-controlled devices that are too expensive for LMICs (33). This could be problematic as TH requires strict temperature regulation within a small temperature range for 72 hours. Any temperature deviations below the target could increase adverse effects, as temperatures above the therapeutic range could lead to a poor therapeutic impact (33).

TH gained some momentum in the LMICs as more resource-scarce facilities utilise cooling as part of their HIE treatment. Often these neonatal units use local solutions to achieve and maintain TH. Air conditioning, phase-changing material (PCM) or even ice packs (IP) are used to reduce the core temperatures manually. The effectiveness of these adjuncts is questionable and potentially more labour-intensive than a computerised cooling unit. Manually removing or adding adjuncts could lead to fluctuations in and out of the treatment range, reducing the treatment effectiveness (33).

In a retrospective study, Prashantha et al. investigated the efficacy and safety of TH using IP or PCM. This study used two different types of PCM as adjuncts to facilitate cooling. PCM was described as a substance with a set melting point of 21 or 29°C, depending on the type selected. PCM is composed of salt hydrate, fatty acids and esters that changes from a solid into a liquid when exposed to a heat source like body heat. The PCM absorbs the energy, drawing heat away from the patient, resulting in a drop in core body temperature (34)

TH was initiated in this study by placing the selected material, either IP or PCM, on the patient's head, abdomen, and back as the patient is turned lateral. The IP and PCM were covered with cloth to mitigate thermal injuries (34). Continuously, rectal temperature monitoring was used in this study with vital monitoring intervals of 15 minutes. A targe temperature was set at 33. 5°C that was maintained by adding or removing either the IP or PCM. Removing the cooling adjunct was indicated if the temperature was at 33.2°C, and more adjuncts were added when a temperature of 35.8°C was recorded. Treatment duration was kept at the standard 72-hours (34).

In this study, 62 patients were assigned to either IP or PCM cooling (IP 29, PCM 33), with a total of 49 patients successfully cooled and discharged. Interestingly, there was a significant difference in the number of discharged patients from the PCM group compared to the IP group (90.9% vs 65.5%, p=0.03).

The number of patients discharged against medical advice was 17.7%, and the recorded overall mortality was 3.2%. There was also a noticeable difference in cases where TH was prematurely ended due to complications. In the PCM group, only 6.2% of patients in the PCM group vs 17% in the IP group had TH terminated due to disseminated intravascular coagulation (34).

In this study, PCM was superior over IP by reaching the target temperature in 30 minutes (IQR 20-40) compared to the IP group with 35min (IQR 25-45). Furthermore, the PCM with a set melting point of 21°C was less labour intensive compared to IP (5.2 (1.5) vs 8.1 (4.1) changes per day (34).

Despite the IP and PCM differences, the study found that both techniques effectively initiate and maintain target temperatures for the entire treatment duration. The study also indicated that PCM is perhaps the better option in LMIC due to the reduced labour intensity and fast target body temperature reduction.

Oliveira et al. investigated the Feasibility of whole-body cooling in India using low-cost servo-controlled units for birth asphyxia neonatal patients. This study enrolled 82 patients that met the inclusion criteria. These patients were classified as moderate (74% (61/82)) and severe (26% (21/82)) encephalopathy. This study concluded that using these low-cost devices is feasible and could reduce the labour intensity of individual cases. Furthermore, fewer temperature fluctuations occurred, making this alternative to manual cooling control more attractive. The downside is that the estimated cost of such a cooling unit is roughly US$1000 but is still a tenth of the price of a top-end modal used in HIC (33).

Despite the availability of this low-cost cooling technology for TH and comprehensive monitoring, the cost may be beyond the reach of many facilities within the LMIC. Sub-Saharan Africa, like India, has a high number of neonatal deaths related to birth asphyxia (35).

Ghana, for example, is a Sub-Saharan country with an estimated 800 000 births per annum. Almost a third of neonatal deaths are related to intrapartum hypoxic events. Furthermore, birth asphyxia is the major cause of Ghana's disability in surviving children (35).

A prospective observational cohort study conducted at a neonatal unit at the Korle Bu University Teaching Hospital (KBTH) in Ghana found that 30% of the 966 neonates admitted were related to birth asphyxia over six months. The study also reported that 22% of birth asphyxia neonates referred for further care to TBTH died. The study also stated that 80% of neonatal deaths of inborn neonates are associated with intrapartum-related events (35).

This study described the outcomes of the passive cooling of neonates to a TH target of 33-34°C for 72 hours over a study period of one month. Passive cooling refers to a

cooling method where all external heat sources are removed to facilitate heat loss. Active cooling uses external mechanisms to actively cool the neonate to the target temperature using whole-body cooling like in the TOBY trial or head cooling like the ICE-cap trial (29, 30).

In this study, patients who recorded temperatures outside this range were either referred to as hypothermic (< 33°C) or above the therapeutic range (>34°C). Rectal temperatures were electronically measured and stored continuously at 1-minute intervals. Commencement of temperature data ranges was from 1.2-26-hours (median 5-hours IQR 3-12- hours) after birth(35).

The study found that during the 72-Hour observation period, a mean time of 18 min (14% of the time) (range 0-44min) was within the TH range. The time spent below 33°C was 11 minutes (18% of the time), and for temperatures above 34°C, 71 min (22%). In 54% (7 patients) were hypothermic, one patient recorded a reading below 32°C, four were between 32.1 -32.5°C and one patient between 32.5°C and 33°C (35). The study's protocol indicated that if a patient's core temperature dropped below 33°C despite adding blankets, the patient must be placed in an incubator. This resulted in one patient that had needed the use of an incubator to prevent extreme hypothermia (35).

The short-term outcome of this study, measured on day four of life, showed that four patients (30%) had persisting moderate encephalopathy. Two patients were indicated as severe with one mortality. In six patients (46%), the outcome improved as measured against the Thomson score. The study also documented mortality of 23% before discharge, two patients in the severe group and one from the moderate group (35).

The neonates in this study had continuous core temperature management. However, this specific neonatal unit used for this study did not have the resources to do routine core temperature readings before the trial. The neonates enrolled in the study were kept separately, which could have led to a treatment bias. Although this study enrolled only 13 cooled patients, the study indicated that passive cooling effectively lowers temperatures to TH ranges. The recommendations that came from this study advised

that temperature monitoring is essential if TH is to be considered a treatment option in an LMIC setting (35).

A systematic review and meta-analysis by Rossouw et al. looked at the efficacy of low-technology TH methods within an intensive care setting in LMICs in reducing mortality. The data indicated that cooling with low technology adjuncts is safe and effective in the setting with access to mechanical ventilation with intensive monitoring capabilities (36).

Rossouw concluded that neonates who were cooled showed a reduction in mortality before discharge from hospital compared to standard treatment [RR 0.60 (95% CI 0.39, 0.92), RD – 0.08 (95% CI 0.14, 0.02), NNTB 13 (95% CI 6.9, 81.7)]. Furthermore, two other studies concluded a reduction in mortality of children between ages of 6-24 months [RR 0.63 (95% CI 0.43, 0.93), RD 0.10 (95% CI 0.19, 0.02), NNTB 10 (95% CI 5.2, 63.3)] (36). This study also showed a remarkable reduction in neurological morbidity at the time of hospital discharge in those patients that were treated with low technology devices compared with standard treatment [RR 0.49 (95% CI 0.033, 0.63), RD 0.24 (95% CI 0.33, 0.15) and NNT 4 (95%CI 2.9, 6.3) (36).

A more recent retrospective cohort study by Shipley et al. (2022) compared the outcome of BA neonates born at a facility providing TH to those who needed transport to such a specialised unit. This study looked at a total of 5059 neonates, of which nearly half (46.7%) were outborn and needed transport. Interestingly the study found that inborn neonates had an advantage with increased survival without seizures (35.1% vs 31.8%; OR 1.15, 95% CI 1.02 to 1.31; p=0.02) compared to outborn peers. The study further noted a reduction in seizures of (60.7% vs 64.6%; OR 0.84, 95% CI 0.75 to 0.95, p=0.007). The study further noted that the two groups' mortality rate was almost similar (15.8% vs 14.4%; OR 1.11, 95% CI 0.93 to 1.31, p=0.20) (37).

It is important to note that the study found that 67.1% of neonates arrived at the receiving facility with optimal therapeutic temperature, although only 12.7% arrived so within the 6-hour window period (37). The reduced time from incident to cooling in the inborn patient could have contributed to the advantages in survival without seizures compared to the outborn.

Looking at the data mentioned above, it seems that cooling effectively reduces mortality and morbidity in the birth asphyxiated neonates, regardless of the preferred method. The literature leans more towards the strict maintenance of TH ranges for better results. Careful monitoring of core temperatures will reduce dangerously low temperatures and fluctuations that may reduce the therapeutic effect.

Transport and cooling.

Not all neonates that suffer BA are born at the dedicated cooling facility and therefore requires transportation to such a facility. The birth asphyxiated neonatal patient that is born at a referring unit could potentially face three outcomes. One of the options is to transport the patient to a cooling facility to initiate TH on arrival; the second option is to initiate passive cooling on the arrival of the neonatal transport team; the third option is to initiate passive cooling at the referral unit as soon as possible under the guidance of a neonatologist.

A few studies investigated the safety and outcome of active and passive TH during the transport phase. In a historic control group cohort, Szakmar et al. evaluated the safety and feasibility of active cooling during transport compared to standard intensive care transport. This study, led by the Semmelweis University in Budapest, looked at 214 term neonates diagnosed with moderate to severe HIE. The historic control group consisted of 78 newborns and was compared to 136 newborns that received cooling. The outcome measurements for this study were the time of initiation cooling, including the temperature profile and recorded vital signs (38).

The findings were that the cooling was started in the cooled group on average 2.58 hours earlier than compared to the control group (median 1.42 [IQR 0.83-2.07) vs the control, 4.0 [IQR 2.08-5.79]; p <0.0001). The cooling group also reached the target temperature 1.83 hours earlier than the control group (median 2.42 [1.58–3.63] vs 4.25 [2.42–6.08] respectively; p < 0.0001) (38).

The study also reported that 58% of the patients in the cooled group arrived at the cooling facility within the target range of 33-34°C (79/136). Furthermore, 11.8%

(16/136) were overcooled to temperatures below 33°C. The APGAR scores, pH and mortality indicated more towards severe HIE cases in the overcooled neonates. This observation leads to the suggestion that temperature control in the most severe HIE cases might be more difficult in this subgroup (48%; 7/16) (38). The overall conclusion of this study is that TH during transport is feasible and would shorten the time from injury to treatment that is well within the 6-hour treatment window.

This study used retrospective data subjected to the accuracy of data capturing during transport. However, the same transport team was used for all the transfers. This could have potentially reduced the risks of inconsistencies during transfers data charging. The authors acknowledge that neonates with less severe HIE also received cooling, leading to a better outcome profile favouring TH during transport.

A retrospective study by Leben et al. evaluated the quality of passive cooling of birth asphyxiated newborns and looked at data collected over ten years. The study found that only 15% of the transported patients were in the therapeutic target temperature range of 33-34°C on the arrival of the transport team at the referring facility. Whereby 52% were in the set target range on arrival at the cooling centre, indicating that many patients were adequately cooled during the transport phase (39).

This study also found that the excessively cooled patients before transport stayed excessively cold during the transport phase. This implies that those extremely cold neonates arrived at the cooling facility below the minimum temperature of 33°C degrees centigrade. The study found that 22.8% of the neonates had temperatures below the target range.

The study further found that 33.3% (13/39) of the patients that were not adequately cooled arrived at the cooling facility above the treatment temperature target. The study also identified three incidents where the patient's temperature was above the target temperature before departure that recorded an increase in temperature during transport (39).

This study also indicated that longer transport times resulted in a reduction in body temperature. This observation was more prominent in patients within or near the target

range. This study recommended that both the referral and the transport team attain patient temperatures in or as close as possible to the target range (39).

Potential Barriers to early transport

Birth asphyxia neonates born at a cooling facility might be more privileged to receive timely cooling treatment within six hours than outborn peers. Despite all the efforts to minimise the delay between the initial hypoxic injury and the onset of TH by implementing pre-transport cooling and maintaining TH during transport, the outborn still faces challenges. Furthermore, one can speculate that a referral facility that seldom deals with birth asphyxia might not recognise subtle signs and symptoms or risk predictors. This delayed recognition may lead to a late neonatal specialist consultation and activation of the transport team.

The delay in timely treatment could be multifactorial for the outborn and encompass different roleplayers' input. These roleplayers include the referral and receiving facilities, transport company, transport team, and medical aid. Poor communication between these roleplayers and the limited availability of ICU beds might adversely affect early cooling.

Even though a large pool of literature that focuses on BA and HIE exists, including treatment and transport recommendations, literature regarding barriers to care, specifically in HIE, is scarce. However, some literature describes the barriers and difficulties associated with general neonatal and paediatric inter-hospital transfers and transfers.

A South African study by Ashokcoomar and Naidoo investigated paediatric and neonatal transfer delays with associated adverse events and highlighted several issues. This study looked at a total of 120 neonatal transfers over 43 days, calculated to an average of 2.79 transfers per day. Ashokcoomar and Naidoo conducted their study within the public healthcare sector, including government ambulance services. The authors emphasised that this transfer total is higher than the average transfer frequencies recorded in Europe, with neonatal transfer rates between 0.482 and 0.487

per day. The authors speculated that the higher transfer rates seen in the study are potentially due to the lack of specialised local neonatal care facilities (40).

This study identified some barriers that could lead to delays in dispatching ambulances. The problems identified were ambulance non-availability in 47.3% of the cases and equipment shortage in 15.5%. The study further noted that 4.7% of delays were due to a lack of ambulance support staff, including paramedic non-availability, responsible for 32% of delayed calls (40). The study noted that only 60% of the delayed calls, due to paramedic non-availability, actually required a paramedic (40). This gives the impression that other ambulance personnel could have serviced 40% of those calls earlier, provided they are equipped to do so. The study recommended that improved information gathered by the ambulance control centres could mitigate these delays in future neonatal transfers. The study stated that these centres are mainly staffed by Basic Ambulance Assistants (BAA) or Ambulance Emergency Assistants (AEA). The terminology BAA and AEA are also internationally referred to as Basic Life Support (BLS) and Intermediate Life Support (ILS).

Ashokcoomar and Naidoo also reported that the average time of an ambulance to complete a transfer was three hours and 49 minutes (range 55 min to 10 hours and 34 min) (40). By deductive reasoning, ambulance availability seems to be directly related to the total mission time of a neonatal transfer, coupled with the neonatal transfer frequency and staff availability.

Although this study was conducted within the public healthcare sector in the eThekwini District (Durban) of the KwaZulu-Natal Province, South Africa, there is a high probability that the issues highlighted by this study would correlate with other geographical areas within public healthcare. One must also understand that South Africa currently has a dual-healthcare system that is divided between public and private healthcare. Private healthcare differs from public healthcare and is funded mainly by medical aid, paid by the private paying patient. The private-healthcare sector may vary significantly from the public sector as the latter experience different challenges. No literature was found during the research period that addressed these

issues within the private healthcare system, specifically in birth asphyxia and transportation delays

Another South African qualitative study by Vincent-Lambert and Wade looked at the challenges of inter-facility transport in high acuity pediatric cases. In their study, four main themes emerged: Time delays, low education levels and BAA training, communication breakdown between role players and lack of equipment (41).

This study provides a deeper insight into the complexity of inter-hospital transfers by the combined perspective of both the receiving and referring facilities, including management from the EMS. The contributing factor for the delays was that a transfer needed multiple levels of approval before authorisation was granted. The authorisation process could take up to several hours, even for gravely ill patients and include processes like motivation for transport documentation, approval from the referring hospital CEO and transfer office. Only when all the roleplayers approve the transfer can the patient be transferred to an appropriate facility (41).

Furthermore, the lack of transport vehicle availability added to the delay of transfers, which Ashokcoomar and Naidoo also highlighted in their study as a barrier to care. Further insight from an EMS perspective is that there were only four intensive care transfer vehicles to do the complicated cases at the time of the study (41). The small number of dedicated intensive care vehicles could contribute to a delay in transport in some cases.

Like Ashokcoomar and Naidoo, Vincent-Lambert and Wade also reported equipment shortages and undertrained EMS staff arriving to facilitate patient transport in the public health sector (41). The equipment restraints and case complexity can lead to delays as additional time is lost waiting for trained staff and equipment to arrive. In BA and HIE cases, these types of delays will undermine timely treatment and may have a negative impact on treatment outcomes.

Vincent-Lambert and Wade further reported that communication between all the roleplayers is ineffective and attributed to unnecessary delays. Ashokcoomar and

Naidoo also highlighted communication breakdown as a barrier to care that adversely affects transport to an appropriate facility (40).

Some international studies also highlighted the importance of appropriate communications during the planning and arrangement of the transport of critically ill patients. A prospective observational case series study to describe the process of interhospital transfers from the emergency department of West Gippsland Hospital in Australia noted that the number of phone calls to arrange a transfer was 4.7 (95% CI 3.96-5.43). The study further indicated a need to contact several hospitals multiple times, with an accumulative time-delay effect.

The average time spent by patients in the ED was calculated at 307 min (95% CI 32.9-372.6 min) with the time of acceptance for transfer 56.7 min (95% CI 19.1-94.8). The term "time to acceptance" refers to the period from first contact with the receiving facility to verbal confirmation by the receiving facility accepting to continue further care on arrival (42). Idealistically, a transfer should be initiated by a single phone call, followed by the timely arrival of the dedicated transfer team (42).

Furthermore, the study noted inequities in specific subgroups of patients. The study showed that younger patients require fewer telephonic calls than the elderly. The authors indicated that the small sample size might have led to underestimating the outcome measures associated with these findings. Although this study is older (2005), it seems that the availability of beds and communication difficulties are echoing themes, despite the advances made in modern communication.

A later prospective observational study (2014) by Gillman et al. that looked at IHTs over 14 days also noted an increased frequency in communication to arrange transfers. This study documented that transfers communication can take 1-11 calls to a range (median 2) with an increased frequency for urgent transfers (median 4, IQR 3.5-9.4, n=69) and less urgent calls (median 3, IQR 2-4, n=160, P=0.04). In 23.5% of the observed cases, four or more calls were required to arrange a transfer (N=54), in which 20 (9%) involved critically ill patients (43).

Gillman also documented a median acceptance time for both urgent and non-urgent calls and found similar outcomes for urgent calls (10 min IQR 4-24, n=69) and non-urgent cases also 10 minutes (IQR 5-23, P=0.48, n=155). Post-hoc analysis of IHT that took more than 60 min showed that non-urgent transfers took 120 minutes (IQR 79-157; P=0.07) compared with urgent IHTs that took longer at 155 minutes (IQR 132-213) (43). No specifics were provided for this finding. However, a reasonable explanation is that more complex transfers might require more communications and transport arrangements. Case urgency might also positively correlate with case severity with specific equipment and intensive care needs. The receiving hospital might only accept the patient if all the required equipment is available at the bedside before final acceptance.

Both Graig and Gillman concluded that the transfer delay due to increased communication associated with arranging critical care transfers is related to the number of roleplayers who must agree to the transfer and the receiving hospital's bed availability. Difficulties in contacting the appropriate receiving specialist or staff with authority to initiate the transfer process also contributed to multiple calls, subsequently adding to the transfer delay. Gillman stated that their inability to observe after-hours transfers was one of the limitations of the study. He speculated that transfers after-hours might be more challenging, further contributing to transfer delays (43).

Both Graig and Gillman did well to capture the challenges associated with the IHT arrangements; however, their study design did not focus on the logistics of the transport phase. The transport phase would incorporate assigning a specific transport vehicle (ambulance/air transport), the time needed for the assigned vehicle to arrive at the referring facility from the time the call was received (response/reaction time), the time spent at the referring facility (scene/stabilisation time), followed by the travel time to the receiving facility (intervention/transport time) as mentioned by McEvoy (44). The study by McEvoy specifically focused on the evaluation of neonatal transfers.

Response and transfer times are subjected to traffic considerations and distances, whereby appropriate staff, vehicle and equipment availability can influence the time to assign transport for a specific transfer (40, 44). McEvoy noticed a longer stabilisation time is needed at lower care facilities - 57 minutes (median 45 min, range 15-220 min).

This study had a sample size of 175 neonatal transfers. Of this sample group, 71.6% was related to respiratory distress, of which 112 (64%) neonatal patients required mechanical ventilation support (intubated 13.7%) and neonatal nasal CPAP (45.7%). The mean response time was 62 minutes. Transport times was 107 minutes (SD 50min) with a median of 93 minutes (range 28-314min) (44).

Understandably, the transport team's time spent at the referring facility for the most critically ill exceeds that of neonates that require transport only. Setting up ventilation equipment and infusions for transportation and, at times, help with further stabilisation may prolong the stay. Essential tasks like communication with the parents, history taking and handover procedures to the transport team, including other therapeutic interventions, also occur during this phase (45).

None of the above studies specifically focused on the perceived barriers to care for HIE or BA related injuries. However, it is reasonable to assume that the birth asphyxiated neonate that requires urgent transport would be subjected to the same barriers. It is also reasonable to speculate that other aforementioned factors could contribute to transfer delays unique to specific healthcare systems or within a geographical area.

Conclusion

TH, with an ideal temperature range between 33.5 and 34.5 degrees Centigrade, effectively reduces mortality and morbidity of neonates exposed to birth asphyxia with early treatment initiation. The therapeutic window period of 6 hours for BA and HIE may seem to be ample time to identify, stabilise and transport the neonate to the appropriate dedicated facility. However, the inborn neonate still appears to have an advantage compared to their outborn peers who face barriers to proper treatment, notwithstanding the advances in cooling strategies and in-transport cooling. There is literature supporting pre-transfer cooling and various other approaches to care for outborn BA and HIE, but none from LMIC.

No articles were found that specifically describe the barriers to care for outborn neonates with BA or HIE that require transport. However, the literature described general transfer barriers from both the HIC and LMIC over all age groups, with some overlapping barriers that came forth. The overlapping themes mainly pertain to vehicle availability, lack of education and training, staff and equipment restraints, and communication breakdowns.

From a South African perspective, no literature was found on barriers to transport in the private healthcare system, nor studies describing the perceived barriers to care of BA or HIE patients. Therefore, this study intends to investigate the perceived barriers to timely care for BA and HIE neonates born outside a cooling facility within the private healthcare system in the Western Cape. South Africa.

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PART B

THE PERCEIVED BARRIERS TO TIMELY THERAPEUTIC HYPOTHERMIA TREATMENT FOR NEONATES DIAGNOSED WITH HYPOXIC-ISCHAEMIC ENCEPHALOPATHY WHEN BORN OUTSIDE THE COOLING FACILITY WITHIN THE PRIVATE HEALTHCARE SETTING

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Abstract

Background

Hypoxic-Ischemic Encephalopathy (HIE) is a debilitating neurological injury at birth due to a hypoxic event. The recommended treatment is therapeutic hypothermia (TH) provided at certain neonatal facilities and should commence within the treatment window of 6 hours (1). The outborn neonates are at a disadvantage because they require timely transport to a TH-capable neonatal ICU. The study aimed to identify the perceived barriers to care of HIE neonates born outside the cooling facility within the private healthcare setting.

Methods

This study made use of one-on-one structured open-ended interviews that were recorded on two separate digital recording devices. All the interviews were transcribed and stored within a cloud-based secured folder. All the interviews were subjected to qualitative content analysis using dedicated qualitative software. All audio files were destroyed after transcription to ensure participant confidentiality, including participants' names and locations.

Results

A total of seven participants were interviewed during the data collection phase of this study. The participants were all employed in South Africa within the private healthcare system and comprised of paediatricians, neonatologists, and neonatal nursing staff. The participants represented both the referral and receiving facilities.

The descriptive analysis of the data obtained showed overlapping of emerged themes, ranging in repetitive strength. During the data analysis, three main themes were identified, with other supporting themes providing additional insight: HIE recognition and decision-making, navigating the referral process, and communication barriers.

Discussion

Despite the availability of resources within the private healthcare system and private patient transfer services, there are perceived barriers to timely care for HIE or Birth

Asphyxia (BA) neonatal patients needing an urgent interhospital transfer. This study concluded that changes within the referral system are needed to mitigate the perceived barriers to time-sensitive care. Further research is required to motivate changes and must include the roleplayers' input within the referral process to match the patient's best interest.

Background

An estimated 45% of 5.9 million global deaths in 2015 were in the neonatal population group, with birth asphyxia being one of the causes of neonatal mortality (2). Asphyxia poses a severe risk to a child's survival globally, with an even higher risk for neonates in low to middle-income countries (LMIC) (2). An estimated 23% of the global neonatal population dies due to perinatal asphyxia, especially in countries with a low-income status.

Hypoxic Ischemic Encephalopathy (HIE) can be defined as a brain injury directly associated with a period of hypoxia during or shortly after birth (3). Hypoxic-Ischemic Encephalopathy (HIE) has potential long-term effects or causes premature death in neonates. A study done in South Africa found that of the 21 086 live births evaluated, 8.7 to 15.2/1000 suffered asphyxia, with HIE ranging between 8.5 to 13.3 per 1000 live births. It was calculated that 60% of HIE cases were moderate to severe, while mortality rates within this group were as high as 7.1% (4, 5).

The primary insult is neurological (6), and HIE must not be viewed as a single lone standing event but rather an evolving cascade of events at a molecular level that was put in motion by the hypoxic event. This "continuous neurological roll-over-injury" (CNRI) can span over 3-4 days with the involvement of more structures of the brain as time progress (7). In order to minimise this damage, therapeutic hypothermia (TH) has been recommended (8). Evaluation and cooling should commence in a timely fashion to ensure treatment begins within 6 hours to maximise therapeutic success (8). Supporting these recommendations is a recent randomised controlled trial (Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY)) that sought to determine mortality or severe disability recorded at 18 months following TH treatment versus standard care. This study concluded that patients who received TH had a more favourable outcome than the control group (odds ratio 0.47; 95% CI 0.26-0.87. p=0.021; NNT 6 (95% CI 3-27)) (9).

TH is the preferred treatment with more promising outcomes than only a supportive approach in the past, as no pharmacological therapy is available (10).

However, owing to resource limitations and centralisation of neonatal intensive care services, neonates born at facilities that do not have the equipment or trained staff to provide TH may experience considerable delays in its initiation. The lack of interfacility transfer resources has been cited as one of the top ten preventable causes of neonatal deaths in South Africa (11), while a recent study from the private sector ranked transfer for HIE and birth asphyxia the sixth most prevalent diagnosis encountered (12).

While limited data exists regarding the challenges to timely transfer for HIE specifically, some data related to neonatal transfer has been published more broadly. Challenges related to ambulance availability (13), equipment shortages (13), unavailability of paramedical staff (13), poor levels of education and training, and breakdown in communication (14) were all cited as barriers to neonatal transfer leading to considerable delays. While these studies were all conducted in the public health sector of South Africa, it is unclear whether similar barriers may be observable in the public sector with seemingly greater resources (15, 16). To this end, this study aimed to identify the perceived barriers to timely care for outborn HIE neonates within the private healthcare setting of the Western Cape, South Africa.

Methodology

Research Design

This qualitative study used semi-structured interviews to obtain data from individual participants. Descriptive phenomenology formed the study's theoretical orientation, aiming to describe the perspectives of neonatal clinical staff within the private healthcare system on the barriers to timely TH for HIE.

Setting

South Africa has a dual healthcare system, namely private and government healthcare systems. Private healthcare encompasses patients who use medical aid to cover medical costs, including those who choose to pay out of pocket for care. The government healthcare system provides healthcare to all individuals who do not have medical aid. The majority of the South African population uses the government system,

roughly 80%, whereby private healthcare will cover approximately 18% (17). The Western Cape province has a population of 6.7 million people, with 28% of the population possessing medical aid (17). This study was conducted within the private healthcare setting in the Western Cape province of South Africa, employing interviews with private healthcare providers.

Each individual interview was held at a time and private location convenient to the participant. The most suitable participants for this study were identified by the recommendations of the neonatal unit managers of each facility. Following permission, the participants were contacted telephonically at their workplace to confirm their willingness to participate and arrangements were made for the interviews to follow. Only neonatal staff within the private healthcare setting were selected for this study as they would provide the best data pertaining to the research question. The participants were chosen for their expertise in neonatal care and years of experience, specifically in private healthcare, as the aim was to describe the perspective within this setting. The participants represented both the referral and receiving facilities.

Data collection

The data for this study was obtained by conducting seven individual interviews from four separate private hospitals, that represented both the referring and receiving facilities. The primary investigator conducted the interviews by using semi-structured open-ended questions. The interview consisted of five main questions based on the perceived barriers to care for outborn HIE neonates and was supported with complementary prompts to gain a deeper understanding. This semi-structured interview guide was specifically developed for the study by Wardi de Wet (WdW) and Willem Stassen (WS), based on the contextualisation of the limited literature available and their own experiences. Prior to data collection, WdW underwent training in interview techniques, and a pilot interview was conducted between WdW and WS. Data from this interview was not included in the final analysis.

The scheduled interviews ranged from 25 to 35 minutes and were conducted between April and August 2021. The interviews were recorded on two separate recorders and transcribed verbatim by WdW.

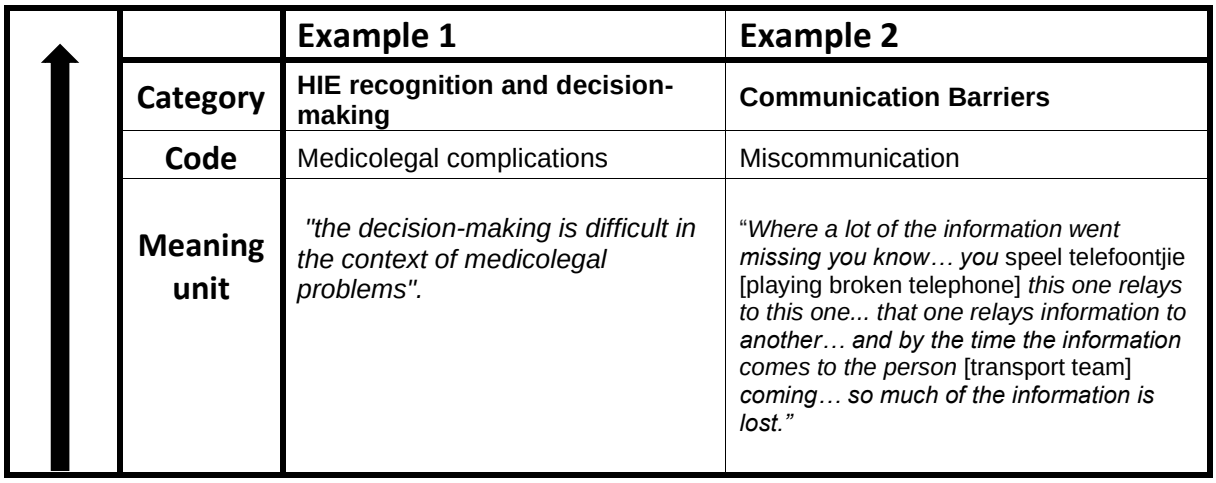
This study only included neonatology staff members with two or more years of experience in neonatal intensive care settings from the referring and receiving facilities within the private healthcare setting. Referring facilities were defined as those that do not have TH capabilities, while receiving facilities were those with TH capabilities. The participants included neonatologists, paediatricians and neonatal nursing staff. The exclusion criteria encompass all neonatal staff from the government healthcare setting and staff with less than two years of experience, including ad hoc staff.

Informed consent

Before commencing the interview, the participant was allowed to read through the consent form carefully, and were asked questions to ensure that they, as the participant, fully understood the document's contents before signing. The consent form briefly explained the focus of the research with additional information regarding participant information and data security, including withdrawal from the study procedures. All the participants were made aware that the interview would be audio-recorded, to which they expressly consented. Ethical approval was provided by the University of Cape Town Human Research Ethics Committee (HREC REF 117/2020).

Data analysis

Content analysis of transcriptions was performed using nVivo (QSR International, Melbourne, Australia) qualitative data analysis software. Inductive dominant content analysis to the manifest level was undertaken by first submersion in the data, whereafter meaning units were identified, condensed, coded and categorised (18). Data codes and categories were discussed and refined during researcher triangulation, as displayed *(*Figure 1*)*. Data saturation was obtained within seven interviews, gauged by repetitive comments and perspectives that emerged during the interviews (19).



	Example 1	Example 2
Category	**HIE recognition and decision-making**	**Communication Barriers**
Code	Medicolegal complications	Miscommunication
Meaning unit	*"the decision-making is difficult in the context of medicolegal problems".*	"*Where a lot of the information went missing you know… you* speel telefoontjie [playing broken telephone] *this one relays to this one... that one relays information to another… and by the time the information comes to the person* [transport team] *coming… so much of the information is lost."*

Figure 1: Ascending categorical development from higher levels to abstraction.

Reflexivity

I Wardi de Wet (WdW) was aware of the potential for bias within qualitative research. I came from the pre-hospital emergency care setting and was deeply familiar with the transport barriers within the private as well as governmental services. More specifically, I currently work in neonatal transport in the private sector. During analysis, I ensured that these experiences and potential for subjectivity were bracketed and discussed with Wilem Stassen (WS). Results obtained were also interrogated through researcher triangulation.

Trustworthiness

Trustworthiness was ensured by following the framework as described by Shenton in the following manners:

- Credibility: The interview was piloted and practised before collecting the data generated by the planned interviews. A personal journal was kept to reflect and investigate the developing categories, and reflexive commentary was also provided. Lastly, credibility was ensured through regular debriefing sessions between investigators and researcher triangulation.

- Dependability: The research process is described in full and in accordance with the Consolidated Criteria for Reporting Qualitative (COREQ) research checklist (20).

- Confirmability was bolstered through strategies used for improving credibility. A coding tree (Figure 1) is also provided to diagram the categorical development.

Transferability: The research setting, participants and data collection periods are described. Results are also contextualised in relation to existing literature. In this manner, the reader may determine whether results are transferable to their own setting.

Results

A total of seven interviews were conducted, lasting between 25 and 35 minutes. Participant demographics are contained in Table 1. Following analysis, three main categories emerged from the data (Table 2), namely, 1) HIE recognition and decision-making, 2) Navigating referral processes, and 3) Communication barriers.

Table 1: Demographic details of participants.

	Qualification	Experience (years)	Facility
Participant 1	Neonatologist	27	Receiving
Participant 2	Paediatrician	20, 1 year abroad	Referring
Participant 3	Paediatrician	20	Referring
Participant 4	Neonatologist	20, 5 years abroad	Receiving
Participant 5	Senior Neonatal Nurse	10	Referring
Participant 6	Paediatrician	14	Referring
Participant 7	Paediatrician	10	Referring
Interviewer	Critical Care Emergency Care Practitioner	8	Transport
a) All the participants (N=7) are fully employed within the private healthcare setting. b) All the participants indicated that they have experience within the government healthcare system during or after training.			

Table 2: Categories and subcategories emerging from the interviews.

Categories	HIE recognition and decision-making	Navigating referral processes	Communication Barriers
Subcategories	a) Diagnosis and decision-making b) Medico-legal considerations c) Parental involvement	a) Bed availability b) Referral from Private to Government c) Funding and authorisation	a) Repetition of information b) Misinformation

Main category summary

Category one: Barriers to HIE recognition and decision-making

Barriers to HIE recognition pertain to any direct or indirect obstacle, preventing an early recognition of BA or HIE that could delay referral for cooling. Barriers that may influence the decision-making process are also described. Both the described barriers collectively act as barriers to timely care that could lead to late, delayed cooling.

The participants also described the following subcategories: 1) Failure of early recognition of BA or HIE could have multiple root causes and are dependent on case presentation and training background; 2) Previous experience in HIE may further influence treatment thresholds; 3) External factors that may influence early decision making is the medicolegal environment, as well as parent participation in the decision-making process. Medicolegal considerations are considerations based on the legal implications of the treatment choices made by the treating physician. Parent involvement pertains to the parents' role in the final decision regarding the treatment option.

Category two: Navigating referral processes

The category “Navigating the referral processes” describes the perceived barriers experienced by neonatal hospital staff regarding the referral process itself. The participants described these processes and how they influence the time to cool. Participants noted that multiple factors during the referral process could act as barriers

to treatment. The subcategories that emerged were thus: 1) Bed availability, the term bed availability plays a vital role in the referral process that could be influenced by the lack of a physical open space within a receiving facility, or it could mean that there are insufficient staff to take care of the patient at the receiving facility; 2) Cross referral from a private facility to a government facility may have further associated complications in finding a bed. Cross-referral refers to the transfer of a patient across the boundaries of healthcare systems. This cross-over may have separate associated barriers to care; 3) authorising the transfer may have financial barriers as medical aid acts as gatekeepers within private healthcare. The terms and conditions stipulated by medical aid may profoundly affect the theoretical treatment window.

Category three: Communication barriers

Communication barriers consist of barriers perceived by different roleplayers involved in the referring process. In this study, communications are essential to the transfer process and significantly impact all involved. Communication forms a significant part of the referral process as information is relayed between key roleplayers. Poor communications significantly affect the treatment window and are perceived as a barrier to care. The following subcategories were described: 1) Repeating information on first contact with a call centre by the referring facility was mentioned as a barrier to care as this process is described as time-consuming; 2) Misinformation refers to the quality and accuracy of the information that is relayed to the transport team due to a process of information-sharing.

HIE recognition and decision-making

Three subcategories emerged in the HIE recognition and decision-making category: diagnosis and decision-making, medicolegal considerations, and parental involvement.

Participants indicated that the diagnosis of HIE and whether to refer the patient is not a straightforward process, especially in mild to moderate cases. Mild to moderate HIE cases may take longer to diagnose due to the subtle signs and symptoms that are less pronounced than in the more severe cases (21).

The participants indicated that the mild to moderate HIE cases might delay decision-making as not all the physiological and neurological markers are present. This aligns with the findings of Chalak, feeling that the absence of a standardised definition for mild HIE might be a contributing factor in a late diagnosis, also stating insufficient biomarkers that could reliably identify mild HIE cases within the treatment window (21).

The participants stated that deciding to initiate cooling or the transfer process is not just based on personal opinion and results of a single test or criteria. The case is often discussed with a neonatologist, advising to wait an hour and evaluate to get a clearer HIE picture or to transfer immediately. *"It's not like you get a test done… it is a bit of a process. Especially with the ones who are borderline… It takes a bit of time to decide whether they are going or not going."* - Participant 3.

To complicate matters further, some mild to moderate HIE cases respond well to resuscitation and slowly progress to a delayed encephalopathic picture. "*Your patient looks a lot better… after the resuscitation and tends to... slowly deteriorate into an encephalopathic picture in the hour that follows."* - Participant 4.

The above statement from the participant explains the terminology *"evolving HIE*" used by Chalak, strengthening the need for further investigation of biomarker development as an early diagnostic criterion for this subset of HIE patients (21).

Delays in referrals were also reported to be related to when a clinician was trained. *"We see that our colleagues that were trained before cooling was a treatment modality are very slow to make a decision… Where the colleagues that were trained... after cooling was introduced… are much faster to refer."* - Participant 4.

Another barrier to recognition and decision-making related to the frequency with which referring clinicians encounter these patients. "*Also, because it only happens once in a blue moon -I'm talking once every four years- it is just one of those situations that we don't actually do drills for... in a small unit like ours."* - Participant 3. This lack of regular exposure resulted in feelings of being under-prepared, especially given that HIE

"happens too soon, or too close to the birth itself, that one cannot really prepare in advance for this type of thing." - Participant 4.

A potential mitigation strategy to reduce the time of referral by the referral facility for likely HIE patients is to initiate refreshing training sessions. Continuous Professional Development (CPD) sessions could be scheduled to encourage early consultation with a neonatologist, especially for mild to moderate cases. Medicolegal training could be incorporated as a CPD topic. Furthermore, due to the low HIE frequency reported by the participants, HIE case simulations can be hosted at the referral facilities to improve preparedness (22). These case simulations will also incorporate the neonatal staff that are often involved with these cases.

A retrospective cohort study by Mohammad et al. was conducted after implementing an educational outreach program regarding HIE neonates and found a reduction in mortality and morbidity in infants with moderate-to-severe HIE. The key interventions were early identification, patient referral by telemedicine and utilising a more centralised communication system. The outreach education program included hands-on patient simulations and in-depth discussions on training guidelines and clinical management (22).

Participants from referring facilities also reported that they lack appropriate diagnostic equipment such as electroencephalography (EEG) to guide their referral decisions. *"We also don't have a brain monitor… I know some other referral institutions that have a monitor where they can look at the EEG and say, you know this baseline is worse as what it is supposed to be. "* - Participant 6.

However, receiving clinicians felt that EEG monitoring was not always necessary to make referral decisions. *"Ja" (yes) for the evaluation process to make the decision, you can use an EEG, but it is not necessary. So, it is a simple clinical call".* and *"If you can do the cord pH… that... plus your APGAR, is usually sufficient."* -Participant 4.

One of the primary markers in diagnosis is the blood pH taken from the umbilical cord shortly after the delivery (23). The assumption is that a poor cord pH will set off the HIE investigation and timely consultation with a cooling specialist. Further literature

suggests that an arterial cord blood pH below 7.00 combined with low 5-minute APGAR scores and a base deficit exceeding 12mEq/L may indicate poor neurological sequelae (24).

However, the absence of blood chemistry may force the treating physician to evaluate the patient's APGAR and needs to conduct a neurological examination. This will heavily rely on their experience and knowledge of HIE to make a diagnosis, as BA and HIE might not be that common within private healthcare. Some peripheral hospitals that also refer to larger cooling centres may not have access to immediate blood results. "*Ja" (yes), not all of the hospitals are doing a cord pH, so for someone in the periphery who doesn't have a cord pH at their disposal, the APGAR is the best starting point.*" - Participant 6. Waiting for pending blood results to decide whether to initiate the referral for cooling can be perceived as a barrier to care.

Interestingly, both the receiving facilities feel that the brains monitor does not play a definitive role during the diagnostic process, but could aid in the decision-making if cooling is indicated. The general feeling is that during mild to moderate cases, the referral facility would prefer more supportive evidence indicative of an HIE diagnosis based not on a "*simple clinical*" evaluation alone. The need for supporting evidence during borderline cases could be multifactorial.

One potential reason is the low frequency of HIE at referral facilities, which could limit physicians' exposure. Referral facilities may have one to two cases a year, if not less. Whereby the receiving facilities may see two HIE cases a month from referral facilities. Furthermore, neonatologists at TH neonatal ICU are trained in HIE and TH and might feel more confident in making an early diagnosis. It appears that there is a sense of uncertainty in mild to moderate HIE cases, whether to refer the patient for invasive cooling or not, especially if there is a scarcity of supporting equipment, like pending blood results or EEG (Electroencephalogram) "brains monitor." The referral facility might monitor the patient closely before concluding a definite diagnosis.

It is important to note that the transport arrangements for this patient group can only commence after the decision is made that cooling is needed and transport to a cooling facility is indicated. It is also important to note that there might be some elapsed time

before the initial neonatologist consultation. This elapsed time will further delay the timely treatment and may cause the late initiation of TH.

One other factor that may play a role in the final decision-making is medicolegal complications; *"the decision-making is difficult in the context of medicolegal problems".* - Participant 6, as clinicians seek certainty as to *"whether these babies really need it* [TH].*"* - Participant 6. This consideration could play a significant role in the time elapsed before making the decision to refer a patient and could potentially be a barrier to referral, as clinicians. *"Medico-legally… often have to think it through quite a bit..."* - Participant 7. However, from this study, it is not clear to what extent the medicolegal aspect affects decision-making and how it contributes to delays.

Some participants indicated that they wish this landscape could change to reduce the anxiety associated with care, including the financial burden. *"I wish we could change that kind of landscape… where you know… at the moment we pay... I think about 15 times more medical protection society fees a month as the doctors in Government, and it is just escalating tremendously. So, I wish we could change some of the medical-legal setup and take that anxiety associated with it away."* - Participant 6.

These concerns are not without merit as Tylor and Betinna note that healthcare in South Africa *"is on the cusp of a perfect storm"* due to the sharp increase in medicolegal claims against public and private healthcare providers that accelerated from 2008, particularly in maternal and child health services (25). Taylor and Betinna strengthened the point that indemnity insurance and fear of litigation are stress factors associated with obstetrics and gynaecology (25).

Lastly, parental involvement in the decision-making process was also reported to be a potential for referral delays. This may be because parents have personal preferences related to the birthing process and strong feelings on what they expect the outcome should be, *"there is a lot of cases where… I mean… where people literally tell you that I do not want a caesarean section, I only want a normal delivery."* - Participant 7.

Parents may also ask to be referred for a second opinion regarding a diagnosis or proposed treatment plan, "*parents in private often ask for a second opinion.*" – Participant 3. With HIE, this process could delay treatment beyond the window period as the parents might not understand the gravity of the situation. In instances where parents are amenable to the care, information-sharing related to HIE and TH *"can lead to very long discussions… so that can also delay… because sometimes parents will say… give me more* [Information]*… it is quite a hectic experience"*. - Participant 3.

Parent involvement in child health decisions are not uncommon in medicine and could be challenging. Several considerations could influence the decision-making process, like the cognitive and emotional ability to process information and understanding of the risk versus benefit. Post procedural sedation shortly after giving birth may also play a role in the parental ability to make clear decisions regarding HIE (26, 27). Decision-making could be made easier by early discussion between the physician and the parents during maternal care visits regarding the risks associated with birth (27). A pre-informed parent may consent to treatment earlier, compared to the unexpected, where complex decision-making happens on the spot.

Navigating referral processes

In this category, three subcategories emerged: bed availability, referral from private to government, and funding and authorisation.

Once the diagnosis of HIE is made, the patient is referred to a dedicated cooling facility that provides therapeutic hypothermia as the primary treatment option. Part of the referral process is finding a cooling facility to continue care. This process is informally referred to as “finding a bed”. Finding a cooling facility to continue patient care is time-consuming, may take multiple communications with different institutions, and is a perceived barrier to care. One participant from a receiving facility said: *“Then they will phone one* [hospital] *and that person can't accept then they have to look for another place… So, they often phone two (2) or three (3), four (4) different people before they actually get to the place they need to be."* - Participant 4.

Several factors are at play here and may differ from day to day and between cases. Factors affecting bed availability include physical space in large Neonatal ICUs with

TH capabilities that often operate at total capacity. "*Well, obviously we've got to have space, that's the one thing."* - Participant 1.

Participants stated that finding an open space at a cooling facility is challenging as "*in private, you don't know if you're going to find a bed somewhere* [in a cooling facility] *."* - Participant 7.

This may be compounded by the fact that facilities also admit neonates born within their own hospital. For this reason, perhaps it might be useful to refer high-risk pregnancies antenatally, to minimise delays if the need arises.

Challenges exist with navigating the referral process, regardless of whether the referral is to a Private or Government facility. One participant mentioned that "*if it's, ...I mean, a child that needs cooling is a private patient (private paying), then you're going to struggle to get it into a public facility."* - Participant 7; while another noted, *"if it's a private patient (private paying), we have to use public, so it's… it takes a long time to refer and transferring anyone anywhere is difficult."* - Participant 6.

Therefore, difficulty in "*finding a bed"* results in a need for multiple communications during the referral process and echoes other international studies' findings which indicate the need to contact several hospitals multiple times, with an accumulative time-delay effect (28).

In order to overcome these barriers in the referral process, participants suggested that a standardised referral protocol and network be developed within private healthcare. *"I think the problem... the bigger problem to me is that there is not a known cooling network. There should be a cooling network, the hospitals that do cooling should know who cools and should know who got beds available."*
- Participant 4.

The participants agreed that neonatal units work as separate entities in siloes and that a cooling network would encourage more robust unison. Besides the potential patient benefits that could stem from a cooling network, the smaller neonatal units will not feel so isolated … *" in Private, you are completely alone."* - Participant 7.

Funding and authorisation

Medical care is funded either through out-of-pocket expenditure or by specific healthcare insurance or medical aid in the private healthcare sector (17). In this manner, these medical aids play a gatekeeper role prior to a transfer being activated in that all transfers and admission to a receiving facility should be pre-authorised. For these reasons, it is important to note that communication by the referring facility is not just confined between the referral and receiving facilities, but may include communications to medical aid and emergency medical services companies.

Failure to obtain timely authorisation, or authorisation at all, results in transport delays, thus minimising TH's benefit. In some instances, the medical aid may completely reject the transfer request if the patient is not being referred to a designated service provider hospital, as "*hospitals has a list of medical aid with every option… whether it is accepted or not accepted, so you just need to be aware you are referring to and what their policy is."*- Participant 6.
Complicating these matters further, Emergency Medical Services and hospitals may not wish to take the patient, given the financial risk and costs involved in having unsettled hospital bills. "*I know that a (private hospital group) are not prepared to take the case and argue the case later. If it is not authorised beforehand, they don't want the patient."*- Participant 4.

Besides the time it takes to get the needed authorisation, it appears that the time of day can further slow down the process. Some participants mentioned as medical aids may not be reachable after office hours. *"Look… medical aid is definitely; authorisation is getting them to understand what is actually happening… and then… I don't know if anyone mentioned it but like after 16H00 the medical aid close… it is over, you can't do anything.*" - Participant 7.

To further complicate matters, the medical aid is under the misconception that all neonatal intensive care units within the private sector are the same. "*They (medical aid) think that every ICU cools. They don't understand that there are only certain ICU's that cools."* - Participant 4.

This misconception leads to a poor understanding of why a neonatal patient needs to be transferred out. Furthermore, if cooling is initiated at the cooling facility without pre-authorisation, the referring facility must motivate their treatment options to receive payment for the services rendered. One participant said: *“I've got a thing now for a baby that came out with a pH of 6.9. He's got- he was cooled, that was last week or the week before. And with (specific medical aid) now, I must motivate for it, why?"* - Participant 1. Interestingly, this patient was an inborn patient born at a cooling facility and did not need transport authorisation. This indicates that medical aid authorisation processes influence the care of even inborn patients.

Obtaining authorisation before treatment is not an unknown phenomenon. In an article by Corder, *Streamlining the Insurance Prior Authorisation Debacle*, he describes the tedious process of pre-authorisation. He also mentioned that after-hours authorisation is a concern, stating that the authorisation process is a waste of the physician’s time and noted that there is often a need to repeat information without additional information actually being required or relayed (29). Corder further notes that 92% of physicians surveyed feel that pre-authorisation affects their ability to practice medicine appropriately. Medical treatment was altered in 93% of the cases due to restrictions placed by the medical insurance provider. The big concern is that there is a risk that the patient may deteriorate whilst waiting for transfer approvals (29) and thus negating the benefit of timely TH.

The participants in our study stated that medical aid involvement is a barrier to care, and if the medical aid is not part of the decision-making process, more patients would be able to make the treatment window, even if referred over longer distances. Some participants stated that medical aid should not be part of the transfer and decision-making process at all. *“The main answer is cutting out the medical aid out of the equation so that they can't prevent the transfer or delay the transfer."* - Participant 4.

Communications barriers

Participants described communication-based barriers that resulted in the need to repeat information and/or misinformation be relayed.

Communication plays an important role in making arrangements for timely interfacility transfer but comes with different challenges. Transfer arrangements involve communication with a transfer company, usually, an ambulance service. Importantly, this can only happen following consultation with a specialist neonatologist and finding a bed at an appropriate facility.

Participants described transport communications as a tedious process that is time-consuming and challenging for the referral facility, with one participant describing it as *"frustrating and they* [call centre]*… takes a long time. There's one word to describe this* [transfer communications]*: frustrating*." - Participant 2.

The participants showed strong emotions when they shared their experiences regarding the transfer communications stating that they had to repeat information and perceiving this process as a barrier to care. *"What is your name? How do you spell your name?* [spelling letter for letter]… *What is the temperature?… What is the… I mean… it's not things that's relevant, and you need to go through that process of calling, and they're asking 120 questions- that is, that is extremely time-consuming… its extremely time-consuming."* - Participant 2.

During this phase, critical information about the patient's condition and equipment requirements are not relayed to the transport team despite clear instructions. *"So you tell them* [transport company] *it is an intubated, ventilated… or whatever… and to send an incubator box and oxygen… so there is that also… they don't understand what you are asking for… then they send the wrong… transport team*." - Participant 7.

The general feeling was that the personnel at the call centre do not understand the urgency of the case, nor do they understand the requirements for the call. This may be due to limited medical training for call-takers who rely on generic call-taking software interfaces to gather case information rather than their own medical knowledge that can be applied. "*Well, the problem is who you're dealing with. These people, they've got no actual medical background."* - Participant 1.

Similar communication challenges were also reported in other studies regarding transfer delays. In a South African study, Ashokcoomar and Naidoo recommended that improved information gathered by the ambulance control centres could mitigate these delays in future neonatal transfers. The study stated that these control centres

are mainly staffed by ambulance personnel with basic emergency medical training (13).

To minimise the communication challenges and to make the process more streamlined, the participants felt that the information could be filled in on a pre-designed sheet and emailed to the relevant call centre. Another suggestion is that the patient's case requirements are sent via a dedicated mobile or computer application. *"So, the transfer information is critical, and it should not be telephonic. There should be a written version as well. So, my feeling is that…either an application via an app, or written application that is emailed or WhatsApped, or sent in an electronic format to the medical aid, so that the receiving ambulance crew can also see what they're going to do. I mean if the ambulance crew sees that…they going to…know that they are the wrong guys for the transfer*." - Participant 4.

Communication challenges are often a concern as this can directly or indirectly affect patient care. Regardless of the advances made in communication technologies, miscommunication is a regular occurrence (30). This is especially more probable if the information is handled and processed multiple times (30). Some participants feel that information is lost during the relaying of information from the referral facility to the transfer team. "*Where a lot of the information went missing you know…you speel* telefoontjie [playing broken telephone] *this one relays to this one... that one relays information to another… and by the time the information comes to the person* [Transport team] *coming…so much of the information is lost."* - Participant 6.

Literature indicates that communication-based errors are not uncommon when arranging an interfacility transfer. One study that looked into the communication process of aeromedical transport noted multiple areas where critical information errors can occur, especially in the call-taking process (31). Miscommunication may lead to errors in diagnosis, medication administration, and poor equipment choices and preparation (31). Vincent-Lambert and Wade reported that a lack of call-takers understanding basic terminology and inexperience led to poor call prioritising, resulting in delays. As a result, inappropriate neonatal staff and equipment are assigned to facilitate the transfer (14). Vincent-Lambert and Wade also reported that poor communication feedback regarding the transfer status led to frustrations and delays.

It would often happen that after the transfer arrangement with a call centre, the ambulance does not arrive. The referral hospital is not informed about the transfer status and is unaware of a potential delay (14).

In this study, participants also shared their experience regarding miscommunications and errors to follow. *"Sometimes you get it where they sent the wrong crews… wrong equipment… wrong bus* [ambulance/transport vehicle] *as they say. So that is another problem."* - Participant 7. This was attributed directly to communication barriers that existed.

Importantly, literature has shown that most communication errors cannot be attributed to any individual but rather to organisational processes and practices, suggesting that system change may result in improvement and mitigation (31). Participants in this study agreed and noted that direct communication with the transport team could mitigate some of the miscommunications regarding the equipment needs and level of care. "*The more, uhm… more specific questions are asked by that transport team when we are phoned by them, to just know what the current condition of the child is, what equipment is needed."* - Participant 6.

One participant mentioned that if the transport team received a transfer handover from the receiving facility, the transport team would be well-prepared for the transfer. This may minimise any information lost, decrease dispatch and response times, and lead to timely transport for TH. *"So, I think he [receiving neonatologist] sort of skips that whole part [call centre], and I think maybe that's why it's faster to designate a proper neonatal team to come and fetch the baby*." - Participant 5.

Discussion

This study aimed to determine the barriers to timely TH treatment for outborn neonates with HIE within the private healthcare setting of the Western Cape, in South Africa, as perceived by neonatal clinical staff. Although this was a small study within the private healthcare system in the Cape Town metropole, the assumption is that similar results will emerge if the study is replicated elsewhere in the same setting. The immediate

conclusion is that perceived barriers to TH care for HIE and BA outborn neonates do exist.

This study found that the decision-making of whether or not to refer for TH is not a straightforward process at a referring level, especially in mild to moderate HIE cases lacking a clear clinical HIE picture. The decision-making process is further complicated if the mild to moderate patient does respond to initial treatment before lapsing into a delayed HIE picture. The added complication during such cases is that a significant time is lost, leaving less time to transport and start treatment before the end of the treatment window. Furthermore, the low frequency of HIE and BA within the private healthcare setting at a referring level may be a contributing factor influencing the decision-making process. Experience practitioners and training in HIE and BA may reduce the elapsed time in decision-making compared to practitioners who qualified before TH became the standard treatment for HIE. During times of uncertainty, less experience referring practitioners may rely more on additional indicators like EEG and follow-up blood results before a consultation, leading to delayed treatment. In contrast, the more experienced practitioner may initiate early consultation based on Poor APGAR scores and cord blood pH alone.

Parental involvement in the decision-making process can be a barrier to care. Parent birth preferences and choice of treatment may act as barriers, especially if a second opinion is requested regarding TH as a treatment.

Medicolegal implications also influenced the decision-making process, and these findings are in line with international studies (25). Still, it is difficult to conclude to what extent this may influence the decision-making process within this study. However, it seems that medicolegal issues are less prominent within the government healthcare system with less influence during the decision-making process.

Funding and transport authorisation was also identified as a barrier to care. There is a significant time delay at the medical aid level during the authorisation period. Medical aid's accessibility after hours and poor differentiation between the capabilities of a referring and receiving neonatal unit were also contributing barriers to care. Reducing the medical aid participation during the treatment plan decision-making and choice of

receiving facility, including the transport team selection, will reduce the time to treatment.

Bed availability plays a vital role during the referral process as physical space at the receiving facility seems to be a barrier to care. The participants feel that it becomes more complex to secure an open bed if a patient is referred from a private facility to a government facility. Furthermore, transport arrangements were also a barrier to timely care as miscommunication is common. Some of the barriers identified are poor closed-loop communications between the transport company and referral facility, including a lack of understanding at a call-taker level that leads to poor transport vehicle allocation and inadequately trained staff.

Conclusion

Outborn HIE neonates requiring transport to a dedicated cooling facility for further care experience complex perceived barriers which differ from one case to another. Holistically, the referral process lacks fluidity and cohesion between the different roleplayers, indicating that the current system fails to benefit the patient. The complexity becomes evident when peeling back the obvious barriers to treatment. Once the obvious outer barriers are removed, the root causes of delayed care lie exposed. These multi-layered and interwoven difficulties form the fabric that are the perceived barriers to care for outborn neonatal patients. A systematic approach is needed to address these issues and may require simultaneous input from multiple roleplayers.

More could be done to reduce these barriers to care to ensure that all eligible outborn neonates receive cooling within the treatment window. Further research is needed to fully describe this phenomenon within private healthcare in South Africa. Future studies could investigate mitigation strategies to address the perceived barriers to care and should include the input of all the roleplayers involved.

Reimbursement of participants

All participation was voluntary, with no reimbursements offered for their participation.

Limitations and recommendations

This qualitative study aimed to capture and state the participant's perspective on outborn neonatal care for BA and HIE. This relatively small study was done within Cape Town and mainly focused on one private hospital group. This study did not capture the view of other private healthcare groups within Cape Town. However, the authors feel that similar results are possible if replicated within those settings. The authors recommend that further studies are needed to understand the barriers to care.

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Conflict of interest

The study's author is permanently employed within the private healthcare sector as part of a Critical Care Retrieval Service (CCRS) team tasked with transporting neonatal and paediatric patients.

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PART C: Appendicies

Appendicies A

Journal and author information

The intended journal for publication is the South African Journal of Child Health (SAJCH). This study is aimed at Neonatal and Paediatric care specialists within the South African context, including the international audience.

Relevant journal Instructions to Authors can be found at the following link
http://www.sajch.org.za/index.php/SAJCH

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Appendices B

Research proposal

THE PERCEIVED BARRIERS TO TIMELY THERAPEUTIC HYPOTHERMIA TREATMENT FOR NEONATES DIAGNOSED WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY WHEN BORN OUTSIDE THE COOLING FACILITY IN THE PRIVATE SECTOR

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This study is in partial fulfilment of the MPhil Emergency Medicine degree.
A phenomenology approach in qualitative research.

I, Wardi de Wet, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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1. Title

The Perceived Barriers to Timely Therapeutic Hypothermia Treatment for Neonates Diagnosed with Hypoxic Ischemic Encephalopathy when Born Outside the Cooling Facility in the private sector.

2. Background

Childbirth is a natural event and an essential aspect of the circle of life and our existence. Childbirth, however, comes with risks to both mother and baby, despite medicine's best efforts to reduce mortality and morbidity (66).

Although there are many risks to neonatal health during childbirth, hypoxia remains a well-known contributing factor in neonatal mortality and morbidity (67).

Hypoxic-Ischemic Encephalopathy has potential long-term effects or causes premature death in neonates. The primary insult is mostly at a neurological level due to the brain's inability to cope during a prolonged hypoxemic event during or shortly after birth(24).

Hypoxic Ischemic Encephalopathy (HIE) can be defined as a brain injury that is directly associated with a period of hypoxia during or shortly after birth(46).

Hypoxic Ischemic Encephalopathy must not be viewed as a single lone standing event but rather an evolving cascade of events at a molecular level that was put in motion by a hypoxic event. The findings following the initial hypoxic insult are subtle and only visible with diffusion-weighted imaging during the first few hours after the injury (19). However, MRI studies have found that the lesion progresses in size in the following days. This "continuous neurological roll-over-injury" can span over 3-4 days with the involvement of more brain structures as time progresses (19).

It is safe to say that mortality and morbidity are directly proportional to the final injury's extent over time and the severity of the initial hypoxic event.

An estimated 45% of 5.9 million global deaths in 2015 were in the neonatal population group, with birth asphyxia being one of the causes of neonatal mortality(45). Asphyxia

poses a severe risk to a child's survival globally, with an even higher risk for neonates in low to middle-income countries (LMIC) (45).

An estimated 23% of the global neonatal population dies due to perinatal asphyxia, especially in countries with a low-income status (68). This finding further strengthens the fact that asphyxia is still a global disease burden (69).

A study done in Southern Africa found that of the 21 086 live births evaluated, 8.7 to 15.2/1000 suffered asphyxia, with HIE ranging between 8.5 to 13.3 per 1000 live births. It was calculated that 60% of HIE cases were classified as moderate to severe, while mortality rates within this group were as high as 7.1%(47, 48).

Recommended treatment for neonates who show early signs of neurological fallout or those exposed to a suspected hypoxic event during or shortly after delivery should be transported to a cooling facility to be evaluated by experts capable of initiating therapeutic cooling if needed (25). Evaluation and cooling should commence in a timely fashion to ensure treatment commence within the window period of 6 hours (25).

There is currently no pharmacological therapy available for the treatment of HIE. Target temperature management is the preferred treatment with more promising outcomes compared to only a supportive approach in the past(23).

Unfortunately, babies are born at facilities that do not have the equipment or trained staff to provide this specialised care. The preferred practice is to transport these patients to designated facilities that are capable of providing therapeutic cooling. The one factor that adds to the complexity of HIE treatment is time.

Therapeutic cooling yields the best results if initiated within a 6-hour window period(46). It appears that the neonates born at the cooling facility have minimal delays in treatment compared to those born outside the cooling facilities(25).

The initiation of Therapeutic Hypothermia (TH) therapy within the 6-hour window period is vital (46). During this period, cerebral damage may still be limited with an early start of TH treatment before the onset of the "continuous neurological roll-over-injury". Therapeutic treatment may reduce the overall size of the insult with a reduction

of adversely affected brain structures (23). This preservation of neurological tissue may reduce the debilitating effects, with a possible decrease in mortality and morbidity (23).

There is evidence that indicates that there might be neuroprotective effects of Therapeutic Hypothermia (TH) in babies with Hypoxic Ischemic Encephalopathy (HIE) if treated within the 6 hours after birth or a hypoxic event. (23, 46).

Other studies also stress the importance of timely treatment. HIE treatment is time-critical, and the study advocates TH initiation within the first 6 hours after the insult (23).

The first 6 hours is known as the primary phase, also called the "*primary energy failure*" followed by the secondary phase 6 hours later. Research indicates that if initiation of treatment commences within the primary phase (0-6 hours), there might be a prospect of a better neurological outcome. TH aims to reduce "*secondary energy failure*" following an ischemic event (23, 24). There is a possibility that this window period may be less in severe cases due to a shortened latent phase with an increase of severity in the secondary phase (70).

Therapeutic cooling is a well-controlled process where the core body temperature of the HIE diagnosed neonate is lowered to a target temperature of 33-34 degrees Centigrade. Once the patient reaches the target temperature, the temperature will be maintained for 72 hours under stringent monitoring (71).

Two types of cooling techniques could be utilised as a treatment: Complete Body Cooling, which involves cooling the whole body, and Head Cooling, which focuses on the cooling of mainly the head. These treatment options target the brain as the primary focal point (71).

Currently, there are a limited number of cooling facilities in the private health sector within the Cape Town metropole that are capable of providing hypothermic treatment.

Mediclinic Louis Leipoldt is located in the northern substructure with Netcare Christiaan Barnard Memorial hospital that is more situated in central Cape Town Metropole. Netcare Blaauwberg Hospital is situated in the Western perimeters of the Cape Town metropole. Mediclinic Panorama will fall on the southern border of the northern suburbs.

The limitation of cooling facilities results in an increased need for HIE neonates that require prompt transport to one of the above hospitals.

Neonates with complicated ventilation requirements or neonates with additional congenital comorbidities are transferred to Mediclinic Panorama, Netcare Christiaan Barnard Memorial- or Netcare Blaauwberg hospital.

Hospitals like Mediclinic Cape Town, Mediclinic Stellenbosch, Mediclinic Vergelegen, Mediclinic Hermanus, Mediclinic Worcester, Life Vincent Pallotti, Melomed Tokai, Melomed Gatesville, including Netcare Kuilsriver do have neonatal ICU units with 24-hour care. However, they are likely to refer HIE patients to one of the cooling facilities mentioned above.

In this study, the researcher will seek the opinions of the following referral facilities. Life Vincent Pallotti, Mediclinic Vergelegen, Netcare Kuils River and Mediclinic Stellenbosch.

HIE neonates with other congenital abnormalities, eligible for cooling may pose a higher risk for complications during the cooling process. Therefore, there is a preference to transfer these cases to the highest tier in neonatal care.

In a study done in a single Neonatal Intensive Care Unit (NICU) in 2010 found that 80% of HIE neonates were born outside a cooling facility and required transport (25). The study also mentioned that some of those patients did not make the 6-hour time frame (25). This study was conducted in a low- to medium-income country, and this specific NICU had access to specialised transport teams and rotary-wing services.

Due to the lack of accurate data within the South African context and, more specifically, the Western Cape, it is difficult to make a comparison. However, anecdotal reports indicate that many of these neonates may require transport for further investigation or cooling treatment.

Therefore, the purpose of this study is to identify and understand the barriers that exist within the private health system in providing Therapeutic Hypothermia treatment in neonates born outside the cooling facilities diagnosed with HIE.

3. Research aim

The aim is to describe the barriers to timely Therapeutic Hypothermia treatment for neonates diagnosed with Hypoxic-Ischemic Encephalopathy (HIE) when born outside the cooling facility within the private healthcare system.

4. Objectives of the study

4.1. To describe the perceived barriers from the neonatal staff's perspective, responsible for arranging timely transport of HIE neonates who need TH. The researcher will be describing the perceived barriers in detail as this will provide insight into the phenomenon.

5. Methodology

5.1. Philosophical assumption

Based on the researcher's own experience and informal discussion with staff at both referring and receiving facilities, the researcher is under the assumption that some of the newborns, which require TH treatment, may arrive at the designated cooling facility close to the 6-hour treatment window or shortly thereafter. If a neonate misses the suggested window period, the researcher assumes that the perceived barriers investigated are involved.

The researcher wishes not to speculate on the actual numbers of neonates that miss the therapeutic window as this is not the aim of this study. However, the researcher assumes that the perceived barriers do play a role in the timely treatment of neonates eligible for cooling.

The researcher strongly believes that there are indeed barriers to the timely care of HIE neonates and that identifying these potential barriers is possible. Once those barriers are identified, only then solutions can be investigated in the future.

The researcher wishes to describe these perceived barriers and to gain a more in-depth insight into this phenomenon, as described from the participant's perspective.

6. Methodological orientation

The researcher believes that there are perceived barriers regarding the timely treatment of HIE neonates in the private healthcare system needing treatment at another facility. However, these barriers are observed but not formally identified within the Western Cape private healthcare system, making it difficult to define these margins clearly.

The researcher believes that it would be difficult to completely define the margins of the phenomenon due to the complexity and the dynamic nature. The researcher believes that it is possible to describe these barriers and that by conducting this study, a more profound insight will be gained.

A phenomenological approach in qualitative research is interested in understanding, intending to clearly describe a particular experience within a specific context (72).

The aim is to describe the interviewed neonatal staff's experiences regarding the perceived barriers in HIE neonates. A phenomenological approach will provide an in-depth understanding and deeper meaning of the experienced phenomenon. Phenomenology within a qualitative setting will allow findings to emerge as the study progresses, leading to a more detailed insight and knowledge (72).

The researcher will include the participants' opinions and recommendations obtained during the research process on how they feel these barriers can be managed and mitigated. The researcher believes that they will provide possible solutions for future mitigation due to their in-depth involvement with HIE neonates.

6.2. Research design

This study is a qualitative descriptive study that will investigate and aims to describe a perceived phenomenon.

6.3. Reflexivity

The researcher is aware of the potential for bias within qualitative research. He will work closely with the experienced supervisor to mitigate and reduce the bias footprint during the study. The researcher will draw on the supervisor's expertise and experience within this qualitative study as a second analyser of the study's data. Conclusions drawn from the gathered data will be scrutinised to eliminate potential bias.

The researcher comes from the pre-hospital emergency care setting and is deeply familiar with the transport barriers within the private and governmental ambulatory services. The researcher is aware of potential bias towards this aspect to further treatment and is mindful that transportation difficulties might be one of the perceived barriers. However, the researcher feels that more complex aspects of the phenomenon contribute to the perceived barriers to timely care.

The researcher is aware that due to his professional background in emergency care and his neonatal transportation experience, the participants might answer questions within the interview with a potential bias towards interhospital transport.

The participants in the study are familiar with the researcher's professional background. He is involved with interhospital transfers of neonates and often transports neonates to or from some of the mentioned hospitals. The study will be done within the private healthcare system that is independent of the governmental sector.

Furthermore, the researcher is aware of his assumptions and opinions of what the phenomenon consists of and what he feels the perceived barriers might be. This personal bias can potentially skew the analysis and conclusions drawn from the

obtained data, which will be mitigated by following a structured approach in the study's processes.

The researcher will obtain additional training in qualitative research by making use of an online training platform. The researcher will complete an online course on qualitative research and show proof before or during the intended research proceedings or in the study's final write-up. The researcher believes that this will ensure that potential bias is further mitigated.

The researcher will make use of dedicated software to analyse the data collected during the qualitative study. The researcher will make use of the NVivo qualitative analysis software in this study.

6.4 Study population

The study will recruit permanently employed neonatal staff (doctors and nurses) working primarily in the private healthcare system's neonatal units. The neonatal staff will be from four different referring hospitals within the City of Cape Town Metropole. Mediclinic Cape Town is located within the Central Business District (CBD). Life Vincent Palotti hospital, Netcare Kuilsriver, and Mediclinic Vergelegen in the eastern substructure.

All of the hospitals mentioned above have Neonatal Intensive Care Units but do not provide cooling therapy. They will rely on transport if cooling is indicated.

Due to these facilities' general similarities, the assumption is that all may experience some overlapping internal and external barriers to timely care.

Internal factors may encompass factors like adequate staff or equipment shortages. External pertains to the availability of beds at the receiving hospital and the availability of dedicated specialised neonatal transfer units. All of the above plays a vital role in the referring process and onset to timely treatment.

Furthermore, the researcher will include insight from various receiving facilities within the Cape Town Metropole area in this study. These facilities are capable of providing therapeutic cooling for HIE neonates.

This study will incorporate insights from Mediclinic Panorama, and as well as Netcare Blaauwberg- and Netcare Christiaan Barnard Memorial Hospital, including Mediclinic Louise Leipold who are all capable of therapeutic cooling.

For a broader understanding and more in-depth insight, the researcher wishes to incorporate a combined perception from the referring and the receiving facilities.

The researcher wishes to recruit a minimal total of 10 participants for this study, but sampling will continue until saturation (outlined below). The participants will be equally distributed between the referring and the receiving facilities. The combined experience of neonatal staff from the referring- and receiving facilities will provide a more in-depth understanding of the perceived barriers to timely care.

The referring neonatal care doctors in these respective units are responsible for identifying potential HIE patients and arranging for further care as part of their duties, including thorough documentation of these arrangements. Therefore, the researcher feels that the referring doctors can provide valuable insight regarding the perceived barriers to timely care. Furthermore, the researcher wishes to supplement a deeper understanding of the perceived barriers by incorporating neonatal nursing staff.

Due to the structure of individual care provided by the neonatal nursing staff, the researcher feels that they also have a vantage point to give a holistic insight to any barriers regarding treatment and transport of the HIE diagnosed neonate. They are also often tasked with arranging the transfer in the private sector by contacting ambulatory services. The nursing staff will provide information regarding the patient's transport needs and level of care requirements.

The researcher will evaluate the data obtained and will monitor if any new themes emerge during the interviews. Once the researcher is satisfied and there are no new themes during the meetings, he will conclude that the data have reached saturation.

The interviews will be done by utilising the same open-ended set of questions to all the participants within the study (73).

Inclusion criteria

The researcher intends to include:

- Neonatology staff members with two or more years of experience within the neonatal intensive care setting from the referring facilities.
- Neonatology staff members with two or more years of experience within the neonatal intensive care setting from the receiving facilities.
- The participants must have experience within a private healthcare system because the study will be conducted within this setting.

Exclusion criteria

The study will exclude staff based on the following criteria:

- Staff providing neonatal care services on an ad hoc basis.
- Neonatal nursing staff permanently employed with less than two years of neonatal unit experience within the private sector.
- Provincial neonatal staff due to the vast differences in opposing transport and resource settings.
- Pre-hospital staff.

The researcher feels that the perceived barriers in the private sector would differ from the governmental healthcare systems. Therefore, he believes those two health systems may not be comparable in this study. The researcher believes that combining the governmental health system with the private sector in one combined study would skew the results and may lead to inaccurate conclusions and undermine the study's trustworthiness.

Pre-hospital staff exclusion

The pre-hospital emergency personnel are not involved with the transport arrangements before the ambulance control and dispatch centre's call placement. The

researcher believes that the ambulance emergency control centre will have different perceived barriers other than that of the in-hospital neonatal staff.

However, the researcher is aware that some of these barriers experienced by these separate entities might overlap. As the hospital staff often initiate the referral process, this study will focus on their perspective as an initial point of departure.

The researcher is aware that a need may arise to investigate other role players not identified at the beginning of the study to deepen the understanding of the perceived barriers to timely care for HIE neonates born outside the cooling facilities.

6.5. Recruitment of participants

The researcher will correspond with hospital managers as well as operational managers of the hospitals of interest. The correspondence will include the study's aim and objectives, with a brief description of how the study will be conducted.

This documentation will include permissions from the identified hospital groups with supporting approval documents of ethical clearance. All communications will be well-documented and filed.

The research will only proceed once written permission is obtained from both the hospital and the operational managers with complete approved ethical clearance. Recruitment of participants will follow the operational manager's recommendation and snowball effect up to a sub-minimum of 10 participants.

This hospital's structured shift system will allow the researcher to schedule interviews with the respective shift units within a window period of four weeks. The researcher aims to interview five participants from the day shift and five from the night shift.

The researcher believes that there might be some unknown differences or barriers related to the time of the day. The researcher speculates that there might be a difference in resource availability at night. The researcher assumes that a potential barrier to timely transport or treatment is possible during the handover from day shift

to night shift. The hospital handover time from day shift to night shift and visa-versa is in sync with the transport units and the control centre. This transition from one shift to the other may potentially have a negative impact on timely care.

These interviews will incorporate the neonatal doctors and nursing staff in both the referring and receiving hospitals. The researcher aims to interview a minimum of five neonatal care doctors from the referring hospitals and five from the receiving hospitals. The researcher believes that the essential data would be obtained within this group of participants. This group will be more exposed to the perceived barriers as they are directly involved with the transfer arrangements.

6.6. Research procedures and data collection methods

Data collection will be done by conducting personal interviews with participants on an individual semi-structured interview.

Interviews will be conducted on a time and place that is convenient to both the researcher and participant. The ideal location must provide continuous privacy during the interview without possible interruptions during the session. The primary researcher will lead the interviews and be responsible for collecting and safekeeping the gathered data during the planning phase.

Due to the current restrictions and social distancing protocol at play, as a result of the Covid-19 pandemic, other platforms could be incorporated as an interview option. Microsoft Teams, Skype or Zoom meetings are available to facilitate these meetings. These options will eliminate exposure and could take place at a time and place convenient to both the researcher and the participant.

The researcher decided that the semi-structured interview would yield better trustworthiness than a group interview or a combination of both. The researcher believes that a more personalised approach would allow the participant to answer more openly and provide a more in-depth perspective on the perceived barriers in definitive continuous care for neonates diagnosed with HIE who require TH therapy. The more personalised approach will reduce external factors that could alter the

information provided by the participant. Participants may feel influenced by colleagues and superiors if interviewed within a group context, leading to data that may lead to misinterpretation of the truth.

Furthermore, the semi-structured interview will allow the researcher to ask additional questions if needed to comprehend the participant's response and allow for consistency.

The interview questions will be open-ended, and the researcher will encourage the participant to reveal their personal opinions and experiences regarding the main topic. The researcher also wants to fully understand and appreciate their views on how they feel these barriers could be addressed in the future.

The researcher and supervisor will develop a structural approach to optimise the interview process to ensure that the questions asked will answer to the research question.

The interview process will then be simulated by using an exploratory rehearsal interview with the supervisor. The simulated interview rehearsal will allow the researcher to make changes if needed before commencing with data collection interviews. The interview process will be constructed in such a way to provide in-depth, meaningful information from an individual perspective.

6.7. Data safety and monitoring

During the interviews, the researcher will use a dual digital recording system as a fail-safe method in case the primary audio recorder fails. Upon completion of each interview, the audio recording data will be captured onto the researcher's private laptop.

The dedicated laptop is password-protected, and all information will be stored in a password-protected folder located within a cloud-based database. Access to this folder will be restricted to the researcher and supervisor only. After successfully capturing the data within this cloud-based folder, the data will be erased from both

audio recording units to eliminate any accidental leakage. All written copies of the processed audio files will be anonymised to eradicate any form of identification and will be stored and locked up in a secure location with restricted access. Consent documentation will be stored separately from other documents at a different secured location.

6.8. Data analysis

The data in this study will be obtained by making use of a well-constructed interview process. Content analysis will be performed, and the researcher will identify any repeated categories within the data.

6.9. Trustworthiness

The researcher is interested in the participants' opinions regarding the research question and will document the findings after the interview. However, the researcher will make field notes during the interviews, as additional information, to add a more in-depth perspective. The researcher will follow structural guidelines during the data collection strategy to ensure the trustworthiness of the study. This structure will include aspects like Credibility, transparency, Dependability and lastly, Confirmability (74).

6.9.1. Credibility

The participants are going to be sampled, as previously explained. The researcher will ensure that every participant understands the data collection process and the intended purpose thereof. The participants will indicate their willing participation in the study by completing the provided consent form.

The consent form will briefly explain the interview process, including that both audio and written data will be collected. The participant can then decide if he/she wants to partake in the study.

The researcher will also make use of a personal journal to reflect and investigate the developing categories. This journal inscriptions will aid the researcher in his elaboration on how he came to various conclusions. The researcher will rehearse the

intended interview before the interview with guidance from his supervisor. This procedure is to ensure that the research and the research questions adhere to the proposed research aim and methodology.

6.9.2. Transferability.

The researcher understands that qualitative research is based on the analysed data obtained from opinions. However, by a careful description of the setting in which the research took place and the recruitment procedures, the researcher will ensure that the reader will be able to contextualise the content to their context (74).

6.9.3. Dependability

This qualitative study aims to describe a phenomenon within a specific setting. The researcher will base his conclusions on the participant's opinions and the researcher's interpretation.

This process will be under supervision by the supervisor. Although the study's methodology can be repeated, the outcome may differ to some extent if the same study is replicated with the same participants. The researcher will also reflect in the final write-up of how effective the research methodology was to gain new insight and conclude its findings.

The researcher will describe how he comes to conclusions, including the coding methods utilised during data analysis, to indicate the processes. The complete process will be fully documented in the final write-up (74).

6.9.4. Confirmability

The researcher will ensure that the participant's opinions are captured and portrayed in the research. The researcher is aware of possible bias toward the research that could skew the results. To minimise potential bias, the research supervisor will objectively act as a secondary data analyser and quality control to minimise the potential bias. The researcher will ensure that the participant's opinions and views are captured with a detailed description and not that of the researcher.

6.10. The solution to perceived barriers

The researcher wishes to describe the perceived barriers in this study and believes that if this phenomenon is better understood and described, only then can recommendations be made for further actions.

However, the researcher will include opinions and recommendations from the participants on what they feel should be done in the future to eliminate these barriers.

Due to their in-depth knowledge of these barriers, they might be able to provide potential future solutions. Their contributions and insight can potentially aid in the changes needed to mitigate these perceived barriers. The researcher will make the findings of this study available to the relevant facilities, potentially leading to changes with a potential positive outcome towards better timely care.

7. Ethical considerations

7.1 Risks

However, the researcher does not foresee any risks to the participants, given that medical staff involved with children, especially the very young, may develop a bond with children they intensively cared for over some time. There might be a small risk that negative emotions may be provoked during participation in the interview due to a traumatic or previous emotional experience.

The researcher will terminate the interview immediately if the participant experiences any form of discomfort. The researcher will advise the participant to seek professional assistance.

Participant confidentiality is of paramount importance, and the researcher will ensure that anonymity is maintained throughout the research period and beyond. The participants will be referred to as numbers and not names during data processing. The names of the participants will be known to the researcher only. Furthermore, the information will be in a secure location in a locked personal safe. The researcher will

describe findings in such a way that readers will not be able to tie information to a specific individual.

Participation in the intended study will be conducted voluntarily, following a signed consent form that will be handed to the participant before the planned interview. A copy of the consent form will be given to the participant for personal use. This consent form will provide information regarding the withdrawal of participation and procedures to follow if a participant wishes to do so. This documentation will also include general information regarding the study.

By signing the consent form, the participant will agree that participation is willing without external peer pressure with an additional signature consenting to an audio recording of the interview. The researcher will allow enough time before the interview for the participant to read through the consent form and ask any questions to clarify any uncertainties. Participants will be able to ask questions during and after the interview if he/she requires additional information or if any further explanation is needed.

The participant will be ensured that they will be quoted anonymously. Data will be portrayed in a way that the identity of the participant cannot be identified by any means.

The researcher will ensure all participants that all identification information will be kept confidential and that only the primary researcher will know the participant's identity. Furthermore, he will ensure the participants that this information will be stored in a secure location.

7.2 Informed consent

If a participant is identified and willing to dedicate his/her time to partake in the study, the researcher will arrange a time and date that will be convenient. Before commencing the interview, the participant will be allowed to read through the consent form carefully. The researcher will make sure that the participant fully understands the document's contents before signing. The researcher will answer any questions that may arise to clarify any uncertainty. The consent form will briefly explain the focus of

the research with additional information regarding participant information and data security, including withdrawal from the study procedures. The researcher will inform all participants that the interview will be audio-recorded and that the researcher must obtain consent before the interview process (Annexure A).

The consent form will underline that the participant voluntarily partakes in the study and that no negative consequences will follow when his/her right to withdraw from the study is being exercised. The researcher will provide a complete copy of the consent form to the participant to take home.

7.3. Privacy and Confidentiality

The identified participant will be approached in private and ensure that his/her decision to participate in the study will be kept confidential.

The researcher will ensure that the participants remain anonymous and that they will only be known to the researcher. This sensitive information will be kept in a safe location with restricted access to the researcher alone. The audio recordings will be uploaded in a restricted access cloud folder password-protected and accessible by the researcher only. The information provided during the interview will be documented as a participant number only. The researcher will only know the allocated participant number and corresponding name. In the unlikely event that the participant withdraws from the study, the researcher will be able to identify the interview and eliminate the specific data from the study. The participants will not be able to view any of the completed interviews, nor will any names be made available.

7.4. Reimbursement of participants

The participants will be informed that no financial or other benefits will stem from their participation. The agreement to partake in the study is entirely voluntary in nature, which will be disclosed before signing an agreement at the start of the interview.

8. Dissemination of findings

The researcher intends to make the study results available with the prospects of a journal publication.
The research will also be made available on the Open-UCT research platform with open access to the PDF format. The final paper will also be made available to the Head of the Department and those who deal with Open access journals.

The researcher hopes that the findings will promote awareness and stimulate further research investigating strategies on how to address the perceived barriers to timely treatment of HIE neonates who require cooling.

Transcription

The preferred language during the interviews will be English. However, the researcher is aware of the dual language use in most of the hospitals within the Western Cape. All the targeted participants of this study are believed to be bilingual and can understand English, but the researcher will incorporate Afrikaans if the participant feels more comfortable in doing so.

The researcher believes that a more profound expression and richness of data can be obtained if the participant is expressing him/herself in their primary language of choice if needed. The researcher will translate and describe all the Afrikaans during the analytic procedures of the study. The researcher will translate the intended question in Afrikaans during the interview if the need arises to ensure that the participants fully understand the questions.

9. Project timeline

Research phase	**Date**
EMDRC	2019/10/30
Ethics	2021/02/30
Data gathering	2021/04/14 – 2021/10/15

Data Analysis	2021/11/01
Draft for review	2022/01/15
Final draft	2022/05/10
Submission	2022/05/20

10. Resource utilisation

The researcher will use private transport during the study duration and be responsible for the costs involved, including the procurement of a reliable digital audio voice recorder and printing. The researcher will use a personal laptop with access to a cloud-based data storage application. The researcher will pay for the data used during the research period if no Wi-Fi access is available.

11. Budget

Transport costs				**TOTAL**
Printing costs				
Protocols				
Informed consent forms				
Informed consent supporting				
Documentation				
Manuscript				
				R 450
Transcription costs	Self			
Audio	15/minute	45 min x 20		
Language editing				
Other				
Data				R 700
Recording equipment	1 unit			R 700
		Estimated TOTAL R 2666.00		

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12. Appendices

Appendix A
CONSENT FORM

THE BARRIERS TO TIMELY THERAPEUTIC HYPOTHERMIA TREATMENT FOR NEONATES DIAGNOSED WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY WHEN BORN OUTSIDE THE COOLING FACILITY IN THE PRIVATE SECTOR

Name of Primary Researcher: Wardi de Wet

Name of Affiliations: University of Cape Town

Name of Research Supervisors: Dr Willem Stassen and Dr Ricky Dippenaar

This **two-part** consent form is for the participants partaking in this study and will be interviewed using an individual semi-structured interview structure.

Part one of this consent form will contain all relevant information on the study, as well as contact numbers for further information details if needed.

Part two of the consent form will be the section of the consent form that is signed by the participant when he/she gives consent to his/her participation in the study. Two copies will be provided, one for the researcher and one for the participant.

Part One.

I, Wardi de Wet, am the primary researcher in this study that will research *"The Perceived Barriers to Timely Therapeutic Hypothermia Treatment for Neonates Diagnosed with Hypoxic Ischemic Encephalopathy (HIE) when Born Outside the Cooling Facility."* This study is part of my Masters in Philosophy: Emergency Medical Care at the University of Cape Town.

This document will provide you with information about the research. The researcher invites you to partake in this study and will value your contribution.
Your participation in this study will be entirely voluntary, and you are under no obligation to partake in the study. If you feel that you do not want to continue with the study, you may withdraw, even if the consent form was signed.

Interview process

The interview process will follow a specific structure

1. Background information on the research.
2. The interview is based on a one-on-one interview, done virtually
3. Consent documentation discussion.
4. The interview will last no longer than an hour.
5. The interview will incorporate 5-8 questions.
6. The interview will be recorded on an audio recording device.
7. There will approximately be 10 participants in this study.

Risk and benefits

The researcher does not foresee any direct or indirect risks to the participant. All the information will be handled by the researcher alone and stored in a private and secure location, including all audio recordings and the consent documentation. Names and other personal information will not be made available to any other persons, including the supervisor of the study, to mitigate and prevent any risks.

There will be no financial benefits to any of the participants or the affiliated hospital or specific unit in the hospital.

Ethics Clearance and Approval

This research project will be submitted to the "*University of Cape Town's Human Research and Ethics Committee*" to ensure that all ethical criteria are met before approval is granted.

This research study follows the ethical guidelines as described in the "Helsinki Declaration" and the "*South African Good Practice Guidelines*."

Contact details

The researcher invites you to contact him if further information is needed or any other questions you may have regarding the research.

Cell no.: 072 622 2088
Email: DWTWAR001@myuct.ac.za

The Human Research Ethics Committee

G 50
Old Main Building
Groote Schuur Hospital
Observatory, 7925

Tel +27 21 406 6340
+27 21 650 3002

Part 2

CONSENT CERTIFICATE

THE PERCEIVED BARRIERS TO TIMELY THERAPEUTIC HYPOTHERMIA TREATMENT FOR NEONATES DIAGNOSED WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY WHEN BORN OUTSIDE THE COOLING FACILITY IN THE PRIVATE SECTOR

I, _____, the participant has read and understand the content of the consent form and had the opportunity to ask questions or seek deeper understanding. I understand that my participation is completely voluntary and that I was informed that I may withdraw at any stage from the study.

I am aware that I will not receive any remuneration for my participation in this study at any point in time, even if my information is used in this study.

I am also aware that my interview is audio-recorded for data gathering purposes and will be analysed later.

I am aware that the researcher will keep a signed copy of my consent form for safekeeping.

Name_____

Date_____ Place _____

Signature_____

Researcher signature _____

Interview schedule

THE PERCEIVED BARRIERS TO TIMELY THERAPEUTIC HYPOTHERMIA TREATMENT FOR NEONATES DIAGNOSED WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY WHEN BORN OUTSIDE THE COOLING FACILITY IN THE PRIVATE SECTOR

INTERVIEWER NOTES:

For the interviewer's ease of use, all notes to the interviewer will be in *ITALIC* font. All the questions and information to the participant will be in **BOLD**. Additional information regarding the questions will be in a textbox under the heading "Further Prompts" and can be used to encourage further dialogue.

FACILITATION:

The interviewer is responsible for the audio recordings and taking additional notes during the interviews. Therefore, the interviewer must be familiar with the interview process. The primary researcher will lead all the planned interviews and are responsible for the accurate capturing of the gained data.

Due to the sensitivity regarding neonatal care and treatment of children, the researcher is aware that past negative experiences may trigger an emotional event.

The researcher is responsible for the safety and wellbeing of the participant during the interview. Therefore, the interviewer must be sensitive to emotions that past experiences could provoke. The interviewer must stop the interview if any signs of distress are noted.

PREPARATION:

The researcher must ensure that audio recording equipment is in good working order and that the equipment's placement is optimised to record both the interviewer and participant. Ideally, the equipment must be tested before the interview.

The researcher must ensure that all legal documentations are available before commencing with the interview. This documentation will include two (2) copies of the consent form (one for the participant to take home for personal reference). The researcher must ensure that the content of the consent form is understood and signed before the interview. Furthermore, consent must be recorded on the audio recording as part of the interview process.

CONFIDENTIALITY STATEMENT

Thank you for the time and effort to participate in this research project. Your valuable input will always be kept confidential. There is no right or wrong answer to any of the questions. This interview aims to obtain your opinion and thoughts, and you may add additional information to any of the questions later.

Please take note, that you are entitled to withdraw at any time from the study if you wish to do so, even if you have signed the consent form.

I further need to inform you that the interview will be audio recorded.

Ask the participant if there is any objections or concerns.
"Do you have any concerns or objections, and is there anything else that you want me to explain further?"

Make sure that the participant understands "consent" and answer any questions regarding this topic.

SESSION INTRODUCTION

It is essential to ensure that the participant introduces him/herself on the audio recording at the beginning of the interview for good recordkeeping. This information will also include the interview number with time and date information that the interviewer will state.

The interviewer will state the time and date, followed by the interview number.
Start the recording.

Good day, thank you for taking part in the interview on the (date/time interview no. -----). Will you please state your name and surname for recording purposes.

Do you partake in this study willingly?
Did you read the consent form and understand all the content?
Are you aware that you can withdraw from the study at any time, even if the consent form was signed?

Read the following introduction statement to the participant.

Thank you for partaking in this study. I would like to use this time to obtain your opinion regarding the:

"THE PERCEIVED BARRIERS TO TIMELY THERAPEUTIC HYPOTHERMIA TREATMENT FOR NEONATES DIAGNOSED WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY WHEN BORN OUTSIDE THE COOLING FACILITY"

Childbirth is seen as a natural event and an essential aspect of the circle of life and our existence. However, childbirth comes with risks to both mother and baby, and despite medicine's best efforts to reduce mortality and morbidity, not all uncertainties are being eliminated (66).

Although there are many risks to neonatal health during childbirth, hypoxia remains one of the well-known contributing factors in neonatal mortality and morbidity (67).

Hypoxic-Ischemic Encephalopathy is known for having potential long-term effects or causing premature death in neonates. The primary insult is mostly at a neurological level due to the brain's inability to cope during a prolonged hypoxemic event during birth or shortly thereafter (67).

A study done in South Africa found that of the 21 086 live births evaluated, 8.7 to 15.2/1000 suffered asphyxia, with HIE ranging between 8.5 to 13.3 per 1000

live births. It was calculated that 60% of HIE cases were classified as moderate to severe, while mortality rates within this group were as high as 7.1%(47).

Once recognised, the treatment of HIE neonates should commence as soon as possible. The treatment of choice for HIE is Therapeutic Hypothermia (TH) and should only be done in health care facilities which are capable of providing such treatment. Unfortunately, the most significant percentage of babies are born at facilities that do not have the equipment or trained staff to provide this specialised care. The preferred practice is to transport these patients to designated facilities that are capable of providing therapeutic cooling. The one factor that adds to the complexity of HIE treatment is time.

I would like to obtain your opinion and past experiences regarding those babies that are diagnosed with Hypoxic Ischemic Encephalopathy or those suspected to have been exposed to a hypoxic event.

If you do not understand the question or need more clarity, you can inform me, and I will explain the question to you.

There are no wrong answers to any of the questions.

Please read the following questions to the participant.

1. Can you please elaborate on your medical training, background and experiences within the neonatal context?

Further prompts
Your specific training in neonatal care? *Years' experience in neonatal care?* *Neonatal care experience in other settings (maternity units)?*

2. In those babies that do not make the theoretical 6-hour window period for therapeutic cooling, what will you say is the timely treatment's perceived

barriers? In other words, what are the biggest obstacles, difficulties that are responsible for the delay in cooling therapy?

- *Is it an administration problem? Opening of folders, loading of patient information on the health system database before the patient can be transported.*
- *"Booked or un-booked mothers"? Treatment consent from parents/guardians.*
- *Communication problem (between staff and doctors, hospital to hospital)?*
- *Finding a facility to accommodate the patient?*
- *Do you think equipment plays a role (ventilated neonates vs. non-ventilated neonates)? The availability of a ventilator can be a delay.*
- *Second opinion/consultation delays?*
- *Transport complications? Wrong ambulances, call centre's lack of understanding the urgency.*
  In your opinion, do you think that a lack of urgency from the staff could be one of the perceived barriers?

3 If you are tasked to make any changes or suggestions to clear up these barriers, please elaborate on what changes will you make?

Regarding the HIE or potential HIE patient, from the time the baby is born until the time the baby leaves your facility, in your opinion, what are we doing correctly? In other words, is there anything that you will say must stay as it is?

4 In your opinion, what do you think your colleagues feel or say about these perceived barriers?

- *Will you say they all share your opinions, or do you think they have a different opinion regarding the HIE neonates' timely treatment?*
- *What difficulties do you think will **other** referring hospitals or neonatal units experience within the government health system?*

Thank you so much for your participation in this study. Your input is of high value and will be used to help make changes to provide the optimal care for our patient

Appendices D:
Research permission letter

Good Day Dr Du Plessis and DR Van Zyl (head(s) General manager Clinical Service

I hope this email finds you well.

I am currently a Critical Care Retrieval paramedic for Er24 based at Constantiaberg Mediclinic. I am also a student at the University of Cape Town enrolled in a Master's program in Emergency Medicine. My research is mainly focused on neonatal care. The reason for this is twofold. I always had an interest in neonatal medicine, and secondly, a large portion of my patients fall within this patient population, including the micro-premature.

The next step in my research project is the data collection phase. This study's data will be generated utilizing a Semi-structured interview process with neonatal staff at various Mediclinic facilities and other private hospital groups within the Cape Town Metropole. For this phase, I will require written permission from each hospital group.

This research project is registered under the title:
"THE PERCEIVED BARRIERS TO TIMELY THERAPEUTIC HYPOTHERMIA TREATMENT FOR NEONATES DIAGNOSED WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY WHEN BORN OUTSIDE THE COOLING FACILITY IN THE PRIVATE SECTOR"

This research project was also submitted for ethical clearance as part of the registration process. Ethical clearance was approved from the University of Cape Town (REF 117/2020) Student nr DWTWAR001.

Can you please advise me on what steps I must follow to go forward with the project?

Kind Regards

Wardi

From:
Hallick, Juanita <Juanita.Hallick@Mediclinic.co.za>
To:
Wardi de Wet <wardimadel@fastmail.net>
Cc:
Brown, Lynre <Lynre.Brown@Mediclinic.co.za>, **Africa, Michelle** <Michelle.Africa@Mediclinic.co.za>
Subject:
Research approval - Wardi de Wet - Mediclinic Cape Town
Date:
Wednesday, 21 April 2021 10:19

Dear Mr De Wet

Attached kindly find a letter granting you approval to conduct your research at our facilities.
Kind regards

Juanita Hallick (Clinical Services)

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21 April 2021

Mr W de Wet
No.1 Rosecombe Estate
Berghowe Street
Somerset West
Western Cape
7130

E-mail: wardimadel@fastmail.net

Dear Mr De Wet

PERMISSION TO CONDUCT RESEARCH AT MEDICLINIC CAPE TOWN

Your research proposal entitled "The perceived barriers to timely therapeutic hypothermia treatment for neonates diagnosed with hypoxic ischemic encephalopathy when born outside the cooling facility in the Private sector", refers.

It is in order for you to conduct your research at Mediclinic Cape Town and I wish you success with this project.

Yours sincerely
Yours sincerely

pp.

DR CHRIS DU PLESSIS
General Manager Clinical Services

Ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

26 February 2021

HREC REF: 117/2020

Dr W Stassen
Division of Emergency Medicine
F-51 OMB
Email: willem.stassen@uct.ac.za
Student: wardimadel@fastmail.net

Dear Dr Stassen

PROJECT TITLE: THE PERCEIVED BARRIERS TO TIMELY THERAPEUTIC HYPOTHERMIA TREATMENT FOR NEONATES DIAGNOSED WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY WHEN BORN OUTSIDE THE COOLING FACILITY-MPHIL CANDIDATE-MR W DE WET

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 28 February 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Mr Wardi de Wet will also be involved in this study.

Please quote the HREC REF 117/2020 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

HREC/REF 117/2020ss