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Title A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. Abstract Introduction: Hypothermia is a neuroprotective strategy proven to reduce death and disability in children presenting with Hypoxic Ischemic Encephalopathy (HIE). Little evidence exists regarding the long term developmental outcomes of infants who received hypothermia within a secondary hospital in South Africa. Method: This paper describes the long term (up to five years) developmental outcomes of 30 infants with HIE who received hypothermia at the x hospital in South Africa. Developmental outcomes were measured at 3, 9, 12, 24 and 36 months using the Strive Towards Achieving Results Together (START) and at 48 and 60 months using the Early Childhood Developmental Criteria (ECDC). Summary data (variables considered risk factors) are described in relation to developmental outcomes. Results: The results indicate that 20 infants present with typical development, eight presented with cerebral palsy (CP) and two were lost to follow up. Results further support a significant correlation between a severe HIE score and CP with a p-value of 0,008. The children presented with difficulties with spatial perceptual abilities (4 years); number and form concepts (5 years); persistent delays with fine motor abilities (5 years) and difficulties with directionality (4 and 5 years). Conclusion: This study demonstrated that long term occupational therapy follow up of children with HIE is essential to monitor development and provide intervention to prevent barriers to learning at a later stage. This study also advocates the need for clinicians in the public health sector to have access to standardised assessment

tools to closely monitor the development of infants who presented with HIE at birth. Key words: Hypoxic Ischemic Encephalopathy, hypothermia, developmental outcomes, environment INTRODUCTION X hospital is a secondary hospital which collaborates with X Hospital, a tertiary institution, to provide input and guidance in the use of hypothermia for newborn infants presenting with Hypoxic Ischemic Encephalopathy (HIE). In November, 2009 hypothermia was introduced at the X Hospital and the occupational therapists were requested to assist with evaluating the A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 Commented [WU1]: Name the outcome measures used Commented [GAD[2]: Present correlation developmental outcomes of these infants. To date, research evidence has firmly established that hypothermia is effective in the reduction of death and disability amongst infants with HIE, 1,2,3 but the long term developmental outcomes of infants who received hypothermia are still uncertain. This study, which commenced in 2010, describes the long term (up to five years of age) developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital. Data collection ended in 2019. This long term study is unique in its kind as it is one of a few South African studies having followed up on the developmental outcomes of children more than 2 years of age. The objectives of this study were: 1. To document summary data (variables considered risk factors for HIE) and their possible impact on developmental outcomes. 2. To measure and describe the developmental outcomes of infants with HIE who received hypothermia at the GPH at the ages of 3, 9, 12, 24, 36, 48 and 60 months. The context of these children is also unique as they received hypothermia at a secondary hospital in a low resource setting in contrast to the majority of studies which have been undertaken at tertiary hospital settings.4 While occupational therapists in South Africa have been involved in the follow up of developmental outcomes of infants who received hypothermia these studies typically presents on isolated aspects of development such as gross motor development.5 This study adopted a holistic approach to development and evaluates gross motor, fine motor, speech and language as well as cognitive development of the children. While it is widely known that the social context in which development takes place has a direct impact on the development of a child this study did not aim to describe the socio-economic factors impacting on the children's development. The parents of the children accessed the X Hospital where free medical services were provided, which can reflect their socio-economic status. The context in which the children grew up in can generally be regarded as limited in resources with restricted access to high quality early childhood development intervention programs. LITERATURE REVIEW Hypoxic ischemic encephalopathy (HIE) Perinatal asphyxia has been defined as 'a delay in establishing spontaneous respiration upon delivery of a new-born'.6 (p8) HIE is a term used to describe the 'neurological syndromes that occur following perinatal asphyxia'. 6 Perinatal asphyxia is a common and an important cause of death in children in South Africa. 7 Signs of asphyxia at birth contribute to approximately A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 23% of the 4 million neonatal deaths and 8% of all deaths in children under five years of age throughout the world. 6 In developed countries, death or disability has been recorded in 53% to 61% of infants diagnosed as presenting with moderate to severe HIE. 8,9 Various studies have found that HIE following birth asphyxia contributes greatly to neonatal mortality and morbidity including long-term neurodevelopmental

disability in up to 25% to 60% of survivors.1, 9, 10 The HIE Score The HIE score is a clinical assessment tool consisting of clinical signs that are closely associated with the Central Nervous System (CNS). It is used to assess the status of the infant following birth asphyxia. A score between 1 and 10 indicate mild HIE, a score between 11 and 15 is interpreted as moderate HIE and a score between 15 and 22 is considered as severe HIE.11, 12 Most authors refer to this score as the Thompson HIE score. One study showed that, in infants who suffered birth asphyxia, the HIE score can be used as an accurate predictor of neurodevelopmental outcomes at 6 months of age.6 A study by Pin, Eldridge and Galea13 showed that infants with a severe HIE score correlated with a high incidence of death and morbidity, where neonates with a moderate score had varied developmental outcomes and those with a mild score tended to show normal development.13 Commented [GAD[3]: insert numeric reference should go here Hypothermia Hypothermia is a neuroprotective strategy where the core body temperature of a full term infant is reduced by 3 to 4 degrees within 6 hours of birth. The process of hypothermia is sustained for 72 hours before gradual re-warming commences.14 A Cochrane review published in September 2013 included 11 randomized controlled trials comprising of 1505 term and late preterm infants with moderate or severe HIE.15 The use of hypothermia in these infants resulted in a statistically significant and clinically important reduction in the combined outcome of death or serious disability at 18 months of age. Based on South African research, hypothermia has been described as a feasible treatment to use in a resource-limited setting when done within a strict protocol.16 Long term developmental outcomes following HIE and hypothermia Various studies have advocated long term follow up of developmental outcomes to determine the long-term effects of hypothermia. 1,2,3 This is imperative as it is known that subtle neuro- developmental disabilities such as perceptual and learning difficulties only come to light at school going age.13 A study by Shankaran "et al"17 reported on the long term developmental Commented [WU4]: check referencing conventions outcomes of children aged 7 to 8 years assessed by the WeeFIM parent questionnaire, who A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 presented with HIE at birth. Cognitive, attention, executive function and visio-spatial abilities were evaluated with data available for 122 of the participants. Attention-executive dysfunction occurred in 4% of children receiving hypothermia and 13% of those receiving usual care. Visio- spatial dysfunction occurred in 4% and 3% respectively. 17 Newman and DeLoach18 Commented [WU5]: I quite like this way of reporting. commented on the cognitive abilities of infants with moderate HIE who were not cooled when Commented [WU6]: Check referencing comventions compared to those who received hypothermia. No differences were found between the two groups in terms of general cognitive ability, but children who were not cooled went on to demonstrate less ability in language/sensorimotor domains, narrative memory and sentence repetition. 18 Commented [WU7]: What do they mean here? They had no A study by Shankaran published in 201419 reported on the neurological outcomes, cognitive, other obvious impairments? Commented [WU8]: Insert reference attention, executive and visuo-spatial function as well as physical and psychosocial health of children with data available among 190 of 208 of the children. Death or IQ < 70, as the primary Commented [WU9]: Living where outcomes, was noted among 47% of the hypothermia group and 62% of the control group. Neonatal research network trial USA Secondary outcomes included the mortality rate of 28 to 44 %,

death or CP of 41 to 60% and death and severe disability of 41 to 60% in the hypothermia and control groups' respectively. 19 A study performed in Western Australia reported on the outcomes of 65 infants who received hypothermia. Out of the 65 infants, 13 had mild, 35 had moderate and 17 had severe HIE. Nine of the 13 infants who had mild HIE were followed up and had no disability. Among 52 infants with moderate to severe HIE, there were nine deaths and developmental outcomes were available on 39. The incidence of severe disability for this group was 23%. 20 Study population, sampling and sample size The study population consists of all term infants from X presenting with HIE who received hypothermia at the X Hospital. The researchers made use of non-random consecutive sampling as a means to obtain participants for the study. In view of time, staff and cost constraints the study was able to accommodate 30 participants. Commented [WU10]: What was the size of the total population during this period? Was a sample size determined? Commented [S11R10]: It is not known what the size of the Measurement instruments total population was. Non-random consecutive sampling does not require of the researcher to know what the total population was or to determine a sample size. It merely requires the researcher to Based on the literature reviewed the researchers identified developmental assessments obtain one participant after the after (consecutively) until you have reached the sample size determined by the researcher (based on frequently used to determine developmental outcomes of infants presenting with HIE following what he/she can accommodate). By implication, the findings cannot be generalised to the overall population. birth. These include the Bayley Scales, Vineland Adaptive Behaviour Scale, Griffiths and This is an easy way to obtain your sample size, but it has its Peabody Motor scales.6 These developmental assessments are, however, not readily limitations. available to the researchers in their local context. The researchers therefore used the START as a measuring tool to assess developmental outcomes from birth to three years and the ECDC at 4 and 5 years of age as both these tests are readily available in the department of occupational therapy at the X Hospital. Children with CP were assessed by means of the Gross Motor Function Classification System (GMFCS) – Expanded and Revised. The A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 researchers followed the definition for cerebral palsy, as described by Mutch21 et al, as 'an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development. The START is a developmental assessment and intervention program developed by the Sunshine Foundation in Johannesburg, South Africa by Solarsh, Katz and Goodman.22 Its main purpose is to assist caregivers in the identification of areas of development that are potentially problematic (Human and Social Development). Four developmental areas are assessed, namely gross motor development, fine motor development, communication and activities of daily living (ADL). Since the tool is not designed as a measurement instrument there is no published data available on the validity and reliability of the START. As no numerical values are attached to the various developmental areas assessed, the researchers have adapted the START by assigning values. If a child is able to, for example, lift his/her head while in prone at the age of 3 months the child scores 1. Should the child not be able to perform this task, the child scores 0. Within the context of this study, the START was used to assess the developmental outcomes of children from 0 months to 3 years at the following ages: 3 months, 9 months, 12

months, 18 months, 24 months and 36 months. Commented [S12]: See detail added as resquested in previous comment The GMFCS - E&R is based on self-initiated movement, with emphasis on sitting, transfers, and mobility. 6,23 The aim of the GMFCS - E & R is to assess a child or young person's abilities and limitations relating to gross motor function in everyday life.23 It consists of a five-level classification system which indicates the child or young person's ability to mobilise. Level I indicates good mobility whereas Level V indicates severely impaired mobility. Commented [S13]: Insert visual of GMFCS here. The ECDC was developed by a South African occupational therapist, Ingrid Herbst, with the specific purpose of evaluating the extent to which children have accomplished developmental tasks underlying school readiness. Its culture-reduced nature makes it suitable for application in a wide variety of contexts. The ECDC test comprises three subdivisions: cognitive aspects, fine motor co-ordination and gross motor skills.24 With coefficients of r = 0,85 and r=0,93 for the cognitive and motor subsections respectively, the test showed high test-retest reliability. The inter-rater reliability of the test was investigated and correlations of 0,99 were obtained for both the cognitive and combined motor scores of the scales. Component and factor analyses were conducted to establish the factorial validity of the scales. The results supported the construct validity of the scales. The norm group is based upon the data of more than 900 children.24 A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 Commented [WU14]: You can provide some detail as to how you used them specifically. Summary data consists of a list of variables that have been derived from literature on HIE and hypothermia4. The absence or presence of these variables is considered risk factors for developmental delay in children. Summary data described in this study consists of the gender of participants, Apgar scores, HIE scores, possible reasons for HIE, and HIV exposure. The data was collated from the medical folders. As the majority of summary data were collected retrospectively there are incidences where data was outstanding. Analysis The outcomes from the summary data sheet yielded nominal variables. Developmental outcomes as well as certain outcomes from the summary data sheet are expressed as discrete variables. The researchers carefully checked the data collected to identify errors which could possibly influence and bias the results. By examining the graphical display of data the researchers decided which measures to use to summarize and describe the categorical and numerical variables.25 The researchers analysed the data relating to outcomes as measured with the START by drawing stem and leaf plots of every area of development evaluated at every age. Based on the stem and leaf plots, it was evident that, in all areas of development across all age groups, the data was skewed towards high scores. Because of this reason, the researchers decided to use the median rather than the mean to express the data. By implication the children were able to perform the developmental tasks expected of them. The total scores of each area of development differ from each other and between the various age groups. The researchers therefore expressed the median as a percentage to be able to compare the different areas of development with each other and over the various age groups. Statistical analysis was performed with the Fischer's Exact Test by grouping data in 2 by 2 tables. A p-value of less than p = 0.05 was regarded as significant. Commented [WU15]: Reference literature Done Commented [WU16]: Reflect how you managed missing data as per our skype discussion Ethics Ethical clearance was granted by the Human Research Ethics Committee from the Faculty of Health Sciences at the University of Cape Town (HREC REF

number is 261/2012). Results Summary Data The results from summary data variables in relation to developmental outcomes are described in Table I. The only variable which correlated with developmental outcomes is the HIE score, with a severe HIE score indicating a significant likelihood of CP. A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 Table I: Results from the summary data in relation to developmental outcomes Commented [WU17]: Double check against data set The possible reasons for HIE as recorded in the medical folders are listed in Table II. Prolonged stage 2 labour accounted for a third of the possible reasons for HIE. Table II: Possible obstetric reason for HIE as recorded in the medical folder The age of the mothers at the time of the babies' birth is depicted in Figure 1. Seven mothers were younger than 20 years and two thirds of the mothers were younger than 25 years of age. The average birth weight of the babies were 3317 grams. Commented [GAD[18]: Maybe a pie chart or bar graph? Commented [S19R18]: With a pie chart we are going to need too many colours with all the '1' values… not going to be easy to follow. Same with bar graph – when having to type the various reasons on the axis… font is small to fit it all in Figure 1: The age of the mothers at the time of the babies' birth Developmental data When measured with the START the overall developmental data of 30 children indicated that eight presented with CP and 20 children presented with typical development. One child passed away on day six following birth and 1 child was lost to follow up following birth. Of the 28 children who were followed up five children did not attend all of their follow up appointments. Two were followed up at 12 months, one followed up at 6 months, another followed up until 36 months and the fifth child followed up until 9 months. During these evaluations it was evident that the children presented with typical development when evaluated with the START. The researchers went on to assume that these five children would continue to follow a pattern of typical development, and the number of children reflected upon in the sample is provided as 20 (n=20). The assessment results of the children who presented with typical development as evaluated with the START are illustrated in figure 2. Figure 2: Developmental outcomes of typically developing children when measured with the START The median of each developmental area at each age bracket is expressed as a percentage to standardise between the various age brackets figure 2. Gross motor development remains consistently high across all the age brackets with a slight decrease at 36 months. This could be attributed to two of the gross motor tasks namely 'pedalling a tricycle' and 'starts to use a bat and ball'. Both of these activities are dependent on equipment, which many of the children do not have access to due to socio-economic constraints. There is a decrease in fine motor development at 9 months with a return to age expected norms at 12 months and then a gradual decline from 12 months to 36 months. The most common fine motor tasks that children found A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 Commented [S20]: Should we consider the link to HIE here?? Commented [GAD[21]: I was about to ask this. Is age a variable linked to HIE? Commented [S22]: In the discussion we reference a South African HIE study where the average age of the mothers at the time of the babies birth is younger than 28 – similar to our study. Age is therefore not considered a variable link to HIE. Commented [WU23]: Did you follow up these children? Commented [S24R23]: Yes, we did. Their development is described a little further down. Commented [S25]: Is there a more scientific way to describe this? Commented [GAD[26]: Wording? Des

comment: Can we leave this sentence, we already indicate in the START diagram difficult at 9 months were the ability to pick up and hold 2 objects in 1 hand and the ability to hold 1 object in each hand. At 24 months placing a square and triangle into a form board was singled out as the most common fine motor task that this age group struggled with. Again, this is a task dependent on access to educational toys. At 36 months fine motor tasks included more complicated tasks such as snipping with a scissor as well as aspects closely related to cognitive development such as matching colours and pointing to body parts. The development of these abilities are linked to access to quality early childhood development education. The development of communication skills also remained consistently high except for a slight decline at 12 and 24 months. It is likely that the requirements in terms of communication in these two age brackets are slightly high, but that children are able to master communication tasks over a period of time as indicated by the median of 100% at 36 months. Children's' abilities to perform ADL are consistently high except at 24 months where one of the tasks requires children to be dry during the day. Most children were not yet ready for potty training or did not as yet master this task. The children's development was evaluated with the ECDC at the ages of 4 and 5 years respectively. These evaluations were only performed with children who presented with typical development as measured on the START. The results of the ECDC evaluated at 4 and 5 years are reflected in figure 3. The results depict the outcome of the ECDC index cognitive, fine motor and gross motor development. The ECDC does not differentiate between average and above average performance. Figure 3: The results of the ECDC evaluation at 4 and 5 years At 4 years just over half the children scored average and above average on all three domains of development assessed. It is interesting to note that the children performed equal on all three domains at 4 years. This changed at 5 years with poorer outcomes on the ECDC Index and fine motor development and a better score on gross motor outcomes. More children also score below average on fine motor outcomes and the ECDC Index at 5 years (n=9) than at 4 years (n=6). The ECDC cognitive index consists of 10 subdivisions. When looking at the number of children who obtained an average and above average score on the ECDC Index at 4 and 5 years it is evident that they struggled more with particular activities. The activities listed in Table III are arranged in order of those which most children mastered to those with which most children struggled with differences at 4 years and 5 years described. Commented [GAD[27]: Although 36 months is the lesser value? A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 Table III: The components of the ECDC cognitive index in relation to the number of children who obtained an average and above average score at 4 and 5 years respectively Colour concept was the activity both age groups performed the best in, while directionality emerged as the activity in which both groups performed the poorest. Visual perceptual tasks such as visio-motor integration, stick and block building and picture interpretation improved between 4 to 5 years. Children struggled more with number and form concepts at 5 years when compared to their performance at 4 years. The GMFCS is used to describe the development of the children with cerebral palsy. The GFMCS level gives an indication of the degree of functional mobility impairment. Of the eight children who presented with CP, two passed away at the ages of 3 years 6 months and 5 years 3 months respectively. Four of the seven children with CP who were followed up, had a severe HIE score and were on Level V when assessed with the GMFCS. One child with a moderate HIE score

and one with a mild HIE score were both on Level V of the GMFCS. The remaining one child with a moderate HIE score was on Level I of the GMFCS. Discussion and implications Summary data An analysis of the demographic and summary data showed that neither gender nor Apgar score showed a statistically significant correlation with developmental outcomes. The current research concluded that severe HIE scores correlated significantly with CP (p = 0,008). This aligns with the results of a South African study which similarly showed that severe HIE and an abnormal MRI were associated with death and severe impairment. 16 In this study prolonged stage 2 labour accounted for most instances (36%) as possible reason for HIE compared to the South African study by Horn26 where the meconium stained liquor was recorded in most cases (39%) followed by abnormal foetal heart rate in 36% of cases and prolonged stage 2 labour in 20% of infants with HIE.26 It appears that the peripartum complications differ from study to study. It is dependent on the doctor's objective description at the time of labour.26 The current research further supports the results of previous studies, which have shown that infants who present with a mild HIE score will demonstrate normal development9. The study by Pin13 indicated that a moderate HIE score is indicative of varied developmental outcomes. While this study found that 2 out of 3 children with moderate HIE scores presented with normal development, these numbers are too small to draw conclusions on. Commented [WU28]: Check conventions for SAJOT I think when we submit, this is reflected in an appendix A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 Of the four children who were RVD exposed, two demonstrated normal development and two were diagnosed with cerebral palsy. Le Doare27 found that in early infancy to 2 years children who were HIV exposed at birth, did not demonstrate any global delay, however during the preschool years these children had subtle cognitive, motor function, expressive and receptive language deficits. By implication, these children would require follow up and possible intervention during the preschool years. Developmental outcomes When considering the results of the ECDC at four years, the performance of the children in the various categories of development could be indicative of the sequence of development of skills based on children's exposure to stimulation. At 5 years, gross motor development seemed to be developed best followed equally by fine motor development and cognitive development. It is likely that the participants of this study grow up in environments where children are exposed to outdoor play for a large part of the day. This is in keeping with the South African study of Sukha5 who found that infants who presented with moderate HIE at birth had fewer delays in gross motor skills than with fine motor skills when measured at 1 and 2 years. Another South African study by Munro, van Niekerk and Seedat28 also commented on better than expected gross motor skills of South African children from disadvantaged contexts. These authors observed that children from disadvantaged backgrounds are typically not well-supervised and more likely to engage in unrestricted play in open spaces such as the streets of their communities. This kind of play combined with a lack of access to technology such as computer and video games contribute to improved gross motor skills. The South African findings seem to be in contrast to developed countries such as the United Kingdom where fine motor skills seems to be better developed than gross motor skills.28 When interpreting the results of the performance of the children on the subdivisions of the ECDC Index at four years it seems as if the mastery of particularly activities requiring spatial perceptual abilities seem to be problematic. Research has shown that spatial perceptual abilities are

related to visio-motor integration (VMI) and needed for reading, writing, spelling and arithmetic. While the relationship between VMI and academic achievement is not clearly understood29 it is significantly correlated with a child's ability to perform academic work at school. 30 At five years these difficulties are less apparent although number and form concepts seems to be more problematic. The latter should be viewed as problematic as these are foundational concepts for mathematics. Given that the subtest of directionality was the most problematic for both age groups, one should consider whether the task was not clearly understood by the children of whether it is actually still too difficult given their age. Commented [WU29]: What would this then imply? Commented [WU30]: I would discuss this first and then move onto the discussion of the outcome measures. I have thus moved it up Commented [WU31]: Can you discuss the START results, the trends of development noted in line with existing literature A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 Assessment tools When comparing the results of the START evaluation with the ECDC it is evident that study participants performed better on the START than on the ECDC. Three possible reasons will be offered and discussed. Firstly, the START was not originally designed to be an assessment tool, but structured as such by the authors of this article. The authors work as clinicians in a secondary hospital where validated and reliable assessment tools used and described in literature are not available. Using valid and reliable assessment tools between 0 and 3 years would, no doubt, have improved the quality of the research. Yet, when given the choice between no research and making use of what is available the authors opted for the latter. Indeed Sukha,5 an Occupational Therapist who followed up on the motor outcomes of infants with moderate and severe HIE at a tertiary hospital in South Africa commented that mild developmental delays are sensitive to standardised assessment tools while these subtle delays are often overlooked with non-standardised assessments.5 Using standardised assessments will assist clinicians to detect degrees of developmental delays in infants with HIE. 22 The authors argue that having access to standardised assessment tools for the age band between 0 and 3 years would greatly contribute to enabling active contributions towards evidence based practice in terms of early childhood development benchmarking and intervention strategies. A second possible reason for the discrepancy between outcomes of the START and ECDC evaluation is the age group of the population being evaluated. While the ECDC relies on activities presented to the child in a prescribed manner, the START relies to a large degree on parental report of the child's abilities. Infants, even typically developing infants, have a limited capacity to participate in therapy sessions when compared to four and five year olds and therapists are often reliant on parental feedback regarding infant's abilities, which can be subjective and possibly even inaccurate. Thirdly, the ECDC can be considered as a more complex tool in terms of the activities that children are required to perform. While both the START and the ECDC evaluate fine and gross motor development, the ECDC evaluates cognition in greater depth and detail than some of the activities of the START which requires underlying cognitive skills. Limitations An obvious limitation to the research is the small size of the study which limits the generalisability of the results. Acknowledgements Commented [GAD[32]: Would it be possible to detect more subtle developmental delays at an earlier age if different assessment tools are used? Commented [S33R32]: Definitely, see our argument lower down in the paragraph. A descriptive audit of the long term developmental

outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 The authors would like to thank all the medical staff in ward X at the X Hospital, particularly Dr X for her belief in the contribution that Occupational Therapy bring to the quality of life of these children. The authors are sincerely grateful to the parents and children who participated in this study. Conflicts of interest None to declare. Funding Funding was received from Ruth Watson OTASA research grant. References 1. Sculzke SM, Rao S, Patole SK. A systematic review of cooling for neuroprotection in neonates with hypoxic ischemic encephalopathy – are we there yet? BMC Paediatrics 2007; 7;30. https://doi.org/10.1186/1471-2431-7-30 2. Shah PS, Ohlsson A, Perlman M. Hypothermia to treat neonatal hypoxic ischemic encephalopathy. Arch paediatric adolensc med 2007; 16:10. https://doi.org/10.1001/archpedi.161.10.951 3. Blackmon LR, Stark AR. Hypothermia: A Neuroprotective therapy for neonatal hypoxic-ischemic encephalopathy. Paediatrics 2006; 117(3):942-948. https://doi.org/10.1542/peds.2005-2950 4. Padayachee N, Ballot DE. Outcomes of neonates with perinatal asphyxia at a tertiary academic hospital in Johannesburg, South Africa. SAJCH 2013; 7:3. https://doi.org/10.7196/sajch.574 5. Sukha N. "The developmental motor outcomes of infants with Hypoxic Ischaemic Encephalopathy II and III between the ages of 12-24 months at Chris Hani Baragwanath Academic Hospital". Unpublished Master's Thesis 2013. [cited 2017 April]. Available from: http://wiredspace.wits.ac.za/jspui/bitstream/10539/14453/1/The developmental% 20motor outcomes of infants with Hypoxic Isc.pdf 6. Mwakyusa SD, Manj KP, Massawe AW. The hypoxic ischaemic encephalopathy score in predicting neurodevelopmental outcome among infants with birth asphyxia at the Muhimbili National Hospital, Dar-es-Salaam, Tanzania. Journal of Tropical paediatrics 2008; 55:1. https://doi.org/10.1093/tropej/fmn061 7. Pattinson RC, ed. Saving Babies 2008-2009: Seventh Report on Perinatal Care in South Africa. http://www.pipp.co.za/downloads [cited 2014 April]. https://doi.org/10.1016/s0140-6736(09)61123-5 A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019 8. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomized trial. Lancet 2005; 365:663-670. https://doi.org/10.1016/s0140-6736(05)70932-6 9. Shankaran S, Woldt E, Koepke T, Bedard MP, Nandyal R. Acute neonatal morbidity and long-term central nervous system sequelae of perinatal asphyxia in term infants. Early Human Development 1991; 25 (2): 135-148. https://doi.org/10.1016/0378-3782(91)90191-5 10. Robertson CM, Finer NN, Grace MG: School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. Journal of Paediatrics 1989; 114; 753-760. 1 https://doi.org/10.1016/s0022-3476(89)80132-514 11. Sarnat HB, Sarnat MS. Neonatal encephalopathy following foetal distress. A clinical and electroencephalographic study. Arch neurol 1976; 33: 696-705. https://doi.org/10.1001/archneur.1976.00500100030012 12. Thompson CM, Peterman AS, Liney LL, et al. The value of the hypoxic ischaemic encephalopathy score in predicting neurodevelopmental outcome. Acta Paediatrica 1997; 86: 757-61. https://doi.org/10.1111/j.1651-2227.1997.tb08581.x 13. Pin TW, Eldridge B, Galea MP. A review of developmental outcomes of term infants with post asphyxia neonatal encephalopathy. European Journal of Paediatric neurology 2009; 224-234. https://doi.org/10.1016/j.ejpn.2008.05.001 14. Azzopardi D,

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The role of the Authors The primary author worked at x Hospital when the study was initiated in 2010. Having completed her master degree she took the lead in writing the protocol and first drafts of this article. She also contributed to doing assessments of children from 2010 until 2016 when she transferred to another place of work. She continued to provide input to the article up to the point where it was completed. The second author worked at x Hospital as the Chief OT when the study was initiated. She was instrumental in capturing data and doing follow up assessments. She also provided crucial assistance with the writing of the article. The third author is affiliated with an academic institution. She provided unique guidance in the development of the protocol as well during the process of research. She also assisted with the authorship of the article. A descriptive audit of the long term developmental outcomes of 30 infants with HIE who received hypothermia at the X Hospital, South Africa. 30.11.2019