# Evaluating the INTER-NDA for standardised neurodevelopmental screening at 2 years of age for all children born preterm.




A thesis submitted for the degree of Doctor of Philosophy

By

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This thesis is submitted to the University of Oxford in partial fulfilment of the Doctor of Philosophy degree requirements.

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## PART A

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# 1 Acknowledgement

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&

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*Praise the Lord, all you nations; extol him, all you peoples. For great is his love toward us, and the faithfulness of the Lord endures forever.*

*Praise the Lord.*

*Psalm 117 (NIV Version)*

## 1.1 Preface

At the conceptualisation of the DPhil research project, the idea was to determine the feasibility of extending neurodevelopmental screening, currently offered to only a third of children born preterm (i.e. the very preterm) or very ill at the neonatal unit of the Oxford University Hospitals NHS Foundation Trust, to all children born preterm (including everyone born moderate to late preterm, MLPT) using the INTERGROWTH-21$^{st}$ Neurodevelopmental Assessment (INTER-NDA). The research sought to identify if differences in neurodevelopment could be detected at age 2 that would make it clinically worth offering neurodevelopmental follow-up to all children born preterm.

Specifically, the initial primary research questions were to:

- *To establish the effectiveness of the INTER-NDA and the Cardiff Tests of Vision as a standardised neurodevelopmental screening at 2 years of age for all children born preterm;*
- *To compare the INTER-NDA as a viable alternative neurodevelopmental screening tool compared to the Bayley Scale of Infant and Toddler Development, 3rd edition (BSID-III) for children born early preterm (<32 weeks' gestation);*
- *To compare the ease and cost of administration of the INTER-NDA and BSID-III; and*
- *To compare the cost of universal standardised neurodevelopmental screening of all children born preterm using our proposed strategy with the cost of the current standard of care.*

Due to the impact of COVID-19 on research activities, the original research could not be carried out as planned. This meant that in-person assessments could not be offered to eligible children in the study. Therefore, innovative ideas were explored to ensure the

DPhil was successfully completed and contributed meaningfully to the body of science, especially regarding neurodevelopmental follow-up of vulnerable (preterm infants), parental involvement in the care of their children and mixed methods approaches in perinatal research.

**The MLPT infant in the context of the thesis**

In some sections of the thesis, I have highlighted MLPT infants to shed light on this group of relatively vulnerable infants that accounts for the largest proportion of children born preterm. Although MLPT infants have a lower risk of neurodevelopmental deficits compared to children born very preterm (VPT), due to the larger numbers of MLPTs, the collective contribution of their risks places a significant burden on health and educational systems.

Delayed identification of children at risk of neurodevelopmental impairment results in a lost window of opportunity to intervene until these children start showing significant clinical signs of neurological deficits, at which point the potential for targeted therapy to improve the neuroplasticity of the growing infant may have passed [1]. However, it is unclear whether it is feasible or efficient to extend neurodevelopmental follow-up to include all MLPTs as currently offered to VPTs, hence the rationale for focusing Chapter 1 on identifying if there are any early interventions that specifically target the neurodevelopment of MLPT children and their mechanisms of action and effectiveness. The purpose of highlighting the MLPT group in the thesis is to a) shed light on them as an understudied group of vulnerable children, b) contribute knowledge to understanding their neurodevelopmental outcomes, and c) identify which interventions are targeted at improving their neurodevelopmental outcomes (cognitive, neurobehavioural and motor skills), once deficits are detected.

Highlighting the MLPTs this way, however, does not take precedence over VPTs, who are at a higher risk of the associated morbidities and mortalities of preterm birth. There is already a considerable amount of research and early intervention programmes for VPT infants, as noted in Chapter 1. Continued effort is required to ensure the best outcomes for all children born preterm.

All other Chapters of the thesis target all preterm children more broadly – a) Chapter 2 is on neurodevelopmental assessments, b) Chapter 3 is about parent interviews and survey, and c) Chapter 4 describes neurodevelopmental services for all children born preterm in the UK and Switzerland, where the study was carried out.

## 2 Abstract

**Background:** Children born preterm are at increased risk of compromised neurodevelopment. The risk of adverse neurodevelopmental outcomes increases with decreasing gestational age. Neurodevelopmental follow-up can identify preterm infants with neurodevelopmental deficits and deviations to allow early intervention. Children born moderate-to-late preterm (MLPT) do not receive routine neurodevelopmental follow-up despite their increased risk of compromised neurodevelopment compared to their counterparts born at term. Early assessment and interventions increase the chances of improving outcomes among children born preterm. Parents are important stakeholders in the care of children born preterm, yet parent voices are not always considered in neurodevelopmental follow-up services and research. This study, therefore, explores approaches to bridging access gaps to neurodevelopmental assessments for all children born preterm, including those born MLPT.

**Methods:** Through a systematic review, interventions to improve the outcomes of children born MLPT and their efficacies were explored. The feasibility of a novel approach to conducting virtual assessments among preterm infants was carried out. The applicability of the INTER-NDA as a screening tool among children born preterm was ascertained. A mixed methods approach was deployed to understand parent views and perspectives on neurodevelopmental follow-up through interviews and surveys. Finally, a cross-sectional survey of hospitals was undertaken to understand current follow-up practices in the UK and Switzerland, where the research was undertaken.

**Results:** The systematic review ended in an empty review with no literature on specific interventions and their effectiveness for children born MLPT. The INTER-NDA was able to detect preterm children at risk of moderate to severe neurodevelopmental impairment.

Parents prefer a support system, including access to mental health services and a linkage to the health system post-neonatal discharge. Parents would like the opportunity for children born preterm to be offered routine neurodevelopmental assessments to identify any potential problems that may be present and for their reassurance.

**Conclusion**: The empty systematic review increases awareness about the paucity of data and research about MLPT infants, the complexity of early interventions, their effects among preterm subgroups and sustained benefits over time. Virtual assessment is a feasible approach to conducting neurodevelopmental follow-up of young children born preterm. Children with impaired neurodevelopment have been identified and offered a referral for onward care. Incorporating parent voices in follow-up services and studies provides perspectives that can enhance the care provided to children born preterm. Understanding current follow-up practices can show areas of best practices for replication in other settings and areas needing improvement. This study has shed light on research gaps for follow-up and early interventions for children born preterm (including for the MLPT group). It acknowledges the potential challenges to scaling up follow-up services to include all preterm children and therefore presents recommendations for future research on the feasibility and efficacy of extending neurodevelopmental follow-up to include the MLPT, identifying potential early interventions that can improve their neurodevelopment once deficits are identified and the uptake of follow-up services by parents. It also highlights the need for geographical balance in research for children born preterm globally.

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## 6 List of Abbreviations

BAPM: British Association of Perinatal Medicine

BSID-III: Bayley Scale of Infant and Toddler Development, 3rd edition

CBCL: Child Behaviour Checklist

CHERRIES: The Checklist for Reporting Results of Internet E-Surveys

CROSS: A Consensus-Based Checklist for Reporting of Survey Studies

CTRG Clinical Trials and Research Governance

ECD: Early Childhood Development

ECI: Early Childhood Intervention

EPT: Extremely Preterm

GA: Gestational Age

GLD: Good Level of Development

GP: General Practitioner

HDU: Neonatal High Dependency Unit

HIC: High-Income Countries

HIE: Hypoxic-ischaemic encephalopathy

ICU: Intensive Care Unit

IDG: Infant Development Group

IHDP: Infant Health and Development Programme

IMD: Index of Multiple Deprivation

INTER-NDA: INTERGROWTH-21st Neurodevelopmental Assessment

*iSight Pro:* Kay *iSight* Test Professional App

JRH: John Radcliffe Hospital

KS: Key Stages

LBW: Low Birth Weight

| | |
|---|---|
| LDU: | Neonatal Low Dependency Unit |
| LIC: | Low-Income Countries |
| LMIC: | Low- and Middle-Income Countries |
| LPT: | Late Preterm |
| LRF NGN | Larsson-Rosenquist Foundation Centre for Neurodevelopment, Growth and Nutrition of the Newborn |
| MDAT: | Malawi Development Assessment Tool |
| MDI: | Mental Development Index |
| MDT: | Multidisciplinary team |
| MITP: | Mother-Infant Transaction Programme |
| MLPT: | Moderate-to-Late Preterm |
| MPT: | Moderate Preterm |
| NDA: | Neurodevelopmental Assessments |
| NICE: | National Institute for Health and Care Excellence |
| NICU: | Neonatal Intensive Care Unit |
| OT: | Occupational therapist |
| OUH: | Oxford University Hospitals NHS Foundation Trust |
| OX: | Oxfordshire |
| PARCA-R: | Parent Report of Children's Abilities-Revised |
| PICO: | Population, Intervention, Comparator and Outcome |
| PPI: | Patient and Public Involvement |
| NDA: | Rapid Neurodevelopment Assessment |
| SAS: | Specialty and Associate Specialist |
| SDG: | Sustainable Development Goal |
| SEN: | Special education needs |

SGA: Small for gestational age

SURGE: The Survey Reporting Guideline

SwissNeoNet: The Swiss Neonatal Network & Follow-up Group

UK: United Kingdom

USA: United States of America

VPT: Very Preterm

WHO: World Health Organization

# PART B

## GENERAL INTRODUCTION

# 7 General Introduction

## 7.1 Global perspectives of preterm birth

Preterm birth, defined as birth before 37 weeks' gestation, remains a significant global health challenge [2, 3]. Over the past decade, preterm birth rates have remained somewhat static globally, with an estimated 13.4 million (95% credible interval 12.3 – 15.2 million) preterm births in 2020 (9.9% of all births (95% credible interval 9.1 – 11.2)) [3, 4] compared to 13.8 million (12.7 – 15.5 million) babies born preterm in 2010 (9.8% of all births (9.0 – 11.0)) [4-6]. Preterm birth disproportionately affects lower-income countries and impoverished communities [7], with an incidence ranging from 5 to 18%, and the largest burden (more than 60% of preterm births) occurring in Africa and South Asia [3, 7]. Figure 1 shows an estimate of the global burden of preterm birth rates in 2014 [8].

A global trend analysis of preterm infant mortality rates revealed an average annual decline of about 2% between 1990 and 2017. However, disparities in the decline of preterm mortality rates were observed between developing and developed countries, with the highest decline (4%) in high-income countries and the lowest decline of 1% seen in countries in sub-Saharan Africa [9].

Reporting on preterm birth is particularly challenging in the regions with the highest preterm burden. For example, the global estimate of 13.4 million preterm births in 2020 was derived from only 103 of the 195 World Health Organization (WHO) member states and the occupied Palestinian territory, including east Jerusalem (referred to as areas). This estimate includes national administrative data from just 64 countries and 40 research studies, predominantly from developing countries [10]. Additionally, among the 33 countries and areas with the highest quality data on preterm birth, 94% were from high-income countries and areas, with none from southern Asia or sub-Saharan Africa [4].

Regional disparities in healthcare access significantly affect the chances of survival of preterm infants. According to WHO, 75% of under-5 mortality due to preterm birth is preventable with quality newborn care and cost-effective interventions such as warmth, breastfeeding support and basic care for infections and breathing difficulties [3]. Ohuma et al., 2023 reported that neonates born extremely preterm (at 26 weeks gestation) are more likely to survive in resource-rich settings than those born in resource-constrained settings with poor access to care [4]. WHO estimates that 90% of extremely preterm (EPT) infants (born at < 28 weeks' gestation) in Low- and Middle-Income Countries (LMICs) die in the first days of life, compared to less than 10% in High-Income Countries (HICs) [3]. With access to functioning neonatal intensive care units, the survival rate for EPTs born at 24 weeks in most HICs is approximately 50%. In contrast, in many LMICs, the same 50% chance of survival is typically observed for infants born at 34 weeks' gestation [5].

An understanding of the estimates of the global burden of preterm birth, the inequalities in the care of vulnerable newborns and the inverse data law (sparse data where the burden is highest) are important in informing health system policies and programme priorities and targeting interventions appropriately to reduce the burden of preterm birth and its sequelae, especially in developing country and resource constrained contexts [8, 9, 11, 12].

While ongoing efforts aim to improve the survival rates of preterm infants across all gestational ages (GA) and in all regions, [3] the neurodevelopmental outcomes and follow-up of these surviving preterm infants remain an important topic for discussion.

## 7.2 Risk stratification of preterm birth

For this thesis, preterm babies have been categorised into three main subgroups depending on the GA at birth to align with the common preterm classification and the associated aetiology: very preterm (VPT) (born at <32+0), moderate preterm (MPT) (32+0 to 33+6) and late preterm (LPT) (34+0 to 36+6) weeks' gestation [13]. The moderate-to-late preterm (MLPT) group, born at 32+0 to 36+6 weeks' gestation, accounts for up to 85% of the preterm population, and this rate continues to increase [8, 13-16].

Being born too soon increases mortality and morbidity risks to the preterm baby [6, 17]. Complications of preterm birth are the single highest cause of mortality and morbidity among children under 5 (Figure 2) [3, 18]. That said, mortality rates among preterm infants have seen a slight downward trend due to advances in neonatal medicine and perinatal care, and EPT babies survive, especially in resource-rich contexts [3, 4, 19-21]. However, the associated neurodevelopmental impairment among preterm infants remains a challenge [21].

The American Academy of Paediatrics has published a framework by Davis et al., (2023) [22] based on two decades of data from developing country contexts on preterm outcomes where they stratified the risk of prematurity and other neonatal conditions and their related outcomes. Their risk stratification of developmental disabilities in relation to the general paediatric population is informative for clinical decision-making. Risks were arbitrarily classified based on how much more likely a child would develop developmental disability compared to the general paediatric population. Risks were rated as very high (if the prevalence of developmental disability is >10x); high (if > 5 to 9.9x) and moderate-low (if 1.1 to 4.9x) compared to the general paediatric population. Risks

associated with preterm birth were proportional to decreasing GA, with the EPT group being at the highest risk and the MLPTs at moderate-low risk. The term low risk was isolated from the risk categorisation since preterm birth and (other neonatal conditions reported) posed a higher risk compared to the general paediatric population. They identified that the MLPTs had moderate-low risk for intellectual disability, cerebral palsy, hearing loss, and vision impairment compared to the general paediatric population. For example, the prevalence of intellectual disability among MLPTs was 5.3 - 8.2%, i.e. 5 to 8 times more than the general paediatric population, which had a prevalence of 1.1 – 2.5%.

Compromised neurodevelopment can have a long-term impact on a child's educational attainment and economic potential [21, 23, 24]. As the severity of the sequelae resulting from preterm birth increases with decreasing GA at birth, the EPT and VPT infants are at a higher risk than the MLPTs. Similarly, the MLPT children are at a higher risk of neurodevelopmental delays when compared with their at-term counterparts [19, 25, 26].

It must be noted that the preterm cut-off at 37 weeks is ‘somewhat arbitrary as early-term births have higher rates of adverse outcomes than full-term gestations’ [8]. The preterm sub-group classifications VPT, MPT and LPT, as used in the thesis, align with clinical practice as arbitrary cut-off points for follow-up and a guide for clinicians, for example as used by NICE ([27], the Lancet Small Vulnerable Newborns series [10] and WHO [3], and its use is also prevalent in the literature for research purposes [4, 5, 28]. Again, the classification of preterm subgroups by GA allows for stratification of individual risk at a population level and allows for programme planning and identifying subgroups with the most gaps in data reporting [4].

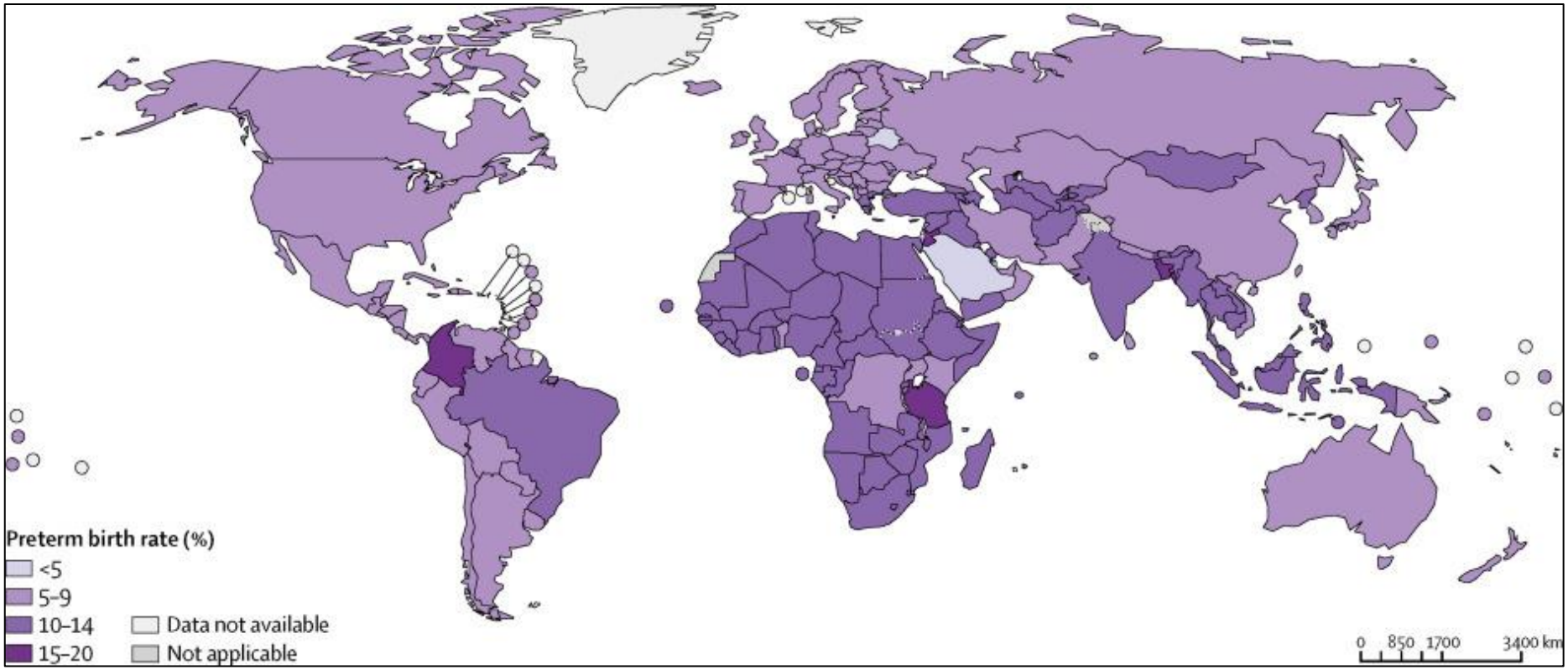



*Figure 1: Estimated global rates of preterm birth in 2014, cited from Chawanpaiboon et al., 2019 [8]*

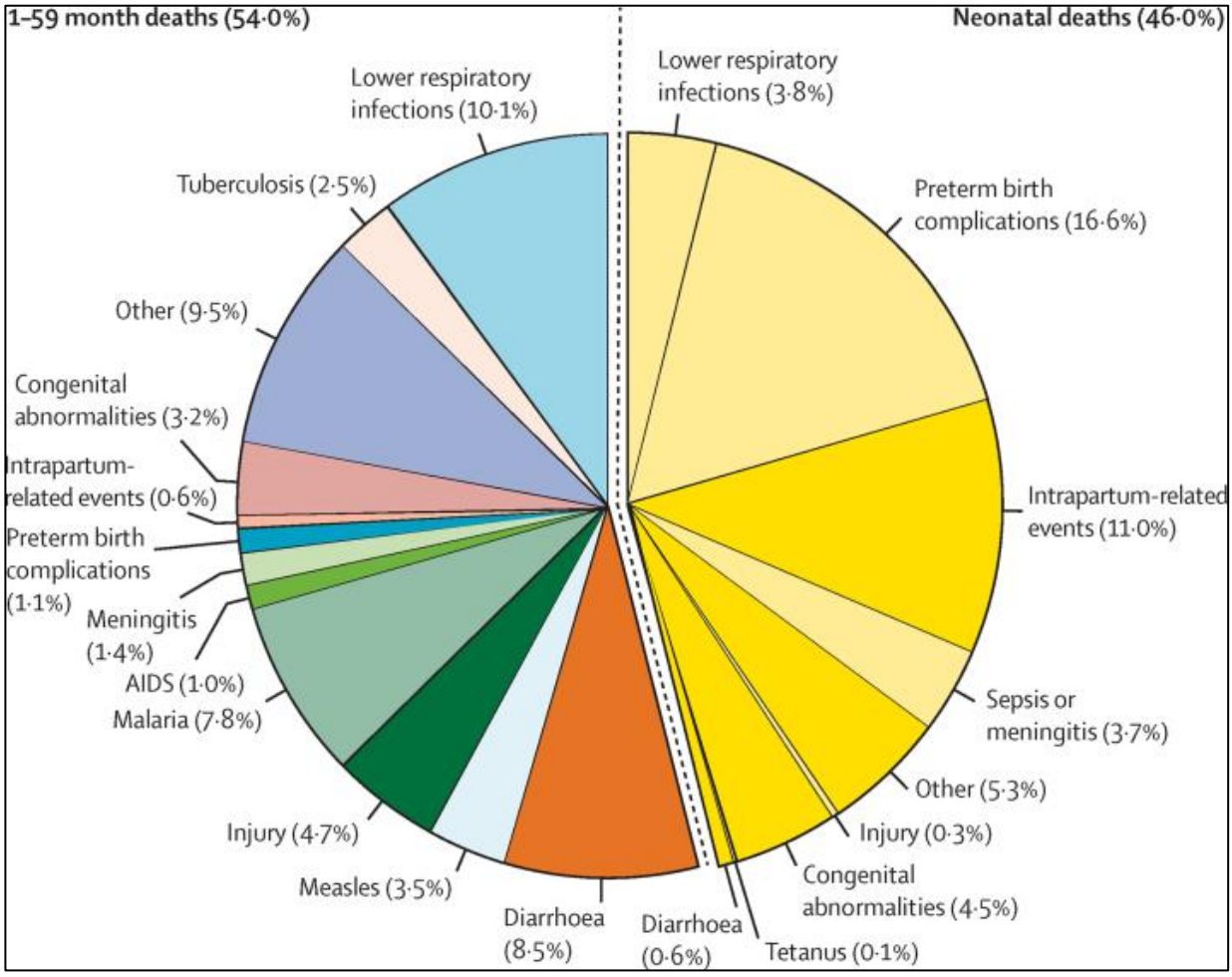



*Figure 2: All-cause mortality among children under 5, adopted from Perin, et al., 2022*

### 7.3 Aetiology of preterm birth

As explained by Villar et al., (2019), preterm birth is a complex heterogeneous syndrome which may have overlapping aetiologies and risk factors with intrauterine growth restriction syndromes and stillbirth [29]. Preterm birth can be due to maternal conditions prior to or during pregnancy, such as antepartum haemorrhage, cervical incompetence, bacterial infections, or due to fetal growth restriction. However, about 30% of preterm births may be from unknown causes [29, 30].

The risk of compromised neurodevelopment among the preterm population could be explained by the brain's inability to develop fully *in utero* before delivery [17, 31]. In the last 6 weeks of pregnancy, there is a rapid development of neurons (the fundamental units

of the brain), myelination[i] [32, 33] and significant networking in the brain [17]. At 34 weeks' gestation, the brain weight is about 65% that of the brain of a term born, and cortical volume is nearly half [34]. Thus, any interference with neural connectivity in the brain in the last weeks before birth can have significant long-term effects on neurodevelopment later in life.

### 7.4 Sequelae of preterm birth

Neurodevelopmental outcomes among children born preterm may include deficits in cognition, language, behaviour, and motor skills [35]. Although not all children born preterm face adverse challenges with their neurodevelopment [6, 36], there is a higher risk of compromised neurodevelopment among children born preterm compared with those born at term, as earlier mentioned [13].

Global estimates by Blencowe et al., (2013) report that 2.7% of preterm infants who survived past the first month experienced moderate-to-severe neurodevelopmental impairment, and 4.4% experienced mild neurodevelopmental impairment. They explained that due to the dearth of data and reporting from regions with the highest burdens of preterm birth, many more children experience learning or behavioural problems that are not accounted for [6].

Figure 3 describes a myriad of the sequelae of preterm birth ranging from no complications to direct and associated morbidities in childhood and adulthood and death in some cases. It underscores the importance of understanding the burden of preterm birth and the multisectoral approach to prevention and appropriate care to promote outcomes for the most vulnerable.

[i] Myelination is the process by which myelin sheaths are produced and act as a layer of insulation around the neuronal axons, it provides the foundation for brain connectivity essential for neurodevelopment.

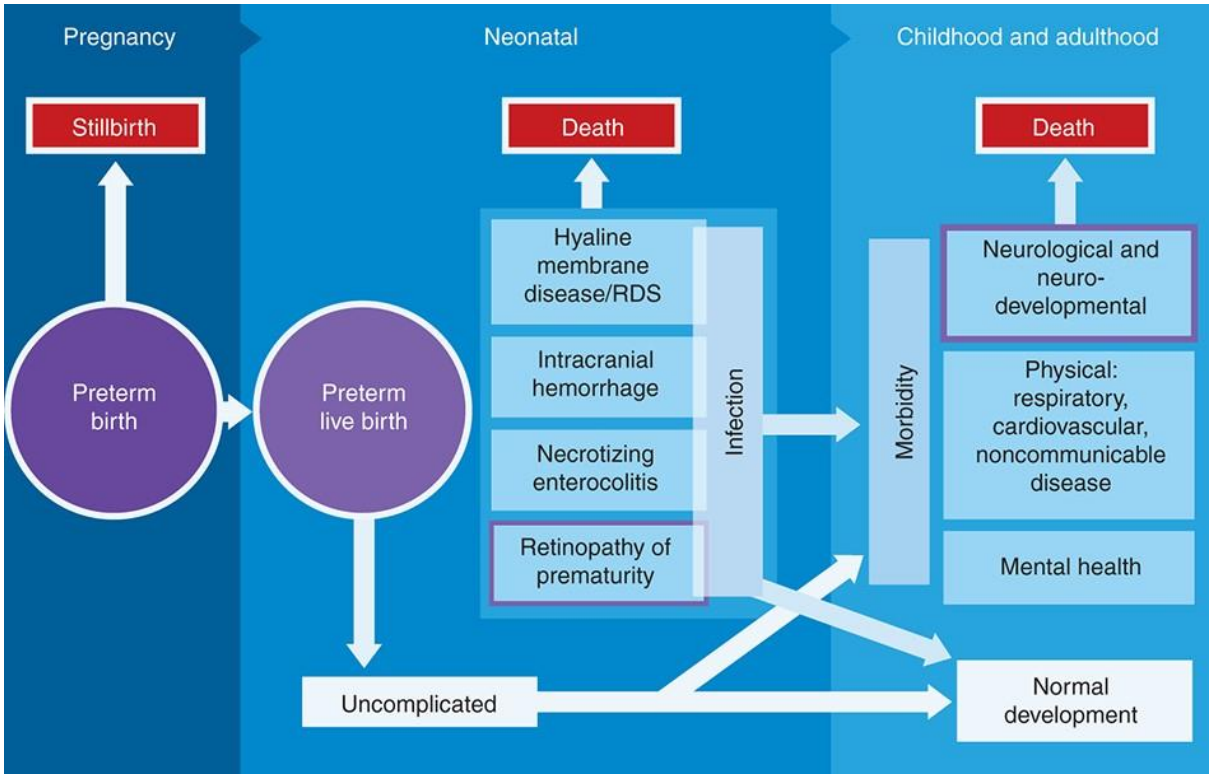



*Figure 3: Disease schema for sequelae of preterm birth, image by Blencowe et al., (2013) [6]*

### 7.5 The numbers: estimation of the burden of preterm birth and its sequelae

Data on preterm birth and its sequelae are limited or lacking in many low and middle-income countries where the burden of preterm birth (in absolute numbers) is highest, thus hampering an accurate estimation of the burden and actions needed to address related problems [3, 7]. Part of the underreporting is due to the challenges with the accurate estimation of gestation, which tends to classify some babies as low birth weight[ii] (LBW) and not as preterm because GA is more difficult to ascertain in many regions [37]. Most preterm babies are born with LBW, and both preterm and LBW babies (small for gestational age, SGA) are generally at higher risk of neonatal mortality compared to term babies and those over 2500g [38]. However, the risk factors and mechanisms of preterm birth are not always the same for LBW babies. Therefore, LBW is not a perfect

[ii] LBW usually used to refer to <2500g weight at birth

substitution or proxy for a preterm birth [37]. Published scoring models of risk prediction cite GA as more highly predictive of clinical obstetric and neonatal risk of viability than birth weight alone [10]. There are calls to improve the accurate and standardised estimation of birth weight and GA (through early ultrasound dating) to inform policies and programmes to effectively target interventions for prevention and improving outcomes, especially in countries with sparse data [37].

According to the published literature, about 10% of children experience neurodevelopmental impairment in the form of deficits in cognition, vision, behaviour, attention, motor skills, sleep, and hearing [39, 40]. However, for preterm children, the rates may be higher as the prevalence of neurodevelopmental impairment is influenced by the degree of prematurity [41]. Some of the reported rates of neurodevelopmental disturbances in the literature include: 35% of EPT to MPT children experienced mild disabilities at age 5 in the EPIPAGE-2 cohort study in France [42], 11-37% of neurodevelopmental impairment was observed among EPT infants in North America at 2-5 years, and 10-13% incidence of moderate impairment in Europe at age 18-24 months of age [43]. In a national large-scale cohort study in Sweden between 1998 and 2012, the neurodevelopmental outcomes of 1,281,690 liveborn singleton children without congenital malformations were assessed to identify the absolute risks according to birth at different GAs. Participants were categorised as MPT, LPT, early term, and full-term [44]. Their findings were similar to the Mackay study that also reported on the risk of developmental outcomes across all GAs [28]. For all domains assessed in the Swedish study - cognitive, motor, vision and hearing - MLPT infants had higher risks of impairment compared with their full-term mates: a hazard ratio of 1.73 (95% CI 1.60 to 1.87) and 1.30 (1.26 to 1.35), and a risk difference of 4.75% (95% CI 3.88% to 5.60%), and 2.03% (1.75% to 2.35%) for any impairment [44]. Their findings confirm the lower

risk of neurodevelopmental disturbances at higher GAs and provide data to support the evidence of the risk of neurodevelopmental outcomes before a fully mature GA of 40 weeks. The long-term follow-up and categorisation adds to the important findings of the adverse effect of earlier GAs on neurodevelopmental outcomes, including among children born preterm and early term. Their study also confirms the lower risk of neurodevelopmental disturbances at higher GAs. The public health importance of this and similar findings is the fact that the MLPT population is the largest group of the preterm population, and therefore, any minimal increase in the risk of neurodevelopmental impairment is important for public health planning and policy considerations for preterm infants.

### 7.6 Preterm birth, educational attainment and the risk of special educational needs

One of the effects of preterm birth is poorer educational attainment. Drawing data from the United Kingdom (UK) Millenium Cohort Study of children born before term in England from 2000 to 2001, Alterman, Johnson et al., (2022) reported that children born MPT and LPT had a higher risk of poorer educational outcomes (lower scores in English and Mathematics) with an adjusted relative risk of 2.13 (95% CI 1.44-3.13) and 1.18 (95% CI 0.94- 1.49) respectively, compared to their counterparts born at term [45]. Overall, 17.7% of children did not achieve expected levels in both subjects at the end of primary school and the proportion of these children increased with decreasing GA at birth. This risk of poor educational attainment continued through primary school to the end of secondary school with significant risk still present for those born VPT. At the end of secondary school, out of the 45.2% of children who had not passed at least five General Certificate of Secondary Education examinations, the VPT were significantly at risk

compared to other GAs. Children born at earlier GAs may require additional educational support throughout compulsory schooling, they concluded [45].

Similarly, a cohort study of 104,065 fetal records in Japan that assessed the risk of neurodevelopmental delays across different GAs showed that, at 6 and 12 months, children who were born at earlier GAs at 37 to 38 weeks had a higher risk than children born at 40 weeks' gestation. Also, there was a higher proportion of children born at 37 and 38 weeks' gestation who did not reach the Ages and Stages cut-off values (J-ASG-3) in all aspects assessed [46]. Thus, birth at earlier GAs and not only preterm birth alone increases the risk of neurodevelopmental delays.

'Special education needs (SEN) refers to children with learning problems or disabilities (including dyslexia, dyspraxia, autism spectrum disorder, and attention deficit hyperactivity disorder) as well as children with physical disabilities that impact learning (including some children with hearing, motor, and visual impairments) that make it harder for them to learn than most children the same age'[28, 47, 48]. The risk of requiring SEN support is higher among children born preterm, with increasing risk proportional to decreasing GAs. Alterman et al., (2021) reported a prevalence of SEN in the UK (Alterman, Johnson et al. 2022) among 11-year-old children between the years 2000 and 2002. The need for SEN may arise from cognitive, learning, physical or behavioural difficulties. The overall prevalence of SEN among the 12,081 children whose data were examined was 11.2%. They observed earlier GAs have increased SEN and, in some cases, may require more complex SEN and support in multiple facets of learning. The VPTs were much more likely to have complex SEN due to the multiple developmental domains that may be affected due to their earlier GA [49].

Another example is the large-scale study by Mackay et al., (2010), involving more than 400,000 children in Scotland, which provides insights into the risk of SEN across all GAs [47]. In their study, GA at birth accounted for 10% of the adjusted population-attributable fraction of SEN. The incidence of SEN was 8.4% among preterm children compared to 4.7% among children born at-term. However, a comparison of the likelihood of requiring SEN was higher among early-term children (born from 37+0 to 38+6 weeks' gestation) than among preterm infants. This was simply because more children are born early term compared to those born preterm. As early-term birth is the highest driving factor for SEN, their study concluded with a recommendation for elective surgeries to wait until 40 weeks' gestation, if there is no indication of danger to the mother or fetus.

### 7.7 Neurological development and trends among children born moderate to late preterm

There have been significant advances in the care of preterm infants, including improvement in NICU practices such as the use of surfactants, antenatal steroids, paediatric ventilators and simple practices such as kangaroo care and infection prevention, all of which have contributed to improvement in preterm survival. Concomitant with improved preterm survival, the preterm birth rate has increased due to late preterm birth [16]. Although MLPTs make up about 85% of the preterm population, their long-term neurodevelopmental outcomes have been poorly characterised compared to the VPTs.

Until recently, little attention had been paid to the MLPTs who were otherwise considered as having no or minimal risk of compromised neurodevelopment compared to VPT infants [17, 25, 50, 51]. In fact, deliveries at 34 to 36 weeks' gestations were considered as near term until the July 2005 Eunice Kennedy Shriver National Institute of Child

Health and Human Development expert panel proposed for infants born in this period to be referred to as LPTs instead of near term, to emphasise their vulnerabilities and increased risk of morbidity [52, 53]. According to a workshop summary report [54], the panel noted that there is no such thing as a 'normal preterm infant' and referring to these infants as LPT conveyed a better sense of their vulnerability rather than being referred to as near-term, which raises the possibility of *'underestimating their risks, (being) less diligent (with their) evaluation, and poor follow-up'* [52, 54].

Recent trends show that all children born preterm are at increased risk of neurodevelopmental insults compared to their counterparts born at term, with decreasing GA proportional to increased risk of compromised neurodevelopment [25]. There is also growing evidence that, compared to children born at term, the MLPTs are at higher risk for long-term behaviour problems, attention deficit and cognitive delays, the latter being more pronounced during school age when children start to perform activities which require higher executive functions, such as learning to read and write [55].

In the Longitudinal Preterm Outcome Project (Lollypop) study in the Netherlands, Kerstjens et al., (2011) observed that at age 4, the prevalence of developmental delay was twice as high in MLPTs compared with at-term controls. The MPT and VPT infants experienced problems in fine motor, communication, and personal social function compared with term controls. On the Ages and Stages Questionnaire scores, only 4.2% of full-term infants had abnormal scores (> 2SDs below the mean), while the rate of delays among the MPTs and VPTs was 8.3% and 14.9%, respectively [56].

In the UK Millennium cohort study that reported outcomes in a sample size of between 12,163 and 14,027 children, the authors observed that cognitive ability is related to the full range of GA with increased risk proportional to decreasing GAs. For example,

compared with the full-term group, the VPTs had a 40 to 140% increased risk of scoring below 1SD below the mean on seven cognitive tests, while the risks were 60 to 80 % and 30 to 40% for getting lower scores in three tests for the MPTs and LPTs respectively. Among children born early term, the risk was only 20% for scoring below 1SD below the mean for two cognitive tests [57]. Similarly, Cserjesi et al., (2012) also reported that MPT infants had lower intelligence and poorer neuropsychological functioning at early school age compared with at-term infants [58].

A large-scale national data analysis of 2-year-old children from the Early Childhood Longitudinal Study-Birth Cohort in the United States of America (USA) in 2011 involving 7,500 term and LPT infants compared neurodevelopmental outcomes of LPTs with full-term counterparts [59]. They observed that a higher proportion of LPTs (21% vs 16% term infants; $p<0.001$) had mental development index (MDI) scores < 70 [MDI score <70 is severe mental impairment]. Also, LPTs had lower MDI (87 vs 89) and psychomotor index scores (88 vs 92); $p < 0.001$, and higher odds of mental (odds ratio: 1.52 [95% confidence interval: 1.26– 1.82] P< .0001) or physical (odds ratio: 1.56 [95% confidence interval: 1.30 –1.89] P< .0001) developmental delay, even after controlling for possible confounders of clinical relevance such as gender, social (maternal race, education, marital status, depression, poverty level) and medical factors (prenatal care, delivery type, fetal growth, infant sex and breastfeeding). They concluded that LPTs have poorer neurodevelopmental outcomes and increased odds to mental and or physical developmental delay compared with their term counterparts [59].

Another study among 161 804 singleton infants born in Florida between 1996 and 1997 that compared outcomes among healthy LPT and healthy full-term infants in the first five years of life reported that healthy LPT infants had a 36% higher risk of developmental

delay or disability compared with healthy-term counterparts. The risk of encountering school-related problems, such as retention at kindergarten, was also higher among the LPTs than the term infants. Additionally, there was a 10 to 13% increased risk among MLPT children of having a disability in prekindergarten at 3 and 4 years, requiring exceptional student education and retention in kindergarten, and the assessment of *not ready to start school* was borderline significant for the MLPTs [51].

In the Avon Longitudinal Study of Parents and Children, Peacock et al., (2012) reported that for 12,089 term infants and 734 MLPTs, 79% of children born at term compared to 71% of MLPT were successful in KS1 assessments, OR 0.64 (95% CI 0.53 to 0.78); $p<0.007$). Adjusting for potential confounders, including maternal education and socioeconomic status, the difference in early school attainment persisted at OR 0.74(95% CI 0.59 to 0.92); $p=0.007$). The conclusion from their study was that children born MLPT, as a vulnerable group of children, *'warrant closer surveillance for early identification of potential education failures'* as they are less likely to be successful in early school assessments compared to those born at term [60].

At the same time, some studies have also reported that they found no or little evidence of differences in neurodevelopmental outcomes among MLPTs compared with term-born controls. In the case of Odd, Emond and Whitelaw's study, MLPTs had similar IQ scores compared to at-term peers, although the risk of SEN was higher among the MLPTS at school- age [61]. Healthy MLPTs showed no burden of neurodevelopmental outcomes, as reported by Gurka, LoCasale-Crouch and Blackman in a prospective cohort study involving more than 1,000 children [36]. In view of the relative paucity of data and conflicting information on neurodevelopmental outcomes for MLTP infants, there is

ongoing advocacy by researchers for large-scale prospective population-based studies to estimate the long-term impact of being born MLPT [13, 16, 44, 62].

Although the thesis highlights the MLPTs as a vulnerable group for neurodevelopmental follow-up, other factors such as socioeconomic status and sex could play a role in the neurodevelopmental outcomes of children. Also, this thesis acknowledges that other risk groups such as small and sick newborns (other than MLPTs alone) may have compromised neurodevelopment. In an ideal world, any child at risk of developmental delay needs to be identified and offered interventions to improve their trajectory.

### 7.8 Effects of other risk factors on neurodevelopmental outcomes

Other risk factors, such as poor socioeconomic status (social deprivation) and the sex of a child, have been shown to be associated with neurodevelopmental outcomes. There have been mixed observations. In a one-year population cohort study in Aberdeen between 1969 and 1970, Illsley & Mitchell (1984), reviewed by Davies (1984) [63], Brouillette (1985) [64] and Nichols (1986) [65] reported the protective effect of the environment on developmental outcomes among LBW children. They found that LBW children, and more so those with the lowest weight or who experienced intrauterine growth restriction, had poorer neurological findings, required hospital admission more frequently and had an increased risk of impairment in intelligence, lower academic performance and poorer behaviour outcomes when compared with controls with a birth weight of over 2500g. The quality of a child's social environment in which they are born, grow and develop was associated with improved physical and intellectual outcomes of the LBW children at age 10.

Similarly, Odd, Evans and Emond (2018) demonstrated using data from 12,586 infants born between 23 and 42 weeks gestation in the Avon Longitudinal Study of Parents and

Children (ALSPAC) that early schooling and (supportive) environment is important among preterm infants and suggests the additional benefit of support on educational outcomes of preterm children in the early few years at school [66]. On average, preterm infants had lower Key Stages (KS) scores than term children (-0.46 (-0.84 to -0.07)). However, the preterm infants demonstrated a catch-up in KS scores in early years compared to term-born mates (0.10 (0.01 to 0.19)). The highest increase was between KS1 and KS2 (p=0.005) and minimal between KS2 and KS3 (0.182) or KS3 and KS4 (p=0.149).

The National Institute for Health and Care Excellence[iii] (NICE) guidance cites the following as independent risk factors for poor neurodevelopmental outcomes: SGA; male sex; a mother from a low-income or disadvantaged background; Black, Asian or other minority ethnic group; and a multiple pregnancy [27]. The Kerstjens Study also observed that low parental education, SGA, male sex, and multiple births were risk factors for poorer developmental outcomes. Poorer socioeconomic status and moderately preterm birth provided a double burden of compromised neurodevelopmental outcomes among the Lollypop cohort [56].

In another study that compared the gender differences in neurodevelopmental outcomes among MPT and at-term controls [58], it was observed that MPT boys and girls had worse outcomes (< 10$^{th}$ percentile) on visuospatial reasoning compared to their at-term counterparts. In addition, preterm girls also had poorer outcomes in intelligence, attention, and executive functioning. Whereas MPT boys did catch up at age 7 compared to full-term boys, the preterm girls still lagged on neuropsychological functions compared with full-term girls. Furthermore, Talge et al., (2010) reported that sociodemographic

[iii] www.nice.org.uk

factors were independent of the effect of preterm birth on poor neurodevelopmental outcomes among LPTs [67].

In addition to the disadvantages early birth may pose on the neurodevelopmental outcomes of children born preterm, the timing of school entry may cause a double disadvantage in the developmental risks faced by children born preterm. In a study report of the Bradford Longitudinal birth cohort data, Pettinger et al., (2020) investigated the impact of GA and school entry age on the likelihood of achieving a Good Level of Development (GLD) in Early Years Foundation Stage Profile among 5-year-MLPT children who started school earlier than anticipated during pregnancy. They reported that MLPT children who started school a year earlier than would have been by estimated date of delivery at term were less likely to achieve a GLD compared to other children born preterm, term summer births and preterm summer births who remained within their anticipated school entry year (fully adjusted ORs were 5.51 (2.85 – 14.25), 3.02 (1.49 – 6.79) and 3.64 (1.27 – 11.48)), respectively. This study's findings add to the evidence of increased risk of poorer educational performance among children born preterm, the double disadvantage of preterm birth and starting school a year earlier than anticipated during pregnancy. In discussing the risk of requiring SEN among earlier GAs, having an understanding of the impact of the reduced chronological and GA on attaining educational outcomes is important to guide educational and health providers' interventions to better support these children [68].

In terms of their burden on the health system, MLPT infants, compared to their at-term peers, have an increased risk of neonatal morbidity that requires admission to a neonatal unit. However, severe neonatal morbidity is not common in contrast to the VPTs. For example, the LAMBS Study showed that MLPT infants contribute a significant neonatal

healthcare burden, considering the large number of infants receiving specialist postnatal care and interventions outside the neonatal unit [69]. They observed that while only 4.4% of term-born infants received all or part of their care in a neonatal unit, the rate was 35.7% among LPT singleton preterm infants. Any modest increase in morbidity requiring neonatal services among the MLPTs, who make up a sizeable proportion of the preterm population, exerts substantial pressure on the health system. Their study recommended further research into how best to deliver cost-effective and efficient services to MLPTs to determine the type of neonatal environment conducive to them and the calibre of providers required to cater for their needs [69].

Aside from the health implications of late preterm birth, there are economic implications involved in caring for an MLPT child. Their average care cost to the NHS is more than the child born at term. For example, from discharge to 6 months of age, Field et al., (2016) report that the NHS spends £334 more on an MLPT child than on a child born at term (£1107 for MLPT compared to £773). Similarly, societal costs involved in caring for MLPT are about £355 more for the MLPT, and there is an overall additional cost of about £3000 for caring for the MLPT than the term-born child [13].

## 7.9 The role of community health services in early childhood development

*This section describes the role of community child health services in early childhood development, including in the detection of developmental problems and early referral in the UK, thus setting the context to understand how children who do not receive routine follow-up (such as the MLPTs) could potentially be identified for onward care.*

In the UK, community health services are usually championed by health visitors who have completed a specialist community public health nursing programme. Their role in early childhood development begins with an antenatal review with parents in the third

trimester of pregnancy [70]. They are the first point of contact to provide (clinical) support to parents in caring for their newborns after hospital discharge. Their role includes identifying health needs to improve the health and wellbeing of children from 0 to 5 years [71]. They also offer developmental assessments between the ages of 2 and 2.5 years with the Ages and Stages Questionnaire [72]. They signpost and inform parents and facilitate referrals and linkages to specialist professionals for children in need or at risk of safeguarding concerns [73]. As such, they are a safety net for identifying children who may require additional developmental support.

From the Institute of Health Visiting written evidence to the parliamentary committee, the health visitors' unique selling point states that (in the UK), '*they are the only service which proactively and systematically reaches all families with babies and young children. They are the most trusted source of advice by families due to their legitimate health functions, providing support for all families and an important safety-net for the most vulnerable' [74].* The Institute further explains that in spite of the vital role of the health visiting service, challenges to the service have had a knock-on effect on some clinical pathways and in the identification and support of families at risk: '*Health visitors are a vital part of the health service; however, the health visiting service has been steadily eroded over the last nine years. Cuts to the health visiting service in England have had knock-on consequences across the system, impacting numerous clinical pathways for pregnancy, postnatal and neonatal care, immunisations, oral health, A&E attendances for minor illnesses and the identification and support for families with babies and children with SEND, to name just a few' [74].*

Community services and health visitor support, when implemented efficiently, help to identify children who may be at risk of developmental delays, but who do not receive routine neurodevelopmental follow-up and are, therefore, not identified routinely and

referred through the mainstream neonatal follow-up process and consequently not linked up with the necessary care.

To ensure the delivery of enhanced developmental support and surveillance for eligible preterm children, the NICE guidance recommends a connection between a child's health visitor or community health nurse and the multidisciplinary team delivering care to the child [27]. This underscores the importance of health visitors and community health services in early childhood development and in identifying developmental challenges sooner where they exist. Early identification and intervention may increase the chances of ameliorating neurodevelopmental outcomes [75], which could otherwise become long-term problems for the preterm child and their family. Some of the early interventions are caregiver-led, may be resource-light, and require little funding [76] and, therefore, could be offered more readily. Chapter 1 explores this further.

The important role of community health services in supporting children and their families at home requires that the educational needs of the community health nurse are adequately planned for and they are sufficiently equipped with the necessary skills and knowledge to better support families [77]. According to the Institute of Health Visiting, 'c*urrently, health visitor pre-registration training does not give sufficient attention to the specific needs of preterm babies and their families. Continuous professional development opportunities for health visitors are determined locally, and this has led to a gap in the workforce's ability to deliver high-quality consistent support to these families' [74].*

The fidelity of implementing health visiting services and the limited knowledge of health visitors in caring for preterm infants is a challenge to realise fully the benefits of health visitors as a safety net for children who may be at risk of developmental delay who do not have access to routine neurodevelopmental follow-up [77, 78].

The Rt Honourable Andrea Leadsome MP summarises the importance and yet the challenges of leveraging the unique opportunity of health visitors and community health services in early development: '*We are fortunate that support for families in England is delivered by many committed midwives, health visitors, social workers and primary care practitioners, as well as thousands of committed volunteers. However, what is clear is that services are patchy, not joined up and often do not deliver what parents and carers need. This must change if we are to truly transform our society for the better'* [73].

The introduction to this thesis concludes with a statement from James Heckman, a Nobel Laureate recipient in Economic Science: "*The highest rate of return in early childhood development comes from investing as early as possible, from birth through age five, in disadvantaged families. Starting at age three or four is too little too late, as it fails to recognise that skills beget skills in a complementary and dynamic way. Efforts should focus on the first years for the greatest efficiency and effectiveness. The best investment is in quality early childhood development from birth to five for disadvantaged children and their families."*—James J. Heckman, December 7, 2012 [79].

## 7.10 The Thesis

This thesis aligns with global health policies and guidelines such as the improving ECD guideline, which highlights the importance of responsive and nurturing care involving family practices to promote health and opportunities for early learning [80, 81], the world disability report goal to reduce disability for the vulnerable [82], the *Born Too Soon* report goal to promote care for children born preterm [7], and the SDG 3 goal to improve health and well-being for all [81].

### 7.10.1 Setting the scene

The original study protocol for the EveryPrem Project which underpins this thesis, aimed to '*establish the effectiveness of the University of Oxford's new neurodevelopment test (the INTERGROWTH-21st Neurodevelopment Assessment; INTER-NDA; www.inter-nda.com) for 2-year-old children who were born preterm (at less than 37 weeks of pregnancy) at the Women's Centre, John Radcliffe Hospital, Oxford.* The research objective and rationale for the study, as indicated in the original protocol, was to *determine whether it is feasible to extend neurodevelopmental screening care, currently offered to only a third of children born there, either preterm (those born at less than 32 weeks of pregnancy) or very ill, to all children born preterm by using a new standardised neurodevelopmental assessment (the INTER-NDA). This is important because children born between 32 and 37 weeks of pregnancy are two times more likely than children born at term to have neurodevelopmental disturbances during childhood, but they are not routinely offered any standardised assessment until these problems begin to significantly impact their function and school performance during later life. The study will involve a 30-minute appointment to the John Radcliffe Hospital where researchers will conduct a series of play-based tasks (the INTER-NDA) to measure children's vision, cognition, language, motor skills and behaviour at age 2 years. The children's results will be*

*compared to the new international child neurodevelopment standards constructed by the University of Oxford to (i) identify those at high, moderate and low risk of neuroimpairment and (ii) characterise impairment in the group of children born between 32 and 37 weeks of pregnancy.'*

However, Covid-19 pandemic disrupted study plans; for example, all (non-Covid-19) research activities had to be halted at the OUH for some months. This meant that 1) neurodevelopmental assessments for this DPhil study also had to be halted. Due to the age eligibility criteria, over 100 eligible children (and their families) were no longer eligible when research activities were allowed to continue. 2) The parent survey and interviews could also not be performed as they were planned to be conducted in person. 3) Over a year of the DPhil primary research work was lost due to Covid-19-related disruptions.

The initial research objectives were therefore adapted, and the following content chapters were employed to achieve the overarching aim of this DPhil research in identifying solutions to improving outcomes of children born preterm and contributing to the global agenda of supporting every child to thrive by:

- identifying interventions offered to improve the outcomes of MLPT children through a systematic review (Chapter 1),
- a virtual approach to bridge the access gap to assessing the neurodevelopment of all children born preterm as well as the suitability of an assessment tool for large-scale screening of all preterm children (Chapter 2),
- highlighting parents as important stakeholders in the care of children born preterm and soliciting their views and experiences on neurodevelopmental follow-up (Chapter 3) and

- understanding current practices of neurodevelopmental follow-up for children born preterm to inform best practices and identify areas for improvement for all children born preterm (Chapter 4).

## 7.11 Thesis Structure

The Thesis has been structured into five parts as follows (summarised in Figure 4):

**Part A**

- Abstract
- Acknowledgements
- Table of Contents
- List of Figures
- List of Tables
- List of Abbreviations

**Part B**

**General Introduction**

This part provides a broad overview of the thesis and briefly introduces all chapters. It further explains the focus of the research.

**Part C**

**The Body of the Thesis**

Each content chapter is presented as a complete study, comprising the Introduction/Background, Methods, Results, Discussion and Conclusion. The content chapters include:

- Chapter 1: Interventions to Improve Neurodevelopmental Outcomes of Children Born Moderate-to-Late Preterm: A Systematic Review.

- Chapter 2: A Virtual Approach and the Applicability of the INTER-NDA for Children Born Preterm.
- Chapter 3: Parental Views on Neurodevelopmental Follow-Up of Children Born Preterm: A Mixed Methods Study.
- Chapter 4: Patterns of Neurodevelopmental Assessments for Children Born Preterm in the UK and Switzerland: A Cross-Sectional Survey of Hospitals.

**Part D**

**General Conclusion**

This section summarises the conclusions from the four content chapters, their policy implications, the direction for future research, and the contribution of the thesis to scientific knowledge.

**Part E**

This part includes supplementary information to the various chapters and the list of cited references in the thesis.

- References
- Appendices

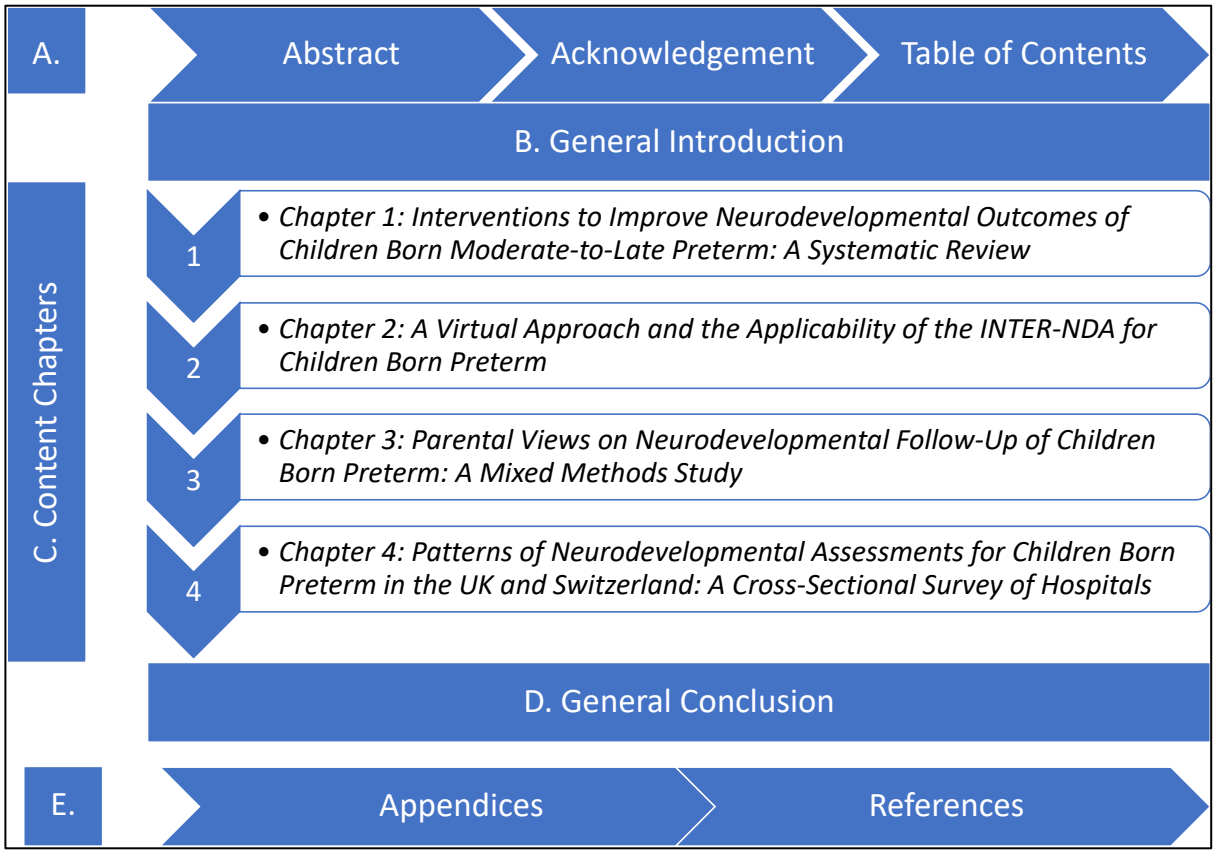



*Figure 4: Overview of Thesis Structure*

# PART C

## CONTENT CHAPTERS 1, 2, 3, & 4

# Chapter 1

# Interventions to improve neurodevelopmental outcomes of children born moderate-to-late preterm: A systematic review.

# 8 Background

## 8.1 Study justification

As part of my DPhil research, I sought to determine the usefulness of extending neurodevelopmental follow-up to all children born preterm, including the approximately 85% of MLPT children who currently do not receive any routine follow-up[iv] (Chapter 2). The premise for conducting the systematic review this way was partly inspired by the strong recommendation from the face-to-face meeting with the ethics research committee that approved the research study for this DPhil study, to identify the usefulness of assessing the neurodevelopment of children born MLPT and the extent of the evidence in support of the interventions that target their neurodevelopment and whether separate arrangements are necessary once problems are identified among the MLPTs. If MLPT children, who would otherwise have been missed or identified later as having developmental deficits, are to be identified as a result of 2-year neurodevelopmental follow-ups, it is necessary to explore the types of interventions that improve the neurodevelopmental outcomes of such children once a problem is identified and their effectiveness.

There is considerable literature on interventions that target the neurodevelopmental outcomes of children born VPT and particularly EPT (due to their relatively higher risk and vulnerability) compared to the MLPT population. Therefore, this review was carried out to determine if there are any interventions that are specifically targeted at the cognitive, motor and behaviour of children born MLPT.

[iv] This excludes MLPT infants who are identified at the NICU because of underlying clinical factors that predict poorer outcomes such as meningitis or brain haemorrhage.

## 8.2 Why is this review important?

This systematic review seeks to contribute to the body of knowledge on interventions to improve neurodevelopmental outcomes among children born MLPT, an important but underrepresented vulnerable group in neonatal and perinatal studies. Findings will inform clinical practice in the field of early childhood intervention (ECI) and preterm birth.

*I conducted the systematic review and served as the first reviewer, took the lead at every stage of the review process, and had the help of an external collaborator as the second reviewer for the title, abstract and full-text review. I conceptualised the study review and wrote the study protocol.*

## 8.3 Introduction

Beyond survival, children born preterm are at higher risk of cognitive, motor and behavioural impairment [83-86]. Some of these neurodevelopmental problems manifest during school-age [87], and domains that are particularly affected include mathematical concepts [88], attentional problems and hyperactivity [89]. These problems may have long-term impacts on their educational attainment, social integration, and self-esteem [17, 90-92]. Some studies have reported lower academic scores, high school completion rates, lower levels of employment and income among adolescents and adults born preterm compared with their contemporaries born at term [24, 93, 94].

MLPT children have a better prognosis than the VPT or EPT. However, they have an increased risk of neurodevelopmental impairment compared to their counterparts born at term – particularly in domains such as language, behaviour, psychomotor development, and education [13, 95, 96]. For example, Huddy et al., (2001) identified that about a third of MLPT children in their Oxfordshire cohort experienced poorer outcomes at school age [95]. Talge et al., (2010) found that, at age 6, children born late preterm were twice as likely to score below the threshold of 85 for intellectual (cognitive) abilities and experience behavioural problems compared to their peers born at term [67]. These observations have important implications for the health and educational systems considering that MLPT children comprise about 85% of preterm births [8, 15] and about 7% of all births in the UK and the US [13, 97]. In England and Wales alone, this translates to about 40,000 MLPT births each year [13].

## 8.4 Paucity of research and perinatal/neonatal data on MLPT children

Research on neurodevelopmental outcomes of children born MLPT is quite limited compared to that of the VPT [14, 15]. This is mainly due to the long-held belief that children born late preterm have similar outcomes as their at-term peers; therefore, research and early interventions have prioritised the VPT [13]. In the UK, for example, there is no routine neonatal or perinatal data collection nor any routine postnatal follow-up for MLPT newborns after they are discharged from the hospital. Thus, there is a paucity of data on interventions and outcomes among MLPT children [13].

In recent years, however, there has been an emerging interest in understanding the factors contributing to LPT births and the outcomes among MLPT children to inform caregivers and clinical care [13, 15]. In light of the large numbers involved, the risk of compromised neurodevelopment and the paucity of research regarding this vulnerable group of children, it may be useful to expand research into 1) understanding the long-term neurodevelopmental outcomes, and interventions that may improve their neurodevelopmental outcomes once deficits are identified, and 2) whether a separate arrangement may be needed for the MLPTs compared to the VPTs and EPTs.

## 8.5 Early intervention programmes

Early intervention refers to the timely identification and provision of effective support to children at high risk of poorer outcomes. A broader definition by Shonkoff and Meidels [98] states that early intervention refers to the "*multi-disciplinary services provided to children from birth to 5 years of age to promote child health and well-being, enhance emerging competencies, minimise developmental delays, remediate existing or emerging disabilities, prevent functional deterioration and promote adaptive parenting and overall family function.*"

Intervention programmes aim to improve the infant's overall outcomes and may be offered by a multidisciplinary team, depending on the developmental domains[v] of concern [100-102]. The interventions may commence while in the NICU and may or may not continue after discharge; in other instances, interventions are initiated in the community [103, 104]. Studies report that intervention programmes that continue post-discharge or with a community focus where the family and home environment are involved may have a better and longer-term impact [87, 105]. This may be because the parents and family are more closely involved in these interventions [100], and therefore they tend to be more sustainable; the interventions may be resource-light or require no additional resources. For example, shared reading intervention involves parents reading out loud to their children to support their language acquisition and cognitive development and behaviour modulation [76, 106], which may require no specific additional resources. On the other hand, intervention programmes offered in the hospital or clinic settings tend to be more resource-intensive, requiring specialist input and limiting their large-scale implementation [105].

### 8.5.1 Characteristics of early interventions

An ideal ECI should require the active participation of the child and involvement of their families, be offered early, at an intensive pace, flexible, resource-light, easily accessible, and tailored towards an individual's needs [107-109]. According to the WHO's world report on disability [82], a model of ECI, as described by Cioni et al., (2016) in Figure 5 summarises the characteristics of an ideal ECI, including the interconnectedness between a child's environment, social relationships and family which are all important to ECI [107].

[v] Examples of developmental domains include motor, cognition, language and behaviour (99. Woodward, L.J. and P.S. Hüppi, *Chapter 11 - Neurodevelopmental Follow-Up*, in *Volpe's Neurology of the Newborn (Sixth Edition)*, J.J. Volpe, et al., Editors. 2018, Elsevier. p. 255-272.

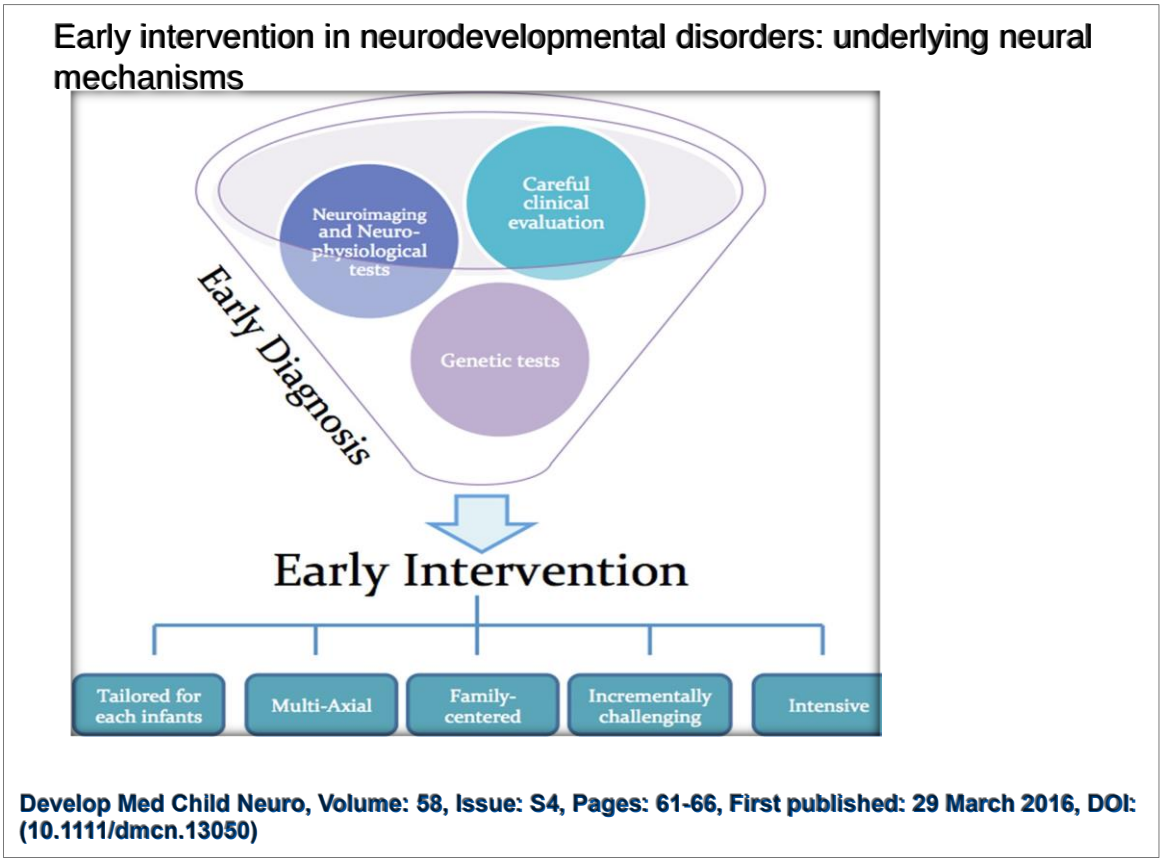



*Figure 5: Underlying neural mechanisms in early intervention in neurodevelopmental disorders, adapted from Cioni et al., 2016*

Neurodevelopmental disorders, as defined by Parenti et al., (2020) are characterised by *an inability to reach cognitive, emotional, and motor developmental milestones* [110]. Different intervention programmes may target specific domains of neurodevelopment, such as cognitive, motor, or behavioural [111]. Some examples of early intervention programmes include the Creating Opportunities for Parent Empowerment[vi] [112, 113], Newborn Developmental Care and Assessment Programme[vii] [114], Infant Behavioural Assessment and Intervention Programme[viii] [115], the Avon Premature Infant Programme [116], and Infant Health and Development Programme (IHDP) [117]. The intensity of these

[vi] http://www.copeforhope.com/nicu.php
[vii] https://nidcap.org
[viii] http://www.ibaip.org

programmes and other factors such as parent-infant engagement, supportive parenting, and the child's environment play a role in how these interventions impact neurodevelopment. However, one common theme that runs through all intervention programmes is that the earlier the interventions are delivered, the better the likelihood of influencing the child's neurodevelopment and optimising outcomes [111].

ECIs have scientific, human rights and global policy backing [118-121]. Many studies [122-124] have reported some positive effects of early intervention programmes on the neurodevelopment of children born preterm. However, further research is required to understand the effect and extent of the impact of early interventions on preterm children (MLPTs), including long-term effectiveness, the mechanisms for effectiveness, and cost implications [111, 125].

### 8.5.2 Interventions targeted at cognitive, motor and neurobehaviour

Interventions targeting the neurodevelopmental domains of a child may be directly targeted at the child, enhancing the parent-infant relationship, or both. The interventions may focus on enhancing the child's development [126, 127], parent-infant relationship or both [128-130]. Some of the interventions that target the cognitive [130, 131], motor [100, 132], and neurobehavioural [133, 134] domains are highlighted in the results section. For example, for cognitive and motor development, interventions may include physiotherapy, occupational therapy, parent-infant interactions, infant stimulation, developmental therapy, early educational intervention, psychological therapy, neurodevelopmental therapy, infant stimulation, infant development, developmental care, home visits, and Kangaroo care [100, 130, 134]. These interventions may be offered by a multidisciplinary team of health

professionals such as physiotherapists, occupational therapists, psychologists, doctors, and nurses [100].

### 8.6 Effects of ECI in the short- and long- term

Many studies have reported on the benefits of ECI and its impact on the lives of vulnerable children, such as those born preterm [135-137]. Studies have reported the effects of ECI on both short- and long-term outcomes. For example, the Vermont Study by Achenbach et al., (1990 and 1993) reported longer-term effects of the Mother-Infant Transaction Programme (MITP) to enhance the mother-infant relationship with the aim of impacting cognitive outcomes. The effects of the interventions were still observed at ages 7 and 9 [136, 138]. On the contrary, other studies have found only short-term effects of ECI on neurodevelopmental outcomes up to 3 years of age or earlier. For example, Haughan et al., (2014) reported short-term benefits of ECI on cognitive outcomes, although interventions did not have a sustained significant effect at ages 7 and 9 [130]. A meta-analysis by Vanderveen et al., (2009), which analysed 25 studies of over 2,000 children, reported that at 12 months there was a clinically and statistically significant difference in physical and mental scores among the intervention group compared to the control group[ix]; in the same study, mental scores were still improved and statistically significant at 24 months although physical scores were not statistically significant. They concluded that, at age 3, interventions had a clinically meaningful effect of more than 5 points, although these were not sustained beyond the age of 5 [137]. Similarly, Spittle et al., (2012) also reported a significant positive effect of ECI on cognitive outcomes at age 2 but a diminishing effect by school age [124].

[ix] The weighted mean difference of the neurodevelopmental outcomes of a population of 961 infants at age 36 months was 9.61 (5.0, 14.31) at $p < 0.0001$, using the McCarthy and Stanford-Binet measure.

## 8.7 Interventions targeted at the neurodevelopment of MLPT infants

The importance of ECI for children born preterm is generally known, but data regarding the specific effect on MLPT children are limited [26, 139]. Most intervention studies have focused on the more vulnerable children, like the VPT and EPT, compared to MLPT children [129, 140-145], who generally have better prognoses than VPT infants. For example, Kerstjens et al., (2011) concluded that the risk of developmental delay among MLPT infants is about half that of VPT infants: their study found that abnormal Ages and Stages Questionnaire scores among MLPT infants was 8.3% while that among the VPTs was 14.9% and only 4.2% among full-term counterparts at school age [56].

Johnson et al., (2015) also reported that the risk of developmental delays among MLPT children at 2 years of age is twice that of term peers [146], and at 7 years of age, the risk is about 36% higher [56]. Other studies have also noted that children born LPT are known to have worse neurodevelopmental outcomes at age 2 [59] and have a higher risk of developmental delay through to 5 years of age compared to those born at term [51].

Against this background of the correlation between the risks of being born MLPT and neurodevelopmental outcomes compared to those born at term, the need for effective and responsible use of current resources, the promotion of inclusive health for all, and the cost implications of ECI vis-à-vis future costs if interventions are delayed [147], further studies are needed to understand the effects of ECI on MLPT children and whether interventions extended to the VPT group are transferrable to the MLPTs in terms of relevance, intensity, duration and extent of impact in the short and long-term [26, 97].

## 8.8 Uptake of ECI by parents of MLPT children

The benefits of ECI may be hampered by a lack of access, which could be due to many factors ranging from the identification of the need for ECI, diagnosis of at-risk children and programmatic factors with the provision of ECI [109]. Identifying the underlying barriers to access helps to address the disparities that may characterise the needs-demands gap to ECI for at-risk children. As described by Sapiets et al., (2021), addressing access to early interventions begins with identifying the underlying factors and barriers to access [109]. In their framework, they describe the interconnectedness of factors influencing the pathway of access to early intervention, including family factors, service issues such as funding, eligibility criteria or referral processes, and contextual factors such as governmental legislation [148].

The Sapiets framework in Figure 6, [109], which describes the factors for accessing early interventions, could be juxtaposed with the conversation about ECI for children born MLPT to provide context about the potential need or gap to ECI, if any. That is, be it in (re)defining the eligibility criteria of who accesses ECI, the policy or guideline implications of ECI and/or family factors that influence compliance, uptake or attrition [148].

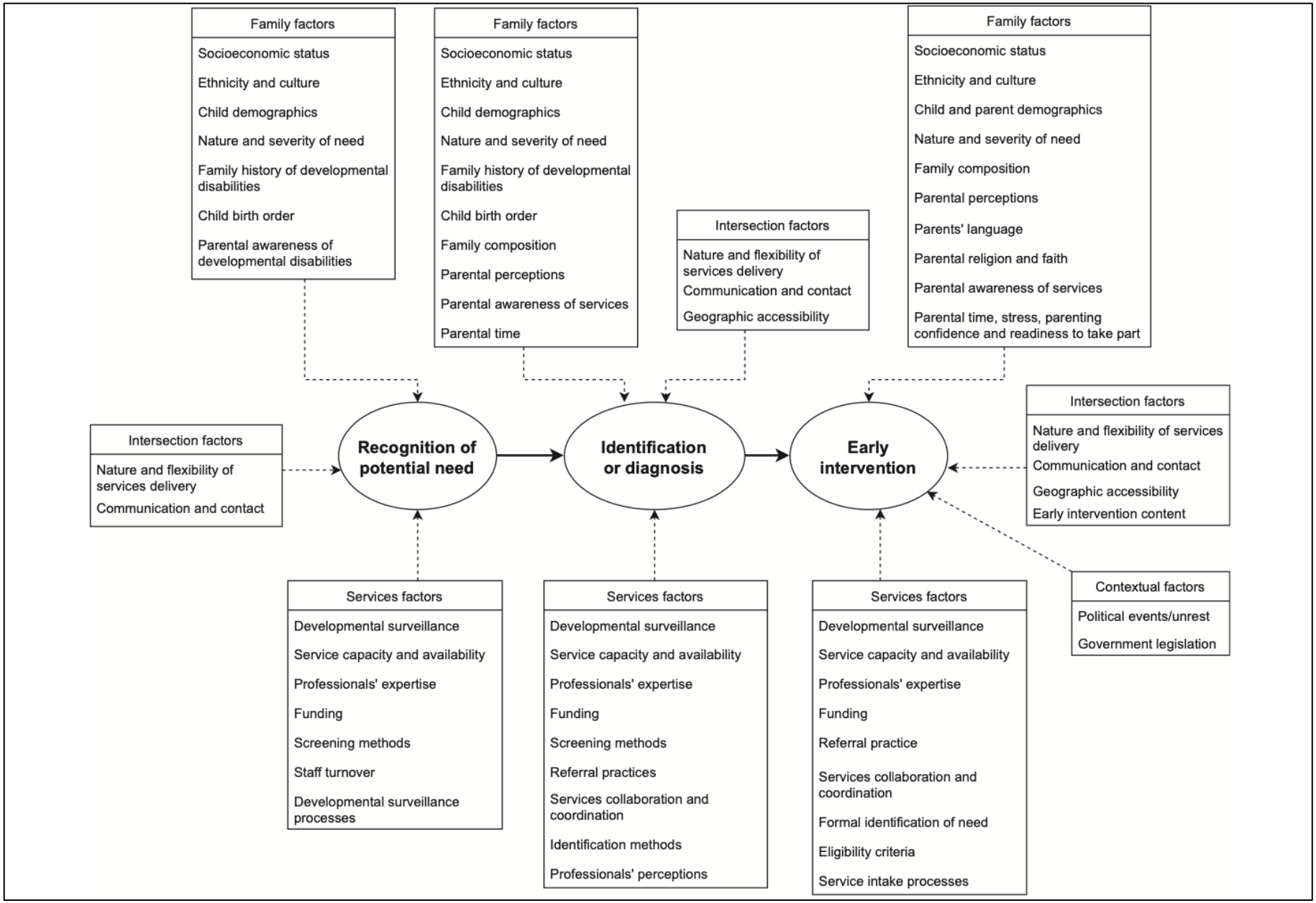



*Figure 6: Factors influencing the pathway of access to early interventions by Sapiets et., al (2021) [109]*

## 8.9 Review question and study objectives

This systematic review sought to answer the question: *Are there interventions to improve the neurodevelopmental (cognitive, neurobehavioural and motor) outcomes of MLPT children?*

The specific objectives were to:

a) Identify which early interventions (from birth until 4 years of age) are being offered to MLPT children (32+0 to <37+0 weeks' gestation) and

b) Evaluate the effects of those interventions on neurodevelopmental outcomes (cognitive, neurobehavioural and motor) up until 18 years of age.

# 9 Methods

## 9.1 Protocol and registration

The methods for this systematic review have been published elsewhere (DOI: 10.12688/gatesopenres.13246.2). The study protocol was registered in PROSPERO[x] with registration number CRD42021227749 on 18 January 2021 prior to commencing the systematic review. The review reporting conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2015 checklist [149].

## 9.2 Search strategy

At the onset of the review, in December 2020, a predefined list of commonly occurring interventions that target cognitive[xi], neurobehavioural[xii] and motor development were considered. Key terms were modified to suit the bibliographic databases used, including applying database-specific filters and externally validated search terms. An experienced librarian provided guidance to refine the search terms. Electronic databases consulted included Web of Science, Medline Ovid, PsycINFO, CINAHL and EMBASE.

The population, intervention, comparator and outcomes (PICO) model used for the search is explained in Table 1 and a sample of the search strategy in Medline can be found here: https://doi.org/10.6084/m9.figshare.14494794.

[x] PROSPERO: International prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/)
[xi] Including language development
[xii] Including socioemotional development

| | |
|---|---|
| Population | MLPT children receiving developmental interventions from birth until 4 years of age. |
| Intervention | Interventions extended to MLPT children (including those involving parents or primary caregivers) |
| Comparator | Children born MLPT who receive no specific early interventions aimed at supporting their cognitive (including neurobehavioural) and motor development. |
| Outcome | Cognitive, neurobehavioural and motor development as measured from birth until the age of 18 years among the population of interest |

*Table 1: PICO model for the systematic review*

### 9.2.1 Information sources

In addition to the electronic databases searched, the reference lists of papers identified through database searches were explored to identify further studies of relevance to this systematic review. Clinical trials registers such as the ClinicalTrials.gov: www.clinicaltrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL): www.cochranelibrary.com and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP): www.who.int/ictrp were further consulted for additional relevant studies. An updated rerun of searches was performed before the final analyses to identify the latest studies that were not indexed during the initial search.

### 9.2.2 Study selection

Records retrieved from databases and registers were saved in EndNote (version X9 and later updated to EndNote 20). After duplicates were removed, the remaining records were uploaded in Rayyan (a Software as a Service, SaaS or a web application), where two reviewers independently appraised the literature in a three-step approach: title, abstract and

full-text review. The full texts of shortlisted records were independently reviewed, applying the inclusion and exclusion criteria to identify relevant studies to this systematic review (see eligibility criteria below). Further to the database and register searches, reference lists of all relevant articles were examined for any studies that met the inclusion criteria, which may have been missed in the bibliographic and register searches.

## 9.3 Data extraction

A data extraction template was developed to summarise key information from relevant studies, such as: study design, GAs and characteristics of child participants, study sample size, study objectives, types of interventions offered, age of children at the time of intervention, duration of the intervention, person delivering the interventions, and outcomes.

### 9.3.1 Strategy for data synthesis

Two primary reviewers were involved at each step of the review process. At the beginning of the review process, they agreed to resolve any disagreements through an iterative process, providing justification for an assigned reason for the inclusion or exclusion of a study. A third reviewer was assigned as a backup in case the two reviewers could not achieve agreement. The heterogeneity of studies included was to be assessed using the chi-squared test (at 0.1 significant level) and I-squared statistics. Further details on the strategy for data synthesis are outlined here: https://gatesopenresearch.org/articles/5-78 [150].

### 9.3.2 Eligibility criteria

**Participants/population:** The population of interest in this systematic review included MLPT children from birth until 18 years of age.

### 9.3.3 Intervention(s), exposure(s)

Interventions of interest included those extended to MLPT children and their parents or caregivers targeted at cognitive, neurobehavioural and motor development. Interventions could have been offered any time between 0 to 4 years of age, but interventions initiated at the hospital needed to include at least one session in the community. Hospital or facility-only interventions prior to hospital discharge were excluded. At the initial database searches, all eligible studies were considered from the inception of the databases searched and without any language restrictions. Eligible literature that included animal studies were included in the initial database searches. The search strategy was informed by a predefined list of commonly occurring interventions that target cognitive, neurobehavioural and motor development. These included interventions extended to children, interventions extended to parents/caregivers which focus on the preterm child, and common intervention programmes (Table 2).

### 9.3.4 Types of studies included

Included in this systematic review are analytical studies (such as retrospective cohort, prospective cohort, and case-control studies), observational studies and experimental studies (such as RCTs and quasi-experimental designs). Relevant studies from conference abstracts and other forms of grey literature that utilised the above study designs were considered. Studies with high evidence of data reported in grey literature sources were further reviewed for eligibility and inclusion. Multiple reports of the same sample were treated as a single study.

### 9.3.5 Exclusion

Studies excluded were those that focused on VPT or term infants only, compared outcomes among MLPT against VPT or term-born children, or only included animals. Studies were

excluded at the title and abstract stage if they did not meet the inclusion criteria. Studies were further perused in the full-text review if their exclusion criteria were unclear during the title and abstract review, such as those that reported outcomes of a preterm population without segregating outcomes on only MLPT children, or studies which reported on LBW infants without a clear GA classification. In such instances, efforts were made to reach the authors for their study database and/or to seek clarification on the outcomes among their preterm subgroups or the characteristics of their study population, respectively. In terms of study design, studies with low evidence of data, such as case series, cross-sectional studies, case reports, editorials, commentaries, qualitative studies, and literature reviews, were excluded. Systematic reviews were excluded; however, reference lists from those studies were examined for potential studies of interest.

| Interventions for children | Interventions for parent/caregiver which focus on the preterm child | Intervention programmes |
|---|---|---|
| • Developmental therapy | • Parent education | • Avon Premature Infant Project |
| • Neurodevelopmental therapy | • Information given | • Curriculum and Monitoring System |
| • Educational therapy | • Guided observation | • Creating Opportunities for Parent Empowerment NICU Program |
| • Early intervention | • Active involvement | • Infant Behavioural Assessment and Intervention Program |
| • Infant stimulation | | • Infant Health and Development Programme (IHDP) |
| • Physical therapy | | • Newborn Individualised Developmental & Assessment Programme |
| • Occupational therapy | | • Neonatal Behavioural Assessment Scale, Brazelton |
| • Speech therapy | | • Nursing Systems for Effective Parenting-Preterm |
| • Psychology | | • Maternal Infant Transaction Program |
| • Exercise | | • Modified Mother Infant Transaction programme |
| • Rehabilitation | | • Parent Baby Interaction Program |
| | | • Parent Child Interaction Therapy |
| | | • Premie Start |
| | | • Sensory Integration and Neurodevelopmental Therapy |
| | | • State Modulation |
| | | • Victoria Infant Brain Studies |
| | | • Supporting Play Exploration and Early Development Intervention |
| | | • Traditional Holding |
| | | • Parent-infant psychotherapy |

*Table 2: Predefined list of interventions for the systematic review*

## 10 Results

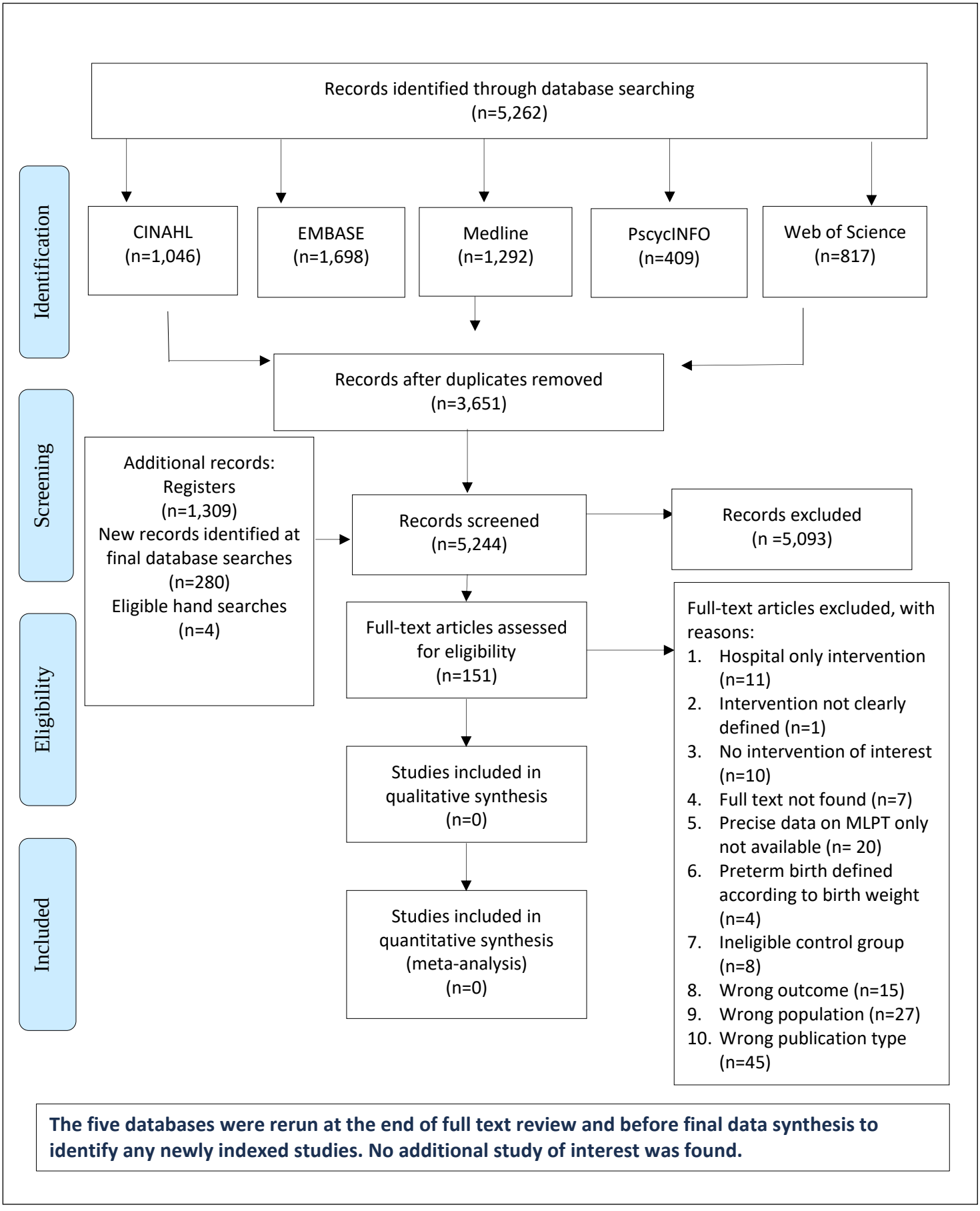



*Figure 7: Systematic review flow chart*

The database searches yielded 5,262 records (Figure 7). The records were exported into EndNote for further processing and storage. After removing duplicates in EndNote, the remaining 3,651 records were exported into Rayyan software[xiii] for further review. Rayyan proved to be a more efficient platform for performing blinded reviewing of the records.

A further 346 duplicates were detected in Rayyan and through a manual review of the records. The remaining records were then independently screened for title and abstract against the agreed study eligibility. A further 3,496 records were excluded after the title and abstract screening. A total of 151 records were shortlisted for a full-text review. At the end of the review, none of the 151 full-text records/studies had reported results explicitly for the defined population of MLPT children. Reasons for exclusion have been noted in the PRISMA flow chart in Figure 7.

Following the full-text review, 31 records were found to potentially meet the eligibility criteria for the systematic review. However, the GAs of the children in those studies were mixed, including VPT, MLPT and, in some instances, at-term infants, or GAs were simply not defined. Efforts were made to solicit the GAs, and the data from the MLPT group alone. The authors either did not respond to the request or were unable to share the data[xiv] with us. Therefore, it was not possible to proceed with the meta-analysis.

An alert system was set in the databases searched so that new records that met the eligibility criteria of the systematic review were received periodically. None of the new studies that came through the alert returned any promising record that met the criteria for this systematic review [150]. Since no study met the review criteria for inclusion, the

[xiii] https://www.rayyan.ai
[xiv] For example, to confirm GA eligibility of study participants such as those indicated as being LBW infants for whom GAs were not indicated

present study is reported as an empty review. Therefore, the risk of bias assessment of individual studies was not completed.

## 10.1 Reasons for exclusion

The following are the reasons for excluding records after the full-text screening:

1. Hospital only intervention (n=11)
2. Intervention not clearly defined (n=1)
3. No intervention of interest[xv] (n=10)
4. Full text not found (n=7)
5. Precise data on MLPT only not available (n= 20)
6. Preterm birth defined according to birth weight (n=4)
7. Ineligible control group[xvi] (n=8)
8. Wrong outcome (n=15)
9. Wrong population[xvii] (n=27)
10. Wrong publication type[xviii] (n=45)
11. Wrong study design (n=3)

[xv] These include studies which offered no interventions at all or that the interventions offered were not targeted at the domains of interest to the review (for example, some of these studies looked at effects of maternal IQ, maternal age, maternal depressive symptoms, the home environment, socioeconomic status on child outcomes).
[xvi] Ineligible control group include non MLPT children born such as those born at term or very preterm.
[xvii] Non-MLPT Population
[xviii] Wrong publication type: for example, reviews, meta-analyses, and conference abstracts.

## 10.2 Selected articles of interest to the study

### 10.2.1 Geographical spread of selected articles of interest to the study

The shortlisted studies of some relevance to the study objectives, namely those whose interventions targeted the cognitive, motor or neurobehavioural development of preterm infants were from high-income countries, including the USA, Canada, Finland, France, Italy, Japan, Norway, Spain and Russia and upper-middle-income countries including China, Thailand and Turkey (Table 3). The USA alone accounted for more than half of the countries shortlisted (17/31; 54%). There were no studies from low-income countries or regions where the burden of preterm birth is highest, such as in sub-Sahara Africa and southern Asia [3].

**Geographical spread of selected articles of interest to the study**

| Study # | Name of article | First Author | Year of Publication | Country of Study |
|---|---|---|---|---|
| 1 | A randomized clinical trial in preterm infants on the effects of a home-based early intervention with the 'CareToy System' [151] | Giuseppina Sgandurra | 2017 | Italy |
| 2 | Early Intervention Services Improve School-age Functional Outcome Among Neonatal Intensive Care Unit Graduates [152] | Jonathan S. Litt | 2017 | USA |
| 3 | The effects of family-centred physiotherapy on the cognitive and motor performance in premature infants [153] | Bulent Elbasan | 2017 | Turkey |
| 4 | Improved Cognitive Development in Preterm Infants with Shared Book Reading [76] | Susan Braid | 2015 | USA |
| 5 | Cognitive outcome of early intervention in preterm at 7 and 9 years of age: A randomised controlled trial [130] | Lisbeth Hauglann | 2015 | Norway |
| 6 | Preschool motor skills following physical and occupational therapy services among non-disabled very low birth weight children [154] | Stephanie Watkins | 2014 | USA |
| 7 | Early multi-disciplinary intervention reduces neurological disability in premature infants [155] | CHEN Guang-Fu | 2014 | China |
| 8 | Treadmill training in moderate risk preterm infants promotes stepping quality--results of a small randomised controlled trial [156] | R.M Angulo-Barroso | 2013 | Spain |
| 9 | Association between types of play materials and cognitive development among 12-month-old Thai infants: the prospective cohort study of Thai children [157] | Bandit Thinkhamrop | 2012 | Thailand |

| Study # | Name of article | First Author | Year of Publication | Country of Study |
|---|---|---|---|---|
| 10 | Effect of early intervention programs on neurobehavioral outcome in premature infants after discharge [133] | B. Guillois | 2012 | France |
| 11 | Effect of an early intervention programme on development of moderate and late preterm infants at 36 months: A randomized controlled study [158] | Nina Kyno | 2012 | Norway |
| 12 | Intervention with African American premature infants: four-month results of an early intervention program [159] | Douglas Teti | 2009 | USA |
| 13 | Massage interventions and developmental skills in infants born with low birth weight [160] | Kelmanson I. A | 2006 | Russia |
| 14 | A randomized controlled trial of an early intervention program in low-birth-weight children: outcome at 2 years [161] | Per Ivar Kaaresen | 2008 | Norway |
| 15 | Early Intervention in Low-Birth-Weight Premature Infants-Results at 18 Years of Age for the Infant Health and Development Program [162] | Marie C. McCormick MD | 2006 | USA |
| 16 | Early Intervention: The Moderating Role of the Home Environment [163] | Robert Bradley | 2001 | USA |
| 17 | Transitions on and off AFDC: implications for parenting and children's cognitive development [164] | Judith Smith | 2001 | USA |
| 18 | Cognitive performance and attachment patterns at four years of age in extremely low birth weight infants after early intervention [165] | N. Sajaniemi | 2000 | Finland |
| 19 | Early intervention for very-low-birth-weight infants [166] | Toyojiro Matsuishi | 1998 | Japan |

| Study # | Name of article | First Author | Year of Publication | Country of Study |
|---|---|---|---|---|
| 20 | Neurodevelopment until the adjusted age of 2 years in extremely low birth weight infants after early intervention - A case-control study [167, 168] | Teija Salokorpi | 1998 | Finland |
| 21 | Results at age 8 years of early intervention for low-birth-weight premature infants - The infant health and development program [168] | McCarton Cecelia | 1997 | USA |
| 22 | Examining observational measures of emotional support and cognitive stimulation in black-and-white mothers of pre-schoolers [169] | Lisa Berlin | 1995 | USA |
| 23 | The effects of experience of early intervention on low birth weight, premature children: The infant health and development program [170] | Samuel Meisels (Fong-ruey Liaw) | 1995 | USA |
| 24 | Early Intervention in LBW Premature Infants: Results Through Age 5 Years from the Infant Health & Development Program [171] | Jean Brooks-Gunn | 1994 | USA |
| 25 | Early educational intervention for very low birth weight infants: Results from the Infant Health and Development Program [172] | Marie C. McCormick MD | 1993 | USA |
| 26 | Enhancing the development of low-birthweight, premature-infants - changes in cognition and behaviour over the 1st 3 years [173] | Jean Brooks-Gunn | 1993 | USA |
| 27 | Effects of early intervention on cognitive function of low-birth-weight preterm infants [174] | Brooksgunn, J | 1992 | USA |
| 28 | Enhancing the outcomes of low-birthweight, premature infants. A multisite, randomized trial. The Infant Health and Development Program [175] | Ruth T Gross | 1990 | USA |
| 29 | Early physical therapy effects on the high-risk infant: a randomized controlled trial [176] | Martha C. Piper, | 1986 | Canada |

| Study # | Name of article | First Author | Year of Publication | Country of Study |
|---|---|---|---|---|
| 30 | Home intervention for premature infants of low-income families [177] | Gail Ross | 1984 | USA |
| 31 | Effects of Brazelton demonstrations for mothers on the development of preterm infants [178] | Susan M. Widmayer | 1981 | USA |

*Table 3: Selected studies of interest to the review*

### 10.2.2 Some reported interventions

| Study # | References | Cognitive | Motor | Neurobehaviour |
|---|---|---|---|---|
| 1 | [151] | home visits by dedicated nurse | physical therapy | |
| 2 | [152] | providing parent and family support | | |
| 3 | [153] | family centred physiotherapy and neurodevelopmental treatment | family centred physiotherapy and neurodevelopmental treatment | |
| 4 | [76] | shared book reading (reading aloud to children) | | |
| 5 | [130] | 1. active parent involvement 2. home visits by a dedicated nurse | | |
| 6 | [154] | | occupational therapy | |
| 7 | [155] | coordinated games and activities | rehabilitation training, regular development monitoring | |
| 8 | [156] | | treadmill training | |
| 9 | [157] | stimulation through play activities | | |
| 10 | [133] | parent infant interaction | | parent infant interaction |
| 11 | [158] | emphasising each infants uniqueness and developmental potential. Supporting parents in their care of their infants (MITP) | | |
| 12 | [159] | infant tactile kinetic stimulation, psychoeducational intervention (providing parents with information about preterm infants and their interaction with the world) | | infant tactile kinetic stimulation, psychoeducational intervention (providing parents with information about preterm infants |

| Study # | References | Cognitive | Motor | Neurobehaviour |
|---|---|---|---|---|
| | | | | and their interaction with the world) |
| 13 | [160] | | massage therapy | |
| 14 | [161] | 1. active parent involvement 2. home visits by dedicated nurse | baby massages | 1. active parent involvement 2. home visits by dedicated nurse |
| 15 | [162] | routine homebased preschool educational programmes | | homebased preschool educational programmes |
| 16 | [163] | 1. home visits, 2. providing parent and family support, 3. information provided about health and development to caregivers, 4. children attending child development centre from age 1 5. coordinated games and activities | | 1. home visits, 2. providing parent and family support, 3. information provided about health and development to caregivers, 4. children attending child development centre from age 1 5. coordinated games and activities |
| 17 | [164] | study assessed the effect of public assistance and poverty on cognitive development (relational rather than interventional) | | |
| 18 | [165] | 1. occupational therapy 2. promoting parent-child interaction | | |
| 19 | [166] | children attending child development centre from age 1 | | |
| 20 | [167] | occupational therapy | occupational therapy | |
| 21 | [168] | home visits, child development services, parent group meetings (IHDP) | home visits, child development services, parent group meetings (IHDP) | |

| Study # | References | Cognitive | Motor | Neurobehaviour |
|---|---|---|---|---|
| 22 | [168, 169] | parent support meetings including providing information on age-appropriate games, home visits, intensive child educational centre activities | | parent support meetings including providing information on age-appropriate games, home visits, intensive child educational centre activities |
| 23 | [169, 170] | home visits, child development services, parent group meetings (IHDP) | | |
| 24 | [170, 171] | routine homebased preschool educational programmes | | homebased preschool educational programmes |
| 25 | [171, 172] | 1. home-based visits 2. educational interventions, | | 1. home-based visits 2. educational interventions, |
| 26 | [172, 173] | parent support meetings including providing information on age-appropriate games, home visits, intensive child educational centre activities | | parent support meetings including providing information on age-appropriate games, home visits, intensive child educational centre activities |
| 27 | [173, 174] | parent support meetings including providing information on age-appropriate games, home visits, intensive child educational centre activities | | parent support meetings including providing information on age-appropriate games, home visits, intensive child educational centre activities |

| Study # | References | Cognitive | Motor | Neurobehaviour |
|---|---|---|---|---|
| 28 | [174, 175] | parent support meetings including providing information on age-appropriate games, home visits, intensive child educational centre activities | | parent support meetings including providing information on age-appropriate games, home visits, intensive child educational centre activities |
| 29 | [175, 176] | | physical therapy: individualised treatment, demonstration and instruction to parents | |
| 30 | [176, 177] | 1. teaching mothers games and exercises to promote cognitive and motor skills,<br>2. caretaking skills for parents including providing information about developmental milestones and behavioural capabilities of preterm infants<br>3. enhancing parent interactions with their babies through customised games and exercises for preterm infants | | 1. teaching mothers games and exercises to promote cognitive and motor skills,<br>2. caretaking skills for parents including providing information about developmental milestones and behavioural capabilities of preterm infants<br>3. enhancing parent interactions with their babies through customised games and exercises for preterm infants |
| 31 | [178] | Parent-infant interaction | | |

*Table 4: Reported interventions that target cognitive, motor and neurobehaviour*[xix]

## 11 Discussion

This systematic review aimed to identify the type of ECI (from birth until 4 years of age) offered to MLPT children and to evaluate their impact on neurodevelopmental outcomes (cognitive, neurobehavioural and motor) as assessed during childhood.

### 11.1 Summary of the main results

Table 4 is a review of the shortlisted studies of interest that did not meet the exact criteria of the systematic review as specified for children born MLPT in this study, but which describe interventions that target the neurodevelopmental domains of cognition, motor and neurobehaviour. Out of the 31 papers that were shortlisted (Table 4), 27 reported on interventions that targeted cognitive development (studies 1-5, 7, 9 to 12, 14 to 28, 30 and 31); 10 targeted motor skills (1, 3, 6 to 8, 13, 14, 20, 21 and 29) and 12 were on neurobehaviour (10, 12, 14 to 16, 22, 24 to 28 and 30).

Cognitive interventions included activities extended to children and/or their parents. Some of the activities were home visits by a dedicated nurse, shared book reading, coordinated games and activities, stimulation through play activities, parent-infant interaction, coordinated game activities and intensive child educational centre activities.

Motor skills activities: interventions were offered mainly to children but with the support of parents. These included physical therapy, family-centred physiotherapy, occupational therapy, rehabilitation training, regular developmental monitoring, treadmill training, massage therapy including baby massages and individualised treatment. The aspects of the interventions that targeted parents included demonstrating activities to them and providing targeted instructions for their children's therapies.

Neurobehavioural interventions included strengthening parent-infant interaction, providing parents with information about their preterm child and their interaction with the world, active parent involvement in the care of their child, and home-based visits by dedicated health workers. These were sometimes offered as composite interventions targeting more than one neurodevelopmental domain. For example, home-based visits and information sharing with parents targeted all three domains reviewed: cognitive, motor and neurobehaviour.

None of the literature reviewed met the full criteria of the systematic review; therefore, this was an empty review, i.e., a systematic review with no primary studies of interest. In view of this limitation, the quality of studies could not be assessed. However, a narrative review of the topic is described in the next section to appreciate some of the underlying complexities of early interventions for children born preterm and the stratification of the impact of interventions for preterm subgroups. The significance of empty reviews is that they identify an important gap in evidence and inform research priorities.

Another observation from this review is the regional (geographical) bias in the representation of intervention studies, where the majority are conducted in upper-middle-income and high-income countries. Inverse data reporting was also observed where regions with the highest burden of preterm births are not well represented in these intervention studies (Table 3).

.

### 11.2 A narrative review of the literature on early interventions among children born preterm.

The following sub-sections present two studies that comprised significant populations of MLPT infants but which did not meet the inclusion criteria for this review. Their findings and implications to this systematic review are discussed.

## 11.3 Lessons from this systematic review

### 11.3.1 GA not clearly indicated or ascertained

The findings of this systematic review highlight the need for a harmonised classification of preterm birth (based on accurate pregnancy dating with an early ultrasound scan). For example, 31 of the 151 studies identified for full-text review closely matched the population, interventions and/or outcomes of interest (Table 3). However, either the specific GAs at birth of the study participants were not reported or it was unclear whether they were MLPT children. Therefore, attempts were made to reach the authors of the 31 studies to clarify the GAs and inclusion of MLPT infants if the information was not provided, or where birth weight rather than GA was the criterion for classifying prematurity.

The accurate classification of preterm birth is important in ascertaining neonatal outcomes, including their associated morbidities. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal–Fetal Medicine (SMFM) endorse the classification of birth according to GA and recommend its use https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5139808/*.

In this review, some studies classified preterm birth by birth weight and not by GA, or they combined the two populations as a common group in determining ECI outcomes. There was also no clear categorisation of outcomes by GAs or preterm subgroups. This classification or the lack of distinct differentiation between these preterm and LBW populations makes it challenging to compare interventions and related outcomes [179].

Preterm babies and babies born LBW are at risk of neonatal morbidity and mortality. GA is a better predictor of neonatal and child mortality but is more difficult to ascertain than birth weight. Globally, preterm birth contributes to 75% of neonatal mortality [37] and is directly responsible for 35% of neonatal deaths worldwide [2]. Although not a perfect proxy, LBW

has sometimes been used as a crude estimate of preterm birth when it has not been possible to ascertain GA accurately [37]. However, not every child born LBW is preterm, and some children born at term can be LBW. Studies have reported a 67% overlap between preterm birth and LBW [180]. Despite the substantial overlap in incidence, the mechanisms and risk factors for prematurity and LBW may differ.

Another reason [2] why LBW is not a good proxy for preterm birth is that it has the potential to overestimate preterm birth in settings such as South Asia, where a proportion of the population will be born SGA simply because of intrauterine exposures such as malnutrition and infection. Also, there is a range of normality for birth weight assigned to a given GA and sex, making LBW not a suitable indicator of prematurity and, therefore, cannot be used interchangeably.

According to Blencowe et al., studies use LBW as a proxy for preterm birth because of the challenges of accurately estimating GA [2]. The best estimate of GA is an accurate early ultrasound measurement of fetal crown-rump length in the first trimester, up to 14 weeks' gestation [2, 181]. Interpretating scan does also require the expertise of a sonographer or trained personnel, and is therefore not easily accessible, especially in rural and remote areas in developing country settings [182].

Although some sites may still use LBW as a proxy for prematurity, this method of pregnancy dating is suboptimal. Accurate dating by ultrasound scan in the first trimester is considered the gold standard and WHO's recommendation is that every pregnancy is dated with ultrasound, "One ultrasound scan before 24 weeks of gestation (early ultrasound) is recommended for pregnant women to estimate GA, improve detection of fetal anomalies and multiple pregnancies, reduce induction of labour for post-term pregnancy, and improve a woman's pregnancy experience" [10, 181, 183].

## 11.4 Some important observations about ECI

### 11.4.1 Interventions that target cognitive, motor and neurobehaviour development

Table 4 highlights some identified interventions that were targeted at the cognitive, neurobehavioural and motor development of at-risk children, including those born preterm or with LBW in the 31 shortlisted studies. Interventions were targeted directly at either the child, parent, or both. Either way, the outcomes of interest were intended to impact the neurodevelopment of the child. Some interventions were targeted at more than one domain. For example, active parent involvement and home visits by dedicated health personnel were aimed at improving the cognition, motor performance and neurobehaviour of study participants. The common themes that underpin the interventions that were reviewed in this study are:

- customising interventions to suit each child and family's needs,
- active involvement of the mother (parent), caregiver or family in extending interventions to the (preterm) child,
- consistency with interventions provided, and
- maintaining a reasonable amount of follow-up time in order to reap benefits.

Ascertaining the duration of interventions to yield a significant outcome was beyond the scope of this review. The evidence was limited on which interventions impact the neurodevelopment of the MLPT children [26, 139]. Thus, future research on ECI for MLPT will be useful for gathering evidence in identifying which interventions (including for example, their frequency, intensity and mode of delivery) impact the neurodevelopment of MLPT children and their effectiveness [139].

### 11.4.2 The Vermont Study

The Vermont Study was carried out in the 1980s to evaluate the effect of LBW on behaviour and cognition. Participants included babies born < 2,250 g and 37 weeks' gestation and who were hospitalised for more than 10 days in the intensive care unit. Matched controls were children born with a normal birth weight > 2,800 g and > 37 week's gestation [184]. [184]The study has had a significant impact on the field of developmental psychology and has influenced the field of child behaviour. The Mother-Infant Transactional Programme [185] was developed for and used in the Vermont Study [136, 138, 186]. Interventions are based on the transactional model of development, and its conceptual design is predominantly informed by the neonatal behavioural assessment scale [185]. It included 11 sessions offered by a neonatal intensive nurse, seven of which were delivered a week prior to discharge and four sessions at home after discharge. Each session lasted an hour and involved the nurse supporting the mother to be acquainted with their child's behaviour and supporting the parent to be more confident in handling their child.

Measures assessed [184] at the end of the intervention programme included outcomes such as maternal anxiety, maternal perception of infant temperament and satisfaction with the mothering role. Infants were assessed for cognition at different periods. The interventions had a positive effect on mothers' adjustment and degree of responsivity to their LBW infants and a longer-term positive effect on the cognitive outcomes of the children in their intervention group. At age 4, the McCarthy General Cognitive Index scores for the LBW intervention group (after adjusting for socioeconomic status) were 12.9 points higher compared to the LBW control group and identical to the scores of the normal birth weight infants [184]. At age 7, the LBW experimental group scored significantly higher on the Kaufman Mental Processing Composite Scales than the control group and did not differ

from the normal birth weight infants. These findings suggest a longer-term protective effect of the interventions on LBW and preterm infants.

The Vermont Study, however, was not eligible for this systematic review as the control group included children born VPT and at term, i.e. the data were not specific to those born MLPT as per the specification of this systematic review [150]. Also, the results of the Vermont Study looked at the effects of LBW on outcomes rather than on GA, which is the focus of this systematic review. As noted earlier, birth weight is not a good proxy for preterm birth [37]. Therefore, the Vermont Study [136, 138, 184] did not qualify to be included in this review.

### 11.4.3 Lessons from the IHDP study to this systematic review

Although the IHDP Study did not meet the criteria for this systematic review, it presents important findings in ECI which are relevant. The IHDP [171, 187-189] was a landmark research study that started in the 1980s to examine the long-term neurodevelopmental outcomes and the effectiveness of early intervention for children born preterm (≤ 37 weeks' gestation) and LBW infants (< 2,500 g) [172, 187]. The study recruited preterm infants from birth through to 36 months. The study was a randomised, controlled multicentre trial in eight socioeconomically heterogeneous clinical sites. Out of the 985 eligible infants enrolled in the study, about a third, 377 infants, were randomly assigned to the intervention group and 608 to the follow-up on group. Within each of the two groups, children were further divided into two strata: LBW, < 2,000 g (two-thirds of each group) and the heavier tier, weighing 2,001 to 2,500 g (one-third of each group) [171].

Interventions in the IHDP Study included home visits after neonatal discharge, centre-based schooling from age 1 to 3 years and paediatric follow-up. Children in the follow-up (non-intervention) group only received paediatric follow-up care. Children were assessed for their

cognitive development, behavioural competence and health status. Participants were assessed in four phases at ages 3, 5, 8 and 18 [189].

Although the IHDP Study did not qualify to be included in this systematic review, it presents important contributions to the field of early childhood development and interventions:

1. Neurodevelopmental outcomes: LBW (compounded with preterm birth) is associated with an increased risk of neurodevelopmental problems such as behavioural, cognitive and language impairment and long-term impact on educational outcomes. For example, at age 5, children in the higher birth weight tier had higher cognitive and language scores compared with those in the lower birth tier [171]. In relation to this systematic review, these findings highlight the higher risk of neurodevelopmental challenges among LBW children who were more likely to be of lower GAs. A limitation of the extrapolation of the IHDP Study to this systematic review is the fact that outcomes were described according to birth weight and not GA, which is the focus of this review. However, safe assumptions could be made that, generally, children of lower GAs may be the ones more likely to have LBW.
2. Early interventions: The IHDP Study emphasises the importance of early interventions, which can mitigate the effects of risk factors such as LBW (and preterm birth) on a child's development [171].
3. The home environment mediates the neurodevelopmental outcomes of children born LBW and preterm [188], and maternal participation in early intervention programmes indirectly influences child outcomes and is critical in sustaining the outcomes [173].
4. Timing and duration of interventions: The IHDP Study offered interventions over three years from birth. At age 3, children in the intervention group had lower behaviour problem scores compared with the follow-up group [173]. There were significant

differences in cognitive scores at ages 2 and 3 for the intervention group but not at age 1, suggesting that home visit interventions for LBW children may have no significant early cognitive gains [173]. At age 5, children in the higher birth weight tier had higher verbal and IQ scores compared to the lighter birth weight intervention [171]. These observations highlight the importance of timing and duration of early interventions for different developmental domains.

5. The study was also based on the premise that LBW infants would benefit from educational interventions successfully extended to children with socioeconomically disadvantaged backgrounds.

Despite the useful information on early interventions on preterm infants in the IHDP Study, it did not meet the criteria for this review because it did not specifically indicate the effects of the outcomes of their interventions for MLPT children. Attempts were made to reach the authors for the primary data to analyse the effect of early interventions among the MLPT. The authors who responded did not have the data to share. As such, it was not possible to differentiate the benefits, frequency, scope or depth of early interventions for the MLPT preterm, and that is why the IHDP Study and all other similar studies were not included in this systematic review.

### 11.4.4 Long- vs short- term benefits of ECI

ECI has been shown to be effective in improving developmental outcomes such as motor and cognitive development, with stronger effects observed in infancy than later in childhood. Sometimes, the benefits do not persist in adulthood. The systematic review by Orton et al. (2024) [190], which included 44 eligible studies on the effectiveness of early developmental intervention programmes provided post-hospital discharge in preventing motor and cognitive impairments in preterm infants, has important findings that can be extrapolated to

this review. They observed that ECI improved cognitive outcomes in infancy, with 25 studies showing a positive effect (standardised mean difference, SMD of 0.27, 95% CI 0.15 to 0.40; P< 0.001) among 3,132 participants (low-certainty evidence). The cognitive benefits persisted into preschool age, where nine studies reported SMD of 0.39 at 95% CI 0.29 to 0.50; P < 0.001 among 1524 participants (high-certainty evidence). At school age, it was not clear if cognitive benefits are sustained. Only six studies involving 1453 participants showed an SMD of 0.16, 95% CI -0.06 to 0.38; P = 0.15 (low certainty evidence).

For motor outcomes, there was a small positive effect during infancy, with an SMD of 0.12, 95% CI of 0.04 to 0.19; P = 0.003 reported by 23 studies, including 2737 participants (low-certainty evidence). There was little evidence supporting the benefits of ECI in improving motor outcomes beyond infancy. For example, at preschool, three studies involving 264 participants showed an SMD of 0.008, 95% CI -0.16 to 0.32; P = 0.53 (moderate-certainty evidence), and at school-age, an SMD of -0.006, at 95% CI -0.31 to 0.18, P = 0.61 for 265 participants (low certainty evidence) were observed.

### 11.4.5 Variation in effectiveness of ECI programmes

The effectiveness of ECI programmes was not fully proven due to the considerable heterogeneity arising from variations in intervention focus, intensity, participant characteristics, and length of follow-up. Therefore, it remains to be determined which specific early developmental interventions and mode of delivery (such as frequency and intensity) are most effective, the longer-term effects of these programmes on child development, and how to optimise these interventions.

The lack of sustained benefits from ECI later in life [87, 124, 190] can be attributed to several factors:

- Variability in intervention quality and intensity: Interventions during infancy may vary significantly in quality, intensity, and duration; this variability can influence the long-term sustainability of their benefits. High-quality, intensive interventions are more likely to have lasting effects, while less intensive programmes may not provide sufficient support to maintain gains over time.
- There is considerable heterogeneity in how different preterm subpopulations respond to early interventions. The variability in GA, birth weight, and other health factors influences the effectiveness and sustainability of these interventions. Variations in the benefits of ECI among preterm subgroups may be that interventions extended to VPTs are typically of higher intensity due to the greater developmental vulnerabilities of the VPTs compared to the MLPTs. Similarly, the relatively lower baseline risk of MLPTs compared to VPTs can explain the relatively smaller impact of ECI among the former.
- Changing Environmental Influences: As children grow older, they are increasingly influenced by their broader environments, including home, school, and community settings. The quality of these environments can play a critical role in sustaining early cognitive gains. For instance, ongoing educational support, parental involvement, and enriching home environments are crucial for maintaining early intervention benefits and the influence of these can cause variations in the outcomes of intervention programmes.
- Follow-up and Continued Support: Many early intervention programmes focus primarily on the first few years of life without adequate follow-up and continued support. For example, sustained cognitive benefits may require ongoing interventions and support mechanisms that extend into the school years. Short of this, the impact of such interventions may not be observed well into childhood or even early adulthood.

- Developmental Catch-Up in Control Groups: Children in control groups who initially did not receive early interventions may eventually catch up to their peers who did receive interventions. This catch-up can occur due to natural developmental processes, improved care environments, or other later interventions that were not part of the initial study
- Measurement Sensitivity and Study Designs: The methods used to assess cognitive outcomes at different ages might vary in sensitivity. Some measures may not fully capture subtle cognitive gains or declines over time. Additionally, differences in study design, sample size and follow-up duration can influence the observed long-term effects.
- Compounding Effects of Socioeconomic and Health Factors: Socioeconomic and health factors that emerge or persist after the early years can affect cognitive development. Children from disadvantaged backgrounds or those with ongoing health issues may face additional challenges that hinder the sustainability of early cognitive gains. Sustaining cognitive benefits from early developmental interventions requires high-quality, long-term support that adapts to build children's changing needs as they grow. Environmental influences, continued intervention, and comprehensive support systems are essential to maintaining and building upon the early gains achieved through these programmes.

### 11.4.6 Interventions for VPT vs MLPTs

Considering the different baseline risks of preterm subgroups, tailoring ECIs to meet the specific needs of preterm subgroups might be required to optimise outcomes for each subgroup. For example, whereas VPTs may require more intensive and sustained interventions with therapists and specialised developmental programmes such as specialised physical and occupational therapy, more frequent home visits by healthcare providers, MLPTs might benefit from less intensive programmes which focus on developmental surveillance, parental education and providing support services, periodic home visits and community services, as needed.

Even with common interventions such as parental education and involvement, parents of VPTs may require intensive training and support to handle their infants' relatively complex medical and developmental needs. In contrast, for parents of MLPTs, parental education may focus on monitoring developmental milestones, nutrition, and routine care. The specific factors contributing to the differential effectiveness across preterm subgroups remain to be explored (Orton, Doyle et al. 2024).

Some considerations for extending ECI to MLPTs, despite the benefits being less pronounced compared to VPTs include:

- Early Detection and Mitigation: Although MLPTs are at lower risk for severe developmental impairments, they still face increased risks compared to their full-term counterparts. Early interventions can help detect and mitigate potential developmental delays or issues before they become more pronounced.
- As ECI can contribute to the holistic development and well-being of infants in need, MLPTs may benefit from interventions that contribute to social and emotional growth and overall well-being, not just specific domains such as cognitive and motor development, which may be less of a problem for MLPTs compared to VPTs.
- MLPTs have been observed to require SEN more than term infants. ECIs can enhance school readiness and performance, leading to better educational outcomes for children in need. Children who receive early support are more likely to succeed academically and socially in school. Providing early support can reduce the need for special education services later, which can be both costly and less effective than early interventions. Investing in early interventions is often more cost-effective than addressing developmental delays and health issues later in life. Thus, early interventions can reduce long-term educational costs and societal burden.

- Also, as ECI includes parental support, involvement and education, parents of MLPTs would have the opportunity to be equipped with the knowledge and skills to better care for their children through the ECI platforms. This support can have a lasting impact on family dynamics and child development [136, 171]. Also, the interaction with community health services can alleviate parental stress and anxiety associated with uncertainties and worries they may harbour about their infants, which has a knock-on effect of creating a supportive home environment for the child.
- Indeed, extending interventions to all preterm infants based on need would help address disparities in healthcare access and outcomes. It would ensure that all vulnerable children, regardless of their specific level of prematurity, receive the support they need to thrive. In addition, comprehensive early intervention programmes promote inclusive policies that recognise the needs of all preterm infants, fostering a more equitable healthcare system.

In summary, while ECI generally benefits all preterm subpopulations, the magnitude and sustainability of these benefits vary, with VPTs typically showing the most significant improvements. As fewer studies focus on the LPTs, the benefits of ECI among this population are less clear, as observed in my systematic review. Extending early developmental interventions to MLPTs in need would likely ensure comprehensive support, prevent potential developmental delays, improve long-term outcomes, support families, and promote equity in healthcare. These interventions would help create a foundation for healthier and more successful lives for all preterm infants, regardless of their initial risk level.

## 12 Conclusion

The specific objectives of the systematic review were to:

a) Identify which early interventions (from birth until 4 years of age) are being offered to MLPT children (32+0 to <37+0 weeks' gestation) and

b) Evaluate the effects of those interventions on neurodevelopmental outcomes (cognitive, neurobehavioural and motor) up until 18 years of age.

The systematic review did not identify any study that extends early intervention (from birth until 4 years of age) to MLPT children as defined in the systematic review protocol. Hence, objective 2 could not be carried out to evaluate the effects of any identified interventions on neurodevelopmental outcomes (cognitive, neurobehavioural and motor) of MLPT children until 18 years of age.

However, from the shortlisted studies of close interest to this systematic review, the thesis summarises some observations such as early interventions that targeted the cognitive, motor and behaviour domains of preterm infants and other at-risk infants generally. Lessons from landmark studies on early interventions for preterm and other at-risk infants have also been drawn to highlight their relevance to this subject.

The effects of ECI on preterm outcomes are complex, with mixed observations regarding the extent of effectiveness and the waning of benefits in later childhood and/or adulthood and differences in effects among preterm subgroups. Variations in the quality of intervention implementation, the influence of the environment, and the degree of the baseline risk of compromised neurodevelopment among preterm subgroups may account for the mixed observations.

Future studies will be important to understand which early interventions will most efficiently target the cognitive, motor, behaviour and other neurodevelopmental domains of MLPT children and whether MLPT infants and their families would require different interventions in terms of dose, frequency and mechanism of action from those offered to VPT children. As early follow-up and interventions at scale may be resource intensive, it will also be important to appreciate the investments required for early interventions of preterm subgroups and the implications for large-scale implementation.

This systematic review has identified that there are no published data or grey literature in the recognised databases which report solely on interventions that target the cognitive, neurobehavioural and/or motor outcomes of MLPT children. The findings highlight the need for a harmonised classification of preterm birth, and the paucity of data on ECI dedicated to MLPT children and the related mid-to-long-term outcomes (related to cognition, neurobehaviour and motor skills) until 18 years of age.

Some ECI are caregiver-led and require minimal resources compared to the costs of needing interventions later in life and the associated economic costs when human capital is lost (for example, as a result of neuroimpairment among the large MLPT population if ECD is not maximised). ECI may have multiple advantages for: 1) MLPT children, 2) parents and caregivers who may be impacted psychologically while caring for relatively vulnerable children (such as the MLPT), 3) health systems as ECI may offer long-term savings when interventions are offered early, and 4) improving human capital by maximising ECD.

# Chapter 2

# A virtual approach and the applicability of the INTER-NDA for children born preterm

# 13 Background and rationale

## 13.1 Neurodevelopmental follow-up and assessments

Neurodevelopmental follow-up is "a critical component of the evaluation of the neurological development and ongoing clinical needs of the high-risk newborn", as defined by Woodward and Hüppi, 2018 [99]. It also includes services for high-risk children from birth until 18 years [27]. It is a surveillance and intervention programme, which forms part of neonatal care, encompasses community services and involves the child and their family [191]. Follow-up involves the neurodevelopmental assessments of high-risk infants using standardised tools. The purpose of follow-up is to provide the opportunity for the early detection of neurodevelopmental impairment among high-risk children. Beyond the assessments, follow-up also offers the opportunity for parental counselling, where parents can interact with the health provider, ask questions and receive information to better support and advocate for the needs of their child [192].

Standardised neurodevelopmental assessments may begin in the NICU. This early identification of infants at risk of impaired cognitive, motor and behavioural development is important for early interventions to maximise their neurodevelopment [193]. In the neonatal period, it is not always possible to predict accurately which infants will have neurodevelopmental problems. Therefore, the standardised assessments are extended through infancy, typically at age 2, and may continue until school age for high-risk infants. According to the NICE guidelines, children born before 30 weeks' gestation or who have underlying conditions should have routine neurodevelopmental follow-up at age 2 and at age 4 for the EPT infants [27]. This allows for early identification and subsequent care for high-risk infants [194, 195]. The routine neurodevelopmental assessments (NDAs) are generally not extended to MLPT infants who are at least 2-3 times at higher risk of compromised neurodevelopment compared to their term peerse, partly due to resource

implications. Neurodevelopmental follow-up sessions can entail tests of vision, hearing, cognition, motor skills, behaviour and language development [196].

## 13.2 Tools used in this study

### 13.2.1 Bayley Scales of Infant and Toddler Development, 3rd edition

The Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III) are considered the gold standard for NDA of children [197]. They include tests of cognition, motor, behaviour and language development [1]. A standard BSID-III assessment can take 60-90 minutes and requires specially trained assessors to administer the test. Therefore, a universal follow-up scheme for all children born preterm may not be feasible in the near future or sustainable at scale if using the current gold standard tool.

According to a study by Sand et al., [198], paediatricians cited the main barriers to standardised developmental screening to include limited resources such as staffing, time constraints and inadequate funding. To bridge the missing opportunity for MLPT to be routinely assessed, there is a need for a tool that could be as sensitive and specific as the gold standard and which could satisfy the requirements for large-scale implementation in terms of resource implications. The INTER-NDA tool has attributes suitable for large-scale NDA screening, as described below.

### 13.2.2 INTERGROWTH-21st Neurodevelopmental Assessment

The INTER-NDA [40] is a novel multidimensional tool developed by the University of Oxford in 2012 for ECD assessment[xx]. '*It is an internationally valid, rapid, standardised assessment of cognitive, motor, language and behaviour skills for children aged 2 years whose norms are the first standards of early child development, constructed according to*

[xx] https://www.inter-nda.com/about.html

*the WHO Multicentre Growth Reference Study's guidelines*[xxi] [xxii]. As a package, the INTER-NDA is complemented by the Cardiff Test to assess visual acuity and contrast sensitivity [199].

The INTER-NDA is designed to allow non-specialist staff to be trained to administer the test, making it suitable for large-scale ECD research and surveillance. Assessment with the INTER-NDA is through direct administration, concurrent observation, and caregiver report [197]. The strength of combining these psychometric techniques is that they minimise potential recall or reporter biases that are common with caregiver interviews [200].

#### *13.2.2.1 Clinical input in the development of the INTER-NDA and virtual assessment*

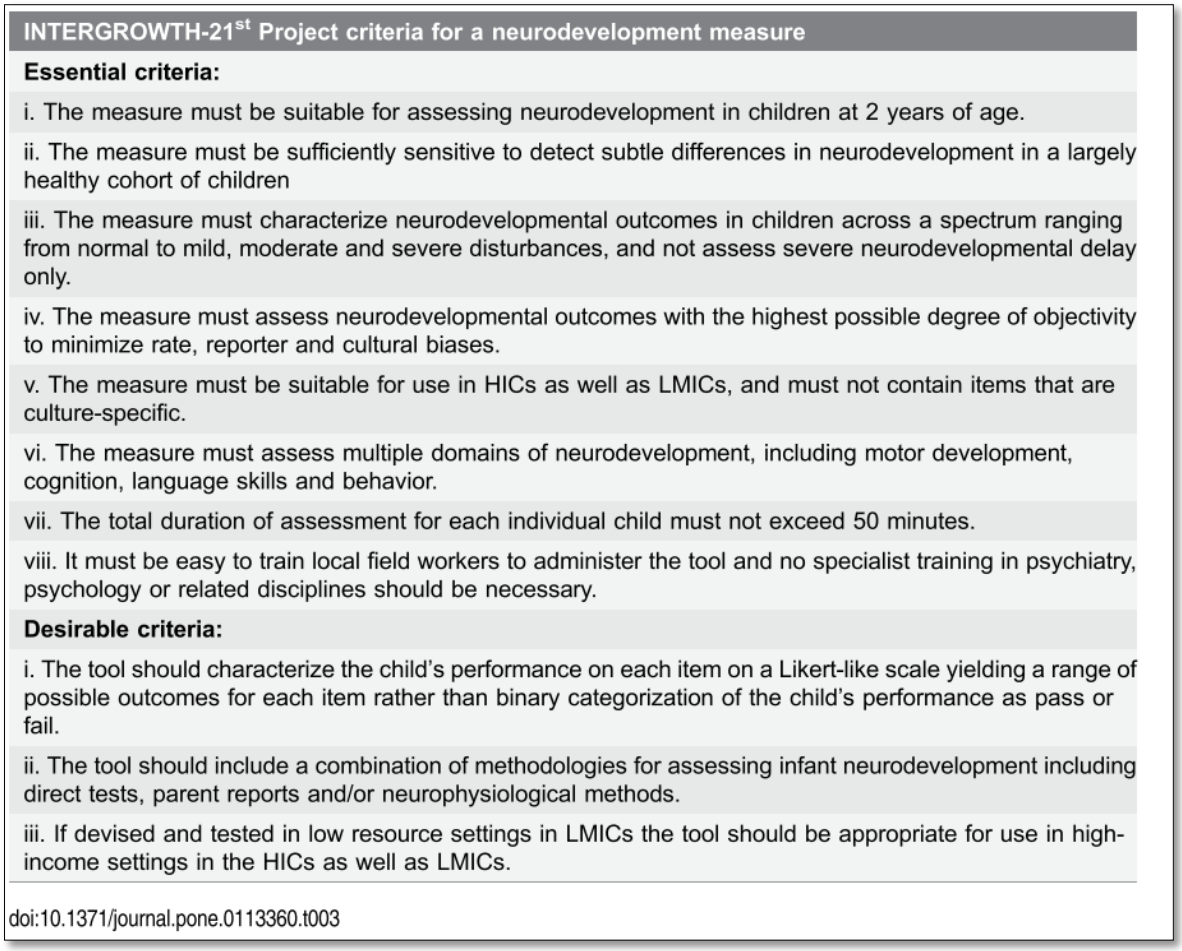
In the development of the original INTER-NDA, an expert group, the Infant Development Group, headed by Alan Stein, Professor of Child and Adolescent Psychiatry, University of Oxford, was consulted to review existing psychometric tools for assessing the neurodevelopment of children aged 24 months. The age of 24 months was selected because it: a) coincides with conventionally used tools, such as the BSID-III; b) has an acceptable level of medium to long-term predictive value, and c) is the age at which neurodevelopment is not confounded by transient outcomes of prematurity [40, 201]. The criteria for selecting suitable tools for the INTERGROWTH-21st Project are presented in Image 1. First, the expert group identified 47 well-established psychometric tools for measuring neurodevelopmental outcomes at 24 months in an international sample. Matching this list against their agreed criteria in Image 1, 13 tools fulfilled some of the criteria.

Further, a scientific advisory panel of independent international experts in neurodevelopment, paediatric neurology, child psychiatry, child psychology, vision,

[xxi] https://www.inter-nda.com/
[xxii] http://189.28.128.100/nutricao/docs/geral/artigo_oms_curvas_ingles.pdf

neuroscience, ophthalmology, sleep research, perinatal medicine and epidemiology critically appraised the list of 13 shortlisted tools. The scientific advisory panel recommended five of the 13 tools as fulfilling most of the project criteria: the BSID-III [202], the Rapid Neurodevelopment Assessment (RNDA) [203], the Malawi Development Assessment Tool (MDAT) [204], the Griffiths Mental Development Scale [205, 206], and the Child Behaviour Checklist (CBCL) [207, 208].

Secondly, the expert group constructed a multi-dimensional package for neurodevelopmental assessment. Neurodevelopmental outcomes were considered if they have long-term predictive value [209, 210] and if well-established psychometric, neurophysiological and clinical tests are available to measure these outcomes, which were categorised into domains, with the rationale for selecting them [40]. Details of the construction of the INTER-NDA, including the clinical and quality considerations, are reported in Fernandes, Stein et al., (2014) [40]. The components of the INTER-NDA tool are described in Image 2.



| INTERGROWTH-21st Project criteria for a neurodevelopment measure |
|---|
| **Essential criteria:** |
| i. The measure must be suitable for assessing neurodevelopment in children at 2 years of age. |
| ii. The measure must be sufficiently sensitive to detect subtle differences in neurodevelopment in a largely healthy cohort of children |
| iii. The measure must characterize neurodevelopmental outcomes in children across a spectrum ranging from normal to mild, moderate and severe disturbances, and not assess severe neurodevelopmental delay only. |
| iv. The measure must assess neurodevelopmental outcomes with the highest possible degree of objectivity to minimize rate, reporter and cultural biases. |
| v. The measure must be suitable for use in HICs as well as LMICs, and must not contain items that are culture-specific. |
| vi. The measure must assess multiple domains of neurodevelopment, including motor development, cognition, language skills and behavior. |
| vii. The total duration of assessment for each individual child must not exceed 50 minutes. |
| viii. It must be easy to train local field workers to administer the tool and no specialist training in psychiatry, psychology or related disciplines should be necessary. |
| **Desirable criteria:** |
| i. The tool should characterize the child's performance on each item on a Likert-like scale yielding a range of possible outcomes for each item rather than binary categorization of the child's performance as pass or fail. |
| ii. The tool should include a combination of methodologies for assessing infant neurodevelopment including direct tests, parent reports and/or neurophysiological methods. |
| iii. If devised and tested in low resource settings in LMICs the tool should be appropriate for use in high-income settings in the HICs as well as LMICs. |

doi:10.1371/journal.pone.0113360.t003

*Image 1:Eligibility criteria for a neurodevelopment measure to be included in the INTERGROWTH-21st Project (adopted from Fernandes et al., 2014)*

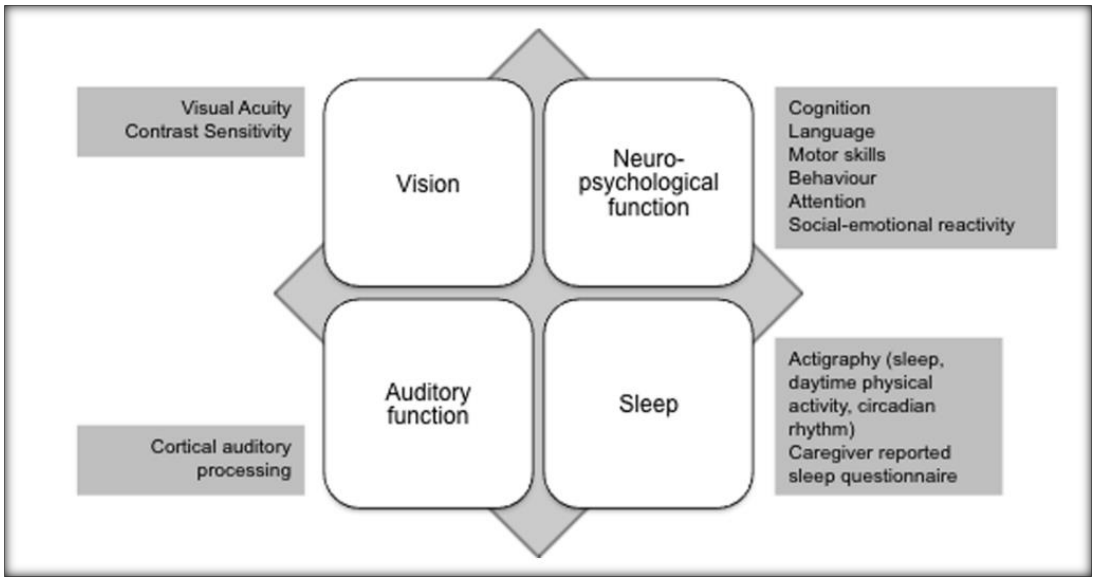



*Image 2: Components of the INTER-NDA Package*

#### *13.2.2.2 Validation of the INTER-NDA against the BSID-III*

The INTER-NDA has been validated against the BSID-III among children born at term. It has a strong agreement of interclass correlation coefficient of 0.75 - 0.88, p< 0.001 for all domains with little or no bias on the Bland Altman test. The INTER-NDA has good inter-rater and test-retest reliability [196]. To date, it has been used to assess over 30,000 children in 21 countries globally[xxiii].

The agreement between the BSID-III and INTER-NDA was evaluated based on four statistical analyses as recommended by Lee [211] and Bland and Altman [212]. Murray and Fernandes (2018) [197] cite these analyses and results as below:

i. *Repeated t-tests showed no significant difference between the INTER-NDA and BSID-III across all subscales* (Image 3)

ii. *single measure interclass correlation coefficients showed a strong association between all INTER-NDA subscales and BSID-III equivalents* (

[xxiii] INTER-NDA - Home

**Interclass correlation coefficients between the INTER-NDA and BSID-III subscales.**

| Subscale | Interclass correlation coefficient (95% CI) |
|---|---|
| Cognitive | 0.85 (0.77–0.90)** |
| Receptive language/communication | 0.74 (0.63–0.83)** |
| Expressive language/communication | 0.88 (0.82–0.92)** |
| Overall language | 0.88 (0.83–0.92)** |
| Global Behaviour | 0.88 (0.82–0.92)** |
| Positive behaviour | 0.84 (0.77–0.90)** |
| Negative behaviour | 0.78 (0.67–0.85)** |

Image 4)

iii. *there was no or very low bias in the subscales, indicating very minimal difference between the INTER-NDA and BSID-III (*Image 5*)*

iv. *Bland-Altman and linear regression analyses of the difference scores between the BSID-III and INTER-NDA shows positive associations between the subscales* (Image 6).

**Interclass correlation coefficients between the INTER-NDA and BSID-III subscales.**

| Subscale | Interclass correlation coefficient (95% CI) |
|---|---|
| Cognitive | 0.85 (0.77–0.90)** |
| Receptive language/communication | 0.74 (0.63–0.83)** |
| Expressive language/communication | 0.88 (0.82–0.92)** |
| Overall language | 0.88 (0.83–0.92)** |
| Global Behaviour | 0.88 (0.82–0.92)** |
| Positive behaviour | 0.84 (0.77–0.90)** |
| Negative behaviour | 0.78 (0.67–0.85)** |

*Image 3: Mean subscale scores, and subscale score comparisons between the INTER-NDA and BSID-III cited from [197]*

**Interclass correlation coefficients between the INTER-NDA and BSID-III subscales.**

| Subscale | Interclass correlation coefficient (95% CI) |
|---|---|
| Cognitive | 0.85 (0.77–0.90)** |
| Receptive language/communication | 0.74 (0.63–0.83)** |
| Expressive language/communication | 0.88 (0.82–0.92)** |
| Overall language | 0.88 (0.83–0.92)** |
| Global Behaviour | 0.88 (0.82–0.92)** |
| Positive behaviour | 0.84 (0.77–0.90)** |
| Negative behaviour | 0.78 (0.67–0.85)** |

*Image 4: Interclass correlation coefficients between the INTER-NDA and BSID-III subscales*[xxiv]

**Bland-Altman analysis showing agreement between the BSID-III and the INTER-NDA.**

| Subscale | Bland-Altman analysis | | |
|---|---|---|---|
| | Bias | Lower limit of agreement | Upper limit of agreement |
| Cognitive | 0.05 | -1.02 | 1.13 |
| Receptive language/communication | 0.00 | -1.40 | 1.40 |
| Expressive language/communication | 0.00 | -0.96 | 0.96 |
| Overall Language | 0.06 | -0.89 | 1.01 |
| Global Behaviour | -0.05 | -1.03 | 0.92 |
| Positive behaviour | -0.01 | -1.13 | 1.11 |
| Negative behaviour | 0.00 | -1.34 | 1.34 |

*Image 5: Bland-Altman analysis showing agreement between the BSID-III and INTER-NDA (image cited from [197])*

[xxiv] ** $p < 0.01$

**Difference scores between the BSID-III and the INTER-NDA.**

| Subscale | Linear regression (difference scores vs BSID-III scores) | |
|---|---|---|
| | *r* | *p* |
| Cognitive | 0.27 | 0.02 |
| Receptive language/communication | 0.37 | 0.001 |
| Expressive language/communication | 0.26 | 0.02 |
| Overall language | 0.23 | 0.04 |
| Global behaviour | 0.28 | 0.01 |
| Positive behaviour | 0.26 | 0.02 |
| Negative behaviour | 0.35 | 0.001 |

*Image 6: Difference scores between the BSID-III and INTER-NDA*

### 13.2.3 Adaptation of the INTER-NDA for virtual use

During the pandemic, when face-to-face assessments were not possible, finding alternatives to offering neurodevelopmental assessments to children, such as virtual assessments and/or offering parent questionnaires, became necessary. Since the original thesis proposal (the EveryPrem[xxv] Study) was to validate the INTER-NDA for use among a preterm population, the most natural choice given the circumstances was to adapt the INTER-NDA for virtual use. The INTER-NDA also offers the double benefit of having a parent/caregiver report component.

The five tools shortlisted by the IDG (BSID-III, RNDA, MDAT, Griffiths Scales and Child Behaviour Checklist) were also candidates for the virtual assessments. A summary of the pros and cons of utilising these five tools, as reviewed by the expert group and presented in Image 7 (adopted from Fernades et al, 2019), informed the decision to use the INTER-NDA for the virtual assessments in this study.

The advantages of the INTER-NDA over these five tools are that the INTER-NDA can be delivered by non-specialists, is less expensive, has a shorter administration time, assesses a broader spectrum of domains, has a paper and tablet/online-based application (for analysis) and is better suited to large-scale ECD surveillance and research. Thus, a decision was made to explore the feasibility of utilising the INTER-NDA as a virtual assessment tool and advancing the overall research objectives of the INTERGROWTH-21st Research Group as described earlier.

[xxv] https://www.wrh.ox.ac.uk/research/everyprem

**Table 5.** Neurodevelopment tools selected following review of candidate tools by scientific advisory panel.

| Tool | Positive Features | Negative Features |
|---|---|---|
| **BSID-III** | • Considered to be the gold standard for psychometric evaluation of children <3 years of age | • Long administration time (60-90 minutes) |
| | | • Specialist training required |
| | • Sensitive diagnostic instrument to detect subtle differences in neurodevelopment in a normal, healthy cohort | • Expensive |
| | | • Concern about the cultural bias of items and norms |
| | • Good predictive and discriminant validity | |
| **24 month version of the RNDA** | • Quick and easy to administer | • Information on sensitivity, specificity and positive predictive value at 24 months not available |
| | • Yield continuous scores | |
| | • Used in LMIC samples | • Not validated in HIC settings |
| | • Administration does not require specialist training | • Not all items are free from cultural biases |
| | • Characterizes neurodevelopmental outcomes across a spectrum ranging from mild to severe delay | • Very few items in each domain |
| | | • No evidence to indicate the measure would be suitable for use within an optimally healthy population |
| **MDAT** | • Quick and easy to administer | • Not validated in HIC settings |
| | • Yields continuous scores | • Not all items are free from cultural biases |
| | • Used in LMIC samples | • No evidence to indicate the measure would be suitable for use within an optimally healthy population |
| | • Administration does not require specialist training | |
| | • Strong items in the language domain | |
| **Griffiths Scales** | • Sensitive diagnostic instrument to detect subtle differences in neurodevelopment in a normal, healthy cohort | • Long administration time (60–90 minutes) |
| | • Validated in a number of international settings | • Specialist training required |
| | • Strong items in the gross motor domain | • Expensive |
| | | • Not all items are free from cultural biases |
| **Pre-school version of the CBCL** | • Sensitive diagnostic tool to detect behavioral, emotional and attention problems | • Subject to reporter/recall bias |
| | • Validated in international settings and available in a large number of languages | • Does not assess cognitive, motor and language skills |
| | • Has a sleep and stress problems scale | • Some items may not be free from cultural biases |
| | • Short administration time (approximately 15 minutes) | |

BSID = Bayley Scales of Infant Development III edition, RNDA = Rapid Neurodevelopment Assessment, MDAT = Malawi Development Assessment Tool, Griffiths Scales = The Griffiths Mental Development Scale, CBCL = Child Behavior Checklist

*Image 7: Pros and cons of neurodevelopmental tools selected by the scientific advisory panel for the construction of the INTER-NDA (adopted from [40]).*

## 13.3 Vision assessments

### 13.3.1 Cardiff Test of Vision

The Cardiff Test of Vision was developed by Dr Woodhouse to measure visual acuity [199]. It is suitable for testing children between the ages of 12-30 months. The test works on the premise that a child will fixate on a picture in a plain background when presented with cards with differing patterns. Based on the technique of preferential looking [213], the assessor estimates a child's ability to see by gauging the child's eye movement rather than what the child says. Therefore, the test is suitable for children with speech and cognitive problems or learning disabilities.[xxvi,xxvii] The Cardiff Test is really used for in-person assessments: therefore, the *iSight Pro* was the preferred tool for virtual vision assessments.

### 13.3.2 The Kay iSight Test Professional App (*iSight Pro*) for virtual vision assessments

The *iSight Pro* was developed by Hazel Kay of Kay Pictures Ltd, one of the leading producers of visual acuity tests in the UK [214]. The *iSight Pro* is suitable for use from 18 months of age to adulthood. The app has international standard letters and Kay picture optotypes that cater to young children and people with a learning disability. It is a fully validated picture vision test with accurate, recognisable pictures and evidenced-based crowding.[xxviii]

The *iSight Pro* app works on an iPhone or iPad. When using an iPad, the app screen can be shared on another device for remote testing. Its testing distances range from 33cm to 6m, and measurements can be done in LogMAR, metric Snellen or Decimal.[xxix] In this study, the *iSight Pro* was pretested among older children and adults before being extended to toddlers in the study. The virtual vision assessment was offered to all children in the study, including

[xxvi] https://kaypictures.co.uk/product/cardiff-acuity-tests/
[xxvii] https://www.bernell.com/product/NCATS/88
[xxviii] https://kaypictures.co.uk/product/kay-isight-test-professional-app/
[xxix] https://kaypictures.co.uk/product/kay-isight-test-professional-app/

the 3-year-olds who were age-ineligible for the INTER-NDA assessment after the study resumed from pandemic-related closures.

### 13.3.3 Quality dimensions of developing the virtual assessments: vision test

The virtual INTER-NDA assessments aligned with the same neurodevelopmental domains described in the original EveryPrem Study, including cognition, gross and fine motor, language, and positive and negative behaviour, complemented by vision assessment. In exploring options for the remote vision assessment, the supervisory team and I reached out to experts who develop vision assessment tools to discuss suitable options. The tool had to enable parents or an independent assessor to assess young children remotely. After consulting with experts in the field, Dr Kay Hazel, the producer of *iSight Pro* and a licensed distributor of the Cardiff test, was identified. A series of meetings were held with her and Dr Frances O'Brien, Consultant Neonatologist and my co-supervisor, to discuss the suitability of the *iSight Pro* app for this study. They concluded that it was appropriate to use the picture optotypes in the *iSight Pro* app for the young population being assessed in the study.

However, the *iSight Pro* requires iOS software (iPhone or iPad) and its use is subscription-based, which made it difficult for many parents to conduct a remote vision assessment at home and share the results with the study team. Therefore, the *iSight Pro* protocol was adapted to enable the assessor to share the test images from the screen of an iPad, which was connected to a video call during the virtual assessment sessions, as described in the thesis. The adaptation process was discussed with Dr Kay Hazel, Dr Frances O'Brien and Dr Maame Gyasiwaa Boa-Antwi, a Specialist Ophthalmologist.

Since this was the first time the *iSight Pro* was used for virtual testing, a pilot study was conducted before extending the test to children born preterm. As it was difficult because of the pandemic to include children with the same characteristics as the study participants in a pilot study, adult (n=5) and child (n=5) volunteers who were more accessible were used.

### 13.4 Care for vulnerable children during a pandemic or where barriers exist

Barriers to neurodevelopmental follow-up are unclear, but some of the cited reasons in the published literature include financial and geographical barriers (longer distance from the health centre to the child's home) and low maternal level of education [215]. Traditionally, NDAs have been conducted face-to-face with a trained assessor administering the test to the child, usually in a health facility setting [195] and sometimes at home. However, for large-scale follow-up, the health centre or hospital has been the preferred venue for such assessments.

### 13.5 Virtual neurodevelopmental assessments

During the assessments, play-based activities were carried out to assess the child's neurodevelopmental domains. During the peak of the Covid-19 pandemic, many health centres halted follow-up clinics, and health workers were reassigned to provide emergency care to combat the pandemic. The high Covid-19 response alert and prioritisation affected essential and non-emergency health services [216], including NDAs. This meant that vulnerable children born preterm lost the opportunity for early screening and any related referrals. To compensate for the limited NDA services, some facilities (as indicated by the hospital survey respondents in Chapter 4), adopted a parent-led questionnaire to report the neurodevelopment of their children.

The need for a virtual platform or alternative approaches for neurodevelopmental follow-up and care of high-risk infants became necessary [217, 218]. As part of this DPhil research, a new modality to assess the neurodevelopment of preterm infants was designed to bridge the barriers to access to essential health services for children born preterm (such as during the pandemic).

### 13.5.1 Benefits of a virtual assessment

For parents concerned about the risk of exposing themselves and their children to Covid-19, a virtual platform for meeting the clinical needs of their children is a positive alternative when barriers to face-to-face encounters exist. During the pandemic's peak, the many benefits of virtual practices [195, 217] included performing medical consultations without the accompanying risk of exposure to vulnerable patients. It also ensured that health professionals could still provide care even when they were in quarantine, for example, as a case contact. For the health system, a virtual practice meant limited use of resources such as office space for consultation and fewer staff involved in care provision, which is the case during a face-to-face outpatient visit [219].

Studies have also cited that virtual assessments (telehealth) are an effective alternative to addressing barriers related to inadequate staffing, such as subspecialties that perform NDAs [220, 221]. As elaborated in Chapter 4 of this thesis, consultants indicated staffing as one of the barriers to neurodevelopmental follow-up in their facilities. Furthermore, virtual assessments create opportunities for parents and caregivers to be closely and uniquely involved in the follow-up and care pathways of their children [220]. For example, the set-up of the virtual platform in the home relies on the parent or caregiver’s intervention and support.

### 13.5.2 Integration of virtual assessments within the neurodevelopmental follow-up pathway

There are considerable benefits of virtual assessments in paediatric care [195, 222, 223]. They ensure continuity of care where barriers to traditional in-person[xxx] assessments exist. However, virtual assessments are an understudied area of care that would benefit from further research and sharing of best practices [223]. A model from Cox et al., (2022) demonstrates aspects of neurodevelopmental follow-up that could be performed virtually [222]. In their framework, they describe three arms of the neurodevelopmental care pathway: the triage/intake stage, the evaluation and care/management pathways, and the opportunity for virtual assessments, as explained in Figure 8. In addition to childhood NDAs, patient screening and consultation, and feedback or follow-up care and monitoring could all be performed virtually.

[xxx] In-person has been used interchangeably with face-to-face

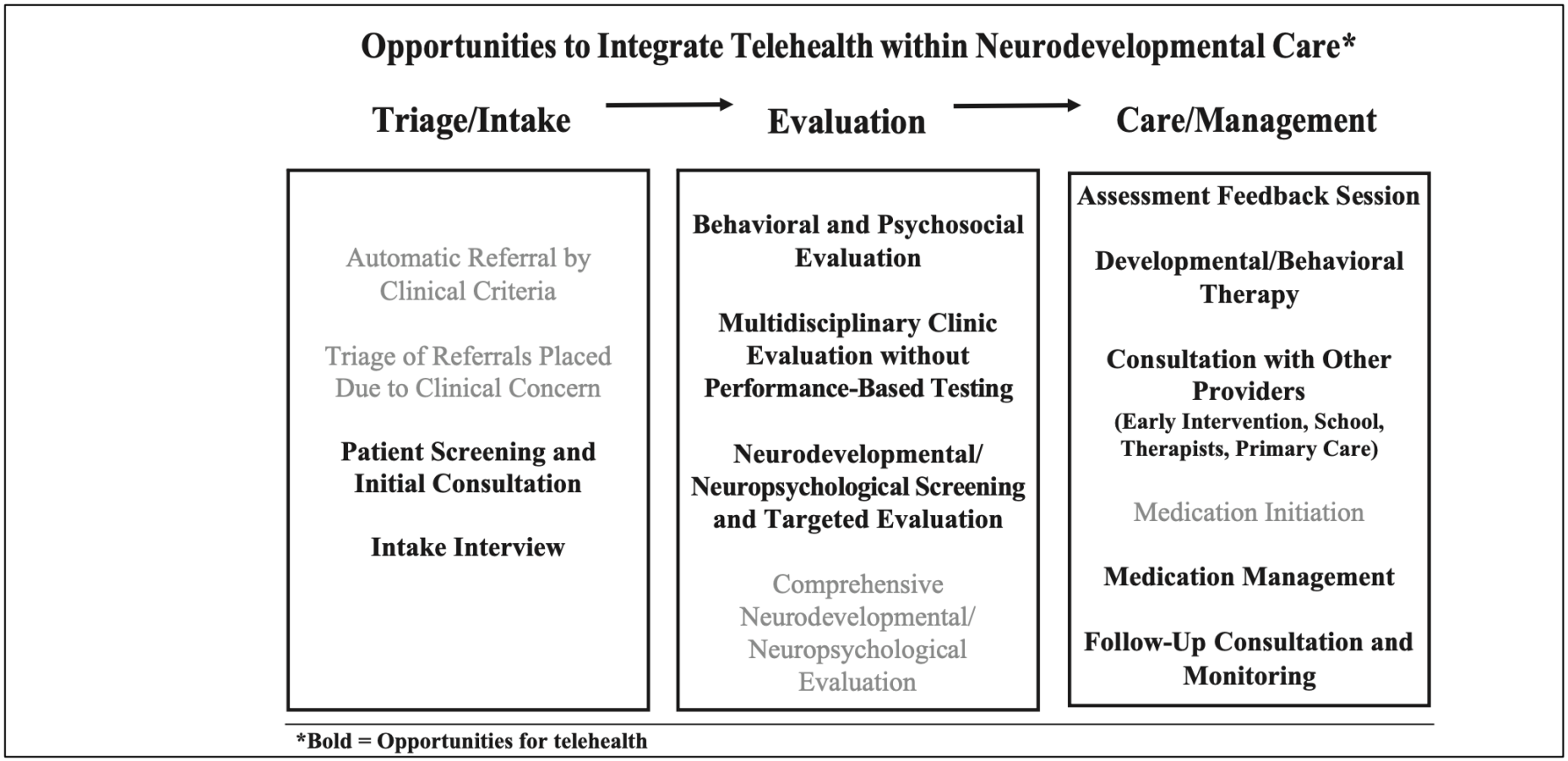



*Figure 8: Opportunities to integrate telehealth within neurodevelopmental care, adapted from Cox et al., (2022) [222]*

## 13.6 Converting in-person INTER-NDA to a virtual assessment: the approach

The INTER-NDA, typically administered face-to-face, was adapted for virtual use, an innovation which received recognition from the British Association of Perinatal Medicine as one of the top three projects for the Gopi Menon Excellence in Research or Innovation Award in 2021 (Appendix I). The Cardiff vision test is the choice of vision assessment that complements the INTER-NDA. However, an alternative tool was required as it is difficult to administer in a virtual or remote setting. After consultations with field experts, the *iSight Pro* became the tool of choice for virtual vision assessments. The next part describes the methodology and approach for the virtual NDA and vision assessments.

## 13.7 Research objectives

*Initially, the research objectives and outcome measures were:*

1. *To establish the effectiveness of the INTERGROWTH-21st Neurodevelopmental Assessment (INTER-NDA) and Cardiff Test of Vision as a standardised neurodevelopmental screening at 2 years of age for all children born preterm.*

*Outcome measures:*

- *For children born **< 32 weeks'** gestation: INTER-NDA domain scores and centiles, and Cardiff Test (LogMAR and contrast %) compared with clinical data (including previous NDAs and parental concerns) and **BSID-III scores**.*
- *For children born ≥ 32 **weeks'** gestation: INTER-NDA domain scores and centiles, and Cardiff Test (LogMAR and contrast %) compared with clinical data (including previous NDAs and parental concerns) and **INTERGROWTH-21st international ECD standards**.*

2. *To compare the INTER-NDA as a viable alternative neurodevelopmental screening tool compared to the BSID-III for children born VPT.*

*Outcome measures:*

- *INTER-NDA and BSID-III scores for participating children*
- *INTERGROWTH-21st international ECD standards*

### 13.8 Modified research objectives due to Covid-19-related changes to protocol

*The following objectives were adopted to mitigate the impact of the Covid-19 pandemic on the DPhil research design. This chapter will therefore report on these modified objectives:*

1. To test the feasibility (practicality) of a virtual platform to conduct NDAs of children born preterm.
2. To test the feasibility (practicality) of virtual vision tests of children born preterm.
3. To estimate the usefulness of the INTER-NDA as a tool for children born preterm.

Primary outcomes

- INTER-NDA domain scores for cognitive, fine & gross motor, language and positive & negative behaviour presented as centiles, and measured against the INTERGROWTH-21st international standards for ECD at age 2 years of age.
- Vision outcomes (visual acuity) measured on Cardiff and *iSight Pro* tests.

Secondary outcomes

- Measure: Parent satisfaction with the virtual assessment measured by % satisfaction and (qualitative) themes from the parent feedback survey.

Outcome measure

- Number of children identified with the INTER-NDA as having a neurodevelopmental impairment (for both virtual and in-person assessments).

### 13.9 Hypotheses

1. Conducting virtual NDAs of children born preterm can be a valuable approach to bridging access where barriers to in-person assessments exist. Valuable refers to added importance or esteemed characteristics or qualities. The value of the approach will be measured by:

- The number of children who could be offered virtual assessments and research activities that could be carried out remotely, which otherwise would not have happened during the pandemic when in-person neurodevelopmental assessments were not possible.
- Parents' feedback and satisfaction with the virtual assessments.
- Learning points from the virtual tests regarding what worked well and areas which could be improved to enhance future virtual assessments and digital healthcare for children and people with neurodevelopmental disturbances.

2. It is feasible to offer a virtual NDA to infants between the ages of 2 and 3.

Feasibility refers to the practicality of performing virtual neurodevelopmental assessments. The hypothesis was tested by setting up and performing the neurodevelopmental assessments virtually. Neurodevelopmental scores for the domains assessed will be presented according to the INTERGROWTH-21$^{st}$ standards for neurodevelopment. Feasibility will be measured by the proportion of children who successfully complete the virtual assessments (regardless of their neurodevelopmental scores). The assessments will be considered feasible if more than 50% of the children who signed up for the study are able to complete their assessments.

3. The INTER-NDA is a suitable tool for assessing the neurodevelopment of children born preterm. Suitable refers to appropriate for a situation or purpose. The domain scores for cognition, language, motor and behaviour will be compared to the corresponding norms of the INTERGROWTH-21st Standards for healthy children. Children whose test scores fall

below the INTERGROWTH-21$^{st}$ threshold for normality for the neurodevelopmental domains of interest will be identified for follow-up care. Parents may accept virtual approaches as suitable alternatives for assessing the neurodevelopment of their young children. This hypothesis will be tested through the parent feedback survey of the virtual assessments.

# 14 Methods

## 14.1 Study design

This section describes the study design and methodology for establishing a virtual NDA for children born preterm. Originally set to be a one-site study, interference because of the Covid-19 pandemic led to a halt in recruitment at the Oxford site. There was no clarity on how soon research activities could resume. Hence, there was a need to have a backup plan to boost data collection for my DPhil research. This resulted in the inclusion of an additional study site in Switzerland, which collaborates with the University of Oxford's INTERGROWTH-21st Project[xxxi]. The Larsson-Rosenquist Foundation Centre for Neurodevelopment, Growth and Nutrition of the Newborn[xxxii] (LRF NGN Centre) focuses on ECD, nutrition, and neurodevelopment, hence a good fit as a second site for the DPhil research.

The NDAs were therefore conducted using two modalities:

1. Virtual assessments at the Oxford site.
2. In-person assessments at the Zurich site.

Further to the assessments, this chapter also reports the parents' feedback survey results of virtual NDAs.

[xxxi] https://intergrowth21.tghn.org
[xxxii] https://www.usz.ch/fachbereich/neonatologie/forschung/ngn-researchcenter/

**Contribution**

*I innovated the virtual assessment methodology for the NDA, did the modification of the INTER-NDA for virtual use, and conducted the virtual NDA and vision assessments, parent interviews and surveys. I trained research assistants who supported the assessments at the Zurich site. I had the help of colleague staff to manage the research logistics, such as sanitising, packaging and mailing test kits to families. I worked under the tutelage of my supervisors throughout the process.*

### 14.1.1 Setting up and pilot testing the virtual vision assessment

The *iSight Pro* is designed to give accurate visual acuity testing on an iPad or iPhone. The test is designed to be suitable for children as young as 18 months. In conducting the virtual vision assessment, the following steps were taken:

**i.** History taking: test participants were asked about any history of vision problems they may have or experienced and if any needed glasses.

ii. Setting the distance: a standard tape measure was used to measure a distance of 1.5m from the screen to the position of the test participant.

iii. The *iSight Pro* was loaded onto the iPad of the assessor who then shared the screen with the parent via a video call.

iv. A virtual pointer on the video calling platform was used to point to the images on the screen.

v. The Kay Picture Test (with images, not letters) was used on the app. It was preferred to the Kay Letter Test as children could describe the images with sounds, or mimic what they saw, rather than being required to name the alphabet, which would have been inappropriate for children at this age. The images included items considered common to a 2-year-old, such as apple, boot, car, duck, house and star.

vi. The test started by showing images from a larger size (3m) and changing to smaller sizes as the test progressed. Sliding to the right of the screen changes the object that appears on the screen, whereas sliding downwards changes the size of the image.

vii. The *iSight Pro* test results are presented in LogMAR and Snellen in the app, and it also shows the distance at which the test was carried out.

The results of the pilot testing are presented in the results section.

## 14.2 Study location

### 14.2.1 Study site 1: Oxford University Hospitals NHS Foundation Trust

The study was carried out primarily at the Newborn Care Unit (also called the Neonatal Unit)[xxxiii] of the Oxford University Hospitals NHS Foundation Trust (OUH)[xxxiv] in Oxfordshire, UK. The OUH is a regional centre for prenatal and feto-maternal medicine. Its NICU is the regional medical and surgical referral centre for complex neonatal care in the Thames Valley Neonatal Network, which has 31,000 births each year. The OUH Neonatal Unit has 16 intensive care units (ICU), 13 high dependency units (HDU), 20 low dependency units (LDU) and four transitional care cots. There are 900 admissions per year and 4,000 intensive care days per year. The NICU provides all newborn care services for the local population with 7,500 deliveries per year.

### 14.2.2 Study site 2: Department of Neonatology, University of Zurich

The second study site was the LRF NGN Centre under the Department of Neonatology, University of Zurich. [xxxv] The LRF NGN was founded in 2019 to investigate the impact of early infant nutrition on neurodevelopment. The Department of Neonatology is one of the nine level-III perinatal centres in Switzerland and the second largest in the country, serving

[xxxiii] https://www.ouh.nhs.uk/children/services/newborn-care/
[xxxiv] https://www.ouh.nhs.uk
[xxxv] https://www.usz.ch/en/clinic/neonatology/

as a referral facility for a 1.5 million catchment area. It operates an 18-bed NICU and 18-bed intermediate care, with 3,000 births and 800 admissions annually. The department specialises in care for VPT infants and high-risk newborns, recording an average of 150 VPT births each year. Furthermore, the level-III centre offers the entire range of care for newborns, including primary and intensive care medicine. It collaborates with the Department of Obstetrics and the University Children's Hospital of Zurich to offer family-centred dedicated care for healthy and sick newborns and their parents and boasts two dedicated family rooms.

Beyond in-patient care, the Department of Neonatology is responsible for outpatient check-ups and offering the first neurodevelopmental visits at age 3 months for infants at the highest risk for neurodevelopmental insults, such as those born preterm or with asphyxia.

## 14.3 Eligibility criteria and study participants

### 14.3.1 Oxford site: child assessments

The EveryPrem Study was set up to recruit all children born preterm with the following characteristics:

#### *14.3.1.1 Basic criteria*

Eligible child participants for the study should satisfy all the following criteria:

- born before 37 completed week's gestation (i.e., up to 36+6 weeks);
- born at or received neonatal care at the John Radcliffe Hospital[xxxvi] (JRH), OUH, Oxford;
- should be aged between 20 and 30 months (corrected age) at the time of the assessment;

[xxxvi] https://www.ouh.nhs.uk/hospitals/jr/

- the parent should have responded positively to the invitation to participate in the study; and
- the parent or legal guardian should provide consent for the child to participate in the study.

#### *14.3.1.2 Geographic area*

- Originally, eligibility by geographical area included residents with an Oxfordshire (OX) postcode at the time of birth and until the time of the assessment. Therefore, children whose families had moved out of OX postcodes were not eligible for the study. The OX postcode eligibility criterion was to ensure that children and their families did not have to travel long distances to be assessed at the JRH.
- However, during Covid-19-related disruptions when the assessments were converted to a virtual platform, the postcode eligibility criteria were waived during the second round of recruitment (in November 2021) so that all children who satisfied the above eligibility criteria but who were living outside the OX postcode area (but within the UK) were invited to participate in the study. This was important as parents no longer had to travel to the hospital to be assessed.

### 14.3.2 Zurich site: child assessments

All children invited for the study satisfied the minimum eligibility criteria described above. Eligibility based on geographical area was not applied. All children delivered at or who received neonatal care at the Zurich University Hospital were eligible to participate in the study. Additionally, language eligibility criterion was applied to the Zurich site so that at least one parent of the child was required to speak (Swiss) German.

### 14.3.3 Parent survey and interview

- All parents whose children were eligible to participate in the study, regardless of whether the child participated in the study or not.
- Parents should have provided consent to participate in the study.

*Findings from the parent survey and interviews are reported in Chapter 3*

### 14.3.4 Exclusion criteria

- Children known or recorded not to be alive.
- Children in the terminal stages of a severe life-limiting condition or those receiving palliative care.
- Children whose parents did not respond positively to the study invitation and/or reminder.
- Non-German-speaking family (for the Zurich site)
- Parents who were unwilling to consent to their or their child's participation in the study.

## 14.4 Recruitment Methodology

### 14.4.1 Oxford site

Recruitment was supposed to begin shortly after all approvals were secured and to last two years (2020 to 2021). Due to Covid-19-related disruption to research work, recruitment was paused between March and September 2020 after the first participant had been assessed face-to-face in March 2020. Recruitment resumed in October 2020 and was extended until March 2022 to compensate for time lost for data collection. The neonatal care team identified eligible participants from the NHS BadgerNet[xxxvii] and Neonatal Unit Transitional

[xxxvii] BadgerNet is an electronic maternity notes system that replaces the paper-based record system: https://elht.nhs.uk/services/maternity-and-newborn-services/what_is_badgernet

Care databases. The neonatal secretary sent out invitation letters signed by the consultant neonatologist responsible for the study. The recruitment flow chart has been summarised in Figure 9 and Figure 10 for the Oxford and Zurich sites, respectively.

### 14.4.2 The Recruitment Pack

The recruitment pack included the following:

- An invitation letter from the consultant neonatologist.
- Participant information sheet with a link to the study website (which contained similar information).
- A reply slip with which parents could register their intent to participate in the study (an online reply slip[xxxviii] was embedded on the study website[xxxix] for parents who preferred to respond online).
- A return-addressed envelope with stamps to mail back the reply slip.
- A reminder slip was sent to parents who had yet to respond to the study a month after initial invitation letters were sent.

### 14.4.3 Responding to the study invitation

On the reply slip, parents could respond yes or decline to participate in the study. Parents could respond via the hard copy reply slip, online link or through the study email addresses indicated in the invitation letters.

[xxxviii] https://www.wrh.ox.ac.uk/research/everyprem/reply-slip/inter-nda
[xxxix] https://www.wrh.ox.ac.uk/research/everyprem

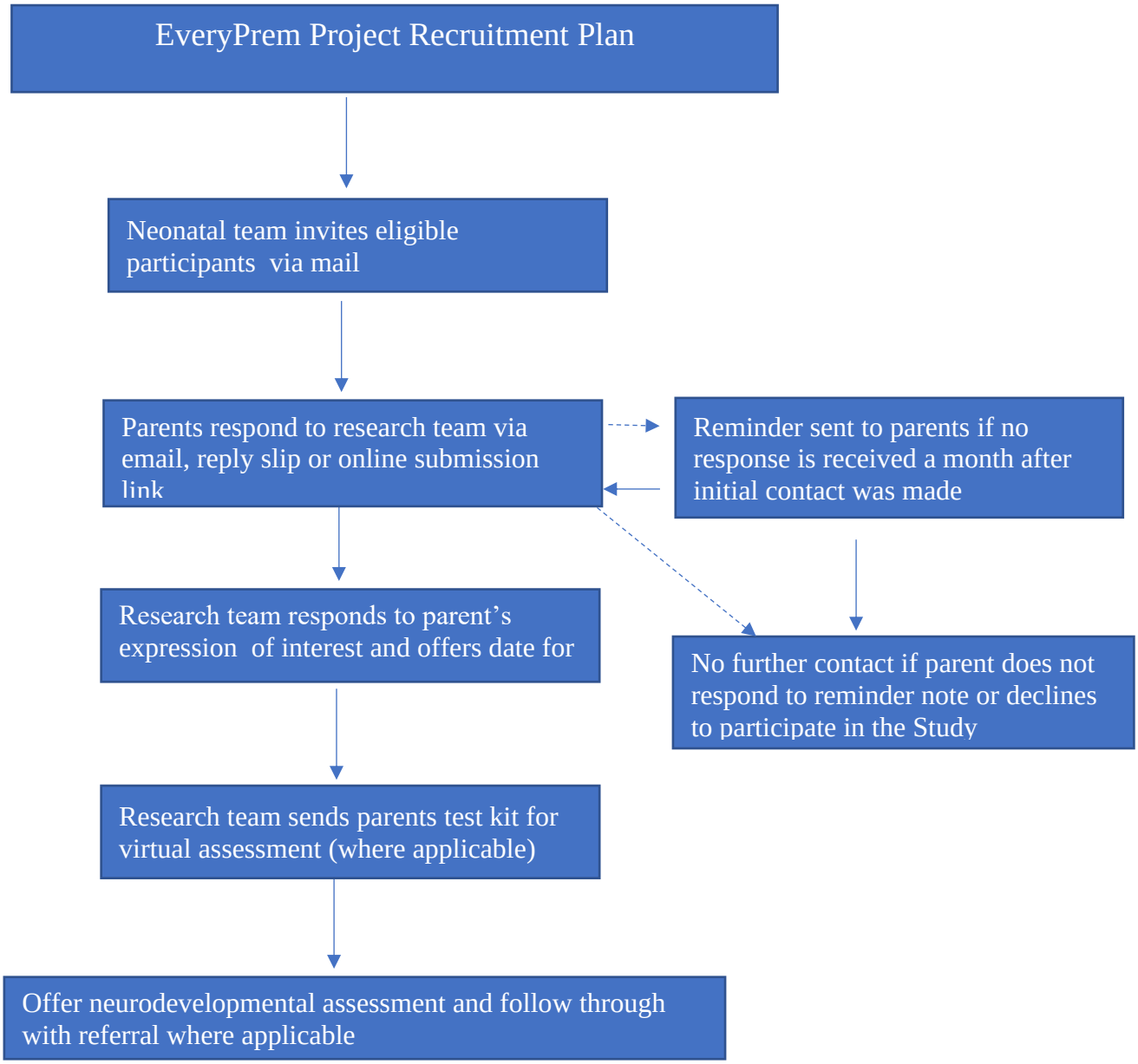



*Figure 9: EveryPrem Recruitment Flow Chart (Oxford site)*

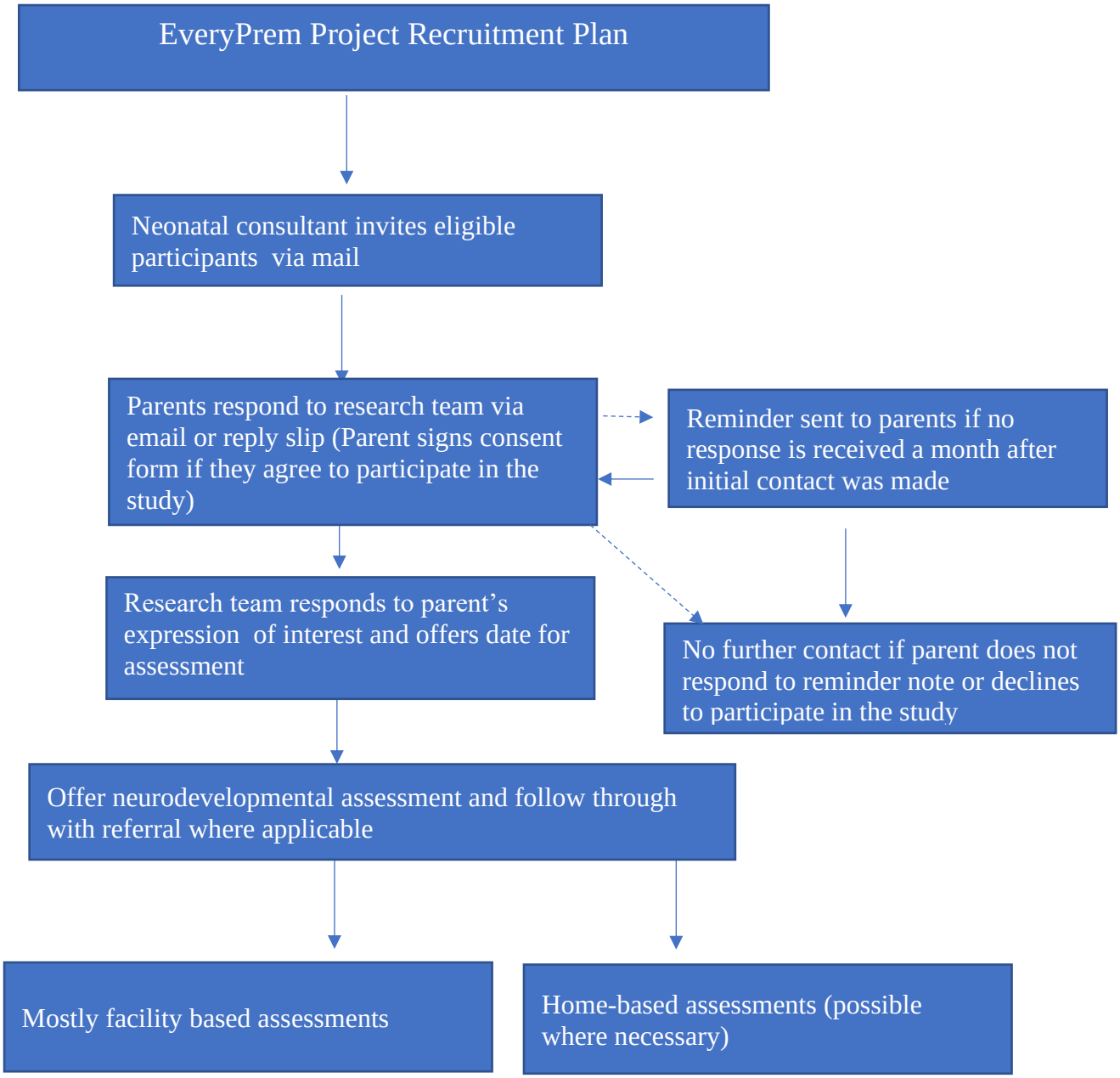



*Figure 10: EveryPrem Recruitment Flow Chart (Zurich Site)*

### 14.4.4 Translation of INTER-NDA assessment tool from English to German: Zurich site

Back translation[xl], also known as reverse translation, is a quality control process in which a piece of text is translated into a target language and then back to the original language. The back-translated text is then compared to the original text for accuracy.

The INTER-NDA manual was translated from English into German[xli] (Appendix II) and back-translated into English to ensure linguistic equivalence of the test instructions [200], Harkness, 2008 [224] cited in Kessler et al, 2009 [225]. The tool was pretested with native speakers to ensure that components of original meanings were preserved.

## 14.5 Virtual Neurodevelopmental Assessment

The need for a virtual NDA became crucial during the Covid-19 pandemic when face-to-face assessments were halted. There was a need to innovate an approach that could mimic the face-to-face assessments for all domains of NDA for the study, including vision, cognition, language, gross and fine motor and behaviour. The first approach was adapting the INTER-NDA for virtual use and finding a suitable vision screening tool that could replace the Cardiff Test of Vision, which complements the INTER-NDA assessments.

[xl] https://lokalise.com/blog/back-translation-best-practices/
[xli] I did the translation in conjunction with the NGN and EveryPrem Zurich teams and student assistants under the supervision of Professor Giancarlo Natalucci.

**FRAMEWORK FOR DESIGNING A VIRTUAL PLATFORM FOR NEURODEVELOPMENTAL ASSESSMENT OF CHILDREN BORN PRETERM**

- Pilot the adaptation of INTER-NDA for virtual use
- Identify a packaging and delivery system for test kit
- Communication with parents and support for virtual assessment
- Vision assessment: identifying a suitable tool (*iSight Pro*)
- Ethics amendment to convert face-to-face child assessments and parent activities to a virtual platform
- Bringing it all together

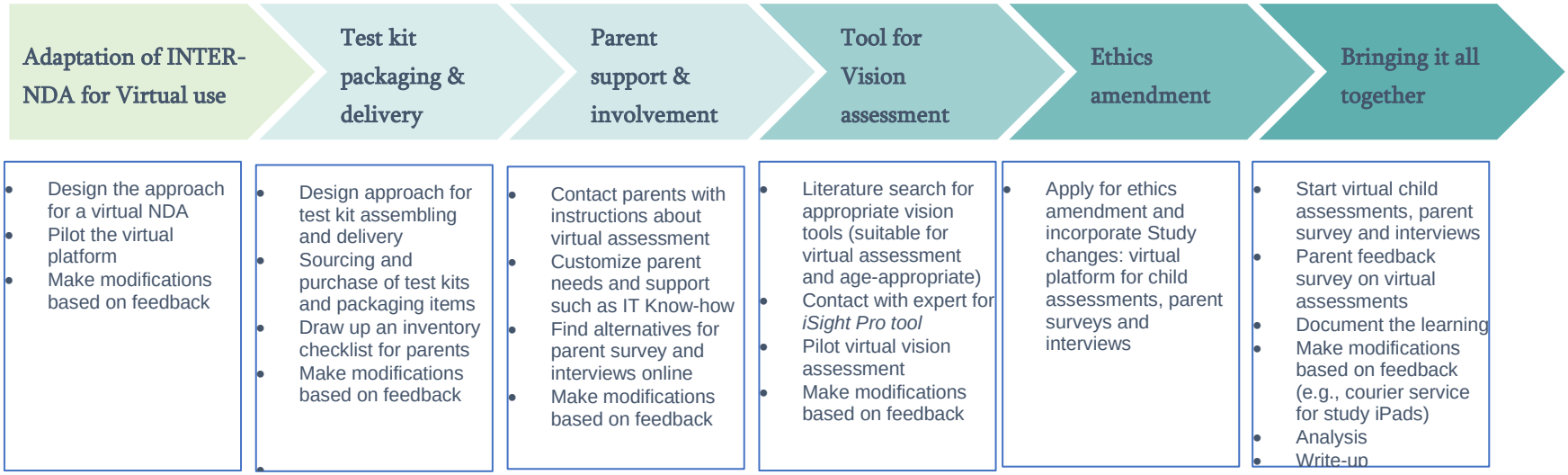



*Figure 11: Framework for designing a virtual platform for NDA*

### 14.5.1 Framework for virtual assessments

The framework for the design of the virtual assessment and research activities has been summarised in Figure 11[xlii]. The framework includes a 6-stepwise approach:

- Pilot the adaptation of INTER-NDA for virtual use
- Identify a packaging and delivery system for the test kit
- Communication with parents and support for virtual assessment
- Vision assessment: identifying a suitable tool (*iSight Pro*)
- Ethics amendment to convert face-to-face child assessments and parent activities to the virtual platform
- Bringing it all together

#### *14.5.1.1 Adaption of the INTER-NDA for virtual use*

Successful adaptation of a screening tool like the virtual INTER-NDA requires pretesting, pilot testing and test modifications to suit the new context [200]. In the design of the virtual approach to testing, the INTER-NDA assessment was pretested with five adult and five child volunteers. Due to the restrictions during the pandemic, it was challenging to find age-appropriate child volunteers for the pretesting. As the INTER-NDA tool is designed for children, this was a limitation in the adaptation process due to the prevailing conditions when this DPhil research was carried out during the peak of the pandemic. However, the learning from this exploratory and feasibility study of virtual approaches for neurodevelopmental assessments has provided invaluable insights for future validation studies of the virtual INTER-NDA.

Adapting the assessment from in-person to virtual involved a transition phase where three child assessments were done in-person and virtually, whereby the children and their parents were assessed in-person by a trained neonatologist, and the primary assessor joined virtually to observe the assessments and make tweaks for the virtual assessment. The two assessors

[xlii] https://doi.org/10.6084/m9.figshare.20422065.v1

debriefed after each session to discuss the assessments. The 'transition' sessions offered the opportunity to make modifications to the virtual assessments.

During this transition period, the opportunity for in-person sessions was limited due to the following challenges:

- The DPhil research was only permitted to continue with the virtual assessments as it was still not possible for parents and children to enter the hospital
- The assessment room in the hospital was converted into a Covid-19 screening room, and so it was no longer available for the study, and
- The primary researcher could not travel to Oxford due to travel restrictions and university closures during the pandemic.

#### *14.5.1.2 Modification of INTER-NDA for Virtual Assessment*

A virtual assessment assessor instruction manual[xliii] (Appendix III) was adapted from the INTER-NDA manual [40] meant for face-to-face assessments. The virtual NDA manual describes the processes for each activity including instructions for the assessor and activity notes to the parents.

Secondly, a standard operating procedure (SOP) (Appendix IV) was designed to document and standardise processes involved in the virtual assessments, including the *before, on the day and after the assessment* activities to organise. The SOP will aid the replication of the virtual NDA assessment in other settings.

In addition, a flowchart (Figure 12) summarising the processes involved in organising the virtual assessments is presented below:

[xliii] https://doi.org/10.6084/m9.figshare.20422065.v1

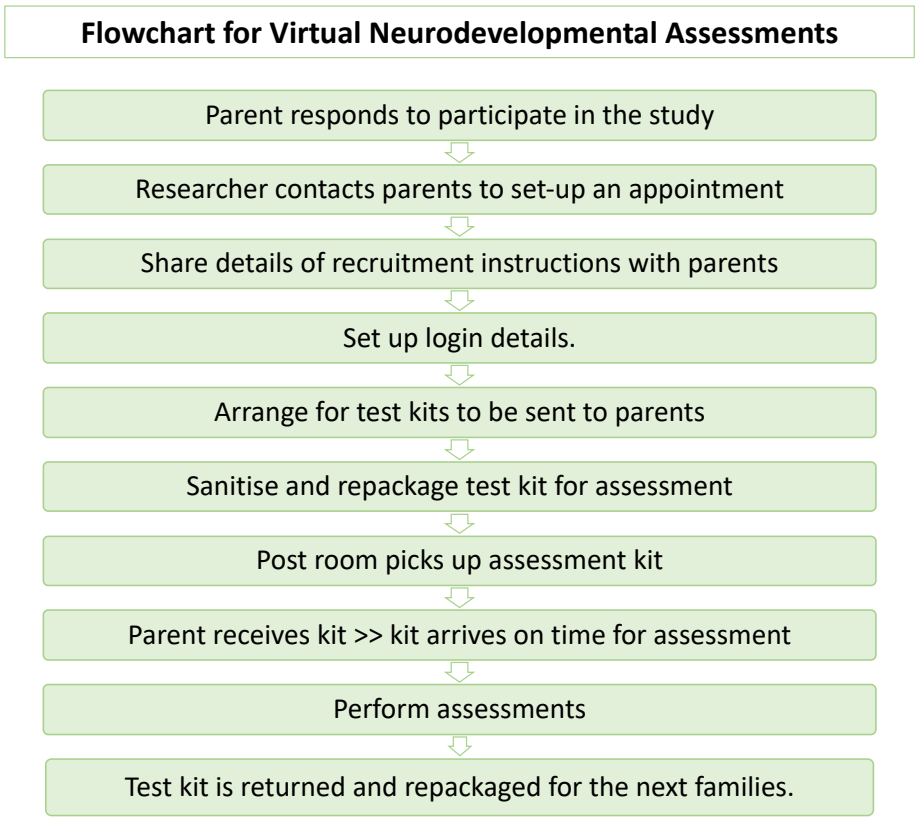



*Figure 12: Flowchart for Virtual NDAs*

#### *14.5.1.3 Test scoring for the virtual INTER-NDA assessments*

The test scoring was taken from the published INTER-NDA test [197], inter-nda_manual_v2.2021.pdf. The INTER-NDA items are administered in sequence. For items 1 to 30, there are five possible outcomes which are scored as 1, 2, 3, and 4 depending on the activity, and outcome 5 is 'unable to assess'. For example, for activity 1: *Builds a tower of 5 cubes in ≤ 3 trials (after demonstration)*, the possible outcomes are:

i. The child builds a tower of 5 cubes in ≤ 3 trials
ii. The child builds a tower of 3-4 cubes in ≤ 3 trials
iii. The child builds a tower of 2 cubes in ≤ 3 trials
iv. The child does not attempt to build the tower in any of the trials or is incapable of stacking more than one cube
v. Unable to assess the child

For INTER-NDA items 31 to 36, there are three outcomes as: *never or rarely*, *some of the time* and *most of the time.* The raw mean domain scores are converted to a standardised scaled score of 0 to 100. For cognitive, fine and gross motor, language and positive behaviour, a higher score reflects better performance; for negative behaviour, lower scores reflect better performance. The threshold of delay (Figure13) is interpreted in the INTER-NDA manual as:

- *'For all domains except negative behaviour, <3$^{rd}$ centile is the cut-off for high risk of severe delay, and*
- *3$^{rd}$ to 10$^{th}$ centile is the scaled score range for high risk of mild to moderate delay*
- *For negative behaviour, > 97$^{th}$ centile is the cut-off for high risk of severe delay, and the 90$^{th}$ to 97$^{th}$ centile is the scaled score range for high risk of mild-to-moderate delay'* (inter-nda_manual_v2.2021.pdf).

'*INTER-NDA 3$^{rd}$ to 97$^{th}$ centile ranges for 2-year-old children are based on scaled INTER-NDA standardised domain scores. Scores falling in the yellow zone* (Figure 13) *correspond to scores between the 10$^{th}$ and 3$^{rd}$ centiles, and scores in the orange zone correspond to scores <3$^{rd}$ centile*' [196].

### 14.5.2 Logistics

A virtual assessment team logistics flowchart (Appendix V) was designed to manage communication with the support staff who helped to organise the packaging of test kits when access to the hospital was limited during the peak of the pandemic. An Excel inventory sheet was also designed to monitor the records of test kits: families who had been sent kits, postage and return dates and the status of kits if they had been returned or otherwise.

#### *14.5.2.1 Logistics flow chart*

Once a date for the assessment was confirmed, a test kit pack was prepared and mailed to the parents' homes ahead of the assessment. Test kits for the virtual assessment were adapted from the INTER-NDA manual and customised to suit assessments in the home setting.

Test items were sanitised and packaged into separately labelled packs according to the order in which the kits would be needed on the assessment day. A test kit inventory (Appendix VI) was included in the packs to aid parents in identifying the order of activities and the kits for each activity during the virtual session.

#### *14.5.2.2 Study iPads for the vision assessment*

For parents without a computer or device larger than a phone screen, a study iPad was sent to them for the vision assessment. Parents were provided with the iPad password after the iPads were delivered. To maintain the safety and security of the iPads, the access point was locked allowing only for connection to Wi-Fi and the online call platform. All browsing sites were blocked.

### 14.5.3 Before the assessment

After parents indicated a willingness to participate, I, as the primary researcher, contacted them to offer an assessment date via email, phone call or both, depending on their preference. Once a suitable date and time were agreed upon, parents were sent an invite to block the date in their calendars. Confirmation was made via text message or a phone call.

#### *14.5.3.1 On the day of the assessment*

On the day of the assessment, the assessor welcomed parents to the virtual assessment room, explained the study, and asked if they had any questions. Parents then provided verbal informed consent, after which the assessment started.

#### *14.5.3.2 Vision assessment*

The *iSight Pro* was used to assess visual acuity from the test iPad. Basic details were keyed in before the vision test, i.e., the participant's study ID, the distance from the screen and the date of the assessment. A phone screen was not used as the images were too small for the child to read at a distance of 1.5m. The *iSight Pro* (2020) recommended two testing distances at 1.5 and 3 m, placing the testing device at eye level [226]. During the pilot testing, it was realised

that testing with a phone screen was not ideal for children in our cohort as the images appeared very small at a distance of 1.5 m. Therefore the screen size of an iPad or a laptop computer was recommended in this study. Hence, as part of the pre-assessment day guide, parents were to inform the primary researcher if they did not have an iPad.

The iPad was connected to the virtual platform, and its screen was shared so the child could see the images also logged on their parents' computer screen in their home. The assessor confirmed with the parent that the child was 1.5 m away from the screen.

### 14.5.4 After the assessment

After the NDA and vision tests were completed, thank you emails were sent to parents with information about and a link to the parent survey, and a reminder to return the study test kit to the research address in the kits. Copies of the verbal consent forms were attached to the emails and sent to the parents for their records.

### 14.5.5 Data management

After the assessments, anonymised vision and INTER-NDA scores, as applicable, were entered into a customised Excel data template for cleaning and processing, after which the relevant data sets were exported into SPSS *(IBM SPSS Statistics Version 28.0.0.0)* for analysis.

#### *14.5.5.1 Update master list*

The master list containing the study participants' personal and identifiable information was updated after the assessments. The master list is delinked from the data collection template so that the results were anonymised before being analysed.

#### *14.5.5.2 Enter data in Siteline*[xliv]

The *Siteline* is a platform to track participation in all OUH-sponsored studies. Right after the assessments, the study ID of the participants is entered into the *Siteline* platform, and the status of the participants is indicated as consent provided, enrolled, or completed.

#### *14.5.5.3 Data cleaning*

One of the duplicate entries with the same IP addresses was included in the analysis and the others were deleted. The status of responses recorded as 'spam' or 'false' in Qualtrics and blank entries, were all deleted.

### 14.5.6 Statistical Analysis

Raw INTER-NDA domain scores have been calculated, standardised, and compared to the INTERGROWTH-21$^{st}$ international standards (Figure 13). The threshold for normality for visual acuity (< 0.2 LogMAR) has been compared to the Cardiff results in the normative sample of the international INTER-NDA standards [196].

### 14.5.7 Ethical considerations

This study received ethical approval from the South Central - Hampshire B Research Ethics Committee (REC reference: 19/SC/0474) and clearance from the OUH to conduct the study at the JRH. The University of Oxford's Clinical Trials and Research Governance (CTRG) provided the approval and ethics sponsorship to the project.

The Study received a minor amendment approval (PID14212-A002-SP001-AC001) from the CTRG in October 2020 to incorporate the Covid-19 related study changes and objectives: transition from the face-to-face to virtual child assessments and parent interviews; and online parent survey (instead of the paper-based survey).

[xliv] https://www.ouh.nhs.uk/researchers/conduct/research-recruitment-reporting.aspx

### 14.5.8 Referral

Children whose assessment scores fell below the INTER-NDA threshold standards [196] for any domains assessed were identified for further onward care. The INTER-NDA international standards were applied to classify the domain scores into *normal neurodevelopment* and *moderate* or *severe impairment*, depending on the centile scores. The results were discussed with Dr O'Brien, who initiated the referral process (Figure 14) where needed, with a parent's consent.

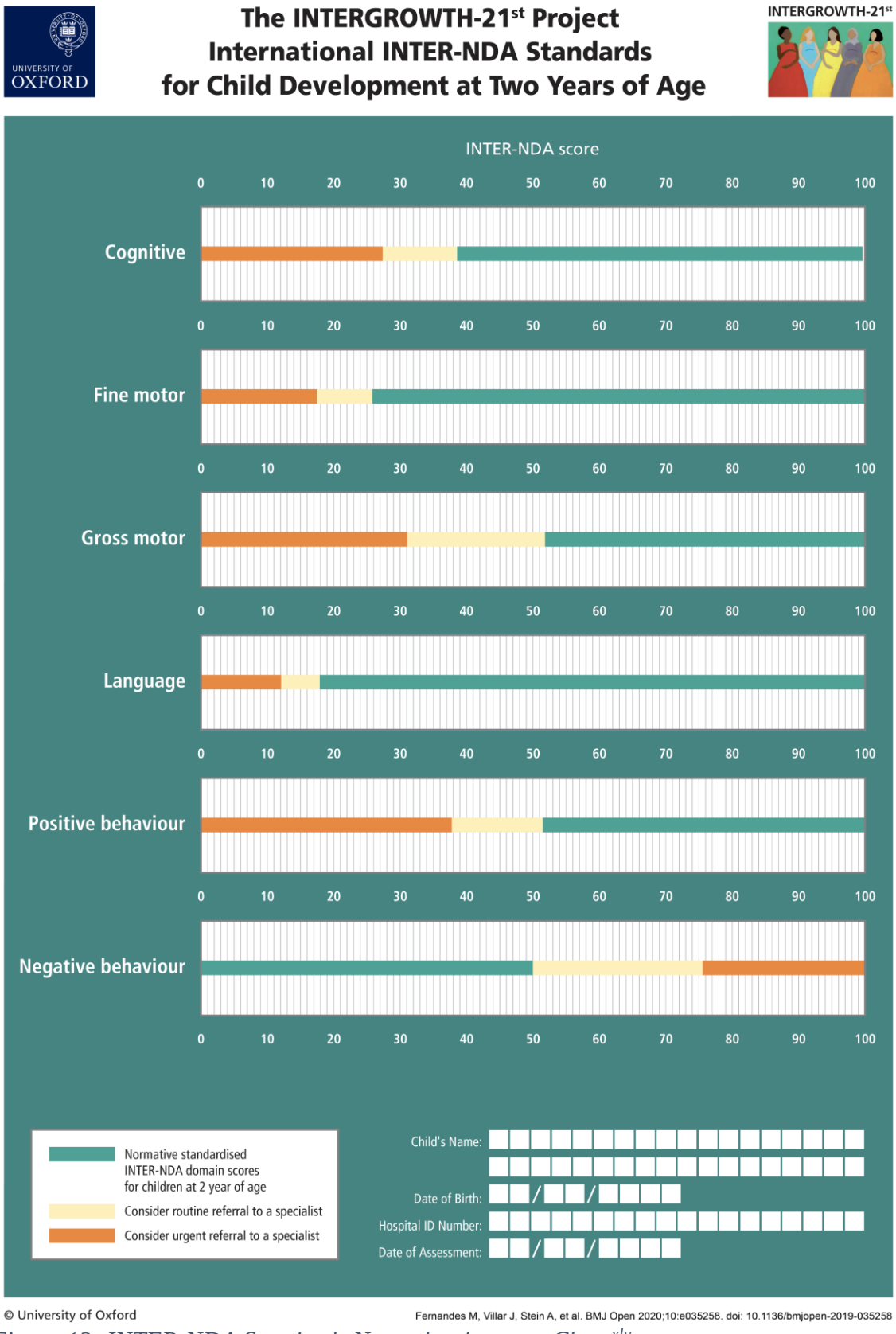



*Figure 13: INTER-NDA Standards Neurodevelopment Chart*[xlv]

[xlv] Figure cited from Fernandes, 2020 at https://www.inter-nda.com/inter-nda-chart.html

#### 14.5.8.1.1 Referral process

For children whose test scores did not meet the threshold of normality, the flowchart (Figure 14) below summarises their pathway for onward care[xlvi]. The threshold of normality, as used here, refers to the INTER-NDA classification of expected or 'normal' neurodevelopmental score ranges, which were constructed based on the prescriptive WHO approach. In constructing these norms, the INTER-NDA excluded children born preterm and those with significant postanal or neurological morbidity. According to the INTER-NDA classification, ''for all domains, except negative behaviour, higher scores reflect better outcomes and the threshold for normality was defined as ≥10th centile. For the INTER-NDA's cognitive, fine motor, gross motor, language and positive behaviour domains these are ≥38.5, ≥25.7, ≥51.7, ≥17.8 and ≥51.4, respectively. The threshold for normality for the INTER-NDA's negative behaviour domain is ≤50.0, that is, ≤90th centile'' [196, 227].

[xlvi] Documents completed for referral include the Single Point of Request for Involvement (SPORFI) Form 2, the adapted BRISC surveillance sheets and the speech sound checklist (for speech therapy referrals), EarlySupportSPORFIFlowchartandGuidance.pdf (oxfordshire.gov.uk).

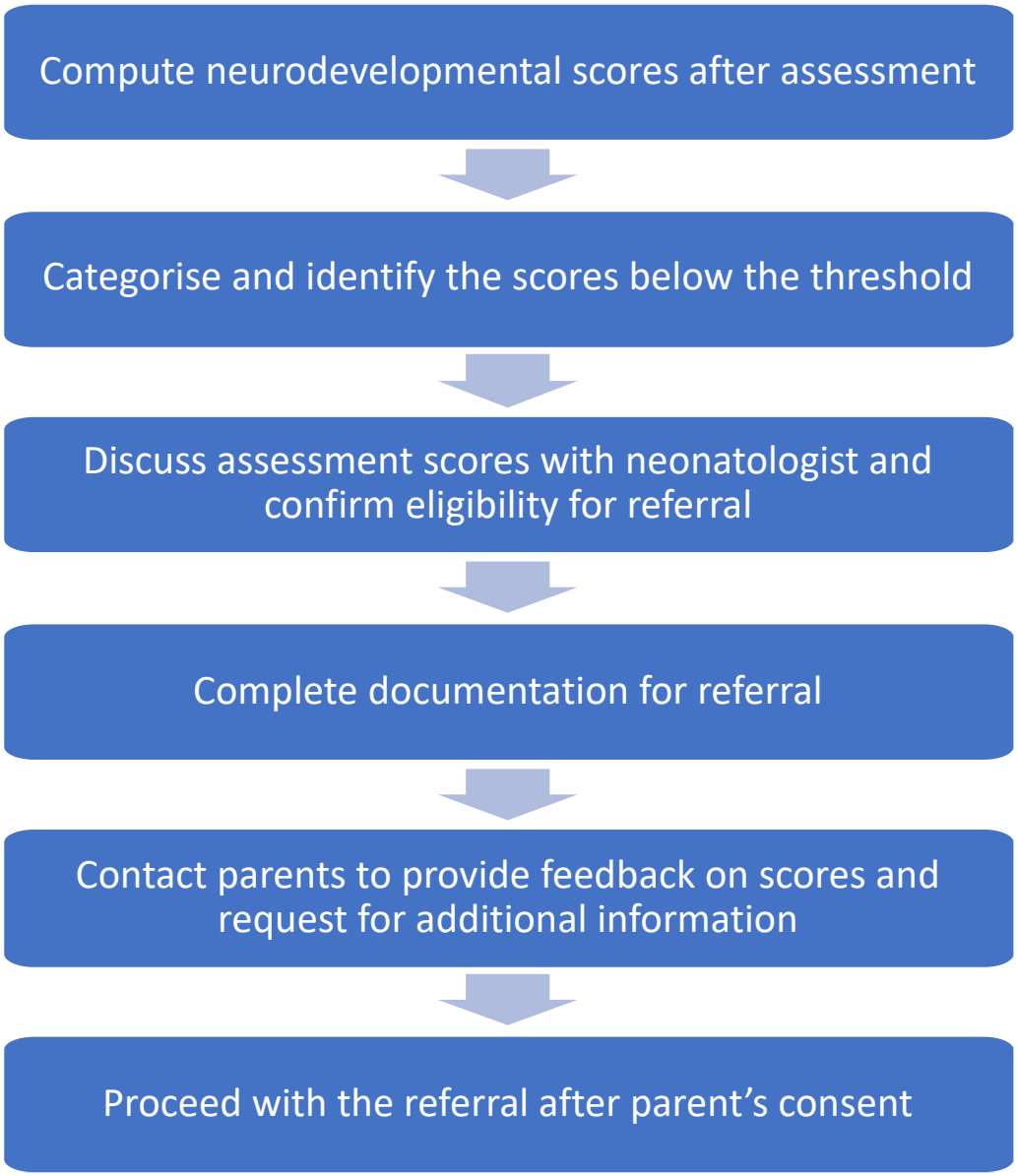



*Figure 14: Referral process for test scores below the threshold of normality*

#### *14.5.8.2 Test kit*

Items were sourced from a local manufacturer, from the shop or online. Items were packaged in recycling bags and labelled per pack to correspond to the label number on the inventory list. The labelled bags were then boxed in sturdy recycling boxes, which were used several times. Stamps for returning the test kits, a return address label, a Royal Mail orange slip for tracking and scotch tape for repackaging the boxes were included in the pack for parents to use to mail back the test kits. iPads were sent to families without laptops to make the vision assessment possible. In this case, a courier service was arranged to deliver and return the iPad.

### 14.5.9 Risk of spread of Covid-19

To avoid the possible spread of the virus during the pandemic, care was taken to ensure the safety of the families who received the packs and that of the research team who received and repackaged kits. The travel time of a few days between contacts with the test kits offered a protective effect on persons who came into contact with the kits. All test items were sanitised thoroughly before they were repacked to other families.

# 15 Results

## 15.1 Overview of study recruitment: Oxford site

**Population characteristics**: For the two recruitment cycles for this study, there were 447 unique households of families with children born preterm who received neonatal care at the JRH within the eligible time frame of the study recruitment. Unique households here refer to children from the same household; this means that twins and triplets from the same parents were counted as a family unit.

Of the 447 unique households, 92 (20.6%) participated in the study. The remaining 79.4% who did not participate in the study included those who declined participation, did not respond to the study invitation or whose postcodes were not considered eligible for the study (due to long distances, only OX postcodes were eligible in the batch 1 recruitment). In batch 2 recruitment, when the study moved virtual, all postcodes of eligible families were invited to participate as distance was no longer a barrier for families participating.

### 15.1.1 Index of Multiple Deprivation

The index of multiple deprivation (IMD) description of the 447 unique families is presented in (Table 5) Families were categorised into three bands depending on the IMD categorisation of their postcodes:

- lower 40% at the bottom of IMD represents the 1$^{st}$ and 2$^{nd}$ quintiles and most deprived areas
- middle 40 to 60% of the IMD decile; 3rd quintile
- upper 40% of the IMD represents the 4th and 5th quintiles and the least deprived areas.

Considering all eligible families together, about 20% of families fall within the lower 40% and of the middle 40 to 60% of the IMD quintile classification, while approximately 60% of unique families belong to the upper 40% of IMD quintiles and the least deprived postcodes in England.

There was no statistical difference between the sociodemographic characteristics of participants and non-participants (p-value = 0.472).

| IMD of study and non-study participants | | | | |
|---|---|---|---|---|
| **P value = 0.472** | | **Eligible households** | | **Total participants n (%)** |
| | | **Participants n (%)** | **Non-participants n (%)** | |
| **IMD Interpretation** | lower 40% at the bottom of IMD, 1st and 2nd quintiles; most deprived areas | 17 (18.5) | 75 (21.1) | 92 (20.6) |
| | middle 40 to 60% of the IMD decile; 3rd quintile | 16 (17.4) | 77 (21.7) | 93 (20.8) |
| | upper 40% of the IMD, 4th and 5th quintiles; least deprived | 59 (64.1) | 203 (57.2) | 262 (58.6) |
| **Total** | | **92 (100)** | **355 (100)** | **447 (100)** |

*Table 5: IMD of study and non-study participants.*

| Interviewee (n=29) | Non-interviewee (n=63) | IMD Interpretation |
|---|---|---|
| 7 (24%) | 10 (16%) | lower 40% of the IMD, representing the 1st and 2nd quintiles; most deprived areas |
| 5 (17%) | 11 (17%) | middle 40 to 60% of the IMD decile; 3rd quintile |
| 17 (59%) | 42 (67%) | upper 40% of the IMD, representing the 4th and 5th quintiles; least deprived areas |

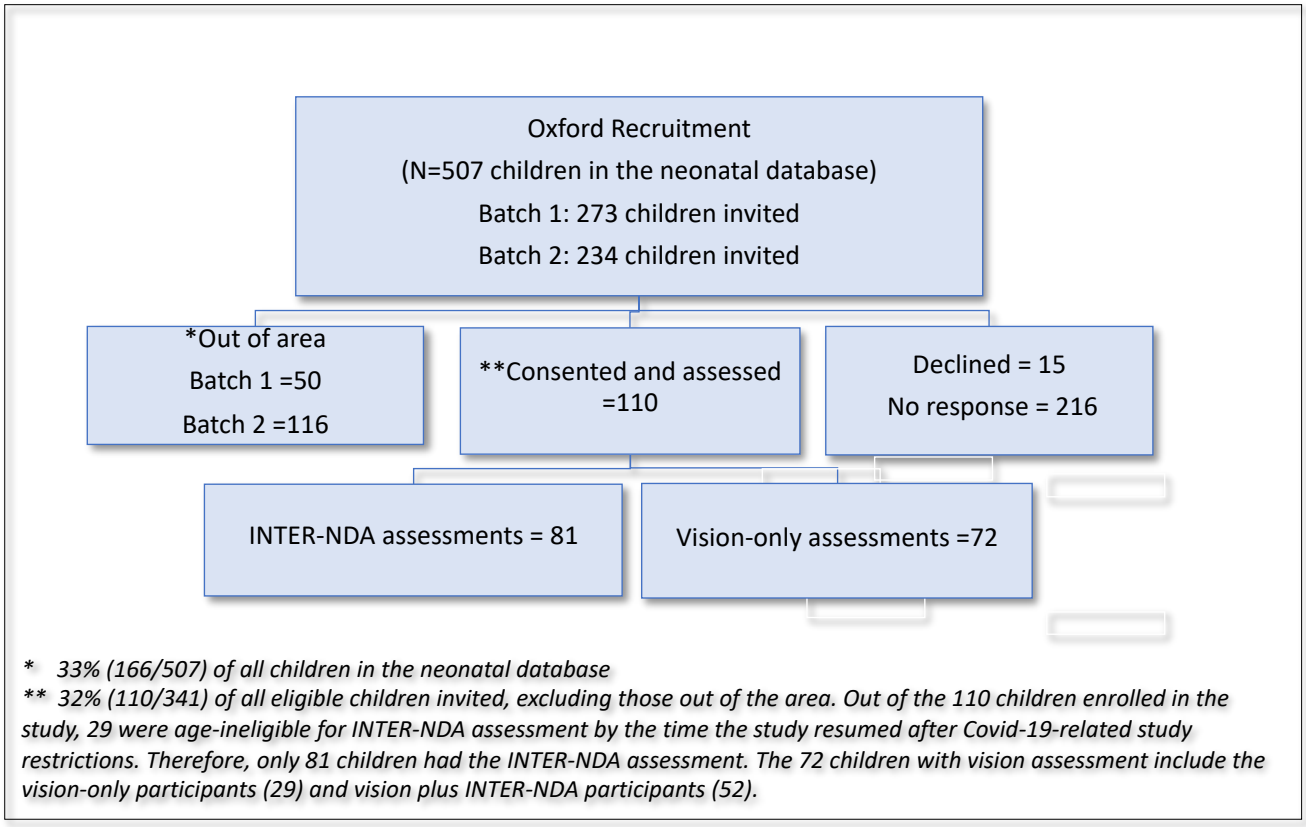
*Table 6: IMD of interviewees and non-interviewees*

**IMD of preterm subgroups**

The IMD of participants have been described according to the preterm subgroups in Table 7. It can be inferred that there were fewer households (about a fifth or less) in the most deprived areas. In contrast, over 60% of participants across all preterm subgroups who participated in the study were from the least deprived areas (4th and 5th quintiles). Representation of households by preterm subgroups was: VPT 35 (38%), MPT 22 (24%) and LPT 35 (38%).

| Very Preterm (VPT, n=35) | [xlvii]Moderate Preterm (MPT, n=22) | Late Preterm (LPT, n=35) | IMD Interpretation |
|---|---|---|---|
| 7 (20)% | 5 (23)% | 5 (14%) | lower 40% of the IMD, representing the 1st and 2nd quintiles; most deprived areas |
| 4 (11)% | 3 (14%) | 9 (26%) | middle 40 to 60% of the IMD decile; 3rd quintile |
| 24 (69)% | 14 (64)% | 21 (60%) | upper 40% of the IMD, representing the 4th and 5th quintiles; least deprived areas |

*Table 7: IMD of households according to preterm subgroups.*




** 33% (166/507) of all children in the neonatal database*
*** 32% (110/341) of all eligible children invited, excluding those out of the area. Out of the 110 children enrolled in the study, 29 were age-ineligible for INTER-NDA assessment by the time the study resumed after Covid-19-related study restrictions. Therefore, only 81 children had the INTER-NDA assessment. The 72 children with vision assessment include the vision-only participants (29) and vision plus INTER-NDA participants (52).*

*Figure 15: Overview of recruitment, Oxford site*

[xlvii] Percent exceeds 100 due to rounding for % IMD of MPT households

## 15.2 Overview of study recruitment: Zurich site

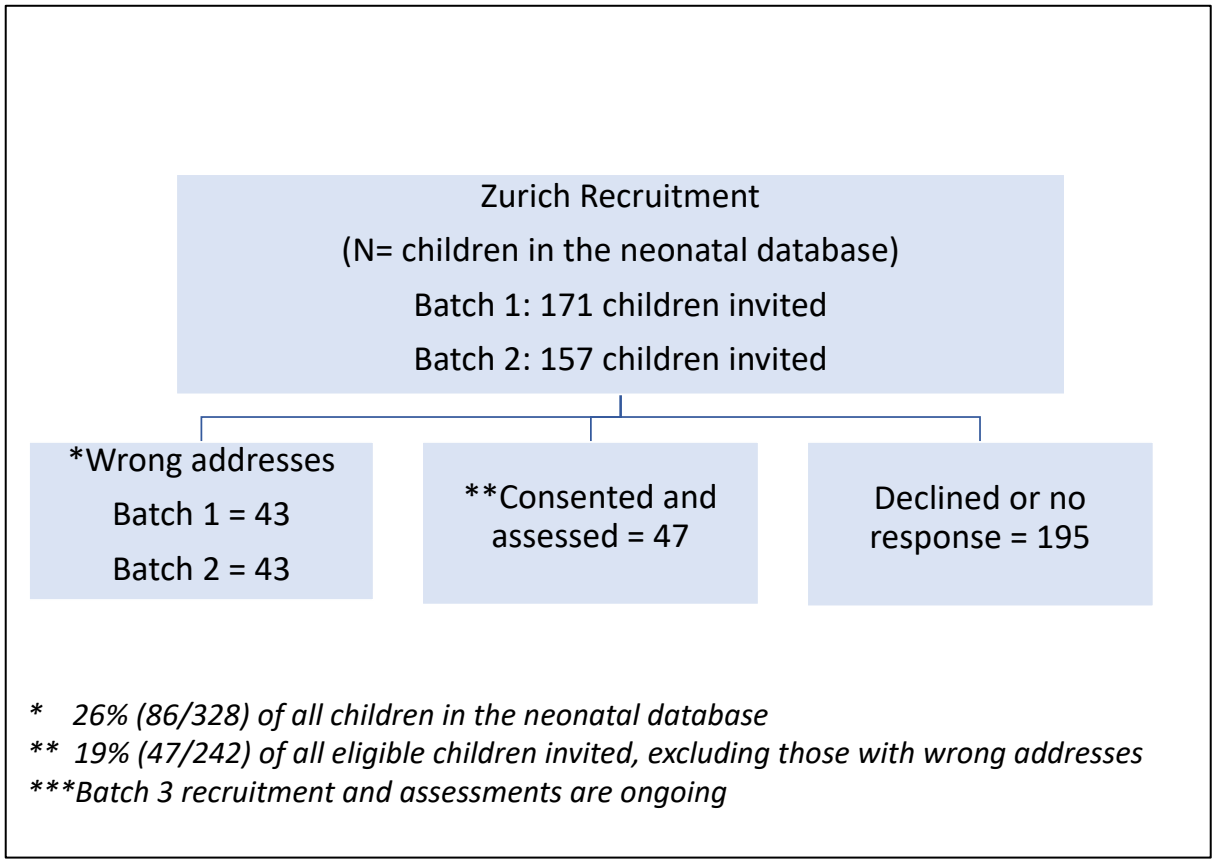



*Figure 16: Overview of recruitment, Zurich site*

## 15.3 Neurodevelopmental scores for children using INTER-NDA tool, Oxford Site[xlviii]

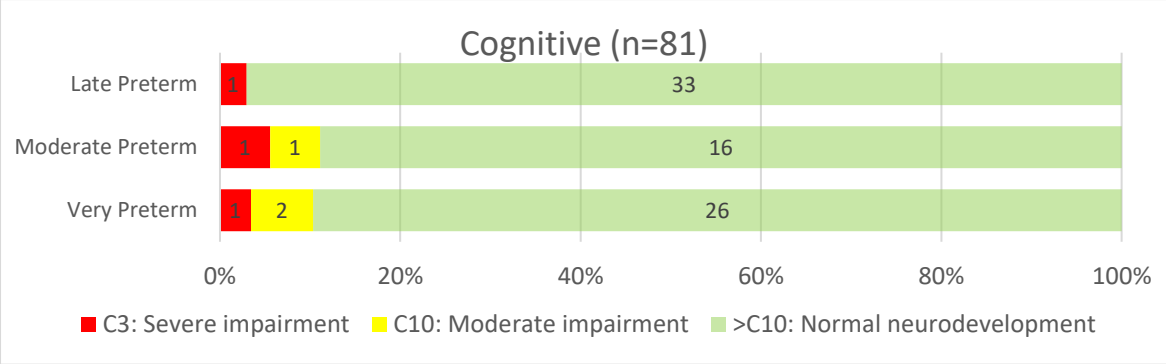



*Figure 17: Cognitive, Oxford*

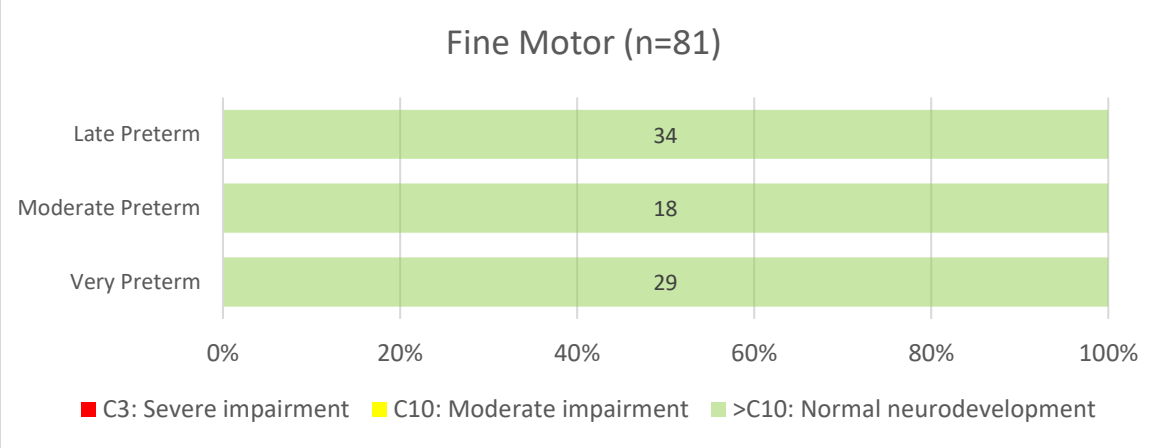



*Figure 18: Fine Motor, Oxford*

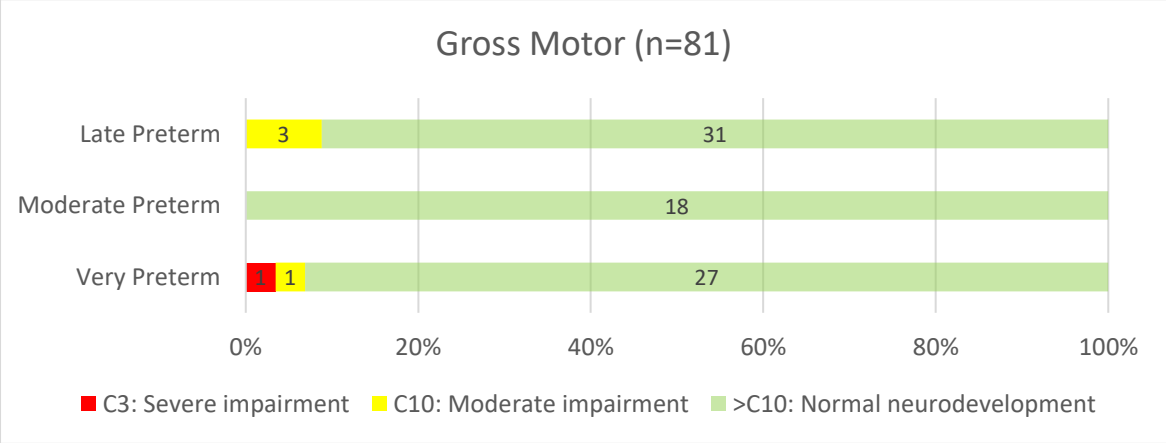



*Figure 19: Gross Motor, Oxford*

[xlviii] n=81

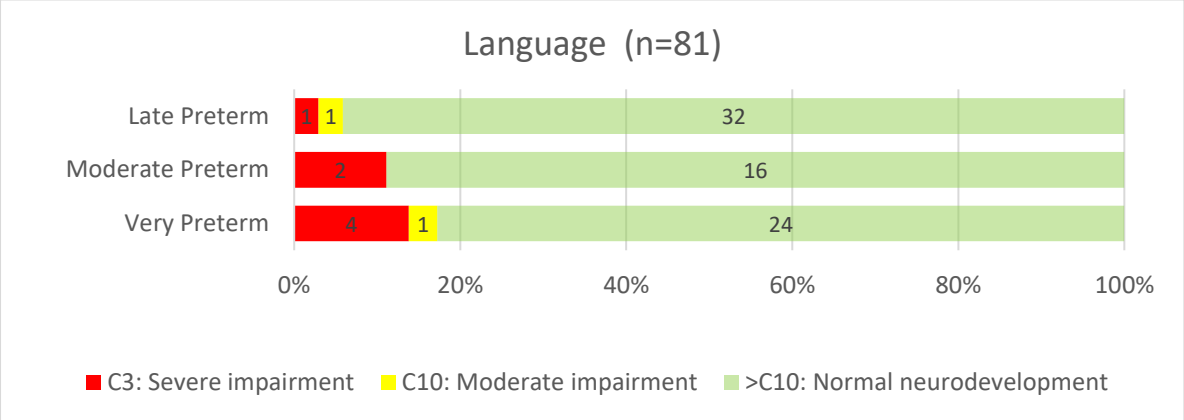



*Figure 20: Language, Oxford*

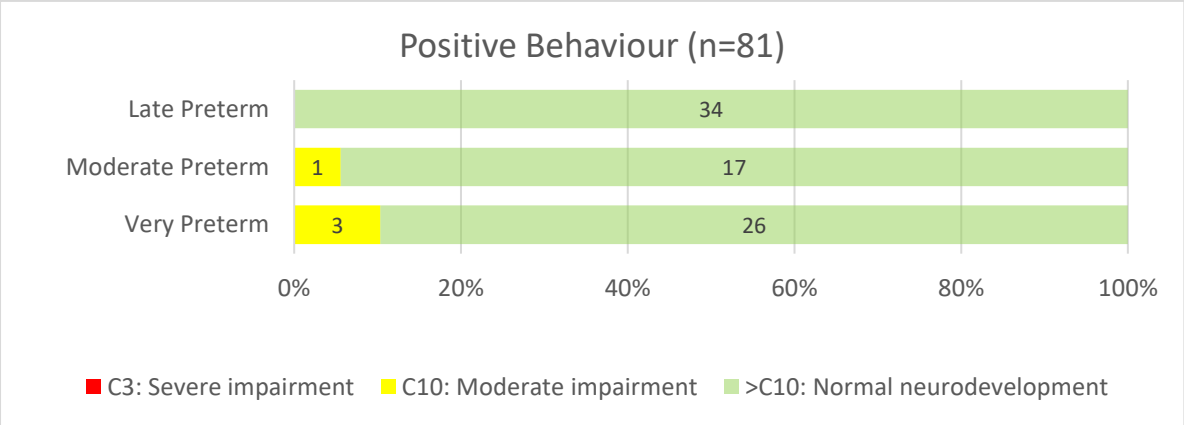



*Figure 21: Positive Behaviour, Oxford*

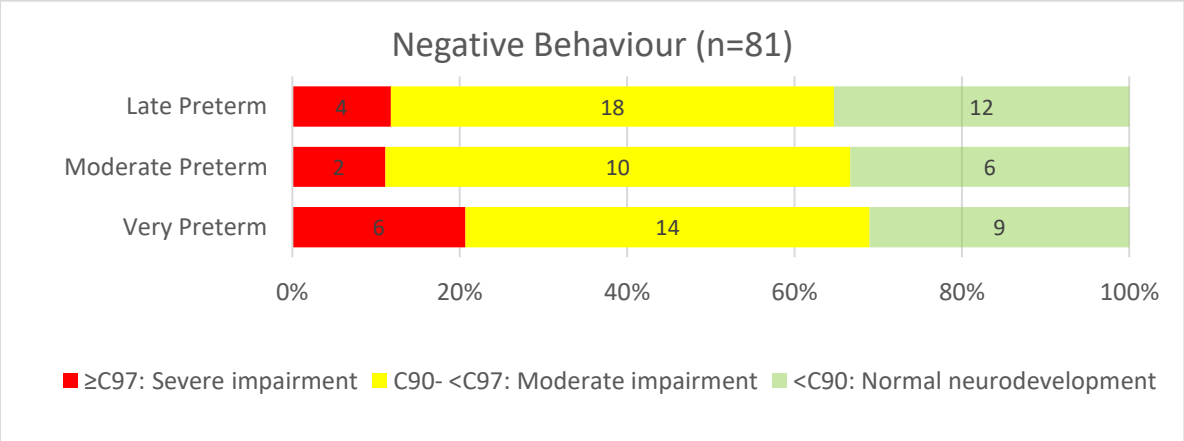



*Figure 22: Negative Behaviour, Oxford*

### 15.3.1 Summary of assessment scores

| Domain | Normal Neurodevelopment | Moderate Impairment | Severe Impairment | Total Impairment[xlix] (by domain) |
|---|---|---|---|---|
| Cognitive | 75 | 3 | 3 | 6/81 (7%) |
| Fine motor | 81 | 0 | 0 | 0 |
| Gross motor | 76 | 4 | 1 | 5/81 (6%) |
| Language | 72 | 2 | 7 | 9/81 (11%) |
| Negative Behaviour[l] | 27 | 42 | 12 | 54/81 (67%) |
| Positive behaviour[li] | 77 | 4 | 0 | 4/81 (5%) |

*Table 8: Neurodevelopmental outcomes and levels of impairment among Oxford cohort*

| Scores segregated by preterm subgroups | | |
|---|---|---|
| **Preterm Subgroups** | **Normal Neurodevelopment** | **Impairment (in at least one domain)** |
| Very Preterm | 8/29 (28%) | 21/29 (72%) |
| Moderate Preterm | 5/18 (28%) | 13/18(72%) |
| Late Preterm | 11/34 (32%) | 23/34 (68%) |
| Total | 24/81 (30%) | 57/81 (70%) |

*Table 9: Neurodevelopmental outcomes by preterm subgroups, Oxford (for all domains combined)*

The study included NDAs of 81 children at the Oxford site using the INTER-NDA tool. Four of these assessments were done in person (one prior to Covid-19 and three during the transition to virtual assessments). The remaining 77 INTER-NDA assessments were carried out virtually and in the comfort of the children's homes. The domains assessed include cognition, fine and gross motor, language, and positive and negative behaviour. Based on the INTERGROWTH-21$^{st}$ international standards (Figure 13) [196], children were classified as having normal neurodevelopment, or (at risk of) moderate or severe impairment in the six domains assessed.

[xlix] Total impairment = moderate plus severe impairment
[l] Negative behaviour domain in INTER-NDA includes distractibility (e.g., poor attention to detail) and negative affect (e.g., shouting angrily)
[li] Positive behaviour domain in INTER-NDA includes positive affect (e.g., smiling, hugging) and cooperativeness (e.g., child performs tasks such as building a tower when requested)
https://www.medscinet.net/Intergrowth/patientinfodocs/INTER-NDA%20Manual%20July%202014.pdf

Domain scores were as follows: 67% (54/81) of the study participants were identified as at risk of moderate or severe impairment in negative behaviour, 11% (9/81) in language, 7% (6/81) in cognition, 6% (5/81) in gross motor and 5% (4/81) in positive behaviour. No impairment in fine motor was observed in this cohort (Table 8).

For all six domains combined, 70% (57/81) of children were identified as at risk of having an impairment in at least one domain (Table 8), and the breakdown is as follows:

- one domain: 48/57 (84%)
- two domains: 4/57 (7%)
- three domains: 1/57 (2%)
- four domains: 3/57 (5%)
- five domains: 1/57 (2%)

#### *15.3.1.1 Neurodevelopment and sex*

Out of the 81 children who had the INTER-NDA assessment, 50 were males (62%) and 31 were females (38%). A breakdown of the level of impairment according to sex is presented in Table 10.

| Domain | Male = 50 (n (%)) | Female = 31 (n (%)) |
|---|---|---|
| **Cognition** | | |
| Normal neurodevelopment | 46 (92) | 29 (94) |
| Moderate impairment | 2 (4) | 1 (3) |
| Severe impairment | 2(4) | 1 (3) |
| **Fine Motor** | | |
| Normal neurodevelopment | 50 (100) | 31 (100) |
| Moderate impairment | 0 | 0 |
| Severe impairment | 0 | 0 |
| **Gross Motor** | | |
| Normal neurodevelopment | 48 (96) | 28 (90) |
| Moderate impairment | 2 (4) | 2 (7) |
| Severe impairment | 0 | 1 (3) |
| **Language** | | |
| Normal neurodevelopment | 44 (88) | 28 (90) |
| Moderate impairment | 2 (4) | 0 |
| Severe impairment | 4 (8) | 3 (10) |
| **Positive Behaviour** | | |
| Normal neurodevelopment | 47 (94) | 30 (97) |
| Moderate impairment | 3 (6) | 1 (3) |
| Severe impairment | 0 | 0 |
| **Negative Behaviour** | | |
| Normal neurodevelopment | 16 (32) | 11 (36) |
| Moderate impairment | 26 (52) | 16 (52) |
| Severe impairment | 8 (16) | 4 (12) |
| **Impairment in at least one domain**[lii] | 37 (74) | 20 (65) |

*Table 10: Neurodevelopmental domains and sex*

[lii] For all domains combined

## 15.4 Vision assessment results

### *15.4.1.1 Pilot testing*

The purpose of pilot testing was to assess the feasibility of carrying out the virtual vision assessment, learn from it, and make modifications as appropriate for the main assessments with the child study participants.

| Volunteer Study ID | Age | Sex | Test 1 (LogMAR) | Test 2 (LogMAR) |
|---|---|---|---|---|
| V001 | 8 | M | -0.10 | -0.10 |
| V002 | 6 | F | 0.00 | -0.10 |
| V003 | 4 | M | 0.30 | 0.20 |
| V004 | 40 | M | -0.10 | -0.10 |
| V005 | 7 | M | -0.10 | -0.10 |
| V006 | 6 | M | -0.10 | -0.10 |
| V007 | 28 | F | -0.10 | 0.00 |
| V008 | 16 | F | -0.20 | -0.20 |
| V009 | 14 | M | -0.20 | -0.20 |
| V010 | 35 | F | 0.00 | 0.00 |

*Table 11: Characteristics and test scores of volunteers for the virtual vision assessment*[liii]

Some of the quality issues that were picked up during pilot testing and addressed were:

i. The screen had to be set at eye level

ii. The recommended screen (size) was that of a laptop computer or iPad. Phone screens were not used as the images would appear too small at a testing distance of 1.5 m.

iii. The test was to be completed as quickly as possible to keep children interested but without rushing them.

When the test was applied in the study itself, children who could not see the images expressed frustration and did not like to look at the screens.

[liii] *Visual acuity scores are presented in LogMAR and at a distance of 1.5m*

### 15.4.2 Main study vision test scores

Out of the 110 children who participated in the study, 72 had a vision assessment (4 with Cardiff test and 68 with *iSight Pro* test), 27 could not be assessed and 11 had no vision assessments due to the reasons explained in Table 12.

| **OUTLOOK OF VISION ASSESSMENTS** | |
|---|---|
| **Vision assessments** | **Number** |
| Cardiff Test | 4 |
| *iSight Pro* | 68 |
| Unable to assess (with *iSight Pro*)<br>Reasons: child factors such as,<br>• *Delayed speech in children*<br>• *Existing vision problems e.g., squint*<br>• *Child too active to focus or not willing to look at the screen* | 27 |
| No vision assessment<br>*Reasons: parent factors and logistics*<br>• *Delays with courier service to send study iPads to parents without a computer*<br>• *Parent only responded to INTER-NDA and not vision assessment* | 11 |

*Table 12: Table of Vision Results*

The vision test scores are presented in two parts: a) individual scores presented in a histogram and tabular form b) aggregate (combined) data of normal and not normal acuity scores.

#### 15.4.2.1.1 Individual vision test scores of participants.

The individual vision test scores of the 73 participants are presented as a normal distribution in the chart below:

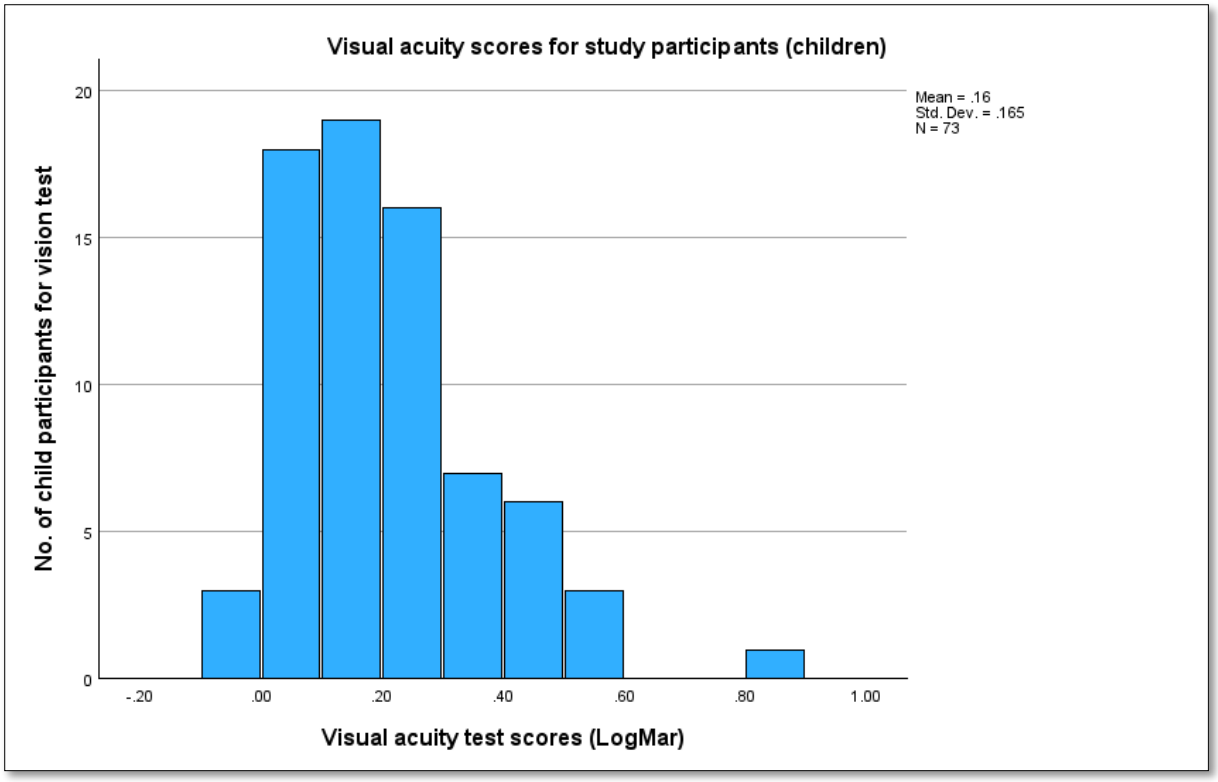



*Figure 23: visual acuity scores*

| Visual acuity scores for study participants | | |
|---|---|---|
| **Visual acuity scores (LogMAR)** | **Frequency** | **Percentage (%)** |
| -0.10 | 2 | 2.7 |
| -0.01 | 1 | 1.4 |
| 0.00 | 17 | 23.3 |
| 0.08 | 1 | 1.4 |
| 0.10 | 19 | 26.0 |
| 0.20 | 16 | 21.9 |
| 0.30 | 6 | 8.2 |
| 0.38 | 1 | 1.4 |
| 0.40 | 6 | 8.2 |
| 0.50 | 3 | 4.1 |
| 0.80 | 1 | 1.4 |
| **Total** | **73** | **100.0** |

*Table 13:Visual acuity scores*

#### 15.4.2.1.2 Vision test scores (per subgroups)

The vision test scores in Figure 24 are presented according to sex, type of birth and preterm subgroups.

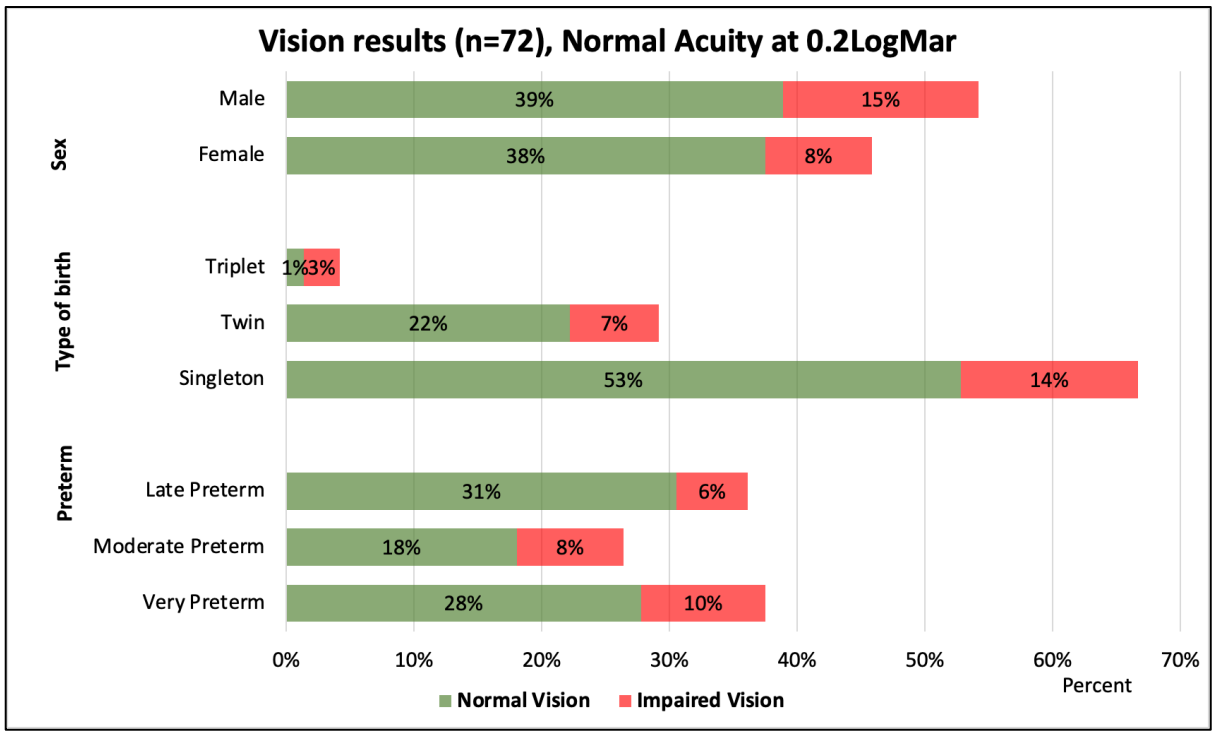



*Figure 24: Results of Tests of Vision (Acuity)*

Figure 24[liv] shows the vision scores by sex, type of birth and preterm subgroups. The overall scores for the 72 participants (Table 14) who took the vision assessment yielded 76% normal vision scores (up to 0.2 LogMAR), and 24% showed signs of impaired vision (acuity at > 0.2 LogMAR) using both the Cardiff and *iSight Pro* Tests.

| **Vision Results: Acuity, n=72 (normality at 0.2 LogMAR)** | | | |
|---|---|---|---|
| **Characteristics** | **Vision Results (Acuity)** | **Normal Vision** | **Impaired Vision** |
| **Preterm subgroups** | Very Preterm | 20 | 7 |
| | Moderate Preterm | 13 | 6 |
| | Late Preterm | 22 | 4 |
| **Type of birth** | Singleton | 38 | 10 |
| | Twin | 16 | 5 |
| | Triplet | 1 | 2 |
| **Sex** | Female | 27 | 6 |
| | Male | 28 | 11 |

*Table 14: Background description of participants for vision test.*

[liv] Percent exceeds 100 due to rounding for preterm subgroup aggregate for vision scores

### 15.4.3 Virtual assessments: logistics management

Appointments had to be rescheduled or cancelled due to 1) kits not arriving in time (n=10), 2) parents being unavailable or missing the appointment (n=4) and 3) child being sick on the day of the assessment (n=1).

## 15.5 Zurich Assessment Results[lv]

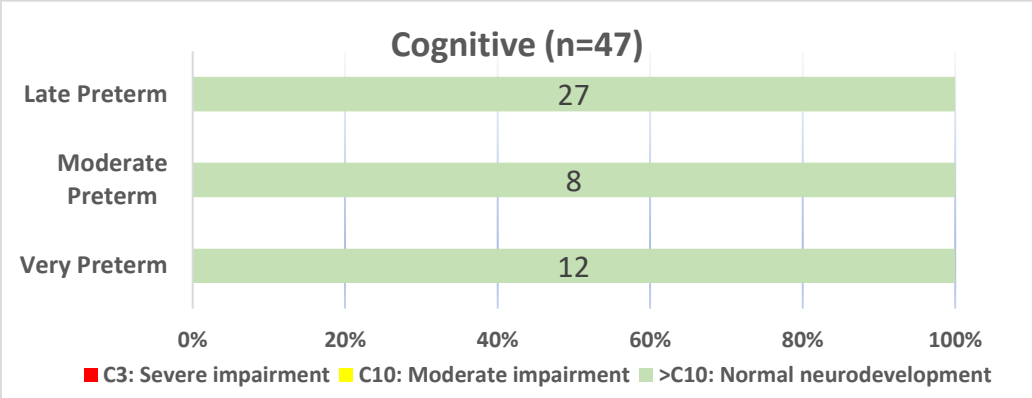



*Figure 25: Cognitive, Zurich*

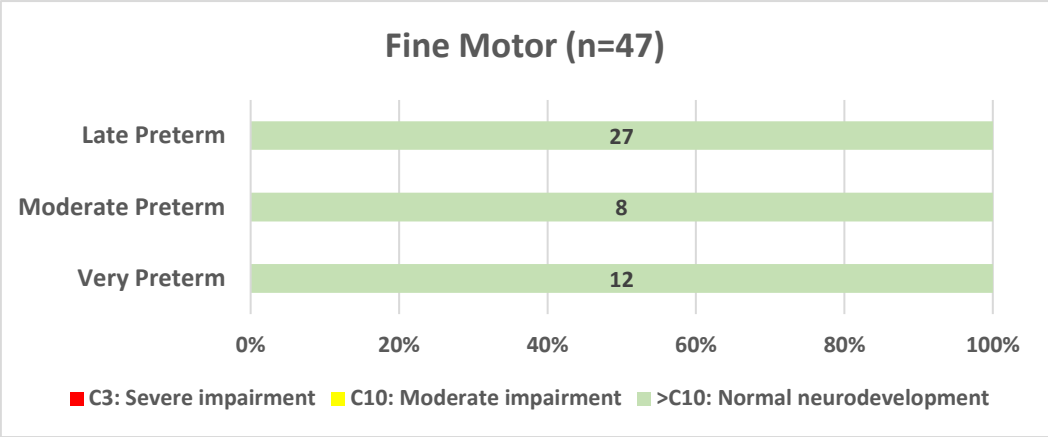



*Figure 26: Fine Motor, Zurich*

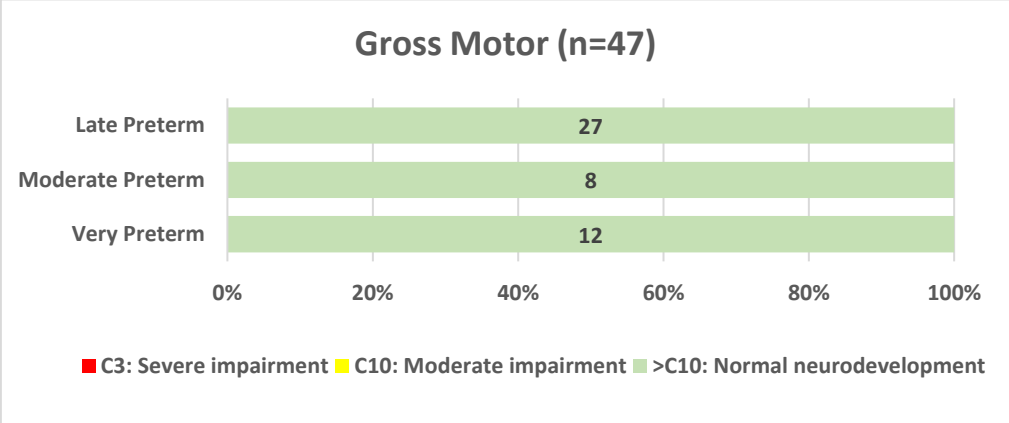



*Figure 27: Gross Motor, Zurich*

[lv] Domains scores for the Zurich site are reported for 47 participants except for positive and negative behaviour, including scores for 46 participants due to missing data for one participant.

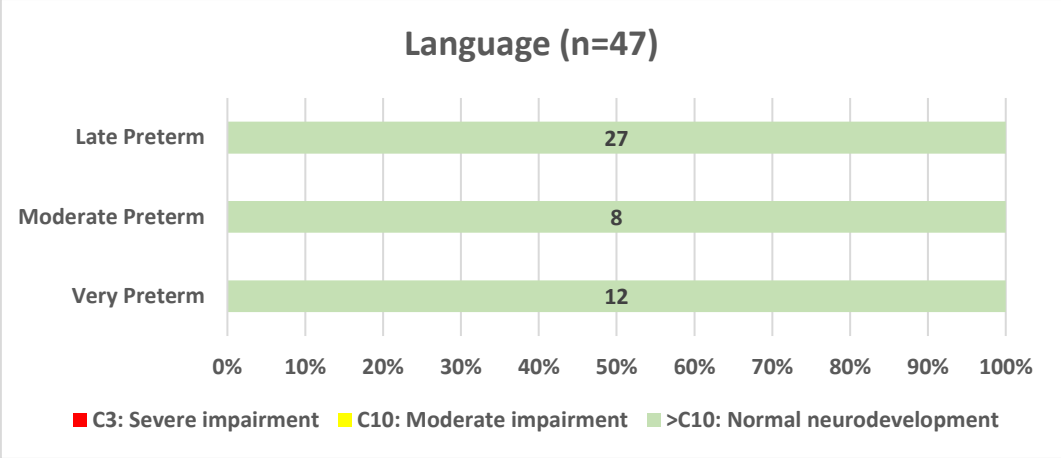



*Figure 28: Language, Zurich*

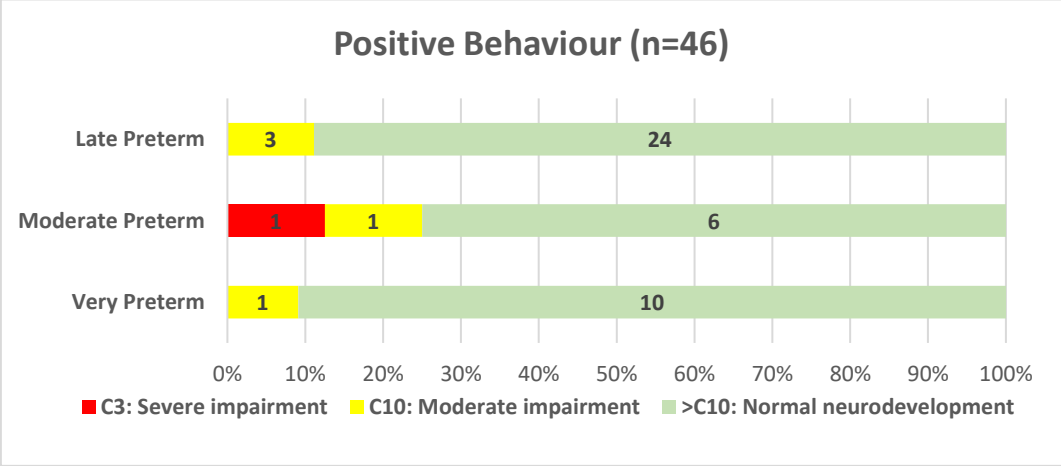



*Figure 29: Positive Behaviour, Zurich*

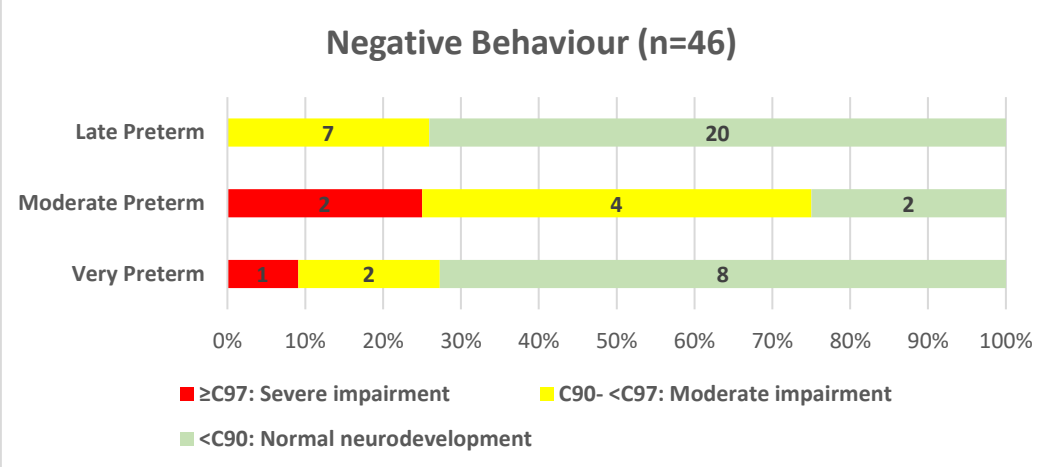



*Figure 30: Negative Behaviour, Zurich*

| Domain | Normal Neurodevelopment | Moderate impairment | Severe impairment | Total Impairment[lvi] (by domain) |
|---|---|---|---|---|
| Negative Behaviour | 30 | 13 | 3 | 16/46 (35%) |
| Positive behaviour | 40 | 5 | 1 | 6/46 (13%) |
| Language | 47 | 0 | 0 | N/A |
| Gross motor | 47 | 0 | 0 | N/A |
| Fine motor | 47 | 0 | 0 | N/A |
| Cognitive | 47 | 0 | 0 | N/A |

*Table 15 Neurodevelopmental outcomes and levels of impairment among Zurich cohort*

| Scores segregated by preterm subgroups[lvii] | | | |
|---|---|---|---|
| **Preterm Subgroups** | **Normal Neurodevelopment** | **Impairment (in at least one domain)** | **Total Impairment (by preterm subgroups)** |
| Very Preterm | 8 | 3 | 3/11 (27%) |
| Moderate Preterm | 2 | 6 | 2/8(25%) |
| Late Preterm | 20 | 7 | 7/27 (26%) |
| **Total** | **30** | **16** | **16/46 (35%)** |

*Table 16: Neurodevelopmental outcomes by preterm subgroups, Zurich (for all domains combined)*

## 15.6 Virtual Assessments Feedback Survey

### 15.6.1 Feedback on Virtual Neurodevelopmental Assessment

The survey ran from February 2021 to May 2022 to solicit parent feedback on the virtual NDA and vision tests. Survey responses have been reported as % satisfaction or themes from the qualitative responses in the survey design.

There were 56 responses from which records with multiple IP records (6 duplicates) were excluded during data cleaning. Hence, 50 participants were included in the present analysis;

[lvi] Total impairment = moderate plus severe impairment
[lvii] Computed with data of 46 out of the 47 participants, behaviour scores were missing for one participant.

29 (58%) of the parents' children had a virtual NDA and vision assessment, and 21 (42%) had only the virtual vision assessment[lviii].

## 15.7 Satisfaction with virtual assessment

Parents whose children participated in the virtual INTER-NDA and/or vision assessments were asked about their satisfaction with both virtual approaches. On a 5-point Likert scale, parents were presented with the options to rank their level of satisfaction as follows: *very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied and very dissatisfied*. Forty-nine parents rated their satisfaction with the virtual assessments: 21 with virtual vision-only assessments and 29 on the virtual NDA[lix] (Figure 31)[lx]. Combining responses on the virtual NDA and virtual vision assessments, the total level of satisfaction (i.e., *very and somewhat satisfied*) was 74%; 22% of the responses were neutral (*neither satisfied nor dissatisfied*), and only 4% of the responses were rated as *somewhat dissatisfied*. There was no rating of *very dissatisfied* with either of the virtual assessments.

[lviii] The children who only had the virtual vision assessment were those who were no longer age-eligible for the INTER-NDA after the study resumed from the pandemic-related research closures.
[lix] Virtual NDA sessions also included virtual vision assessments for most children, exceptions are indicated in Table 12
[lx] Percent for satisfaction with virtual NDA does not total 100 due to rounding.

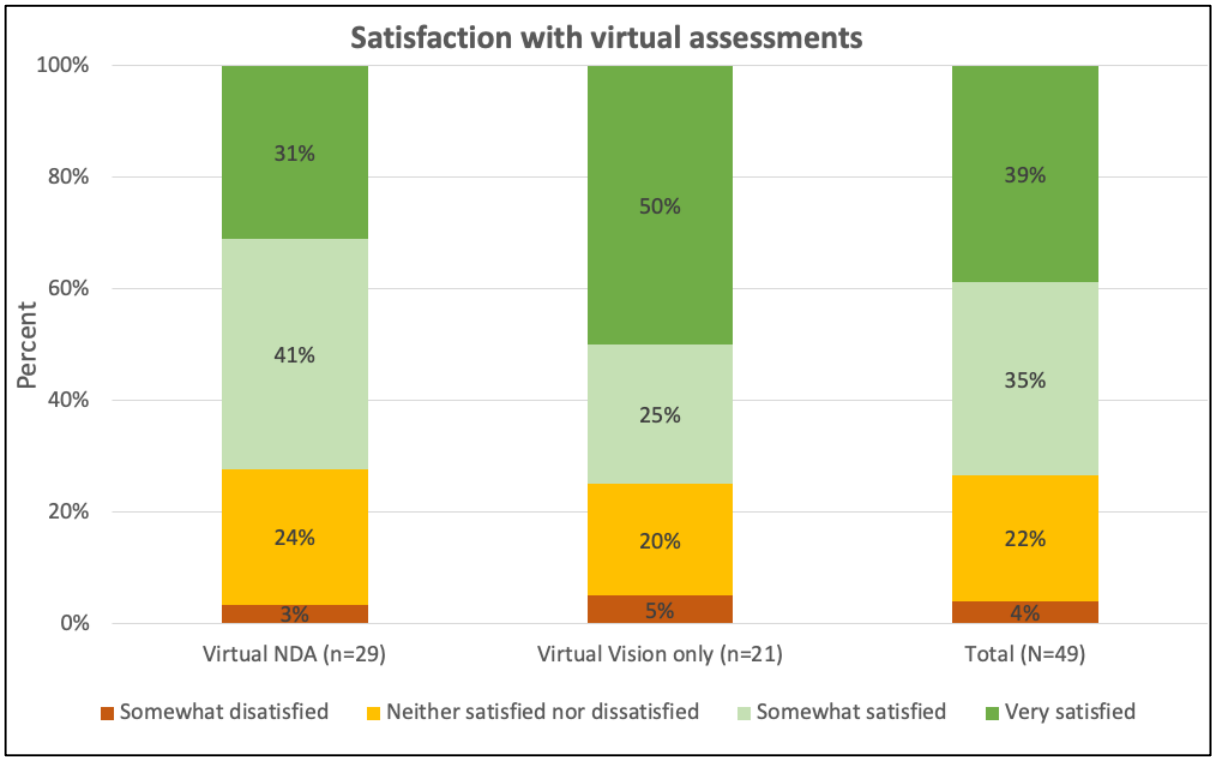



*Figure 31: Satisfaction with virtual assessments*

## 15.8 Themes from parent feedback on virtual assessments

Qualitative themes from the survey are presented in three sections: *home/virtual assessments, face-to-face assessments and virtual vision assessments. Sub-themes further developed from home/virtual assessments, include pros and cons.*

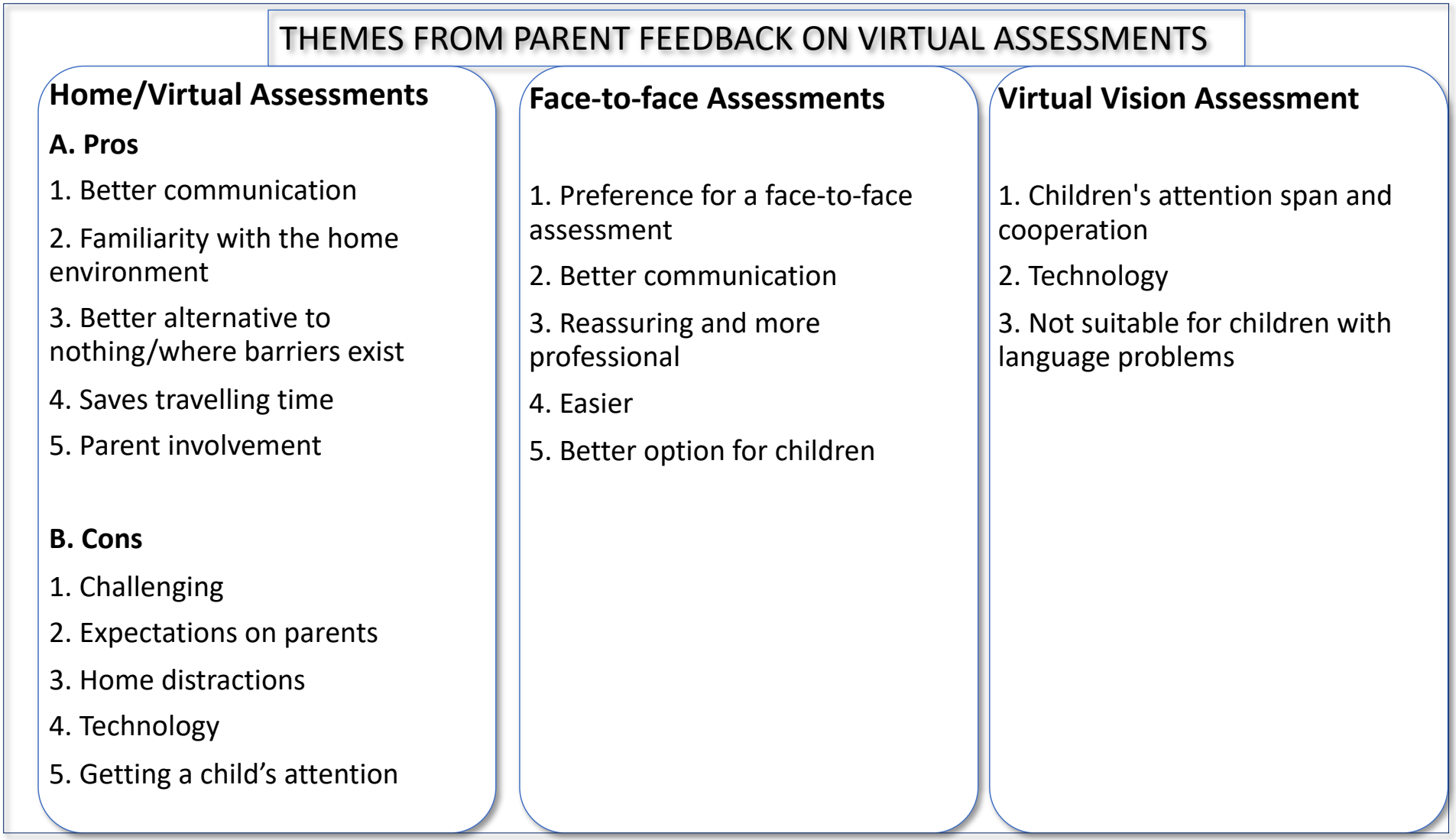



*Figure 32: Themes from Parent Feedback on Virtual Assessments*

### 15.8.1 Parent quotes and subthemes

#### *15.8.1.1 Theme Section 1: Home/Virtual Assessments*

Quotes and subthemes are presented as follows:

| **Home/Virtual Assessment** |
|---|
| **A. Pros of home/virtual assessment** |
| **1. Better communication** |
| *It was easy to follow the instructions and my twins seemed to respond fine to what they were being asked to do.* |
| *The box was great.* |
| **2. Familiarity with the home environment** |
| *Probably easier for the small person to get distracted at home but benefits from being in a familiar place.* |
| *That said, a face-to-face assessment would have been somewhere unfamiliar to my child and that would have affected in some way how he responds to the different tasks, I think.* |
| *I think he was much more confident from the outset than he would have been if it was face-to-face because he was in his familiar environment.* |
| *If face-to-face it would have taken him a little while to feel confident with doing the tasks in front of a stranger maybe* |
| *Possibly virtual means the child is in more familiar surroundings* |
| *..home but benefits of being in a familiar place.* |
| *I felt my son was more relaxed* |
| *The children were comfortable in their own surroundings* |
| *Being in own home may have helped child to settle and perform assessment easier than in a hospital setting.* |
| **3. Better alternative to nothing/ where barriers exist** |
| *I prefer face-to-face but having a virtual one is better than nothing* |
| *face-to-face is much easier but was not practical in my child's case so we had to do it virtually.* |
| *I would have preferred a face-to-face but understand due to covid restrictions a virtual test was a good alternative* |
| *I prefer face-to-face but having a virtual one is better than nothing* |
| *…(I) understand due to covid restrictions a virtual test was a good alternative* |
| **4. Saves traveling time** |
| *I feel that both are able to assess children's development and takes away the travelling stress* |
| *It was much more convenient than having to travel to the JRH.* |

| |
|---|
| *It was much more convenient than having to travel to the JRH. I am not sure we would have been able to participate otherwise. It was easy to follow the instructions and my twins seemed to respond fine to what they were being asked to do.* |
| **5. Parent involvement** |
| *Very informative, thank you.* |
| |
| **B. Cons of virtual assessment** |
| **1. Challenging** |
| *I think that a virtual assessment is very difficult for the parent and assessor* |
| **2. Expectations on parents** |
| *Please provide written instructions on each of the packs with the kit, we sometimes found it hard to understand what we needed to do (bad connection, child being noisy etc.)* |
| *Ensuring that my 2-year-old doesn't run off during the assessment is a bit tricky in our house but would have been easier in a face-to-face assessment (I believe).* |
| *The information provided about the assessment was lengthy and i did not have enough time to read it all, hence was not sure what will be happening during the assessment.* |
| *…so likely to participate better face-to-face; interactions are professionally led and not led by the parent.* |
| *A lot harder to keep child engaged at home compared to at an appointment* |
| **3. Home distractions** |
| *The assessor did a really good job, but I think there are too many distractions at home for it to work effectively* |
| *It was also quite difficult to hear what the assessor was saying at time because of having a noisy toddler in the background.* |
| *(My child) was distracted a few times by the books in his room and I think he was a little bored by the time he did his vision assessment.* |
| *Probably easier for the small person to get distracted at home* |
| **4. Technology** |
| *Zoom/Teams do not work that well with small children around!* |
| *It was really difficult for me and the twins to do the task via video link* |
| *My daughter isn't used to being in front of a computer/zoom call and so wasn't behaving as she normally would. I think she would behave more naturally in person.* |
| *… also, a child's attention and engagement is less when looking at a screen.* |
| *It's very hard to get a toddler to concentrate on a screen* |
| **5. Getting a child's attention (with the virtual vision assessments)** |
| *Doing a virtual vision assessment with a 3-year-old proved to be really difficult.* |
| *It's very hard to get a toddler to concentrate on a screen* |
| *Getting him to focus on a computer screen for that long was hard* |

*Table 17: Parent Survey on Home/Virtual Assessment*

#### *15.8.1.2 Theme Section 2: Face-to-Face Assessments*

| **Face-to-face Assessment** |
|---|
| **1. Preference for Face-to-face Assessment** |
| *I would have preferred a face-to-face* |
| *Face-to-face would be preferred* |
| *I prefer face-to-face but having a virtual one is better than nothing* |
| **2. Better communication** |
| *It makes communication clearer between all parties.* |
| **3. Reassuring and more professional** |
| *Also, as a parent I feel face-to-face is more reassuring as I know a professional can see every aspect of my children's interactions and is professionally led and not led by the parent.* |
| *It would be preferable to do face-to-face as there are many things that can be picked up by watching a child play* |
| **4. Easier** |
| *Face-to-face would have certainly been much easier* |
| *Ensuring that my 2-year-old doesn't run off during the assessment is a bit tricky in our house but would have been easier in a face-to-face assessment (I believe).* |
| *Face-to-face is much easier but was not practical in my child's case so we had to do it virtually.* |
| **5. Better option for children** |
| *I feel children might engage and behave differently face-to-face.* |
| *Children are more focused outside their home environment and have less distractions, so likely to participate better face-to-face.* |

*Table 18: Parent Survey on Face-to-Face Assessment*

#### *15.8.1.3 Theme Section 3: Virtual Vision Assessments*

| **Virtual Vision Assessment** |
|---|
| **1. Children's attention span and cooperation** |
| *Doing a virtual vision assessment with a 3-year-old proved to be really difficult.* |
| *Also, it's difficult making a toddler sit in front of a screen for that much time - more interactive style play might be more natural and also allow a better feel for the child.* |
| *It was difficult to fully engage my child in the vision assessment as there are several distractions at home in comparison to hospital/ GP*[lxi] *surgery* |
| *By the time of the vision assessment the little one was no longer interested in what was going on.* |
| *Also, a child's attention and engagement is less when looking at a screen.* |
| **2. Technology** |
| *Getting him to focus on a computer screen for that long was hard, and variables like brightness, contrast and size of screen were not considered so I'm dubious about its accuracy.* |
| *It's very hard to get a toddler to concentrate on a screen* |
| **3. Not suitable for children with language problems** |
| *Vision test was not included as my child cannot speak* |

*Table 19: Parent Survey on Virtual Vision Assessment*

[lxi] GP: general practitioners

# 16 Discussion

## 16.1 Integration of virtual assessments within the neurodevelopmental care pathway

This chapter presents the feasibility of a virtual platform for conducting NDAs of children born preterm. *The following sections address research objectives 1 and 2 on the feasibility of conducting virtual neurodevelopmental assessments for children born preterm.*

Novel in its approach, the INTER-NDA, traditionally used for face-to-face assessments, was converted to a virtual assessment. The outcome measures were INTER-NDA scores for the domains of cognition, fine and gross motor, language, and positive and negative behaviour presented as centiles and compared against the INTERGROWTH-21$^{st}$ International standards for child development at 2 years of age (Figure 13).

The virtual approach utilised the three-step approach in the Cox framework of opportunities to incorporate telehealth within the neurodevelopmental care pathway: *triage, evaluation, and care management* [222]. For example, in this study, activities such as parent and medical interviews, NDAs of children, and the post-assessment consultation with a neonatologist to discuss test results were all conducted virtually.

### 16.1.1 Learning points identified from the pilot phase.

Learning points and quality issues identified from the pretesting and transition phase informed the adaptation of the virtual INTER-NDA and the instruction manual in Appendix III. Some of these highlights are:

i. The parents' video screen had to be adjusted so that the assessor could see the child's full body, test kits, the surface on which the child was interacting with or playing with the items, and the room as a whole for activities such as throwing or kicking a ball.
ii. It was realised that building blocks (tower game) would sometimes fall if placed on non-hard or non-plain surfaces such as on a woollen carpet. Therefore, the manual

highlighted that the tower game was to be carried out on a plain or hard surface, such as a tabletop, bare floor (e.g. porcelain tile, wooden floor) or a hardcover book to give stability to the tower (Appendix III).

iii. Interference of parents: similar to the in-person assessment, it was noted that there is a tendency for parents to interfere in the assessments: for example, by giving body cues, such as when a child is instructed to hand the parent a block or to put a spoon in the cup, or by parents trying to over-explain the instructions to their children. To mitigate this, parents were reminded at the beginning of the assessments (and during the assessments when it happened) not to interfere with the activities or assist their child as that would invalidate those activities and be marked as 'unable to assess', thus disadvantaging their child.

iv. Distraction by other test items. Another learning was that children were likely distracted by seeing all the play items in the package sent to their parents. To mitigate this, parents were advised to keep all the test items in the box or from the view of their child unless it was time to move to the next activity. Also, the play items for each activity were packaged and labelled separately in zip lock bags according to the order of the assessment activities. This was to help parents to manoeuvre through the test kits more easily. An accompanying test kit inventory was placed in the mailing boxes so parents could familiarise themselves with the package content before the assessment started.

## 16.2 Participation rate

### 16.2.1 Oxford site

The OUH is one of the largest NHS teaching trusts in the UK [lxii], a tertiary hospital serving as a referral site to hospitals within Southeast England. To not overburden parents with long travel times, only those living within Oxfordshire postcodes were invited to participate in the study during the batch 1 recruitment cycle. However, for the second recruitment cycle, geographic eligibility was extended to include families within the UK as a whole, as the assessments were conducted virtually[lxiii]. One of the advantages of the virtual assessment is that it overcomes the geographic access barrier to health services [215]. As was also observed in the parent feedback survey, parents cited some of the advantages of virtual assessments as overcoming travel and access barriers (Table 17 and Table 18).

The virtual approach for screening children at the Oxford site may have boosted participation rates (of 32%; 110/341) in the study. In the parent feedback survey on virtual assessments, one parent's motivation to participate in this study included the opportunity to have their child's neurodevelopment assessed while saving travelling time: *It was much more convenient than having to travel to the JRH. I am not sure we would have been able to participate otherwise* (Table 17).

There were 507 preterm infants in the OUH neonatal databases who were born at or received care at the JRH between September 2017 and December 2019 (Figure 15). During the first batch of recruitment when OX postcode eligibility was in place, about 33% (166/507) of children in the database who had an out-of-area address were not eligible for the study. In both recruitment batches, parents of the remaining 341 children were contacted: 110 (32%)

[lxii] https://www.ouh.nhs.uk/about/
[lxiii] Children who were no longer residing in the UK at the time of the study were not eligible to participate in the study.

agreed to participate and their children were assessed (using the INTER-NDA and/or vision assessment) and 231 (68%) did not respond, declined participation or had left the UK (1 person).

### 16.2.2 Zurich site

Two recruitment cycles (from mid-March to August 2022) were conducted at the Zurich site (Figure 16), resulting in a total of 328 parents being invited to participate in the study. Unfortunately, 86 (26%) of the addresses were wrong, so the letters were returned. Of the remaining 242 parents with correct addresses, 195 (81%) did not respond or declined to participate in the study. Therefore, the results included in this study are those of the 47[lxiv] (19%) children whose parents consented to participate in the study and who had been assessed at the time of writing this thesis.

### 16.2.3 Motivation to participate in research

Published studies of neurodevelopmental follow-up have reported participation rates between 4% and 38% among eligible populations [215, 228, 229]. Considering the potential benefits of early neurodevelopmental screening, the low participation rate in the literature for such programmes is surprising. However, targeted interventions can help raise these numbers. For example, in the Michael et al., (2016) study, the rate of neurodevelopmental evaluation increased from 38% to 52% when specific interventions - such as parental education, scheduling follow-up appointments prior to discharge and setting an automated phone call reminder per their hospital practice - were instituted to promote the NDA of targeted patients [228].

[lxiv] Analyses of positive and negative behaviour domains include data for 46 participants due to missing behaviour data of one participant

For some parents whose children did not qualify for routine neurodevelopmental follow-ups, this study presented an opportunity to have their children assessed. In some cases, these were parents who were nursing worries about their child's development and/or had uncertainties about what a good developmental benchmark of normality is for a child born preterm. The assessments therefore offered relief to such parents (see parent interviews in Chapter 3).

The motivation for participating in research is often an act of altruism, as indicated in Marque et al.'s study (2021) [230], and as reported by parents in this study who wanted to contribute their experiences to help other parents or children born preterm. Knowledge of people's motivation in research studies can certainly inform strategies to increase participation rates in research or follow-up studies and interventions [228].

## 16.3 Neurodevelopmental Assessments

Mortality among children born preterm is decreasing due to advances in neonatal and perinatal health. However, developmental delay remains a problem among children born preterm [42, 231]. Therefore, follow-up of preterm infants must be encouraged to increase their chances of being identified early and to benefit from early interventions, where problems exist.

*The following sections discusses the results of the assessments and addresses research objective 3: to estimate the usefulness of the INTER-NDA as a screening tool for children born preterm.*

### 16.3.1 Neurodevelopmental outcomes among children born preterm

As observed in the results (Table 8 and Table 15), most children recorded normal neurodevelopmental scores in almost all domains (except in negative behaviour), which is consistent with reported literature that most preterm children develop without apparent

problems [231]. Considering (moderate or severe) impairment in at least one domain, the level of neurodevelopmental disturbances was 70% (57/81) at the Oxford site (Table 9) and 35% (16/46) at the Zurich site (Table 16), mainly contributed by negative behaviour domain. The high incidence of negative behaviour results is discussed below, under section 16.9.1.

### 16.3.2 Some domains discussed

#### *16.3.2.1 Motor development*

All children in the study, in both Oxford (Figure 18) and Zurich (Figure 26), had normal development of fine motor skills, i.e. movements related to the small muscles of the hands and fingers[lxv]. Interestingly, compared to a study by Namazzi et al. in Uganda, where they used the MDAT, the domain dominantly susceptible to neurodevelopmental delay was fine motor skills (among 11.9% of participants) [232]. The INTER-NDA[lxvi] conceptually overlaps with the MDAT items for cognition, fine and gross motor, and language, although the MDAT is not validated for high-income settings [40]. In their study, the authors reported on domains such as social behavioural, gross motor and language skills but did not report on cognitive skills. Their study's omission of cognitive scores may be due to the close link and inter-relatedness between cognitive and language development. For example, Liao et al (2015) reported a correlation between language scores and performance intelligence quotient scores, where children with language impairment were associated with lower IQ scores [233]. Webster et al 2004 also report on the coexistence of language and cognitive impairment and suggests that cognitive impairment is an important comorbidity among children with language impairment at preschool age [234].

[lxv] https://www.webmd.com/baby/what-are-some-examples-fine-motor-skills
[lxvi] https://www.medscinet.net/Intergrowth/patientinfodocs/INTER-NDA%20Manual%20July%202014.pdf

In Do et al's study in Vietnam, the Bayley-III neurological examination at 2-year corrected age reported a prevalence of neurodevelopmental impairment at 17% for cognition, followed by language (8%) and motor development (4%) [235]. These findings suggest that preterm children may experience different levels of disturbances in a particular domain of neurodevelopment, such as motor skills.

#### *16.3.2.2 Behaviour*

At the Oxford site, for all domains assessed with the INTER-NDA, negative behaviour was the domain with the highest number of disturbances, 67% of the children were at high risk of moderate-to-severe impairment, followed by language (11%), cognitive (7%) gross motor skills (6%) and positive behaviour (4%) (Table 8). In Zurich, negative and positive behaviour domains recorded 35% and 13% of children being at high risk of moderate-to-severe impairment, respectively. Triangulation data is not available but it would be useful to triangulate behaviour in future studies. All other domains (cognition, fine and gross motor, and language) showed normal development (Table 15).

Behaviour problems in early childhood are predictive of problems in adulthood. In infancy, the problems may manifest as poor social skills, internalising and externalising behaviours, poor emotional self-regulation and emotional difficulties, which may curtail educational attainment and lead to social isolation in adolescence or adulthood [236] [237]. Arpi and Ferrari reported in 2013 that very few studies have paid attention to the behaviour problems of preterm infants in early childhood, including during infancy and preschool age [236]. Including behaviour as a domain to be assessed in follow-up studies is essential to identify children needing interventions and to avert possible problems for the individual and society [236].

Furthermore, studies [237, 238] have shown that sex plays a role in behaviour problems. Stene-Larsen et al., (2016) reported that girls born preterm were at higher risk of emotional problems (OR 1.47, 95% CI 1.11-1.95) than their male counterparts [238]. Other studies reported a higher risk for conduct and externalising problems among males, while emotional and internalising problems are more common among females [237, 239] and the INTER-NDA study also reports higher negative behaviour scores among boys ([196]. The role of sex and behaviour problems is essential information when designing follow-up and intervention studies [238].

#### *16.3.2.3 Sampling*

In the interviews (Chapter 3), some parents of MLPT children with no access to routine follow-up took advantage of having their children assessed in the EveryPrem study. This way, they could confirm their suspicions of possible delay as a result of their children being born preterm. Although speculative, it could be that some parents of MLPT who participated in the study may have had concerns about their children's development.

According to a study by Marques et al., 2021 [230], parents of children born preterm may be motivated to enrol out of gratitude for the care they received from the health system, or through solidarity and altruism to contribute their experiences to improve outcomes for other children. These motives may, therefore, affect the sampling frame for parents who participate in non-randomised research studies as opposed to employing randomised sampling in a controlled study where each child or family has an equal chance of being recruited [240, 241].

To provide certainty about how the study population differs from or is representative of, the non-study participants in the eligible cohort of all preterm children for the study, a comparison of their characteristics such as GA, birth weight, medical and clinical history of

their birth, and socioeconomic status of parents should have been compared. A limitation acknowledged is that research studies like this DPhil work do not have the permission and ethical approval to access the information of parents who do not consent to participate in research studies. A way around this challenge would be for the health system to consider soliciting parents' permission at birth for their anonymised information to be used in research studies, a practice in place at the Zurich Study site in Switzerland (as observed in this study).

### 16.3.3 Vision assessments

The virtual vision assessment enabled the remote assessment of visual acuity among the study participants using the *iSight Pro* App. This proved to be a suitable alternative to the Cardiff test to ascertain the children's vision in the study. A limitation was with children who had delayed speech and could not verbalise the images they saw because, unlike the Cardiff test, which is suitable for children with speech problems, the *iSight Pro* requires that children verbalise what they see. Also, it is designed only for visual acuity testing, whereas the Cardiff test can be used for visual acuity and contrast sensitivity tests[lxvii].

Another limitation of the virtual assessment was the requirement for a larger screen size than provided by a phone. To ensure that families without laptop computers or other screens in their homes are not disadvantaged from participating, the study provided study iPads to be couriered to parents' homes for the assessments, where needed.

[lxvii] https://kaypictures.co.uk/product/kay-isight-test-professional-app/

For all components of the NDA, children were not required to look at a screen except for the virtual vision assessments, where they were required to watch the screen at a distance of 1.5m for up to 2.5 minutes or less to read out the images that appeared on the screen.
The vision assessment posed minimal to no risk to the child participants as their exposure time to the screen for this test was 2.5 minutes or less.[lxviii]

#### *16.3.3.1 Interpretation of vision results*

The study employed the normative values for Cardiff Test (in children aged 24-30 months) for binocular visual acuity at 0.2 LogMAR to classify normal vision or indication of impaired vision [40, 199]. The visual acuity test cut-off of 0.2 LogMAR was selected to align with the INTER-NDA 50$^{th}$ centile, which also falls within the Cardiff test normative values for binocular vision acuity [196, 199]. School evaluations in the UK have referenced the 0.2 LogMAR as the visual acuity pass rate for referral per the recommendations of the British and Irish Orthoptic Society Guidelines (Children's Vision Screening (loc-online.co.uk) and Public Health England states that a *child should achieve a 0.2000 (on the Keeler crowded logMar test) or better for each eye to pass the vision screening'* Screening competencies - GOV.UK (www.gov.uk). Therefore, this study also employed the 0.2 LogMAR to align with standard practice for visual acuity cut-off for needing further vision assessment.

Visual acuity is the most commonly used measure of the visual system [242] and it describes the clarity or sharpness of vision . A good acuity score indicates good sight for distant vision [243, 244] but does not rule out the absence of other vision problems. For research purposes, the visual acuity test gives a good indication of vision problems which warrants further detailed investigation to find out probable causes [243]. Parents should be encouraged to

[lxviii] https://www.aao.org/eye-health/tips-prevention/screen-use-kids

seek detailed assessment of their children whenever they have concerns. Parents of children with a visual acuity of > 0.2 LogMAR were encouraged to see a high street optician to check their child's vision.

## 16.4 Parent feedback survey on virtual assessments

Parents' views were solicited on their children's virtual assessment at the Oxford site. Out of the 57 parent responses, seven records were excluded after data cleaning, and 50 were analysed. The virtual assessments entailed the INTER-NDA assessment and vision assessments. The children who missed the opportunity to receive INTER-NDA assessments due to Covid-19-related interruptions and were age ineligible by the time resumed assessments were offered vision-only assessments. The parent feedback on virtual assessments (Table 17, Table 18 and Table 19) entails responses from parents whose children received vision-only assessments (29/72; 40%) and NDAs (81/110; 74%, with or without vision assessments).

### 16.4.1 Parent satisfaction with the virtual assessments.

Out of the 49 parents who responded to the question about satisfaction with virtual assessments, 74% expressed they were *very or somewhat satisfied*, 22% were neither *satisfied* nor *dissatisfied*, and 4% were *somewhat dissatisfied* with the virtual assessments (Figure 31). The high level of satisfaction among participants in this study is similar to reports in other studies: for example, during the Covid-19 pandemic, Jones et al., (2022) reported great satisfaction for outpatient telemedicine services among caregivers of children at two-time points [245], Cordier et al., (2022) concluded a high level of satisfaction among parents of preterm and at-risk children who attended a video follow-up session for their children [246], Leung et. al., (2021) reported excellent experience with telemedicine among

neurosurgical patients [247] and Schmidtberg et al., (2022) reported a 95.6% level of satisfaction with telehealth in paediatric surgical subspecialties [248].

With the virtual vision assessment, children who had speech impairment could not be assessed as the test requires children to verbalise what they see, unlike the Cardiff vision test, which is based on the principle of preferential looking [213]. Themes and quotes from the qualitative component of the feedback survey shed further insights on what parents thought about the virtual assessments and their recommendations for improvement (Table 17, Table 18 and Table 19).

### 16.4.2 Qualitative responses on virtual assessments

The literature on telemedicine elaborates on the benefits of remote assessments, including bridging geographic gaps to access care and saving parents' commute time to health centres for their children's medical appointments [245]. Through a thematic content analysis, feedback from the virtual assessment survey has been categorised into three main sections (*Figure 32*): *home/virtual assessments,* further subcategorised into *pros and cons*; *face-to-face assessments;* and *virtual vision assessments*.

Parents expressed that the communication for the virtual assessments was easy to follow, and their children responded well to the instructions provided. Assessing children from the comfort of their homes made the children feel at ease to go through the assessments. While this was seen positively by some parents, others found the home environment challenging as they preferred to have their children assessed in a neutral setting such as the health facility. Virtual assessments were viewed as a better alternative to nothing or parent-only evaluations [200], where face-to-face assessments were impossible. Some parents felt their active involvement in the virtual assessments empowered them to be a part of their child's care (Chapter 3) [246, 249]. While some parents viewed their involvement as a strength of virtual

assessments, other parents felt this placed a significant expectation on them, for example, to get their children to be seated through the assessment or take instructions, or the expectation to set up the technology (video call) for the remote assessments (Table 17).

Parents were guided through the setup for the assessments by instructions provided in emails or follow-up phone calls to those who requested additional support. Differences in parent experiences and exposures make them respond differently to tasks for their children's assessments (Table 17, Table 18 and Table 19). Parent factors to promote the ease and success of virtual assessments were beyond the scope of this study. This could be explored further in future studies.

### 16.4.3 Parent response questionnaire

Parent-completed developmental questionnaires [250-253] have a valuable place in neurodevelopmental assessments and give the opportunity for parents to contribute to the assessment of their children by sharing a child's usual behaviour or abilities in the familiar surroundings of their home. Parent questionnaires may be alternatives to traditional in-person assessments, which are costly, time and resource intensive [254]. When used, the parent questionnaires serve as screening approaches to identify children who may benefit from prompt referral for a more enhanced assessment and early intervention services with the potential for improving outcomes [254].

The INTER-NDA tool has an inherent advantage of its psychometric techniques of testing through direct administration and concurrent observation, as well as caregiver reports to minimise potential biases from parental recall, which can arise from caregiver interviews only [196, 200, 255]. Also, the INTER-NDA tool encompasses scoring across the spectrum of a child's abilities and therefore takes into consideration a wider description of a child's

abilities/faculties, another advantage that it presents over a predefined checklist which is common when using only parent or caregiver reported questionnaires.

The design of the INTER-NDA tool already incorporates parental responses through the caregiver report of a child's abilities. Therefore, there appeared to be no added advantage of incorporating a separate parental questionnaire in this study. In fact, the items related to the child behaviour questionnaire, which was a complementary parental questionnaire in the 2013 INTER-NDA manual, have been removed in the revised INTER-NDA manual, version v.2.2021, as the questionnaire is not considered part of/required for the INTER-NDA assessment[lxix].

Identification of developmental delays can be ascertained through routine developmental surveillance through a brief examination to identify children who may be at risk, such as is done by health visitors during the home visits. This type of screening alone is not effective enough to identify developmental delays, where present. A developmental screening using a systematic and structured tool is more effective than surveillance in identifying developmental delays. Beyond the screening, formal developmental tests have diagnostic utility and are more efficient in identifying delays among high-risk populations [16].

Identifying children who are at a high risk of moderate to severe behaviour problems will require a formal diagnostic test using tools like the BSID [16]. Assessor-led assessment is considered the gold standard [17] as children are observed by a specialist with more experience in identifying potential delays using a diagnostic tool. The INTER-NDA follows a similar pattern of administration to the BSID; through direct assessment, it encompasses assessment of different domains, and it has been validated against the BSID among children born at term [13]. A current limitation of the INTER-NDA is its use as a screening and not

[lxix] inter-nda_manual_v2.2021.pdf

a diagnostic tool. Parent questionnaires have a place in developmental surveillance and somehow screening, and parental involvement complements the screening process as parents' knowledge of their children is important. However, parent-led assessments do not replace the benefits of assessor-led screening or formal developmental tests.

### 16.4.4 Self-critique of the current virtual assessments

This DPhil research study has contributed to understanding the limitations of virtual assessments for children potentially at higher risk of neurodevelopmental delays; hence, I have suggested that certain areas need attention or could be improved. For example, a virtual vision assessment is not feasible when children have language or cognitive impairment because they may not be able to verbally describe the images they see. The principle of preferential looking that underpins the Cardiff test (currently offered in-person), may be a better alternative for children with cognitive and language impairment. Preferential looking is not possible to use in a virtual assessment.

Another learning point from the virtual assessment is the fact that the use of technology could limit some families, especially those who may not have access to the internet or who may not be agile in the use of information communication technology (ICT), from participating in such research or accessing health services offered virtually (telehealth). This study presented a mitigating alternative to this limitation by sending study iPads to families without a computer to enable them to participate in the research.

Lastly, although the adaptation of the INTER-NDA for virtual use was innovative and the study demonstrated it is feasible to conduct an NDA virtually, the study's major limitation is that the virtual assessment is yet to be validated (due to the inability to perform face-to-face assessments during Covid-19 there could be no comparison with scores obtained by the 2 methods). Therefore, it has unestablished psychometry validity and before it can be used

outside a research context, the virtual INTER-NDA has to be validated against the original INTER-NDA and other NDA tools.

## 16.5 Conclusion

This study has demonstrated that conducting a virtual NDA for children born preterm and identifying at-risk individuals among this population of 2 to 3-year-olds is feasible. At the time of this study, very little was known or had been reported in the literature about the virtual neurodevelopmental follow-up of children born preterm [195]. Through trial and learning, this study provides rich insights into meeting the essential health needs of high-risk children with alternative approaches.

The virtual assessment feedback survey has highlighted areas for future studies to enhance the approach. Future research should focus on the factors for the success of virtual assessments, such as determining which parent experiences or characteristics may influence their adaptation to technology for remote or virtual assessments.

The virtual vision assessment appears to be an excellent alternative to screen children's vision and identify those with signs of vision problems to be referred for a complete check with an optician. Care should be taken when using the methodology for children with underlying risk factors, such as delayed speech or cognitive development, as these may confound the determination of their visual acuity.

Further, this study has established that it is possible to engage 2-year-old children fully in a virtual and remote consultation. Children demonstrated that assessment from the comfort of their homes might be a suitable option as they are more relaxed in their natural environment.

## 16.6 Feasibility study

The virtual NDA for children born preterm is a novel approach. Therefore, this study was essential to determine the feasibility of extending NDAs remotely and through online platforms. It was also necessary to understand parents' perspectives and acceptability of the novel approach and source their feedback for improvement [256]. As a next step, future

studies can focus on validating the online methodology against face-to-face assessments in estimating its effectiveness in identifying children with neurodevelopmental deficits. Originally designed to be included in the study design at the Zurich site, the ethics approval was not received within the timelines of the DPhil research and therefore the virtual vs face-to-face validation study could not be performed.

This study's findings extend scientific knowledge by highlighting further learning points about the neurodevelopmental follow-up of children born preterm, virtual approaches to conducting NDAs, and parent acceptability of virtual assessments (where barriers exist for in-person assessments).

This study was carried out at a tertiary hospital and within Oxfordshire, where there was no previous experience of virtual NDA for preterm children. Also, it was the first time the INTER-NDA was used for remote and virtual testing. Therefore, this study presents learnings for future adaption of the INTER-NDA for virtual assessments and for neurodevelopmental follow-up of children born preterm and paediatric research more broadly and in different settings.

## 16.7 Implications of study

This study used the INTER-NDA tool to assess the cognitive, language, motor and behaviour outcomes at 2 years of age among children born preterm in the UK and Switzerland. As the first of its kind, the in-person INTER-NDA assessments were converted to virtual assessments where children were assessed remotely and from the comfort of their homes. The virtual approach is an innovation devised during the Covid-19 pandemic. The domain scores for cognition, language, motor and behaviour have been compared to the corresponding norms of the INTERGROWTH-21$^{st}$ Standards for healthy children and children at higher risk of neurodevelopmental disturbances have been identified.

It may be interesting to explore further the high rates of severe and moderate negative behaviour scores at both sites (67% at Oxford, Table 8 and 35% at Zurich, Table 15) to determine whether the INTER-NDA may be highly sensitive for preterm children, or whether a larger sample size would make a statistically significant inference.

**Inter-rater reliability**

Inter-rater reliability [257] is the extent to which scores are identical between different assessors. The inter-rater reliability for the assessors who supported assessments at the Zurich site is underway to determine the extent to which the scores of different assessors could vary. However, the INTER-NDA generally has good inter-rater and test-retest reliability with Cohen's kappas values of k=0.7, 0.95% CI: 0.47-0.88 and k=0.79, 95% CI: 0.48-0.96 respectively, as reported for 21 assessors across five countries [40].

### 16.7.1 Status of hypotheses and implications for future studies

For hypotheses 1 and 2, future work is required to validate the virtual assessments against in-person INTER-NDA (or other suitable neurodevelopmental assessment tools) before it is ready for clinical use. Given the relatively small sample size of the study population, extrapolation of the findings to the general population and their interpretation should be done with caution.

**Hypothesis 1: Conducting virtual NDAs of children born preterm can be a valuable approach to bridging access where barriers to in-person assessments exist.**

The virtual assessments allowed 110 children to be offered neurodevelopmental assessments. This way, the virtual assessment provided a valuable approach to bridging access barriers to in-person assessments. Additionally, other complementary research activities, such as the parent interviews and survey originally planned to be carried out in

person, were successfully offered online, which otherwise would not have happened during the pandemic when in-person research activities were not possible.

Parents have also provided insightful feedback on their satisfaction and suggestions to improve virtual assessments. Parents' feedback on the virtual assessments was accepted for an oral presentation at an international conference under the theme of utilising digital health to improve the care for vulnerable children during the pandemic (Appendix IX).

The virtual tests have provided learning points regarding what worked well and areas which could be improved to enhance future virtual assessments and digital healthcare for children and people with neurodevelopmental disturbances.

**Hypothesis 2: It is feasible to offer a virtual NDA to infants between the ages of 2 and 3.**

All eligible children for the NDAs completed the virtual test. Therefore, it is feasible to offer virtual NDA to infants between the ages of 2 and 3 (using the INTER-NDA tool as explored in this study). For the vision assessments, 68 had *iSight Pro*, four had the Cardiff test, and 38 children could not complete or participate in the virtual vision assessments due to the reasons cited in Table 12. These include child-related factors such as delayed speech, existing vision problems or children unwilling to look at the screen. Additionally, parent or logistical factors such as delays with courier services sending study iPad or parents' scheduling challenges were barriers to accessing the virtual vision assessments.

For a successful completion rate of 64% (68/106), the virtual vision assessments can be considered feasible. The completion rate of the virtual vision test is 71.5% (68/95) when discounting logistical factors not related to the suitability of the test for a child; for example, the impact of Covid-19 on third-party services such as the delays observed with sending

study iPads to some families during the pandemic (11 children had no vision assessments related to logistical factors).

**Hypothesis 3: The INTER-NDA is a suitable tool for assessing the neurodevelopment of children born preterm.**

All eligible children for the neurodevelopmental assessments completed the virtual test. However, the original EveryPrem study objectives of validating the INTER-NDA tool against the standard, BSID-III for children born preterm could not be realised. It remains to be seen whether the INTER-NDA can replace the BSID-III (potentially the BSID IV) as a neurodevelopmental assessment tool for clinical use for children born preterm.

**Hypothesis 4: Parents may accept virtual approaches as suitable alternatives for assessing the neurodevelopment of their young children.**

This hypothesis was tested through the parent feedback survey of the virtual assessments. Parent satisfaction of more than 70% with the virtual assessments is indicative of acceptability with the virtual approach. Further, parents also provided qualitative responses to indicate that they prefer the virtual assessments as alternatives to no assessments where barriers to in-person visits are not possible. Others also iterated a preference for a virtual assessment as it can save travelling time to a health facility.

Further research among a larger parent population with similar or different experiences and in other settings will be useful in determining parents' acceptability of virtual approaches to assessing the neurodevelopment of young children more broadly. With the Covid-19 pandemic over, the proliferation of digital health options now available, and the lessons gained in the telehealth space, exploring parents' acceptability of telehealth for young children and neurodevelopmental services will be beneficial in advancing telehealth

practices and complementing follow-up services for young children and people at risk of neurodevelopmental disturbances.

## 16.8 What this study adds

1. This study has provided useful learning for adapting a novel strategy from existing neurodevelopmental follow-up approaches when access to care is limited, such as during the peak of the Covid-19 pandemic.
2. The study approach has empowered parents to participate fully in the health services extended to their children.
3. Novel in its nature, this study has been presented in scientific meetings to share best practices with health workers on adopting alternative approaches when access to care provision exists, such as geographical barriers, time constraints, or logistical challenges.
4. This study bridges the missing opportunity gap by providing alternative solutions to extend care to vulnerable groups.
5. The virtual testing is feasible on the basis of the work completed to date and the study has identified the limitation of the vision testing among children with cognitive and language impairment. The children seemed distracted or disturbed when they could not read the images on the screen. It will be interesting to find out in future research how visual impairment may impact behavioural observations in non-standardised settings and/or how behavioural observations may influence vision assessment and or results. The relationship between behaviour and virtual vision assessment was beyond the scope of this research.

### 16.8.1 Implications of negative behaviour results

The high incidence of negative behaviour that was recorded in the study aligns with the literature on the impact of the pandemic on learning disabilities, developmental delays and

behavioural disorders among children. For example, Mulkey et al, 2023 explain that the multiple changed experiences during the early years of a child who experienced the pandemic may account for the increase in these developmental problems among children with underlying risks (such as those born preterm) [258]. Some of the ways in which the pandemic affected children were through increased stress and anxiety, disruption of their routine and social isolation (such as school closures), and limited physical activity due to lockdown restrictions [259-261].

Secondly, participation in the study was self-selective (among the eligible population); therefore, it is likely that parents who enrolled their children were those who had concerns with their child's development (negative behaviour). Some studies report that disruptive behaviour is one of the developmental domains of major concern to parents, and that parents' self-report of concerns have moderate agreement with results from behavioural screening instruments [262, 263].

The most common finding of negative behaviour may however not be representative of the entire eligible preterm population for this study. It is acknowledged in the thesis that future studies will be needed to explore the reasons for the high incidence of negative behaviour among a wider population, including whether the assessment criteria are overly sensitive for a preterm population (section 16.7 implications of study). It will also be interesting to know if all of the children with negative behaviour in the study have ended up with behavioural diagnoses.

### 16.8.2 Could the home environment have contributed to the high incidence of negative behaviour results?

The stay-at-home restrictions during the pandemic almost certainly affected children's neurodevelopment: for example, many children did not have the chance to interact with

other children or family members and families also experienced considerable distress [264-267]. It is, therefore, possible that the lockdown restrictions in general and not necessarily the virtual assessments from the home environment could have had an impact on the children and/or their families [268, 269] and potentially also on the test results.

Studies report that the abrupt discontinuation of routine activities and prolonged isolation increases the risk for behavioural problems among children with (or with higher vulnerability to) neurodevelopmental disorders [270, 271]. This stay-at-home restriction could have also impacted or been a confounder with the higher numbers of negative behaviour scores observed among the study population of children born preterm in this research. Studies, however, point to the benefit of ensuring continuity of care for children with neurodevelopmental disorders through telehealth [272, 273].

The relationship between the impact of the stay-at-home restrictions on the neurodevelopmental outcomes or scores from the assessments was beyond the scope of this study and can be acknowledged as a potential limitation. Future studies could assess virtual/home testing in a restricted stay-at-home setting and without restrictions to see any significant differences in neurodevelopmental scores in both scenarios.

### 16.8.3 Home setting vis-à-vis clinic environment

Another important learning from this study was the flexibility to adjust to the home setting of a child for the virtual assessment. It is acknowledged that a 2-year-old may be distracted by the home environment where families do not have a room free of distractions for the assessment as one would have in a clinic setting.

To mitigate the possible distractions at home, a conscious effort was made to conduct the virtual assessments when children were more settled. Therefore, sessions were scheduled

when children were well-fed and well-rested, i.e. in the mornings after breakfast and/or after nap time in the afternoon.

Parents were very supportive throughout the process. Some of the ways they made the adaptation of the home environment suitable for the virtual assessments were for example:

- Families fixed appointments when both parents, a nanny or an older mature sibling were at home to engage younger children (non-study participants) if there were younger siblings at home.
- Parents cleared a portion of their child's room to reduce distractions so that the session was done without the child getting distracted by items getting in their way or lying about in their clear view.
- Parents put their child in a secured seat at the dining table where no items were around to distract the child.

This conscious and flexible scheduling has implications for project planning for large-scale virtual assessments. The good thing was that, during the pandemic, parents usually worked from home, making scheduling more flexible.

## 16.9 Limitations

1. Families without access to technology for virtual assessments may be disadvantaged.

   **Mitigation**: in this study, care was taken to ensure that parents without appropriate technology (device) were supplied to enable participation in the study. Therefore, no participant who expressed interest in the study was disqualified or disadvantaged from participating in the study because of a lack of technology.

2. The study would benefit from larger participant numbers.

# Chapter 3

# Parental views on neurodevelopmental follow-up of children born preterm: A mixed methods study

# 17 Introduction

This chapter presents parents' views, experiences, and expectations for neurodevelopmental follow-up of children born preterm. The study employs a mixed methods approach, which involves a survey and qualitative in-depth interviews with parents as important stakeholders in the care of children born preterm.

- Very little is known about what parents think about neurodevelopmental follow-up for children born preterm. Additionally, the voices of parents with children born MLPT are underrepresented in neonatal and qualitative studies.
- Therefore, this study highlights the expectations of parents of children born preterm (including those born MLPT) regarding the need for neurodevelopmental follow-up.
- The concerns expressed by these parents about the lack of routine follow-up despite the children's risk of compromised neurodevelopment serve as an advocacy tool to prioritise care for all children born preterm.
- As MLPT children make up the majority of the preterm population, their parents' voices provide insights into an understudied area of research and contribute to improving the care offered to these vulnerable children.

# 18 Background

## 18.1.1 Preterm birth, neurodevelopment, and parenting

Preterm birth presents challenges for the mother [274], parents [275, 276] and wider family [277] due to related psychological, emotional, and mental health issues and financial demands. For the preterm child, the risk of neurological deficits can affect their chances of reaching developmental milestones, manifesting as delayed language, motor, and cognitive development.

For parents, caring for children born preterm may be accompanied by stress and anxiety about their infant's chances of survival and uncertainty about their long-term outcomes [278-280]. The tendency to 'assume' *normal* outcomes for MLPT children [278] poses a risk to the child who may not receive any follow-up and will, therefore, miss the possibility for early interventions, where needed. Continued support to parents of MLPT children may be missing or not provided when the children are deprioritised for follow-up care and interventions.

## 18.1.2 Quality of Care

The Institute of Medicine's highly influential quality of healthcare framework encompasses six domains: safety, effectiveness, patient-centredness, timeliness, efficiency, and equitability [281]. In light of these attributes, quality of care should seek to place the patient or users at the centre of care where their voices will be heard and considered in making clinical decisions while making services equitable to all in need of care and provided in a timely manner without delays.

NICE in the UK, in an attempt to provide quality care to vulnerable children born preterm in the UK has provided guidelines, including information-sharing with parents [27]. Translating guidelines into comprehensible and patient-friendly forms would require

discovering from parents what their expectations and preferences are, how satisfied they are with the status quo [282, 283], and what quality of care could look like on the follow-up pathway for their children born preterm [278, 284].

Komoriyama et al., (2019) [283] highlighted the absence of studies that addressed parental views on neurodevelopmental follow-up for at-risk infants, such as those born preterm. The authors stressed the need for parental support as one of their key messages and concluded that parents wish to receive timely information about potential long-term outcomes for their babies born preterm, and for such information and any related support to be appropriate and well-suited to their family needs [283]. Other studies have also highlighted the importance of information sharing and how involvement in the care of their children is regarded by parents [285-287]. One way to involve parents is to ask about their views on [288], experiences of [289] and satisfaction[290] with the status quo, as well as their expectations of what quality care could look like.

Despite the limited literature on parents' views and experiences with neurodevelopmental follow-up, several studies have considered parental experiences of caring for children born preterm [278, 291-293]. Some key highlights from these studies are that parents are pivotal to the care, survival and how well their infants born preterm thrive; parents' views provide invaluable insights to inform care practices for high-risk children, and parents are appreciative when they are involved in the care pathway of their children. Obtaining insights into parental experiences can improve parenting and parent-child relationships and optimise the support to other parents when experiences are shared among parents [278, 284].

Therefore, the present study seeks to gain insights into the experiences, satisfaction, and preferences of parents of all children born preterm regarding neurodevelopmental follow-up. The study also includes parents of MLPT children for whom routine neurodevelopmental

follow-up may not be offered. As with VPT infants, MLPT children can also benefit from routine follow-up to detect early signs of compromised neurodevelopment so that intervention(s) can be offered to avoid possible long-term poorer outcomes [294].

*In the following section, some key research methods and approaches have been explained to give context to the design of this study and their usefulness in addressing the research questions.*

## 18.2 Research Methods: Qualitative Approach

Qualitative research is an interpretative research approach [295] that provides avenues to understand people's views, experiences, and behaviours. The application of a particular qualitative approach is determined by the research question to be answered and the intended outcomes being studied. When appropriately applied, qualitative studies produce credible and trustworthy findings [296].

Mixed methods [297] is the application of quantitative and qualitative research approaches within the same study. Its use is relevant for studies in which a single approach may not be sufficient to address the research objectives. A mixed methods approach creates connections and highlights differences in the findings to better understand participants' experiences [298]. The limitations to using mixed methods include the complexity of analysis and demand on resources, reliance on a multidisciplinary team of researchers, and the appropriate integration of quantitative and qualitative data sources [298].

## 18.3 Survey

A survey is a research approach that gauges opinions from a representative sample of a study population. The quality of a survey may be determined by the sampling frame, also known as coverage bias, the survey instrument, and how any potential sources of bias are addressed [299]. The survey instrument is the data collection tool sent to respondents for their

responses. As the tool is core to the quality of research, its construction and use should demonstrate validity and reliability to minimise potential biases. Validity here refers to the tool's accuracy in measuring what it is intended to measure, and reliability refers to the reproducibility of the results when the tool is repeated in the same or similar populations. A good way to minimise biases in surveys is to ensure that the survey tool is well-designed and adequately pretested with adherence to good reporting practices [299].

The Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [300] is a checklist of recommendations for quality reporting of web-based surveys. However, it may be applied to paper-based surveys as well. Its use is similar to other well-known checklists such as the Consolidated Standards of Reporting Trials (CONSORT), which is used in reporting randomised trials and the Quality of Reporting of Meta-analyses (QUORUM) for reporting systematic reviews.

## 18.4 Interviews

Interview [301] in qualitative research is one of the commonly used methods of data collection to explore people's experiences, opinions or motivations on a topic. Other methods in qualitative research include focus group discussions, observation and textual or visual analysis. Interviews may be conducted with interview guides, which are questions to facilitate the conversation and help address the research objectives.

## 18.5 Study hypothesis and objectives

Given the need for insights into parental experience, satisfaction, and preferences for neurodevelopmental follow-up of children born preterm, the research questions that were explored are:

- What are parents' experiences, opinions and recommendations on neurodevelopmental follow-up of children born preterm?

- How satisfied are parents with the current standard of care (neurodevelopmental follow-up) for children born preterm?
- What are parents' views about neurodevelopmental patterns and outcomes among children born preterm?

Therefore, the specific objectives of this study are to:

- Evaluate satisfaction among parents (carers) with the current standard of care and their opinions on neurodevelopmental follow-up.
- Understand parents' knowledge about neurodevelopmental outcomes for children born preterm.
- Describe parents' experiences, satisfaction, and recommendations for neurodevelopmental follow-up of children born preterm.

## 19 Methods: Parental survey

This study utilised the CHERRIES checklist for reporting results of Internet E-Surveys [300]. The checklist[lxx] follows an eight-step category for conducting surveys, which has been adapted (Appendix XI) as follows:

**1.** Survey design**:** In this study, the target population was parents of children born preterm who were eligible for the EveryPrem Study.[lxxi] A parent/guardian/carer of a child could participate in the survey regardless of their child's participation status in the assessments. Eligibility also included the requirement for respondents to provide informed consent before participating in the survey.

- Ethics approval: The parent survey received ethics approval from the South Central – Hampshire B Research Ethics Committee (REC reference: 19/SC/0474).
- Informed consent process: Participants were given information about the study as part of the recruitment process. On the day of their child's NDA, the study was further explained to the parents, who were then able to ask questions or seek clarification, if required. Verbal consent to participate in the survey was taken from parents on the day of their child's assessment (the consent included a confirmation that parents had read and understood the information sheet and had the chance to ask questions and received satisfactory answers). Survey links were only sent to parents after their informed consent was obtained, after which a copy of the consent form was also emailed to them for their records.
- Data protection: the online survey responses were anonymised (no identifiable details were asked from respondents) so that no one could trace a response to a particular parent. For the four parent participants who did a paper-based survey prior to the transition to a

[lxx] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1550605/table/table1/?report=objectonly
[lxxi] https://www.wrh.ox.ac.uk/research/everyprem

virtual study (during the Covid-19 pandemic), only I, as the primary researcher had access to the master list of parents who had responded to the paper-based survey. Basic characteristics, such as the GA of their child at birth, were required to aid in the analysis. In all instances, parent responses have not been directly linked to them or their children.

2. **Recruitment process and description of the sample having access to the questionnaire:**

   The survey was hosted on Qualtrics[lxxii] platform. The links were not advertised but only emailed to eligible participants. However, the survey was not closed (no restricted access) [300] when hosted online as it was not password protected (to ensure the anonymity of respondents). The usability and technical functionality of the electronic survey were tested with dummy entries to be sure that the adaptive questioning (skip logic function) and all functions were working well before fielding the main questionnaire and sharing the link with interviewees. The responses of the four participants who completed the paper-based questionnaires were later entered into Qualtrics and were not linked to the parent IDs.

3. **Survey administration:** An anonymous Qualtrics link[lxxiii] was emailed to eligible participants. Responses were automatically recorded in Qualtrics once participants logged in to the survey. Participants could log back in to complete their survey later.

- Timeframe: the online survey was active within the period of the virtual child assessments, from October 2020 to March 2022. However, responses were mainly received during the active recruitment for child assessments, from February to December 2021 and from January to March 2022. The last active phase of the survey was in May

[lxxii] https://www.qualtrics.com/uk/
[lxxiii] https://wrh.qualtrics.com/jfe/form/SV_06aUg7ILSjlDX5I

2022, when a reminder email was sent to parents who participated in the last batch of child recruitment for NDAs.

- **Incentives**: Participation in the survey was voluntary, and parents were offered no incentives.
- **Adaptive questioning**: An element of adaptive questioning (*skip logic*) was employed whereby some questions were displayed based on initial responses to reduce complexity and increase the relevance of the questions. For example, questions such as the *age at which the child was assessed* would be skipped if a parent responded *No* to the child not ever receiving an NDA.
- **Structure of survey:** The survey was structured into two main parts with three sub-sections:
  - Part 1: section 1: Child characteristics, e.g., GA
  - Part 1: section 2: Parent knowledge, experiences, and expectations of neurodevelopmental follow-up of children born preterm
  - Part 2: Parent feedback[lxxiv] on virtual NDA.[lxxv]

    The survey was conducted in English.
- **Review step:** the survey was designed such that respondents could review their answers by scrolling up and down the survey page to a particular question or by using a back button. A response request alert was included in the survey so that respondents were reminded to respond to a question if they had left it blank: '*there is 'x*[lxxvi]*' unanswered question(s) on this page. Would you like to continue?*' Respondents had two options to either select *'continue without answering'* or '*answer the question*' before proceeding to the next page.

[lxxiv] https://wrh.qualtrics.com/jfe/form/SV_3K5fPXsOFiG8r54
[lxxv] Survey responses on the virtual NDA have been reported as part of Chapter 2 which describes NDAs of children born preterm.
[lxxvi] X refers to the number of questions unanswered per survey page.

- **Time commitment:** The parent survey consisted of 11 questions and was estimated to last no longer than 10 minutes.

4. **Response rate:** Unique visitors were determined by their computer's IP addresses and the GA of their child, as indicated in their survey responses. Details of the responses have been described in the Results section.
5. **Preventing multiple entries from the same individual:** IP checks were used to identify potential duplicate entries from the same user.
6. **Analysis:** Survey entries were cleaned before the analysis. A detailed description of how the survey responses were cleaned and which responses were deleted is presented in Appendix VII.

# 20 Methods: Parent interview

## 20.1 Context

The study was carried out at the JRH and was intended for all parents of eligible participants in the EveryPrem Study.[lxxvii]

To provide richer insights into parents' satisfaction and opinions on neurodevelopmental surveillance of children born preterm, one-on-one in-depth interviews were conducted to complement the parent survey findings and triangulate the results of parent opinions. The target sample size was to recruit a maximum of 20 parents who consented to participate in the qualitative interviews or until saturation of themes occurred.

To address the research question, the in-depth interview guideline (Appendix VIII) was structured to solicit parents':

- knowledge about neurodevelopmental patterns/outcomes among children born preterm;
- experience in communicating with the NHS regarding care for their children;
- personal experience of NDAs for children born preterm;
- satisfaction with the neurodevelopmental follow-up of all children born preterm in the UK; and
- expectations for universal neurodevelopmental follow-up for children born preterm.

Although the interview questions sought to gather general information and not intimate experiences, it is acknowledged that some parents may have found recalling some experiences sensitive and stressful, as they may be linked to their preterm delivery and postnatal experience. Parents' rights were always respected, and each respondent was free to skip any question they found uncomfortable, sensitive, or stressful to recall and/or discuss.

[lxxvii] https://www.wrh.ox.ac.uk/research/everyprem

Parent interviewees were provided a £10 thank you voucher after the interview. Initially, these were meant to be lunch vouchers if parents had in-person child assessments before the interviews, as they would have stayed longer during their hospital visit. However, during the Covid-19 pandemic disruptions, when the study activities were converted to a virtual platform, parents were still offered the £10 vouchers for their participation. Some parents declined to take the vouchers as they wanted to contribute freely and give back to the NHS.

The reporting format for the parent interviews follows the standards for reporting qualitative research (SRQR) by Equator Network.[lxxviii] SRQR [302] aims to improve the transparency of qualitative research by providing clear guidelines to report on all aspects of a study, including researcher reflexivity and how any potential biases may have been mitigated.

## 20.2 Qualitative Approach and Research Paradigm

The study employed a thematic content analysis [303, 304] approach whereby emerging themes from the interviews were coded and extracted to address the research question. Themes were identified inductively from the research objectives and deductively from new information received from the parent interviews [304].

## 20.3 Researcher Characteristics and Reflexivity

I designed the interview questionnaire and conducted the NDAs and the interviews. However, I did not have access to the children's hospital records and was not aware of the birth or the neurodevelopmental follow-up experience of the child/family before the interview. Parents responded to the survey through a safe and anonymised online link, and I only accessed that information after the interviews had been conducted.

[lxxviii] http://www.equator-network.org/reporting-guidelines/srqr/

To enrich the discussions and triangulate parental responses, the interview questions were designed to follow a pattern similar to the survey questionnaire to gain meaningful insights into parental experiences, confirmatory or contradictory to the survey responses. Parent interviews were conducted after the child's NDAs to avoid introducing any potential biases into the assessments.

### 20.4 Sampling strategy

The study employed both purposive, and convenience sampling approaches [305]. With convenience sampling, invitations were extended to all parents who participated in the study immediately after resumption of research activities (post Covid-19 related disruptions). Interviewing all parents who consented ensured that the study was not severely impacted in the event of any further Covid-19-related lockdowns.

After preliminary analyses were conducted on the initial responses received, a purposive sampling approach was preferred to convenience sampling to ensure that diversity in parent characteristics was fairly represented in addressing the research questions. For example, the purposive sampling was designed to ensure that parents with children of all three preterm sub-groups - VPT, MPT, LPT - were recruited to reflect their experiences and expectations of neurodevelopmental follow-up and caring for children born preterm. Additionally, efforts were made to interview fathers, parents of twins and triplets as well as singletons, twins, or triplets.

Further to describing the parent characteristics of interviewee participants, the IMD has been applied to describe to the sociodemographic characteristics of families who participated in the study. The IMD is the official measure of relative deprivation for small areas (lower-layer super-output areas, also known as neighbourhood level) in England [306]. The IMD considers seven indicators: income, employment, education, skills and training, health and

disability, crime, barriers to housing and services and living environment. There are 32, 844 of these areas, which are ranked into deciles. A lower decile of 1 represents 10% of the most deprived areas, and a decile of 10 represents the upper 10% and the least deprived areas nationally.

## 20.5 Ethical Considerations

All participants gave their informed consent before the interviews. The study was conducted in accordance with the Declaration of Helsinki, and it received ethical clearance from the South Central – Hampshire B Research Ethics Committee (*REC reference: 19/SC/0474*) as part of the ethics approval for neurodevelopmental follow-up for children born preterm. Ethics approval included permission to audio record parent interviews and to quote responses using pseudonyms. Furthermore, the study also secured approval from the University of Oxford CTRG as study sponsor and the OUH Research Unit to conduct the study at the hospital.

## 20.6 Confidentiality and Data Security

The audio recordings of the interviews were anonymised before analysis so that no other person other than the interviewer (and authorised persons) could trace the interview responses back to the participants. Audio recordings have been stored on the University's high-security server.

## 20.7 Data collection methods

During the Covid-19 restrictions, interviews were conducted virtually using a secure video platform. However, only audio recordings were made after parents consented to participate in the interviews. Considering the practicality of organising study activities and the convenience of parents, interviews were usually conducted on the same day after the virtual NDA was completed unless the parent preferred being interviewed later.

## 20.8 Data collection instruments and technologies

A new interview guideline (Appendix VIII) was developed for the study and pretested with a parent and neonatologist to provide feedback on its appropriateness. Furthermore, the questionnaire was reviewed by the Ethics Committee of the University of Oxford and the IRS Research Ethics Committee Panel for suitability. The technical validity of the questions to address the research objectives was reviewed by a senior qualitative researcher, Dr Sara Paparini (Queen Mary University of London), who provided input on parts of the study methodology, including the analysis framework.

As part of the patient and public involvement (PPI) requirement for the EveryPrem Study, the research proposal was reviewed by five mothers of eight children who were born at 28, 32, 33, 34 and 35 weeks' gestation. Their comments can be found in Appendix XII. The study also received an independent peer review.

## 20.9 Data processing

The audio interviews were securely sent to an approved third-party transcription agency to transcribe the recordings into text for coding and analysis. The audio tapes did not contain identifiable information and so the transcribers could not link the responses to any parent or family. The transcription agency transmitted the transcribed files through a secured and closed link. All audio recordings and transcribed documents were deleted from their system after the files were secured on the University's server.

## 20.10 Data analysis

Analyses were run in NVivo[lxxix] (version 12) to codify and identify common patterns and themes through deductive and inductive approaches. Coded texts of interviewee responses

[lxxix] https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home

were pseudonymised and relevant portions have been quoted to support themes where necessary.

### 20.11 Outcome measures

- For interviews: themes emerging from interviews, parental satisfaction and opinions of neurodevelopmental follow-up for children born preterm.
- For the survey: rate of parent satisfaction of neurodevelopmental follow-up for children born preterm.

### 20.12 Techniques to enhance trustworthiness

To mitigate researcher bias, Dr Sara Paparini, an experienced independent qualitative researcher, looked over initial responses for feedback. Additionally, parent interviews were conducted after child assessments to blind the researcher about any family circumstances that could bias the child's assessment.

**Audit trail:** Study ID numbers of parents enrolled in the study were immediately documented on *Siteline*[lxxx], the University's database, to record the participation rate.

Triangulation of methods and responses was employed through the parent survey, in-depth interviews, and NDAs/medical and sociodemographic information.

[lxxx] https://www.ouh.nhs.uk/researchers/conduct/research-recruitment-reporting.aspx

## 21 Results: Parent survey

Responses from the parent survey are presented below. Of the 78 responses recorded in Qualtrics, 65 (83%) were considered unique entries for analysis. Thirteen responses were deleted due to reasons described under the survey cleaning protocol (Appendix VII). The cleaning protocol explains the criteria for cleaning the parent survey responses and the actions to take for different scenarios. For example, responses with the Qualtrics status as 'survey preview' or 'false' were deleted; multiple responses with the same IP address were interrogated to identify if the entries had overlapping information (in this case, duplicate survey responses with the least completed fields were deleted, the most completed survey response for an IP address was included in the analysis).

The survey was open to all eligible parents, including both parents of a child. From the analysis, however, it seems that only one family may have submitted two responses from both parents, judging by the duplicate IP address and same GA of the child and slightly different information submitted in the two entries. Since the survey was anonymous, it is unclear if this duplicate IP entry with the same GA was indeed from two different parents of a child or a double entry by a particular parent. Therefore, the two IP addresses were included in the analysis.

All means possible were taken to ensure that duplicate entries were deleted where detected. Incomplete entries were considered in the analysis if at least the question on the GA of the child was answered. Empty fields or unanswered questions were regarded as valid parent responses. The denominator for each question is stated in the analysis presented below. Unless otherwise stated, the total number of unique entries used for each analysis is 65.

## 21.1 Basic characteristics of eligible families and survey responses

| Items | Number | % |
|---|---|---|
| Total number of parents recruited | 115 | |
| Unique families participating in the study | 110 | |
| Total number of children recruited | 112 | |
| Families with both parents attending the session | 13 (26 parents) | |
| Total survey entries received | 78 | |
| Unique entries for analysis (after data cleaning) | 65 | 83 |
| 100% survey completion | 56/65 | 86 |
| 93% survey completion | 7/65 | 11 |
| 38% survey completion | 1 | 1.5 |
| 21% survey completion | 1 | 1.5 |

*Table 20: Basic characteristics*

## 21.2 Survey responses

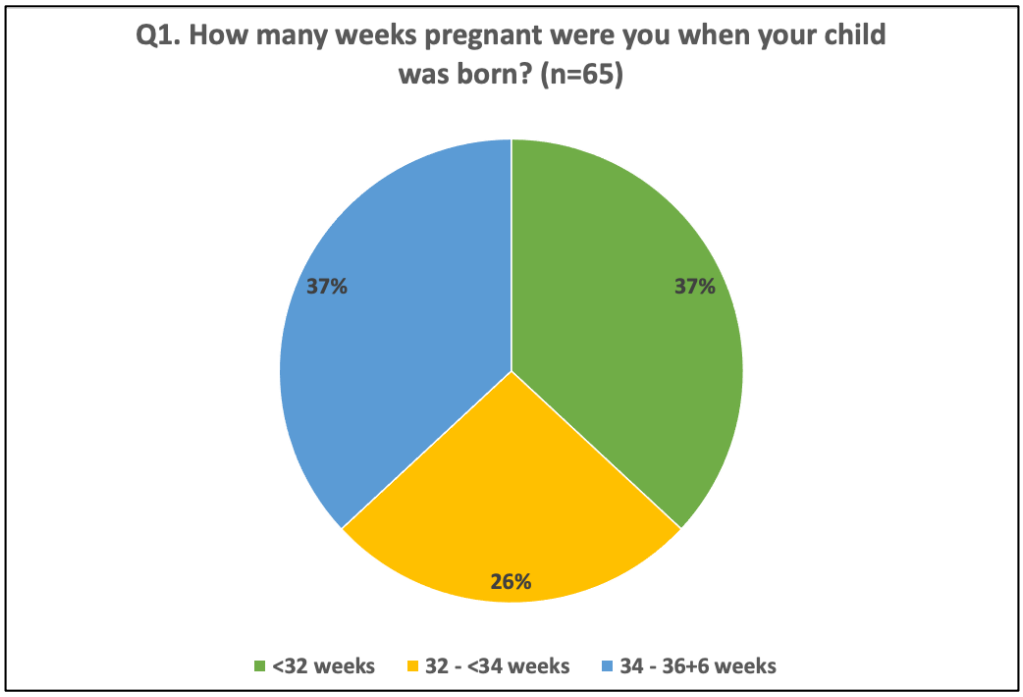



*Figure 33: Preterm subgroups represented in Parent survey (parent characteristics)*[lxxxi]*, (n=65)*

[lxxxi] Very Preterm: <32 weeks' gestation, Moderate Preterm: 32 to 33+6 weeks' gestation, Late Preterm: 34 to 36+6 weeks' gestation

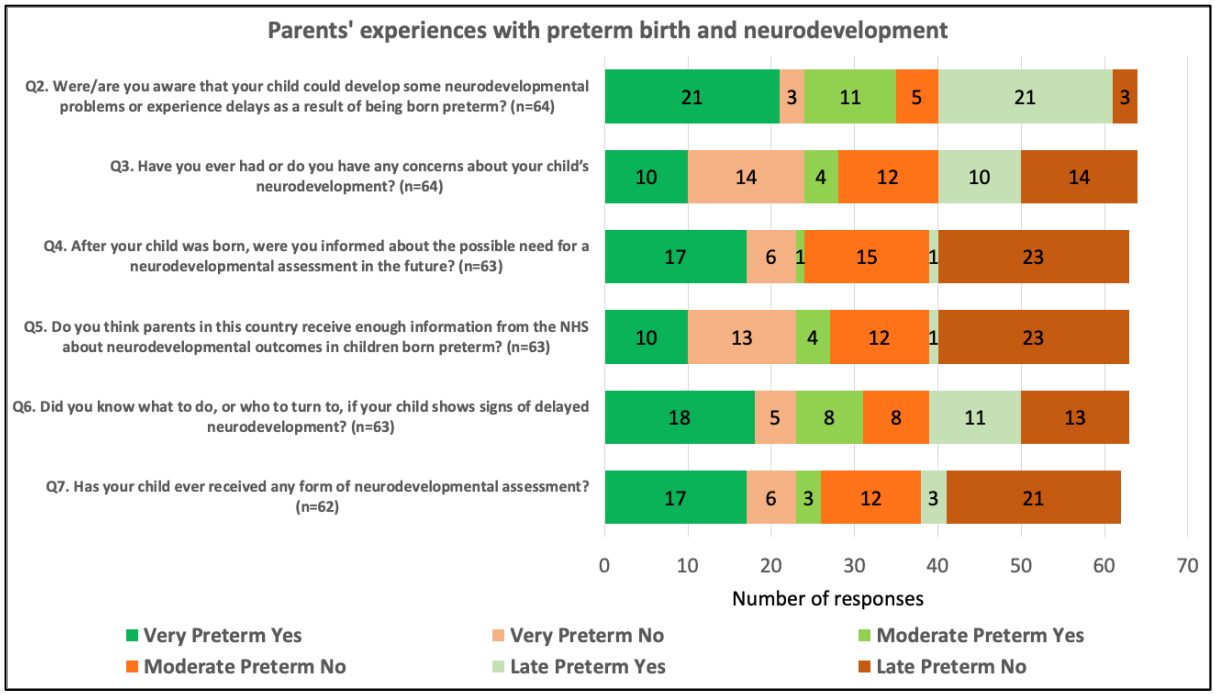



*Figure 34: Parent survey responses-parent experiences with preterm birth and neurodevelopment*

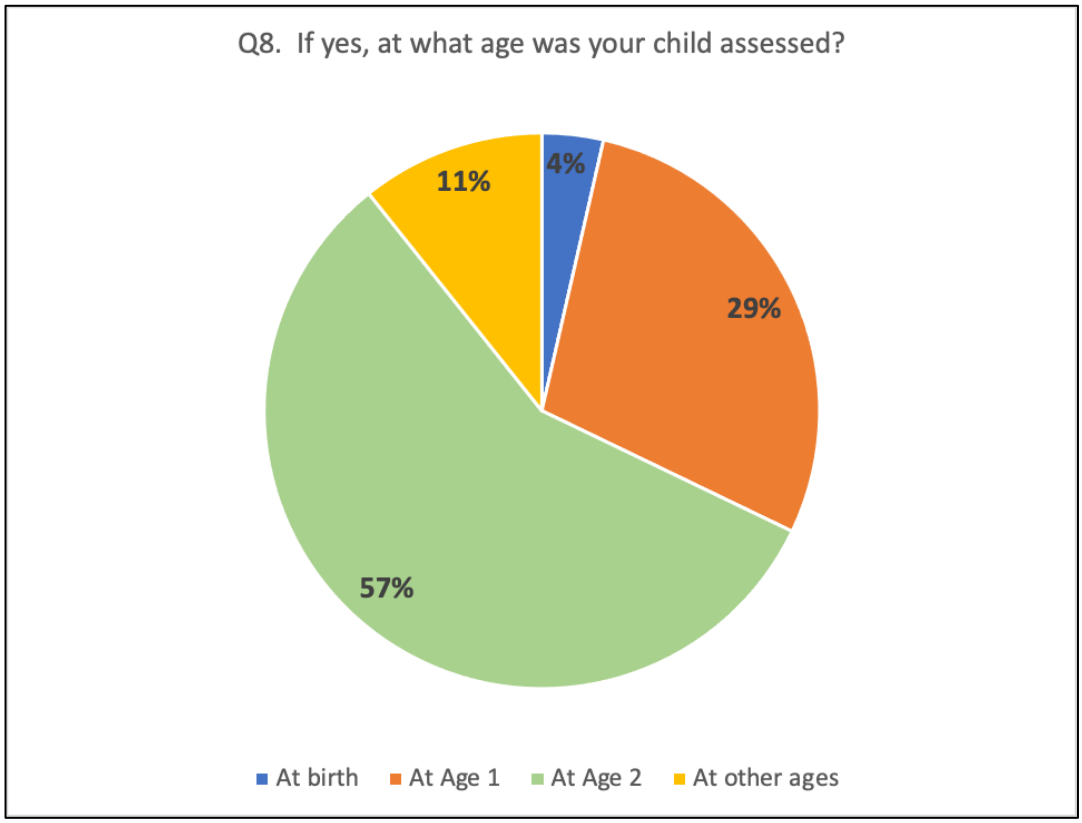



*Figure 35: Age at which respondents' children received NDA (n=28)*[lxxxii]

[lxxxii] Percent exceeds 100 due to rounding

## 21.3 Parents expectations for information sharing

Parents were asked about the kind of information they would like to receive from the NHS.

The total responses from the three options provided were:

- Neurodevelopmental outcomes among children born preterm (77%; 50/65),
- NDAs and future care (88%; 57/65),
- Caring for a child born preterm (78%; 51/65).

Within the preterm groups and for all three areas asked, parents of LPT children selected the highest number of recommendations, followed by the VPT group and then the MPT group (Figure 36).

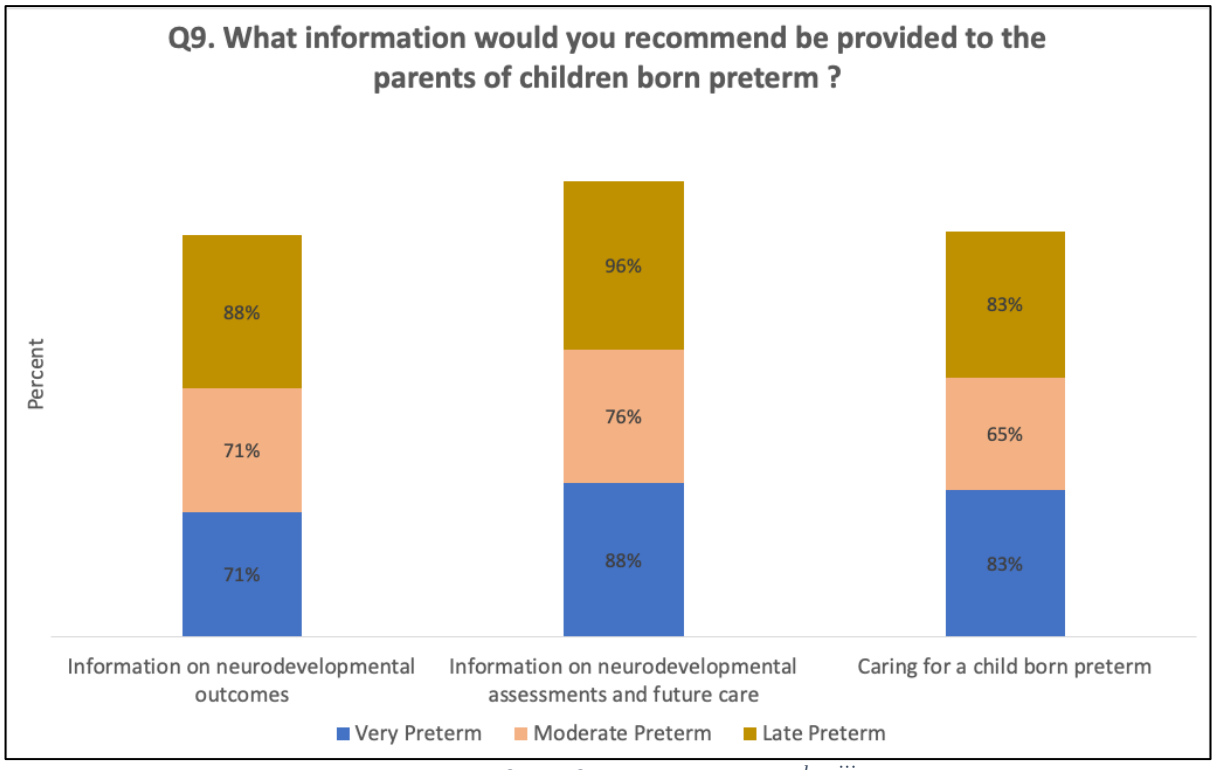



*Figure 36: Parents' recommendations for information sharing*[lxxxiii]

[lxxxiii] Multiple responses were allowed.

## 21.4 Satisfaction with Neurodevelopmental Follow-up

Parents were asked about their general satisfaction with the neurodevelopmental follow-up that children born preterm in the UK receive (Figure 37). Segregating by preterm subgroups (Figure 37), parents of VPT infants were more likely to be satisfied (87% were *very satisfied and satisfied*) than parents of LPT children (17% were *very satisfied and satisfied*). Sixty-seven percent of the LPT parents expressed dissatisfaction (*very dissatisfied and dissatisfied*), while no parent in the VPT group was *very dissatisfied* with the current follow-up children receive. Overall, nearly half of the parents were satisfied with the current neurodevelopmental follow-up: 49% (31/63) (Figure 38).

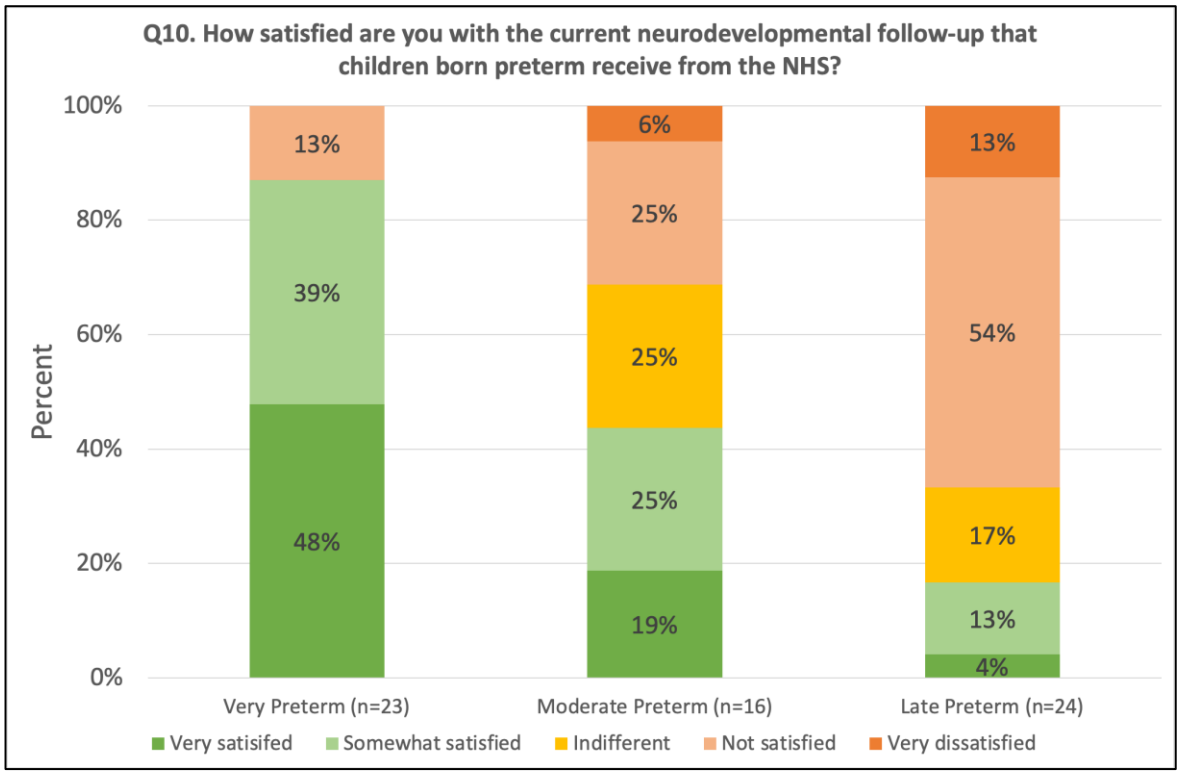



*Figure 37: Parent satisfaction with current follow-up for children born preterm in the UK (according to preterm subgroups)*[lxxxiv]

[lxxxiv] Percentage exceeds 100% due to rounding up

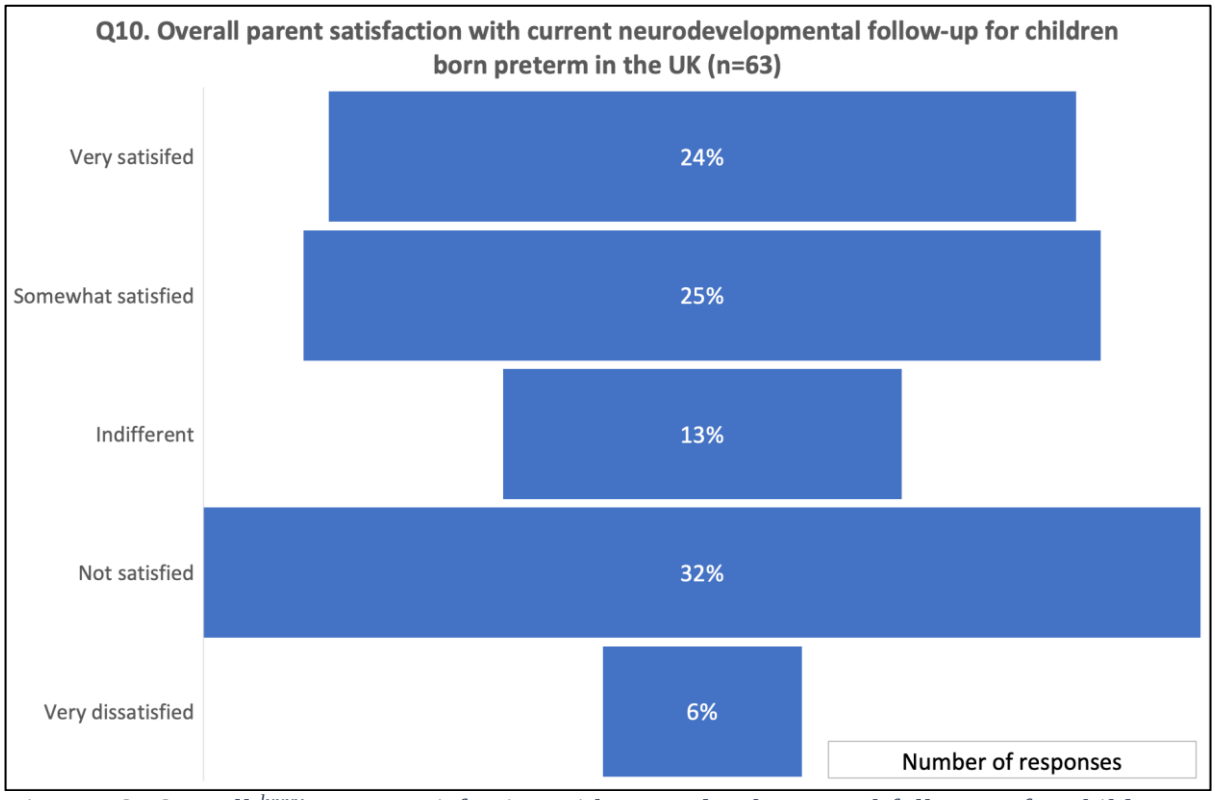



*Figure 38: Overall [lxxxv]parent satisfaction with neurodevelopmental follow-up for children born preterm in the UK*

[lxxxv] All parent preterm groups pulled together

# 22 Results

## 22.1 Parent interviews

In total, 29 in-depth interviews were conducted with 35 parents (mostly with mothers, see Table 21) who have had children born before 37 weeks' gestation. Initially targeting 20 parents, analysis of the preliminary data of the first batch of 17 interviews suggested that saturation had not yet been reached, and so interviews continued until thematic saturation [307] and enough diversity in the parent interviewee characteristics (Table 21) were achieved.

The postcodes (at the time of delivery) of all households participating in the study were matched against the 2019 (latest) version of the IMD score. The 110 children who participated in the study included singletons and multiples (twins and triplets). These come from 92 unique post codes, also referred to as households/families. Out of the 92 unique households of participants in this study (for both children and parents):

- 18.5% were from the lower 40% of the IMD decile (most deprived areas)
- 17.4% were in the middle 40 to 60%, and
- 64.1% were from the upper 40% of the IMD decile (least deprived areas)

Based on the IMD classification of interviewees and non-interviewees in (Table 6), it can be observed that at least more than 55% of interviewees (59%) and non-interviewees (67%) were from the least deprived areas in the UK, while about a fifth of both interviewees (24%) and non-interviewees (16%) were from most deprived areas.

Themes from the interviews were obtained both deductively (a priori) and inductively (emerged from the interview) through a thematic content analysis approach [304].

The predefined themes include:

- Parent knowledge about neurodevelopmental patterns for children born preterm
- Communication with the NHS
- NDAs
- Satisfaction
- Expectations for universal neurodevelopment

The themes that emerged from the interim analysis and the complete set of interviews are described in Table 22 and Table 23 respectively. A sample of the quotes is provided later in this Results section with parent IDs in the format: (*P..X; GA; Type of birth*) where P …X refers to pseudonymised parent ID, GA refers to the preterm subgroup (VPT, MPT or LPT) of their child, and type of birth (singlet or multiple pregnancy: twin or triplet). Where both parents of a child/children participated in the interview simultaneously, their quote identifier is indicated with both parents' IDs.

| **Interviewee Characteristics** | |
|---|---|
| **Preterm Subgroups** | **Number** |
| Very Preterm (VPT) | 9 |
| Moderate Preterm (MPT) | 8 |
| Late Preterm (LPT) | 12 |
| **Type of birth** | **Number** |
| Singleton | 24 |
| Twins | 4 |
| Triplets | 1 |
| **Interviewee Type** | **Number** |
| Mother only | 22 |
| Mother and Father | 6 |
| Father only | 1 |
| **Type of assessment (child)** | |
| Neurodevelopmental assessment | 11 |
| Vision only assessment | 18 |

*Table 21: Parent Interviewee Characteristics*

### 22.1.1 Interim qualitative interview analysis

An interim analysis was conducted to identify emerging themes from the interviews and to determine whether saturation had been achieved. Recruitment was initially through a convenience sampling approach when the study resumed after Covid-19-related interruptions. Through convenience sampling, all parents who attended the assessment sessions of their children were asked if they wanted to participate in the interview. All parents had been informed through the participant information sheet about the interviews. There was no specific effort to recruit parents with particular characteristics during the convenience sampling.

After the first set of (17) interviews had been conducted, an interim analysis was conducted to assess for saturation of themes. Furthermore, I also assessed whether basic characteristics of family types (by preterm subgroup, type of birth and fathers) were fairly included in the interviews. Therefore, a purposive sampling approach was considered to seek families with these characteristics during the virtual assessments. Interview invitations were then extended to such families, i.e., those with fathers attending a session, families with preterm subgroups (VPT, MLT and LPT), and families with multiples - triplets and twins. Most of the assessments were attended by mothers and a few fathers. All fathers who consented to participate in the interview were recruited. Some, although present during the sessions, preferred that the mothers respond to the interview while they simply observed.

The themes from the responses from the 17 parents who had then been interviewed included the predefined themes: parents' prior knowledge of neurodevelopmental outcomes for children born preterm, communication and information flow with the NHS, experiences with NDAs and parental satisfaction with neurodevelopmental follow-up for children born preterm. In addition, emerging themes that were identified from the interim analysis include

parents' experience with preterm birth and the impact of the Covid-19 Pandemic on neurodevelopmental follow-up. The main and sub-themes from the interviews, lessons learnt and recommendations from the preliminary analysis are presented in Table 22. An abstract of the interim findings was presented at the Royal College of Paediatrics and Child Health Conference in 2021 and thereafter published in the Archives of Diseases in Childhood [307].

| | |
|---|---|
| **Prior knowledge of neurodevelopmental outcomes for children born preterm**<br>• *Naïve*<br>• *Minimal*<br>• *Knew there could be a problem but was not sure what to look out for* | **Communication and information flow with the NHS (about preterm neurodevelopment)**<br>• *Received general information but not on neurodevelopment*<br>• *Reassuring care team*<br>• *Never had any conversation on preterm neurodevelopment*<br>• *Limited information and don't know what to expect* |
| **Personal experience with neurodevelopmental assessments for children born preterm**<br>• *Children received health checks but nothing on neurodevelopment*<br>• *Health visitors less knowledgeable and competent to provide preterm neurodevelopmental follow-up*<br>• *Parents feel incompetent to assess their children's neurodevelopment*<br>• *Difficulty in getting referral for neurodevelopmental follow-up*<br>• *Parents need reassurance and encouragement*<br>• *Need for closure before discharge from neurodevelopmental follow-up* | **Parent satisfaction with current neurodevelopmental follow-up for children born preterm (in the UK)**<br>• *Good*<br>• *Dissatisfied*<br>• *Quite poor*<br>• *Unable to rate satisfaction due to the absence of neurodevelopmental follow-up for their preterm child* |
| **Parent experience with preterm birth**<br>• *Depressing*<br>• *Demanding*<br>• *Uncertainties*<br>• *Concerns and worries*<br>• *Unprepared for preterm birth*<br>• *Limited ongoing support*<br>• *No concerns* | **Impact of Covid-19**<br>• *Disappointment with missed opportunity for a comprehensive developmental follow-up due to Covid-19*<br>• *Limited or no interaction with health visitors due to COVID-19 affecting care for preterm* |

| |
|---|
| **Lessons learnt**<br>• Although parents' experience of preterm birth was not the focus of this study, parents spontaneously spoke about their personal experiences and the challenges of preterm birth.<br>• Preference for neurodevelopmental follow-up by the neonatal team to alleviate concerns |
| **Parental recommendations**<br>• Train health visitors on neurodevelopmental patterns of preterm to better support parents<br>• Provide an opportunity for parents to request neurodevelopmental follow-up.<br>• Establish a contact link or hotline for parents to go to if they have concerns.<br>• More information from the NHS<br>• Neonatal team to catch up with parents post-discharge<br>• Provide reassurance to parents about the development of their preterm child<br>• Benchmarking for preterm milestones |

*Table 22: Emerging key and sub-themes from first set of interviews[lxxxvi] (interim analysis) adopted from Agyeman-Duah et. al., 2021[307].*

### 22.1.2 Some emerging themes and participant quotes:

Themes from the interviews have been grouped into three main dimensions:

- Parent factors
- NHS factors
- Child factors

[lxxxvi] In the interim analysis, 17 interviews were conducted involving parents of these preterm sub-groups: at <32 weeks (n=5), 32 to <34 weeks (n=5) and 34 to <37 weeks' gestation (n=7).

| Dimensions | Main Themes | Sub Themes |
|---|---|---|
| **Parent Factors** | Continued contact and support for parents | Postpartum support for parents |
| | | Prenatal support for prospective parents |
| | Parent expectations for neurodevelopmental follow-up for children born preterm | |
| | | Experience with preterm birth |
| | Parent experience with neurodevelopmental follow-up | Impact of Covid-19 on parent and child experiences |
| | Parent impressions about neurodevelopmental follow-up for children born preterm | |
| | Parent knowledge of neurodevelopmental outcomes among children born preterm | Milestone Benchmarking |
| | Parent recommendations for neurodevelopmental follow-up for children born preterm | long term follow-up |
| | Parent satisfaction of neurodevelopmental follow-up for children born preterm in the UK | |
| | Parental concerns | |
| | Parent expectations for neurodevelopmental follow-up for children born preterm | In denial |
| | | Parental mental health |
| | Parents' proactiveness | |
| | Parents' source of information | Charities |
| | Reassurance for parents | |

| | | |
|---|---|---|
| | Dad's voice | Partner support |
| | | Involvement of fathers in research |
| | Motivation to participate in research | |
| **Dimensions** | **Main Themes** | **Sub Themes** |
| **NHS Factors** | Experience with the NHS | |
| | Health visitors | Empower health workers |
| | Health worker-led neurodevelopmental follow-up | Empower parents |
| | Information from NHS about neurodevelopmental outcomes among children born preterm | Knowledge of parents |
| | Parent experience with the NHS on care for children born preterm | |
| | Preference for standardised neurodevelopmental testing | |
| | Satisfaction with general care received | Quality of care received at the hospital |
| | Impact of covid on neurodevelopmental follow-up | Impact of covid on neurodevelopmental outcomes |
| | Neurodevelopmental Assessment- virtual vs in-person | |
| **Dimensions** | **Main Themes** | **Sub Themes** |
| **Child Factors** | Follow-up interventions for children in need | Bundle of care- interventions plus assessment |
| | Neurodevelopmental outcomes among children born preterm | |

*Table 23: Themes and sub-themes from parent interviews (29 interviews)*

### 22.1.3 Dimension one: parent factors

In addition to the predefined themes from the study objectives, emerging themes such as milestone benchmarking, continued contact and support for parents, parental concerns, and parents' lived experiences of having and caring for a child born too soon were well elaborated by the participants.

*'I guess having, once discharged, just a bit more information of what to expect in terms of milestones. I guess I had one of those apps because I guess (I) didn't know much about what to expect in terms of his development compared to other children' (PBBF; MPT; Singleton).*

Parents often highlighted the need for some form of contact or link with the hospital post-discharge to have continued support, given the challenges and uncertainties surrounding their preterm birth.

*'So, I, I think it's just a case of, of perhaps maintaining a contact so that there is somebody to go to if you do have any concerns' (PAAG; VPT; Twin).*

Some quotes could be attributed to more than one theme. For example, on the continued contact with parents, a parent specified mental health support as a form of support that would benefit parents of children born preterm: '*Yeah, I think that would just be so hugely reassuring to so many parents. And, and I, I, that may well be available to people with very preterm babies. But I think when you have a preterm across the board, no matter how preterm they are, it's still a very different experience to having a normal baby. And I think … sorry, a full-term baby, not a normal baby. And I think there are so many mental, you know, mental health issues that come along with that experience, the trauma and stuff. And, and, and I'd, I'd like to see more support in the mental health area. You know, it took me*

*two years to get my treatment after AA*[lxxxvii] *(child's name withheld) was born. And although the treatment was incredible, that two years was very challenging for us as a family. So, I think, you know, that is something that would be extremely helpful if there was more mental health support to parents of premature babies in the first year of life especially' (PADJ, PAEA; LPT; Singleton).*

On the **expectation of future care** and **follow-up for children born preterm**, a theme that emerged was classified as *Dad's voice*, where one father pointed at expanding research to include fathers' opinions and involvement and not only mothers': '*And I think a lot of the research is done between, obviously a lot of research has been done between mother and child. There's little research done between kind of a father and child and, and I think, more information on that and kind of bonding, especially when I went to the neonatal baby groups afterwards, that was great, run by the psychologist, but I feel maybe, you know, looking into that bonding and the brain development afterwards, I know that there's been, there is a lot of research being done on it, but I think that potentially could be a line Oxford University might be able to go down as well' (PAEI, PAEJ; VPT; Singleton).*

**Partner support** as narrated by a father, starts from the prenatal process in cases where couples are aware of an impending preterm birth: *'...(for) a good four months in advance of the baby coming, you are living day-to-day in a, in, in quite a, a heightened sense of, of, of, you know, alarm and, and worry and, and the build-up of the actual birth itself is quite, is quite hard to, to sort of deal with as well as trying to support your partner and, and, you know, basically, and keep everything on balance' (PAEI, PAEJ; Singleton; VPT).*

[lxxxvii] AA is an arbitrary label for all children whose names have been withheld from their parents' quotes.

The subject of **parental concerns** and **experiences caring for a child born preterm** were not the primary focus of this research. However, it was interesting to note how parents spoke passionately and spontaneously about their experiences of caring for children born preterm and their **concerns about their children's development**: '*I was, I was very, very anxious that, that he would have sort of lasting problems' (PAAI; MPT; Singleton).*

*'I know that when his when he had his 12-month check with the health visitor, he was quite, he was behind on a few of his sort of milestone areas and I remember feeling quite stressed about that' (PAAI; MPT, Singleton).*

*'I suppose there's something about, I guess, as a parent, you always kind of want to know whether your children are doing okay, you know, have they kind of ticked the boxes, particularly when they've been born so early' (PAAG; VPT, Twin).*

**Impact of Covid-19 pandemic on parent and child experiences**

Parents also expressed the impact Covid-19 had on neurodevelopmental follow-up experiences on their children's development. Some quotes from parent interviews are presented below: '*He, after the first lockdown, his sleep went really ... wasn't great, still not, to be honest, he was waking up for two, three hours a night refusing to go to sleep, and stopped sleeping through the night, stopped putting himself to sleep, he was a really good sleeper before that' (PADH,ADI; MPT; Singleton).*

*'I suppose it was impacted by, by COVID, so I would really have liked them to have been seen, you know, in person just when they were two, for our own reassurance, I suppose, and was disappointed not to have that' (PAAG; VPT, Twin).*

*"All were due to have a Bayley assessment at age two with the neonatal department but due to Covid that we've still not received anything" (PABD, VPT; Triplet).*

**Parent satisfaction of neurodevelopmental follow-up for children born preterm in the UK**

There was a mixed reaction to the level of satisfaction among parents:

*'I'd have to say, I suppose I didn't really, I don't really feel, like I said, that it's a full or in-depth assessment, given all the things that I know now could potentially go wrong with my preterm child. I have been quite fortunate in that I do have two older children and I can remember what their development was like at similar ages to AA (name of child withheld). So, in a sense, I do feel quite confident about his development, however, I'm not, because I don't know all of the pitfalls of being born preterm, it's kind of difficult to know exactly what I should be looking for. So, I'd say, if I had to sort of score it out of ten, I'd say I'd give it like a six out of ten. Because I wish that there was more information, or certainly that it was given in a more, sort of, you know, layperson's view of what could potentially affect us as a family and him as a, as a child' (PAAJ; VPT, Singleton).*

A parent of triplets had a different level of satisfaction with neurodevelopmental follow-up, which was informed by the assessment tool used for her children. The parent had this to say: *'My son (one of a set of triplets) had, had experience of the Bayley assessment, which I feel is a much more in-detailed and a true reflection of his abilities, especially the fact that it was performed by a paediatric OT (occupational therapist), I feel that there's a real insight into the level he was at, at that point. That was really helpful' (PABD; VPT; Triplet).*

For the second child's assessment, the parent was not as satisfied as with the first. The parent's expectation for standardised testing (with the same tool/under standardised conditions) may be important feedback for follow-up practices. It is noteworthy that different children may respond differently to the same type of test depending on their level of development/prognosis. '*He (one of the triplets) did have an assessment with a consultant*

*paediatric, I'm not sure of what the test was, it wasn't as in-depth as a Bayley assessment. And I, again I feel that one was quite narrow, in the fact that if you didn't do that set of task in the, in the order or in the way the physician believed it should be, I don't know how to explain it, that just, I wasn't, wasn't satisfied that that was a true representation of him and his abilities' (PABD; VPT; Triplet).*

Parents of LPT children were less satisfied with neurodevelopmental follow-up for children in the UK and felt they were supported less: *I would say it was poor… I just don't, I don't feel like I kind of got any support after they, kind of, signed us off from the hospital when she was a baby. I've kind of, had no one, kind of, come to talk to me about effects of being born preterm or anything like that (PABC; LPT; Singleton).*

*Well, if, if we hadn't volunteered to do this (participate in research), I would say there was absolutely zero follow-up... the only follow-up we got was the standard that everyone gets through the health visitor. It wasn't anything specific because he was preterm. So, in that sense, pretty dissatisfied because there was zero follow-up at all (PAEE,45; LPT; Singleton).*

Parents who were not able to have the full NDA and in-person visit (during Covid-19) were not completely satisfied with an alternative assessment through phone call follow-up as they felt it was not adequate: '*…so really satisfied overall but like I said, you know, obviously, it's just unfortunate that he never quite finished; I don't quite feel like he finished that neonatal journey because it ended with a phone call' (PABI; VPT; Singleton).*

### 22.1.4 Dimension two: NHS factors

Themes involving or related to the NHS have been grouped under Dimension Two, described as *NHS factors* (Table 23). Nine themes were identified as NHS-related. Parents generally praised the NHS for **providing excellent service** during hospital stays after delivery. Parents, however, did not always feel the same support when they were discharged

from the hospital: '*And, you know, from when we were in hospital, then arranging for sterilisation stuff to, to be sent over to the children's ward from the neonatal ward so that I could breastfeed him when he was in hospital. Yeah, just so many things that were incredible. You know, it's just hard when all of that slips away and you, you have this incredible support system and then it goes, and you're fed back into the more mainstream system. I think that's where the problems arise with, with parents of preterm babies' (PADJ, PAEA; LPT; Singleton).*

Another parent had this to say about their **experience with the NHS**:

*I don't remember. We were given some leaflets to leave with. But no, not really. I always felt like, that they, the NHS didn't have enough time for the amount of people that were in there. So, anything that there, that wasn't essential to keep somebody alive I felt like while I was in there was probably skipped. So, I think we were handed some leaflets, but I don't remember what they were about or anything like that. They were just given to you, not really explained. So, there could have been some information in there, but I think that this kind of, kind of subject (preterm birth) needs more than just a leaflet (PABJ; LPT; Singleton).*

Parents felt **reassured** when they got the chance to speak with an experienced health worker:

*'I saw a consultant probably about five months after he was born. And he was really kind and he spoke, and he sort of helped me explain … 'because I didn't, still didn't really understand why AA (name of child withheld) was born prematurely and I think I had lots of problems mapped up in that. So, he sort of talked me through and then reassured me that that AA was developing, you know, well, and, and that, yeah, he would be a little bit behind perhaps in, for, for, you know, until one or two when everything had caught up. But he gave me no reason to think there would be a problem, and that was really useful. So, I, I, even though I felt perhaps like I'd just been discharged without really understanding what could*

*have happened and what could happen in the future, I found that reassuring to know' (PAAI; MPT; Singleton).*

***Health visitors*** were a persistent theme that emerged from the interviews and across many parents' responses. Parents generally did not seem to have many positive experiences with health visitors, especially about supporting parents with their children born preterm.

*Yeah, but, but we've had to chase the health visitor twice to get the referral. They just kept fobbing us off (PAAC; LPT; Singleton).*

Parents felt that health visitors who may be their usual point of contact with the health system once they were discharged home did not have **adequate knowledge** about care for children born preterm and, therefore, were not well placed to better support parents: '*And I, I suppose it would be the health visitor ordinarily, wouldn't it, but I, I didn't perhaps feel the health visitor was specialised enough in prematurity to necessarily know answers to some of my questions sometimes' (PAAI; MPT; Singleton).*

*'Because on talking to the health visitors they're always like, "She's fine, she's fine, she's fine." And just, kind of, passing it to the next person. And it isn't until recently now, where I've had to, I've contacted the doctor who's then made a referral to the JRH hospital, for speech and language and sensory problems' (PABC; LPT; Singleton).*

*'I've had, the, the health visitor checks, I feel are, are not in enough detail at all, they're quite outdated, not relevant and quite narrow, in that if you can't do a set task that would mark you either up or down, which isn't a true representation of your abilities possibly. My son had, had experience of the Bayley assessment which I feel is a much more detailed and a true reflection of his abilities, especially the fact that it was performed by a paediatric OT*

*I feel that there's a real insight into the level he was at, at that point. That was really helpful' (PABD; VPT; Triplet).*

*'...I actually made a complaint about her. I think she was rushing, and she hadn't looked at our notes and she ...*Interviewee 2*: I think she was just dismissive of ...yeah, she was dismissive of him being a preterm baby. She kind of was like, "Oh, yeah, I said he was born ..." she asked if he, he was born prematurely, and I said, "Yes, he was born at 35 weeks and one day." And she said, "Well, then hardly, that's not really premature, is it?" And that, again, was extremely traumatic after what we'd been through' (PADJ, PAEA; LPT; Singleton).*

*'Because it was, we were unsure when we did have concerns who to talk to, because the health visitors were just so useless. They really let us down. That was the second let-down we'd had from them. The first was when he was really unwell when he had an undiagnosed pyloric stenosis and essentially, he was fading away. We asked the health visitor to come out to our house and she just never got back to us. So, I, I think we did, we definitely felt let-down from that perspective, for sure' (PADJ, PAEA; LPT; Singleton).*

Also, parents expressed that the care their children received from health workers was not tailored to their needs as children born preterm, but rather the usual standard checks health visitors would offer to all children (without underlying risk factors): *'Well, nothing specific for preterm babies really. AA obviously had the sort of neuro-development test when she was, I've forgotten, she must have been 15 months or so, which was from the health visitors. But it wasn't anything really specific to preterm babies' (PAAE; LPT; Singleton).*

On **health visitors' knowledge of preterm children**, a parent shared her experience as a health visitor and made a recommendation on how to enhance their skills to better support parents: '*I'm, I'm a health visitor, but I know that a lot of my colleagues probably have never*

*worked with preterm babies, so I do wonder if that's something that maybe we could look into. I know the Institute of Health Visiting have just done training for health visitors on how to look after parents' emotional, emotionally when they're on the neonatal unit but I don't think they've looked at the moment about the neurological side of maybe the follow-ups. We do a lot of follow-ups and we know a lot about the brain development in children and a lot about infant mental health, but I do wonder if there was, there was more national guidance maybe and maybe using the same tools, assessment tools between kind of hospitals and in the community might work better as well' (PAEI, PAEJ; VPT; Singleton).*

Some parents expressed **positive feedback** about their encounter with the health visitors, for example one said: *'…we've had the health visitor as well, he was visiting quite regularly once we were at home, from our local surgery. So pretty well supported and pretty well checked, to be honest. So, yeah, fine, good' (PAAG; VPT; Twins).*

### 22.2 Impact of Covid-19 on Neurodevelopmental follow-up and parent experiences

One of the emerging themes from the interviews was the impact of the pandemic on parent experiences of the health system, including neurodevelopmental follow-up. Parents also narrated how the pandemic impacted their parenting experience: '*Because he was born just before lockdown so then we never had much interactions at all, so it's quite an isolated time I guess and perhaps there is a lot more out there for people, but we just didn't have access to it because of when he was born, so yea perhaps there is stuff that we never were able to interact with any of those' (PBBF; MPT; Singleton).*

*'It's been a very difficult year so all of this should have been done a bit sooner, but due to the pandemic it obviously (delayed things). But with the follow-up from our conversation today and with speaking to the local hospital, I'm satisfied that they are now following up any concerns I may have' (PACJ; LPT; Singleton).*

*'.... I think it's a really difficult one, because of Covid, I'd say I was slightly disappointed that we had to do the last one by phone, almost like I wondered whether there was ... I, it's really difficult because ultimately could; obviously, it's a thing that, I guess, none of us could have anticipated and things have had to have been adapted and stuff. But in hindsight, could it have been something he could have just delayed a couple of months and seen somebody a bit later potentially? Or was there a more Covid-secure way to do it? Because I, I do find that, obviously, doing things by phone, this one was, it wasn't even by video with (with the assessor, name withheld), it's, you know, it's ultimately quite hard for any assessment to take place that way' (PABI; VPT; Singleton).*

### 22.2.1 Dimension three: child factors

The themes classified under child factors were *follow-up interventions for children in need* of care and *neurodevelopmental outcomes among children born preterm.*

Parents acknowledged that resources may be limited within the NHS and advocated for **early intervention** as a means to save future costs: '*.... I know, being an accountant myself, the NHS is stretched at the moment in terms of resources but again, I think with the limited resource, those resources should be prioritised ... if something is discovered or is seen in a child at this stage and not corrected for example if his speech is not coming up the way it should be ... and you wait for another 6 months to have him for the referral ..., it has a knock-on effect on other areas of his health and well- being and because of those, now you end up and instead of one thing that you (would) have solved with limited or few resources, you end up having ten in future which you need ten times the resources to solve' (PBBG; VPT; Singleton).*

Parents elaborated on some **outcomes** they have observed with their children born preterm: *'I think he wasn't babbling as much as she would have expected. I think, yeah, he wasn't babbling and there was certain, I think it was two-word instructions or something he wasn't responding to' (PAAI; MPT; Singleton).*

### 22.3 Parent support for children born preterm:

*'And basically, they were, they were telling me what to do and what to not do. For example, I shouldn't ask him to repeat the word. I should just basically speak everything that I'm doing …and if he says it wrong, then I would encourage him by saying, "Bravo. Well done," and I would say it correctly. So, if he says, if he says he wants something from the fridge … I would say, "Yes. Let's get something from the fridge." So basically, this kind of information, things like, kind of like, things to do and not to do' (PADA; MPT; Singleton).*

# 23 Discussion

## 23.1 Parent survey

The objective of conducting the parent survey was to solicit from parents their experience, satisfaction, and expectations for neurodevelopmental follow-up for children born preterm. Parents and caregivers are important stakeholders in the clinical care of an infant, more so for those born preterm who may be at higher risk of compromised neurodevelopment.

### 23.1.1 Representation of parent respondents

At the end of 15 months of recruitment (January 2021 to March 2022) for the parent survey, a total of 78 responses were received in Qualtrics (respondent characteristics have been summarised in Table 21). Attempts were made to encourage the participation of fathers who may be underrepresented in such perinatal and qualitative studies [308, 309]. The interviews were anonymised, so the representation of fathers who took the survey cannot be ascertained.

Respondents had children in the three preterm sub-groups in the study: VPT (37%), MPT (26%) and LPT (37%). An effort was made to interview parents of singletons, twins, and triplets. Thus, there was a good representation of parents' characteristics according to sex, how early their children were born and multiple births [310].

A breakdown of IMD of participants showed no striking sociodemographic difference between the interviewees and non-interviewees in this study (Table 6). The sample size of the study’s participants was not large enough to provide a meaningful statistical inference on the possible associations across preterm subgroups or differences among parent interviewees based on their sociodemographic characteristics, which could have impacted parents' experiences of neurodevelopmental follow-up of their children born preterm and therefore on their responses to the interviews. Future studies could explore the relationship

between parents' socioeconomic status and their experiences, satisfaction and expectations for neurodevelopmental follow-up of all preterm subgroups.

### 23.1.2 Key findings from survey[lxxxviii]

#### *23.1.2.1 Parent knowledge of neurodevelopmental patterns for children born preterm*

**On awareness about the sequelae of neurodevelopmental outcomes**, an equal percentage (33%) of parents of children born VPT and LPT expressed having knowledge about possible delays or developmental challenges children born preterm could experience. With all preterm groups combined, approximately 83% of parents were aware of the association between preterm birth and the risk of compromised neurodevelopment (Figure 34). This high level of awareness may be comparable to a systematic review [311] finding of parental knowledge of child development, which also reported an average of 83% [312]. The mean GA at birth of the children whose parents participated in the Hess et al., (2004) study was 29.5 weeks [312]. The relevance of the findings of the systematic review to this survey is that parental knowledge is influenced by the level of education and socioeconomic status. Although parental income status was not explicitly determined in this study, its setting (in Oxfordshire) may have facilitated a selective pool of parents with at least average to higher-than-average educational level and economic status[lxxxix, xc]. According to the Oxfordshire County Council's 2011 census, 83% of Oxfordshire residents hold some form of qualification, being described as a well-educated county [313].

[lxxxviii] *Findings are presented in the order that the survey questions were formulated. See* Figure 34*4*

[lxxxix] https://www2.oxfordshire.gov.uk/cms/sites/default/files/folders/documents/business/economicdevelopment/LEPbid.pdf

[xc] https://www.oxford.gov.uk/oxsp/info/23/economic_growth_and_regeneration/6/economic_development_growth_and_regeneration

#### *23.1.2.2 Parental concerns about neurodevelopmental outcomes*

An equal number of parents (16%) in both the VPT and LPT groups expressed concerns about their children's neurodevelopment. Parents of children born VPT may be worried due to their knowledge of the literature indicating a higher risk of compromised neurodevelopment among such children [6] compared to their MLPT or at-term peers. Some of this knowledge may have been acquired during the NICU stay [314] and follow-up appointments [288]. However, for the parents of children born LPT, the relatively limited research and information about neurodevelopmental outcomes in this group may create anxiety. The limited support parents of MLPT children receive post-discharge [278] may cause concerns about their children's neurodevelopment and long-term outcomes as highlighted in the Alberta study by Premji et al., (2017) [278].

For parents and families, knowing about the neurodevelopmental outcomes and whether their children are growing normally is good for managing their own stress, making certain decisions, and advocating for further support for their young ones, where needed [99].

#### *23.1.2.3 Q4. Communication with the NHS*

Parents were more likely to be informed about the possible **need for neurodevelopmental follow-up in the future** if their children were born VPT (27%) than parents whose children were born MPT (2%) or LPT (2%) (Figure 34). Consistent with the practice at the JRH, only children born VPT are offered routine neurodevelopmental follow-up.

Considering the likelihood of MLPT children experiencing some delays or neurodevelopmental disturbances later in childhood and beyond, it may be necessary for all parents with children born preterm to be informed about follow-up practices and the availability of early screening to identify signs of compromised neurodevelopment, as well as education about the normal development of a child [315]. For example, the guidelines of

the American National Perinatal Association make recommendations to the healthcare team and for family education for late preterm infants [316]. The guidelines encourage families to be taught about MLPT's increased risk for developmental delays (psychomotor and cognitive delays) and increased SEN. They also recommend stressing to parents the importance of developmental follow-up for MLPT children. To the healthcare team, the recommendation includes performing a regular developmental assessment for MLPTs. Similarly, the SEN34-36 Group of the Spanish Society of Neonatology and the Spanish Paediatric Association have developed follow-up recommendations for LPTs, which include predischarge information sharing with families to understand what is needed for the care of MLPT children, and a recommendation for basic routine neurological screening until 2 years of age [317].

Neurodevelopmental follow-up sessions provide the opportunity for parental counselling on a child's development [192]. They offer parents the chance to interact with a health worker to allay any parental concerns regarding a child's development. A systematic review by September et al., (2016) of the association between parental knowledge of a child's development and parenting highlights the importance of access to information and modulation of good parenting [311].

On the flip side, health providers may have good reasons why parents of MLPT children are not provided with any information on neurodevelopmental follow-up practices as it would inevitably raise parent expectations which cannot be met by the current system or guidelines [27].

## 23.2 Information from the NHS to UK parents on neurodevelopmental outcomes among children born preterm

For all subgroups, 76% (48/63) (Figure 34) of respondents generally felt that parents of children born preterm in the UK do not receive enough information from the NHS regarding potential neurodevelopmental outcomes for children born preterm. Slightly more parents in the VPT group (16%) compared to 6% and 2% (1/63) in the MPT and LPT groups, respectively, expressed a positive response to parents receiving enough information from the NHS.

## 23.3 Who to turn to?

Preterm birth can be a stressful experience for parents when children reach their developmental milestones more slowly. Having access to adequate support and information [286] on managing such difficult moments may be a relief to parents [283, 291]. In this survey, parents were asked if they knew what to do or whom to turn to if their children showed signs of delayed neurodevelopment. Most parents (59%) - mainly from the VPT group (29%) - said they knew what to do or whom to turn to in such instances. Babies born VPT are at higher risk of morbidity and mortality [6], and so research and health services have been prioritised for this group compared to the MLPT [201]. In other words, having a child who was born VPT increases the likelihood of receiving more information from the health system and having a better support system post-discharge than the MLPT group.

## 23.4 Neurodevelopmental assessments

### 23.4.1 Parent experiences with preterm birth and neurodevelopment:

Currently, in the UK and most other countries, children born VPT are prioritised for routine neurodevelopmental follow-up [27, 201]. In this survey, parents' experiences with neurodevelopmental follow-up showed a similar trend with the literature: parents who

responded *Yes*, 27% (17/62 respondents), to their children having some form of neurodevelopmental follow-up mainly were those with VPT infants (Figure 34). This represents 71% (17/24) of VPT parent survey respondents whose children had received neurodevelopmental follow-up. Usually, children born VPT are offered neurodevelopmental follow-up (at 2 years of age) according to the NICE guidelines. The less than 100% expected positive response from VPT parents to the question may be due to Covid-19-related disruptions to follow-up activities where some VPT children missed or had not received the standard 2-year NDA, at least at the time of the survey. Only 5% each of parents of MPT and LPT groups responded affirmatively that their children had received some form of NDA (Figure 34).

As a follow-up, parents specified at what ages their children received an NDA (Figure 35). From the hospital survey (in Chapter 4), UK care providers indicated NDAs are offered at different time points, including: at 3 months (38%), 4 months (8%), 6 months (26%), 8 months (10%), 9 months (13%), 12 months (38%), 15 months (3%), 18 months (26%) and at 24 months (72%). According to the parents, their children received assessments at age 2 (57%) and age 1 (29%). Parents' and care providers' responses suggest that the 12- and 24-month visits are the most popular times for follow-up, although assessments at other time points are possible. Similarly, in Germany, as reported by Albayrak et al., (2020), neurological follow-ups are offered at different times before age 2: at 3, 6 and 12 months. This information is necessary for health services and large-scale planning for neurodevelopmental follow-up for preterm children.

## 23.5 Parents' satisfaction and expectations for universal neurodevelopmental assessment

### 23.5.1 Parents' expectations for information sharing (Figure 36)

Parents of LPT children expressed higher preference for information sharing from the NHS such as caring for preterm children and their birth outcomes. In the study by Premji et al., (2017), they found that often LPT parents failed to recognise the feeding distress and needs of their babies due to lack of knowledge. The biological immaturity of the late preterm can pose challenges, such as inconsistent and poor state regulation, poor sucking and breathing which the mothers may not always know how to handle, and can be a source of stress and worry [278]. In addition, mothers may be inexperienced in monitoring for signs of common problems such as jaundice and dehydration. More information and support would boost maternal confidence in caring for their young infants.

The differences in the parent survey respondents of the LPT and VPT groups may be explained by the fact that VPT parents receive more information and support from the hospital (for example, in the NICU and during follow-up appointments) as the VPTs are generally more vulnerable than the LPTs. As mentioned by Woodward and Hüppi (2018), neurodevelopmental follow-up provides parents with extra advice and support during these sessions [99]. As LPT infants have relatively short hospital stays, Premji et al., (2017) highlight the heightened fears and anxiety among their parents, which may arise from the complexities of caring for a preterm child. These studies [99, 278] and others emphasise the observation of LPT parents in this study, portraying the desire for more information on caring for children born preterm, neurodevelopmental outcomes, follow-up and future care.

### 23.6 Satisfaction with neurodevelopmental follow-up

From Figure 37only 44% and 17% of parents of MPT and LPT expressed satisfaction with the current follow-up. This is understandable as their children are not eligible for routine follow-up. This could be a limitation in the design of the questionnaire if parents are asked about their satisfaction with a service their children do not receive. However, the question about satisfaction was to explore parents' views of the current follow-up design and not necessarily how satisfied they were with a service their child might have received. The fact that the rate of satisfaction among MLPT parents was less than 50% also implies that not all parents of MLPT children were dissatisfied, despite their children not receiving routine neurodevelopmental follow-ups. For example, a few parents of MLPTs felt that their children were doing ok and asking them to do routine follow-up will be over medicalising their children.

The high dissatisfaction rate may be a natural reaction of parents to an expectation that is currently not being met, as their children are not eligible for routine neurodevelopmental follow-up due to their GA. Talking with parents in the interviews and during the assessments, some parents felt that their MLPT children may have missed the eligible cut-off for routine follow-up for VPTs by just a day or a few days. They felt by virtue of being born preterm, MLPT children are at risk of compromised neurodevelopment and would benefit from routine neurodevelopmental assessments. Also citing from the PPI feedback about the EveryPrem Study, one parent commented that: *'My three children were born between 32-37 weeks' gestation, so none were fortunate enough to have received and tests/checks prior to their 2-year health visitor checks. My now ten-year-old son was born at 32 +3, and it was not 'officially' recognised that his speech and language was delayed and that he needed professional assistance until his 2-year check. Had we have been consulted with on a more regular basis as a result of him being born preterm, I do believe*

*this is something that could have been managed, recognised earlier and potentially avoided. I believe as a result of this it has affected his confidence and development'* (Appendix XII Comment 1).

For policymakers and health providers, having evidence-based criteria for offering follow-up would improve the efficiency of the system. As the experience of care is a subjective phenomenon to beneficiaries, the expectations and preferences of parents vis-à-vis recommendations by policymakers may not always be aligned even if such decisions are based on scientific evidence.

The information about parents' satisfaction with the current neurodevelopmental follow-up (Figure 37 and Figure 38) is useful in planning neurodevelopmental follow-up services for children born preterm and a vital advocacy tool for universal neurodevelopmental follow-up [201]. In expressing dissatisfaction, parents of MLPT infants are vocalising their perception of a gap in universal follow-up for all preterm infants [55]. One explanation may be that MLPT children do not have access to routine neurodevelopmental follow-up, which causes dissatisfaction among their parents, i.e. it is not that parents are necessarily displeased with the quality of the neurodevelopmental follow-up itself.

#### *23.6.1.1 Implications of preterm sub-groups from the parent survey*

Parents of MPT children recorded the least number of submissions in all areas asked, such as their expectations for information sharing and satisfaction with the current follow-up from the NHS. It is unclear whether this indicates that parents in the MPT group are generally satisfied or are not expressive of their needs. Further research may be required to understand differences and similarities in parent preferences for their children born MPT and LPT and how this impacts large-scale follow-up assessments or planning of services (for children born preterm).

## 23.7 Parent interviews

The study highlights parents' need for moderated information sharing from the NHS on neurodevelopmental outcomes among children born preterm, caring for children born preterm, and neurodevelopmental follow-up for children born preterm. Through a mixed methods approach, the study has highlighted important perspectives of parents' experience with neurodevelopmental follow-up and their expectation for universal follow-up for all children, including those born MLPT.

The intention was to interview 20 participants or until saturation of themes was achieved. Saturation [318] occurs when no new themes or concepts are observed in the data. Analysis of the first 17 interviews had six themes, four of which were set a priori based on the study objectives, and two new themes emerged from the interviews (Table 22). Analysis of subsequent interviews revealed additional themes observed in (Table 23). Interviews were discontinued when saturation was finally achieved with a purposeful sample of 29 interviews.

The application of mixed methods in this study overcomes the challenges of applying a dichotomised approach to soliciting parents' experiences, which may not always be a *yes* or *no* or only a quantitative approach, which may fail to elicit the complete parent experience [284]. The strength of using mixed methods in this study is that it gives readers a better understanding of, and insights into, parents' experiences. At the same time, the quantitative approach has enabled a wider reach and inclusion of parents' views. Findings from the interviews corroborate aspects of the survey, as discussed below.

### 23.7.1 Some valuable insights from the interviews could inform how neurodevelopmental follow-up is organised for children born preterm.

**Parents felt valued** to be asked as key stakeholders in the care of their children, to share their experiences and recommendations for neurodevelopmental follow-up for children born preterm. Russel et al., (2014) concluded that parents place a premium on being involved in the care of their children, and being provided with information [319]. In the present study, parents expressed quite passionately the need for **continued support** and for relevant information regarding care and follow-up for their children born preterm. Parents of MLPT children in particular expressed their wish to receive some form of follow-up care for their children.

Previous studies that explored parents' experiences of caring for vulnerable children, such as those in the NICU or those requiring additional care or surgery, showed that continued support, good contact with the health system, and good communication were essential for parents [285, 320]. Similar to findings in the present study, the lack of, or infrequent/scanty information sharing impacts parents' emotions, especially during critical phases of uncertainty regarding the outcomes of their preterm or other vulnerable children [285, 287]. Wigert and Bry, (2012) found that, to facilitate **effective communication** and information sharing between care providers and parents, training frontline staff in communication and how to support better the emotional needs of parents is essential as this improves the well-being of parents and, consequently, that of their preterm infants [286].

Some parents were quite concerned about **information overload** and so preferred to have some form of reminder, such as a leaflet to take home on discharge, i.e., information that is relevant, appropriate, and considerate of their family needs and circumstances [283]. They

would particularly appreciate having access to information [285] on neurodevelopmental outcomes, follow-up, and care for children born preterm.

Parents also remarked that having contact numbers for people who are knowledgeable about children born preterm, such as qualified care providers, whom they could contact for support and reassurance, would be helpful. As part of providing enhanced developmental support, NICE recommends: *to provide parents or carers of a preterm baby having enhanced developmental support with a single point of contact within the neonatal service for outreach care after discharge* (NG 72, section 1.3.4). And therefore during discharge planning, parents should be *advised to talk to their health visitor or GP if they have any concerns about their child's development at any stage of childhood or adolescence* (NG 72, section 1.1.14). These recommendations if well implemented can improve parent and children experiences. Feedback received from the parent interviews for a point of contact post discharge could be an indication of limitations in implementing NICE guidance or recall bias with how much parents remember months or a few years after discharge or how much information parents really understand during hospitalisation when they are more likely to be anxious about their baby's health. Future studies to understand the extent to which the NICE guidance is being implemented and or how information should be shared with parents during hospitalisation will be insightful.

Support for parents can be for clinical or non-clinical needs [321]. Support, in this case, can be provided by health workers, as well as support groups or parents in similar situations. Relying on nurses and health personnel to provide all the necessary support may be too demanding [321]. As a learning point and recommendation from the parent interviews for prospective neurodevelopmental follow-up for preterm infants, neonatal units may encourage parent support groups to be established, where these are not already in place;

assigning parents (including those of MLPT children) to an outreach nurse on discharge; empowering healthcare professionals such as health visitors to better support parents; and providing a contact number (hotline) for routine check-in for non-emergencies may be some of the ways parents can be supported through their uncertain days. Ultimately, better support for parents should impact the growth and development of children born preterm [322, 323].

On the theme of mental health support for parents, many parents expressed a need for mental health support (due to the intense emotional distress caused by the preterm birth and uncertainties about their child's health and developmental milestones). Studies have shown that the mental state of parents and high-quality parent-infant interaction impacts the neurodevelopment of children as parental ill health can lead to a parent's inability to cater for their child's physical and emotional needs [324, 325]. Studies, such as the Mother-Infant Transaction Programme [26, 141] and Family Integrated Care [326, 327], which have looked at interventions targeting the parent and/or both the preterm infant and the parent, have reported some benefits of including parents in intervention programmes.

Health visitors and follow-up services provide the opportunity for parental counselling which could be an avenue for parents to interact with their child's care team and get answers about their infant's health and development [192]. In addition to providing psychological support to parents through these interactions, parents in need of additional mental health services can be signposted to their GPs for onward referral to mental health specialists, where required.

A holistic approach (such as providing interventions to both the child and parent) in addressing the neurodevelopment of a child born preterm may have some added value. Careful consideration should be made to resource implications and effectiveness of interventions to determine when to offer interventions to only the child and/or both the child

and parent, i.e. designing neurodevelopmental follow-up service as a paediatric only service or having a comprehensive approach with linkages to perinatal mental health service[xci]. Ultimately, once parents can access mental health services post-birth, the feasibility of either having it as a standalone service or as a family-integrated care should be informed by local systems and preferences.

**Standardisation of tools and follow-up practices:** As per parents' preference, adhering to the same standard of care (referring to the use of the same standard neurodevelopmental follow-up tool), such as the type of test offered and how it is administered, is considered essential for the neurodevelopmental follow-up of children born preterm. However, different tools may be required [197, 329]: for example, to assess an individual child at risk of compromised neurodevelopment or to screen at the population level [329]. There is also the definitive test, administered as a second level of assessment once a child is referred for further testing [330]. Furthermore, the administration modality may require different approaches, such as an NDA led by health workers or parents, face-to-face or virtually [331], depending on many factors. Given that the level of knowledge between health workers and parents may not be comparable, it is important to continue to engage with caregivers and to ensure ongoing communication and education for both providers and caregivers to manage expectations on both sides.

Parents' expectation for standardised testing (with the same tool/under standardised conditions) may be important feedback for follow-up practices. It is noteworthy that children may respond differently to the same type of test depending on their level of

[xci] Perinatal mental health refers to mental health during pregnancy and the first postnatal years (Maternal Mental Health Alliance, 2023) 328. Alliance, M.M.H. *Perinatal mental health*. 2023 14 October 2023]; Available from: https://maternalmentalhealthalliance.org/about/perinatal-mental-health/#:~:text=So%20perinatal%20mental%20health%20refers,exacerbated%20in%20the%20perinatal%20period.

development/prognosis. Therefore, providing parents with enough information before offering NDA or answering their questions during follow-up visits is important [99].

### 23.8 Universal follow-up for all children born preterm: managing expectations-realism vs what's realistic

In the interview, parents were asked about their expectations for universal neurodevelopmental assessments: *If you had the chance to make any recommendations about neurodevelopmental assessments for children born preterm, what would those be, and to whom would you like to make these recommendations?* (Appendix VIII). Although parents were not asked if children needed more assessments or about any specific preterm subgroups, their recommendations included extending (routine) neurodevelopmental follow-up to include children born MLPT.

It remains unclear whether it is possible, or even necessary, to extend neurodevelopmental follow-up services to all children born preterm (including the missing gap of MLPT children) given that follow-up is focused on the relatively smaller population of VPT children [25, 27] (at least in the developed economies where structured neurodevelopmental follow-up is in place). In developing countries, where the burden of preterm birth is highest [3, 6], there are limited data available regarding neurodevelopmental outcomes for children born preterm and routine neurodevelopmental follow-up is rare [332-334].

However, given 1) the emerging evidence of the increased risks in MLPT children [15, 25], 2) the fact that some neurodevelopmental outcomes only become apparent after infancy [21] or during early school years when higher executive functions are required for school, 3) the higher cost implications of intervening late [335], and 4) the potential economic loss that may occur in some cases, the argument for extending neurodevelopmental follow-up to all

children born preterm may be worth considering. The evidence in support of a universal neurodevelopmental follow-up for all children born preterm is, however, inconclusive.

Realistically, valid questions need to be asked about how practical it would be to offer neurodevelopmental follow-up routinely to all children born preterm. For example, what interventions are efficacious to target the neurodevelopment of the MLPT [150]; how cost-effective and justifiable would it be to prioritise all preterm infants for follow-up in terms of how many are actually at risk and can be identified at routine follow-up; how ready is the current system to accommodate these tasks considering the existing barriers to current follow-up practices such as staffing, financing and uptake of neurodevelopmental follow-up services by parents of MLPT children [148, 336].

The NICE guidance recommends enhanced assessment at age 2 for preterm children born before 30 weeks' gestation. The recommendation, however, does not include routine surveillance for those born MLPT unless there is an underlying clinical condition that increases their risk of impaired neurodevelopment [27]. NICE's decision of not prioritising the MLPTs for enhanced neurodevelopmental follow-up may be due to the large relative increased risk of impaired neurodevelopment amongst VPT infants compared to MLPTs and the limited evidence on the overall benefits of routine follow-up and interventions for all MLPT infants.

Secondly, the financial and resource implications of following up all preterm children are substantial, especially bearing in mind that implementation of NICE guidance is still a challenge for the current eligible populations for enhanced follow-up [337]. The 2017 National Neonatal Audit Report quotes that 40% of children born <30 weeks' gestation had no 2-year follow-up clinical information of any type reported to the National Neonatal Audit Programme [338].

As the advocacy intensifies for enhanced surveillance for MLPTs, the balance between the extent of neurodevelopmental impairment among this group, the pursuit of improving care and the financial and practical implications of enhanced follow-up must be taken into consideration [339]. Alternatives in the short to medium term may be intensifying the community health services through capacity building of health visitors and community nurses to be able to identify (MLPT) infants in need of prompt enhanced follow-up/referral [73]. Also, parental questionnaires may be useful for early identification of MLPT children at risk of later difficulties [340].

A longitudinal neurodevelopmental surveillance of MLPT in a research context will be needed to concretise the evidence of the extent and long-term burden of neurodevelopmental outcomes among MLPT infants including the influence of social deprivation and other risk factors, the impact of interventions that target their neurodevelopment and cost benefit analysis of an enhanced neurodevelopmental follow-up as is currently offered to VPT and EPT infants [13].

The fact remains that a better understanding of neurodevelopmental outcomes among MLPT children, the importance of targeted surveillance and follow-up for these children, and the implications of preterm birth on later outcomes for the individual, society, and global public health is needed [96, 341]. Further and timely research and follow-up over longer periods and a good data management system are required to address some of the unanswered questions to scale up follow-up services successfully to include MLPT children and to identify those at the greatest risk of compromised neurodevelopment [25, 97]. In addition, research, clinical and early intervention studies need to be backed by appropriate funding streams to support these initiatives in developing and developed country settings.

### 23.8.1 Potential bias

#### *23.8.1.1 Self-selection sampling and bias*

Self-selection sampling [240] is a non-probability sampling technique where a target population is invited to participate in a study voluntarily. This can be an important approach when people are allowed to sign up willingly and of their own accord. Reasons for participating in research may vary from person to person. They may include people wanting to help advance research by sharing their experiences or feeling strongly about a topic of interest so that they would like to express their opinions. People are more motivated and feel committed when they willingly sign up to participate in research studies.

Pitfalls to self-sampling include the fact that the study sample may not be entirely representative of the target population or that the findings may appear as skewed or extreme depending on the severity or complexity of participant experiences and knowledge. Thus, self-selection bias [241] occurs when non-simple random sampling is used to select the study population. Despite the potential cons of the self-sampling approach, it is an effective technique in experimental or epidemiological research requiring human subjects.

Parents who participated in the present study may have had concerns about the neurodevelopment of their children born preterm or a pleasant experience in the NICU who wanted to give back through their participation in research. For parents of children born MLPT who may not have access to routine neurodevelopmental follow-up, the EveryPrem study presented an opportunity for their children to have NDA. This way, parents who had concerns about their child's development may have been reassured or had the opportunity for their child to be referred, if required.

The basic information available to the research team was the GA of eligible children who were born at or who received neonatal care at the JRH. Nearly a quarter (refer to Chapter 2)

of each of the preterm subgroups participated in the study, highlighting the same likelihood of a parent of a VPT, MPT or LPT child participating in the research. Therefore, in spite of the potential for self-selection bias, the likelihood of all preterm sub-groups participating in the study was similar.

Further, to minimise the potential for self-selection bias, careful planning is required. In this study, all eligible parents had the same chance of being recruited as all were contacted through the neonatal team's usual route of writing to parents. Options such as a prepaid envelope and reply slip, online submission link, email and phone calls or text messages were provided as means through which parents could respond to the study invitation. This way, no parent was disadvantaged in expressing their interest in participating in the study.

Parents were asked about their knowledge and experiences of neurodevelopmental follow-up of children born preterm. There could be a possibility that a parent's comprehension of neurodevelopmental follow-up visits may not be complete and there could be a likelihood that a parent may confuse general health visits with neurodevelopmental follow-up visits. To mitigate this, parents were provided with adequate information through the information sheet at the time of recruitment, and the information given at the time of providing consent to the study. The consent included a confirmation that parents had read and understood the information sheet, and had the chance to ask questions, and received satisfactory answers.

In seeking parents knowledge about neurodevelopmental patterns among children born preterm, parents were for example asked: *What is your view about neurodevelopmental patterns and outcomes among children born preterm?* The interview questionnaire in general served as a guide for the interviews and whenever required, questions posed to parents were explained further for their understanding. There were also follow-up questions whenever needed. In retrospect, the question about parents views on neurodevelopmental

patterns and outcomes among children born preterm may have been difficult to understand despite all best efforts to explain it to parents. Perhaps, it might have been better to phrase the question as: *In what ways do you think the neurodevelopment of a child may be affected by being born preterm?*

## 23.9 Limitations

- The possibility of parental recall bias exists when recounting events that may have happened about 2 years prior to the interview.
- The study focused on parents of preterm infants aged 2 to 3 years. Some findings in this study may not be generalisable to parents of children born preterm who may be younger or older than 2-3 years of age.
- Participation in the survey was voluntary, so there is potential for self-selection bias where the findings may not represent the target population of eligible parents invited to participate in the study. Efforts were made to mitigate sources of selection bias as described earlier.
- For qualitative studies (like the in-depth interview), generalisability is not necessary as it seeks to gain rich insights into the experiences of a select group of people.

## 24 Conclusion

The parent survey and interviews have highlighted the need for policymakers and the neonatal care team to consider parents' knowledge, experiences, satisfaction, and preferences to inform neurodevelopmental follow-up practices for children born preterm. Considering the limitations of the non-randomisation of recruiting survey participants and the relatively small sample size of respondents, further research is required to test the generalisability of these findings to parents of children born preterm. That said, these findings are significant to clinical practice.

Recapping the outcome measures for the study, the parent survey has shown that parents of children born preterm who participated in the study have mixed degrees of satisfaction with neurodevelopmental follow-up practices. Parent experiences may be shaped by their specific characteristics or circumstances. Therefore, it is important to disaggregate the data to pay more attention to different parent groups and their specific needs. For example, relying on data from VPT alone, as seen in this study, may portray an excellent level of satisfaction with the current follow-up for children born preterm, whereas looking at the LPT group alone would show a poorer level of satisfaction. Health providers, managers, and researchers can work around this feedback to improve parents' experiences and manage expectations as well.

The outcome measures for the interviews include emerging themes from parent responses related to their satisfaction, experiences, and expectations for neurodevelopmental follow-up. Findings from the interviews can be summarised as follows:

1) Parents in this study had some level of understanding of neurodevelopmental outcomes among children born preterm. However, the level of knowledge may be influenced by the frequency of exposure of parents to the health system and the support system available to

parents. In all the domains explored and themes identified, parents in the VPT group expressed higher satisfaction and knowledge about the care for children born preterm.

2) Parents would appreciate more information sharing from the NHS on topics such as care for children born preterm, neurodevelopmental outcomes, and neurodevelopmental follow-up practices for children born preterm. Parents would prefer a moderated and diversified packaging of information sharing appropriate to their needs.

Parents expressed anxiety, stress, and uncertainty about their children's development, attaining milestones and long-term outcomes. They voiced their need for continued care and linkage to the health system after hospital discharge to support them through the challenging and uncertain times of their journey caring for a child born preterm. *Partner support* was identified as an avenue mothers or primary caregivers could rely on during their parenting journey to manage challenging times. Other close relatives or friends may provide support.

This study extended the opportunity to fathers as key stakeholders in the care of their children born preterm. They expressed their desire to be involved much more in research and in the care of their children born preterm. Furthermore, some fathers pointed out their vulnerability to stress and anxiety relating to having a child born preterm. Therefore, health workers and policymakers need to consider both parents when planning interventions and support systems, given that mothers alone are usually prioritised in such programmes. Parents mentioned that their mental health is affected due to anxieties associated with experiencing a preterm birth and the uncertainties surrounding the outcomes. Therefore, including easily accessible mental health resources alongside interventions for parents should be considered.

Health visitors are an existing resource or support system available to parents in the UK. However, there was almost a unanimous call from parents for health visitors to be better equipped to recognise that children born preterm have different needs and require different levels of support, including support for parents.

The survey and interviews have highlighted that there is room for improvement in neurodevelopmental follow-up for all children born preterm and support for parents in Oxfordshire. Further research is required to ascertain how these observations may be similar or otherwise across the UK and elsewhere. The contribution of this study (parent interview) is the generation of new constructs that can be tested in a quantitative setting to determine the generalisability of these constructs among a broader population of parents of children born preterm (in the UK or elsewhere). The hypothesis generated from the study is that *considering the parent's voice in the care of children born preterm provides rich insights for improving the care and follow-up of children born preterm.* Future studies will be required to explore how parents' voices can contribute to improving the care and follow-up of children born preterm in a wider population.

The application of mixed methods has achieved its objective of soliciting insightful feedback from parents through the survey and gaining a deeper understanding of parent experiences beyond dichotomising their experiences.

# Chapter 4

# Patterns of neurodevelopmental assessments for children born preterm in the UK and Switzerland: A cross-sectional survey of hospitals

# 25 Background

## 25.1 Why is this study important?

In Chapters 1, 2 and 3, I sought to investigate interventions that target the neurodevelopment of children born preterm, methods of identifying high-risk children through standardised tests, and the parents' voice to determine their satisfaction and expectations of neurodevelopmental follow-up for their children born preterm.

This fourth chapter complements the previous three as it seeks to identify the range of neurodevelopmental practices in the UK and Switzerland to inform healthcare priorities for improving services for all children born preterm, including those born MLPT who are relatively underrepresented in neonatal and neurodevelopmental follow-up research.

Some of the findings in this chapter triangulate the parent survey responses on parents' experiences of neurodevelopmental follow-up and complement the parents' voice in setting priorities and expectations of caregivers and providers in the care for children born preterm, specifically with their neurodevelopmental follow-up.

Early identification of neurodevelopmental impairment improves the chances of treatment and outcomes for children born preterm and affords early parental counselling. Therefore, in identifying current neurodevelopmental follow-up practices, the study will highlight best practices that could be replicated in other settings and could serve as learning points when considering extending neurodevelopmental follow-up to include children born MLPT. Areas of improvement identified through the hospital survey will guide the discourse on priority setting for neurodevelopmental follow-up.

### 25.1.1 Contribution of this study to clinical practice.

At the time of writing this thesis, published studies that focused on describing the spectrum of neurodevelopmental follow-up practices for children born preterm (in the UK or Switzerland) were limited. Most papers on follow-up studies describe neurodevelopmental outcomes among children, or compliance to follow-up services. Therefore, the contribution this study makes to clinical practice and the body of science is in providing an understanding of the extent of implementation of: a) the NICE guideline on neurodevelopmental follow-up ([NG72]) for children born preterm in the UK, and b) the recommendations of the Swiss Neonatal Network & Follow-up Group (SwissNeoNet)[xcii] for high-risk (preterm) infants in Switzerland. This study highlights some lessons on what has worked well and areas for improvement in conducting neurodevelopmental follow-up in these two countries.

## 25.2 Literature overview and current state of neurodevelopmental follow-up

### 25.2.1 What is neurodevelopmental assessment, and why is it essential?

Neurodevelopmental follow-up is the systematic process of assessing an infant's development. It is an important component of the ongoing clinical care of an infant considered high-risk such as those born preterm [99].

Babies who experience neurological abnormalities at birth or experience high-risk factors for compromised neurodevelopment such as preterm birth, LBW, or some clinical diagnosis at birth, for example, hypoxic ischaemic encephalopathy (HIE), may experience neurodevelopmental difficulties that can impact their life course [342]. Although there is a strong correlation between specific risk factors and compromised neurodevelopment, one cannot accurately predict which infants will encounter problems later in life, and no GA is wholly exempt from developing neurodevelopmental problems [343]. The benefit of

[xcii] https://www.neonet.ch/swissneonet/aims-and-description

neurodevelopmental follow-up is, therefore, in offering vulnerable infants the opportunity to be systematically and thoroughly assessed to identify as early as possible those at actual risk of compromised neurodevelopment [99].

Early identification of potential problems improves the efficacy of early interventions and averts the impact of compromised neurodevelopment on the child's quality of life [344]. The longer developmental problems are left unattended, the higher the likelihood of needing further complex interventions, which may involve more specialists and longer treatment time, requiring additional resources and putting a further strain on the health system [99]. Sometimes there may even be the need for additional social support to families and educational services to the child [99].

Neurodevelopmental follow-up has multifaceted benefits for the child, family, and society. Studies have shown that uncertainties surrounding neurodevelopmental outcomes may cause stress and anxiety among parents [345]. Neurodevelopmental follow-up is an opportunity and avenue for parents and care providers to be informed about their child's development, any potential deficits their children may experience as they grow, and interventions that may be helpful for their children in such cases [27, 342]. This way, parents can make informed decisions about their child's needs and advocate for additional support or differentiated care when needed, such as special needs help at school or when an intensive home-based intervention such as shared reading may benefit the child [99, 106]. Information sharing and being up-to-date with their child's care is essential for parents' mental health [99]. Therefore, neurodevelopmental follow-up can benefit the child, their parents, and close families or caregivers.

The advantages of neurodevelopmental follow-up extend to public health and neonatal services in that data collection [342] on most medium to long-term outcomes is only possible

to collect during follow-up when a child accesses neurodevelopmental follow-up services. Furthermore, the efficacy or potential harm of certain practices in the NICU or during early infancy might only be apparent with time. Maintaining a regular neurodevelopmental follow-up system with good data management where outcomes can be observed longitudinally provides crucial information on the efficacy and safety of clinical interventions and their effects on neurodevelopment, which can benefit other children and families. The advantage of collecting longitudinal outcome data is that it improves healthcare planning, saves costs and provides the basis for further research and interventions that can improve care for other children [99].

### 25.2.2 Domains of neurodevelopment

Figure 39 shows the progression of functional domains of neurodevelopment and signals when to prioritise screening and related interventions for a child.

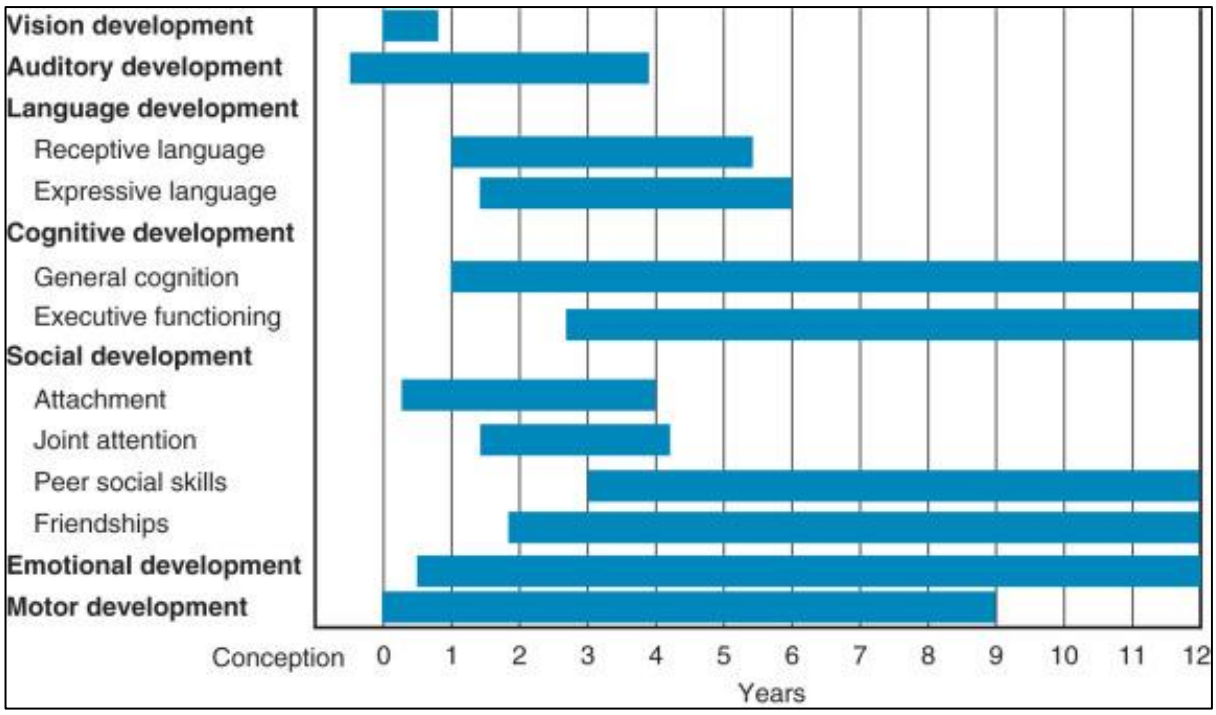



*Figure 39: Developmental progression of different functional domains; figure cited from Woodward, 2018 [99]*

### 25.2.3 Neurodevelopmental Follow-Up in the UK

Prior to the NICE recommendation on developmental follow-up practices for children born preterm in 2017 [27], there was no standardised national guideline for these infants. The NICE guideline provides recommendations to streamline and improve neurodevelopmental follow-up such as information on discharge planning, follow-up services to be offered to categories of at-risk preterm babies, recommended timing of follow-up, recommendations on assessments at each visit and the multidisciplinary team involved in follow-up services. Additionally, the NICE guideline recommends data tracking into a central database such as BadgerNet[xciii], which enhances follow-up practices, data management and research priorities. Recognising the need for parent support, the guideline also recommends that the neurodevelopmental follow-up team provides information to parents on possible risks associated with preterm birth, as well as opportunities for peer support, and providing emotional and psychological support to parents and carers as needed.

### 25.2.4 Neurodevelopmental Follow-Up in Switzerland

In Switzerland, the Swiss network, which comprises the Swiss Society of Neonatology (SwissNeoNet), the Swiss Society of Developmental Pediatrics and the Swiss Society of Neuropaediatrics, made a joint recommendation in 2014 for high-risk newborn children, which includes those born preterm, to be offered repeat, standardised and detailed follow-up examination at specialised centres, complementary to the regular assessments children receive from their usual paediatrician [192]. Similar to the NICE guideline, the recommendations of the SwissNeoNet shape the follow-up of children born preterm in Switzerland. These national guidelines streamline how neurodevelopmental follow-up clinics are offered to ensure a high-quality continuum of care nationwide.

[xciii] BadgerNet is an electronic maternity notes system that replaces the paper-based record system: https://elht.nhs.uk/services/maternity-and-newborn-services/what_is_badgernet

## 25.3 Resources and Planning for Neurodevelopmental Follow-up

Health service planning is essential to maximise value for money, improve efficiency, and reduce waste. Effective planning ensures a good understanding of available and projected resources required for service delivery. Resources include staffing, tools, and database management to document neurodevelopmental follow-up outcomes. An example of efforts to improve resource planning for follow-up is Public Health Scotland's trajectory tool [346] for service planning. The tool estimates staffing needs for assessments and facilitates a multisectoral collaboration of professionals involved in pre- and post-assessment support of young people.

In Switzerland, the SwissNeoNet maintains an online registry of high-risk children for neurodevelopmental follow-up to ensure that all eligible children are reached [192]. Furthermore, the network maintains a limited number of national centres providing specialised developmental assessments that promote inter-centre coordination and communication. There is a conscious effort for centres to use validated and standardised tools to ensure comparability of indicators, and there is continuous professional development of members of the follow-up group with the expectation that its members participate in regular conferences. Such enhanced systems and planning facilitate careful monitoring of at-risk infants, ensure structures for continuity and promote further research of follow-up activities and outcomes.

### 25.3.1 Quality Improvement, a concept for health system strengthening

Quality improvement (QI) is a framework to systematically improve care through standardising processes and minimising variation to achieve results for improved patient outcomes and healthcare system as a whole [347]. Applying a quality improvement (QI)

approach [348] to service planning, the Institute for Healthcare Improvement[xciv] highlights tools, which may help each stage of the planning process. Popular planning tools, such as the driver diagram, support strategic planning; flow charts are effective for viewing systems and processes; the fishbone diagram is useful for organising information; the Pareto for understanding variation; and the value-stream map for identifying potential barriers and solutions for implementation.

In the context of follow-up services, QI approaches and tools have been applied to improve the processes of care. For example, Brachio et al., (2020) demonstrate how they used QI methodology to improve adherence to follow-up visits. The driver diagram in Figure 40 and value stream diagram in Figure 41 show a visual layout of the key drivers for improving their follow-up processes, barriers and solutions that were implemented to improve their neurodevelopmental follow-up compliance from 60 to 76% in a 6-month period.

[xciv] https://www.ihi.org/about/Pages/default.aspx

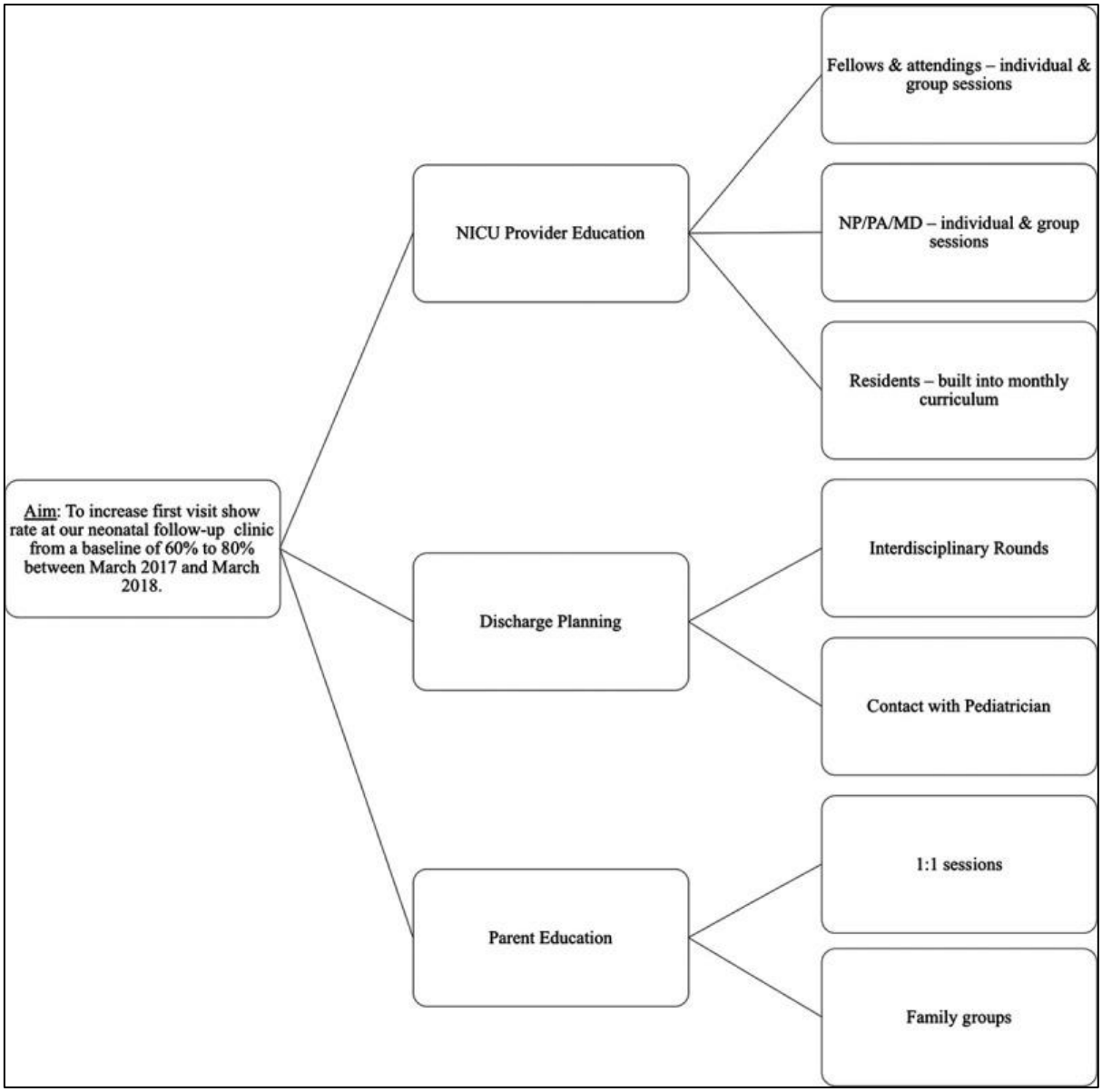
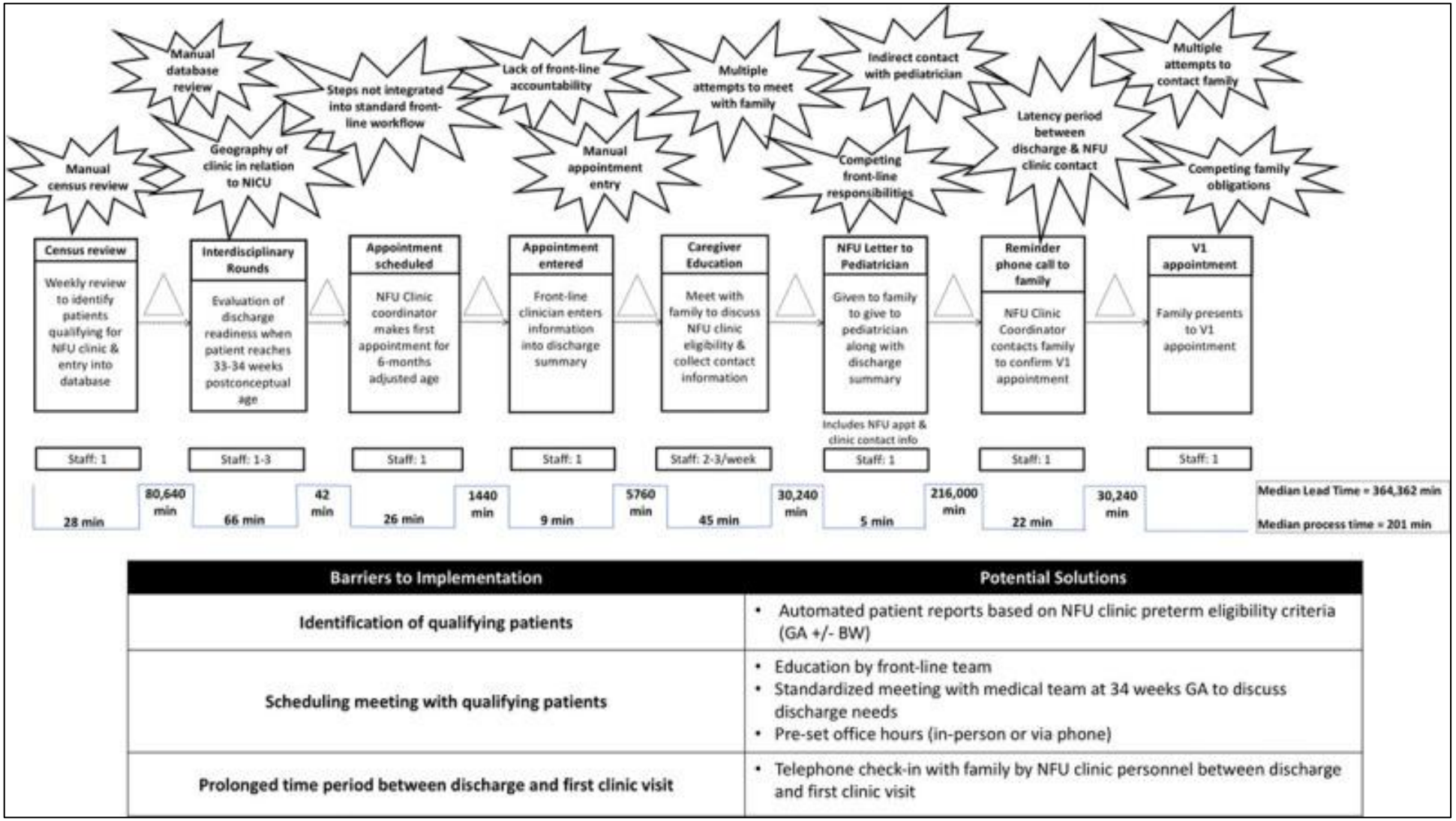



*Figure 40: Key drivers for improving follow-up; figure cited from Brachio et al., 2020 [5]*




| Barriers to Implementation | Potential Solutions |
|---|---|
| **Identification of qualifying patients** | • Automated patient reports based on NFU clinic preterm eligibility criteria (GA +/- BW) |
| **Scheduling meeting with qualifying patients** | • Education by front-line team<br>• Standardized meeting with medical team at 34 weeks GA to discuss discharge needs<br>• Pre-set office hours (in-person or via phone) |
| **Prolonged time period between discharge and first clinic visit** | • Telephone check-in with family by NFU clinic personnel between discharge and first clinic visit |

*Figure 41: Value-stream diagram displaying workflow, barriers, and solutions to improving neonatal follow-up; figure cited from Bachio et al., 2020 [349]*

## 25.4 Impact of Covid-19 Pandemic on Neurodevelopmental Follow-Up

*The DPhil research work was carried out during the peak of the Covid-19 pandemic when neurodevelopmental follow-up services were severely impacted. Most neurodevelopmental follow-up appointments were cancelled, and even when they started to become available, most parents were reluctant to enter the hospital with their child(ren). Therefore, the relevance of this section is to put the thesis in context and showcase some of the peculiarities of the era and how neurodevelopmental follow-up services needed to be adapted to suit those times.*

Neurodevelopmental follow-ups are designed to be offered mainly in person, where the child and their caregiver(s) visit the health facility to meet the follow-up team [195, 201]. During the visits, the child interacts with the care team, who examine and observe the child through standardised tests to determine the trajectory of development and to identify signs of any possible developmental deficits. Where access to care barriers exists, such as geographic barriers due to proximity to the health facility, or barriers such as the Covid-19 pandemic, alternative methods to the in-person assessment become essential [195, 216, 350, 351].

During the Covid-19 pandemic, healthcare services, people's health-seeking behaviour and demand for healthcare were impacted [352]. According to the Clinical Practice Research Datalink[xcv] and the General Practice Appointments Data[xcvi], consultations sharply declined when the UK went into lockdown in March 2020. The health system was overly stretched to meet usual healthcare delivery demands and the additional Covid-19 and related cases [216]. Mitigation measures were instituted to curb the spread of the virus. For example, health staff were redeployed from departments outside the usual emergency care team to be at the frontline of fighting the pandemic. There was an enhanced infection prevention and

[xcv] https://cprd.com
[xcvi] Appointments in General Practice - NHS Digital Appointments in General Practice - NHS Digital

control protocol, and some clinical appointments were postponed or cancelled. Due to the requirement for social distancing, many services reduced footfall or limited the number of visitors allowed per square metre in public places such as hospitals. Switzerland also recorded a similar trend in the decline of patient consultations from March 2020 following the stay-at-home announcement and measures by Switzerland's federal government to curb the spread of the virus [353].

Disruption of developmental services [354] produced cancellations and postponement of appointments, causing delays to interventions where needed or loss of neurodevelopmental follow-up services [355]. Alternative approaches to follow-up were tried, such as parent-led versus health worker-led NDAs and virtual compared to in-person assessments [223], which were often unfamiliar to the child and family. Many health workers were infected with the virus or became contact cases and, therefore, had to be in isolation or quarantine. Average staff absence rates increased in England between March and December 2020, coinciding with the period of the pandemic's peak[xcvii]. Increased working hours, demands and stress at work contributed to a 5-year record-low decline in staff morale, as observed in the 2021 NHS staff survey[xcviii] [352]. These scenarios impacted staff availability, hospital capacity and flexibility for emergency and routine services such as neurodevelopmental follow-up for children born preterm [354].

### 25.4.1 Patient-led behaviour changes on health seeking and demand for services

Health-seeking behaviour changes were observed during the pandemic's peak when patients forwent seeking treatment or non-emergency services [352]. The decline in demand for health services was partly due to the fear of increasing one's risk of exposure to the virus

[xcvii] https://www.england.nhs.uk/statistics/statistical-work-areas/covid-19-hospital-activity/
[xcviii] https://www.nhsstaffsurveys.com/static/1f3ea5c952df62a98b90afcf3daa29ac/ST21-National-briefing.pdf

while in the hospital with other Covid-19 patients or exposed cases. People also felt a social responsibility to postpone hospital visits so as not to overwhelm the already burdened NHS in the early days of the pandemic. Legal regulations and guidance limiting people's movements were also instituted to control the spread of the virus [353]. Thus, the demand for, and provision of, health services was driven by health system challenges, individual preferences, and regulations to curb the spread of the virus.

## 25.5 Frameworks and Concepts

### 25.5.1 Cross-sectional survey: the pros and cons

A cross-sectional survey, also known as a transverse study, prevalence study or cross-sectional analysis, is a type of observational research method whereby data are collected and analysed across a population of interest at a specific time [356, 357]. It is the most relevant research design for determining the prevalence of disease or health outcomes [358] when conducting validation or reliability studies and assessing attitudes and knowledge among groups such as health workers or patients [357, 359]. Data collection may be repeated at different times, and respondents may not be the same each time [360, 361].

Cross-sectional studies may be descriptive, for example, where the study aims to determine disease prevalence or to understand attitudes or knowledge. When employed for analytical studies, the aim may be to understand relations and associations between variables. Cross-sectional studies can be helpful when seeking to uncover trends or characteristics in a population [357]. Multiple variables such as gender, profession, and location may be studied simultaneously.

Cross-sectional studies are relatively quicker to conduct and less expensive than longitudinal studies because data collection occurs at only one point, i.e. the same or similar subjects are not followed over a long period. Furthermore, using a cross-sectional study approach allows

researchers to collect data from a larger sample population and on multiple variables simultaneously. Results from a cross-sectional analysis can provide initial correlations and the basis to catalyse future research or to generate further research hypotheses [360].

The downsides to using a cross-sectional study are that depending on the timing of the study or data collection, the observed characteristics may not be representative of the general population, and the experiences of the sampled population may bias the characteristics of the general population. This may be the case when a survey is conducted shortly after an intervention whose impact is seen in the long term. Cross-sectional studies may not be relevant to establish trends over a longer period, and cannot be used to describe the cause and effect between variables under study [356].

### 25.5.2 Framework for reporting of Survey: A Consensus-Based Checklist for Reporting of Survey Studies (CROSS)

Using a transparent and accurate reporting guideline in research promotes accountability, enhances the reproducibility and quality of findings, and should lead to a greater impact for the intended beneficiaries [362]. Reporting guidelines or checklists help the researcher to identify the most relevant criteria to be included in the report [363]. Checklists and guidelines such as *The SUrvey Reporting GuidelinE* (SURGE) [363], *The Checklist for Reporting Results of Internet E-Surveys (CHERRIES)* [300] and *a Consensus-Based Checklist for Reporting of Survey Studies* (CROSS) [364] are well known for reporting surveys [364]. These checklists provide resources for designing, conducting, and reporting survey studies, ensuring reliability, reproducibility, and transparency at each stage of the survey study. Their recommendations can be applied to both web and non-web-based surveys.

The CROSS Checklist[xcix] [364] is a 19-section checklist with 40 sub-items that provides recommendations for all standard parts of a scientific paper: Title and abstract, methods, results, discussion, and additional sections such as acknowledgement of funding sources conflict of interest statement, and acknowledgement of contributors. The reporting guideline for this study follows the CROSS-Checklist recommendations.

## 25.6 Study aim

The hospital survey described in this chapter aimed to understand the spectrum of neurodevelopmental follow-up practices in neonatal units in the UK and Switzerland. By highlighting follow-up practices that have worked well and areas for improvement in conducting neurodevelopmental follow-ups in these two countries, findings from the survey can inform healthcare priorities for improving services for children born preterm in these two countries and other settings.

A secondary aim was to understand the extent of Covid-19-related disruptions, changes in practices or opportunities for neurodevelopmental follow-up in the UK and Switzerland.

xcix https://www.researchgate.net/publication/353522424_Checklist_for_Reporting_Of_Survey_Studies_CROSS

# 26 Methods

## 26.1 Study design

The hospital survey is a cross-sectional study exploring neurodevelopmental practices in the UK and Switzerland. The reporting of this chapter has been structured according to the recommendations of the Checklist for Reporting of Survey Studies (CROSS) guideline by Sharma et al., 2021 [364].

### 26.1.1 Study setting and participants

The survey was conducted in three cycles in the two countries. The survey tool used for the three surveys was fundamentally the same, with minor adaptations to suit the context and group being assessed.

The first UK survey was open to all staff performing neurodevelopmental follow-ups (e.g. consultant neonatologists, paediatricians, occupational therapists, and physiotherapists) from April to August 2019. All the 196 neonatal units in the 15 neonatal networks[c] in the UK were eligible for the survey (Table 24). Neonatal network refers to the geographical categorisation of hospitals that work together to care for preterm babies and sick newborns.[ci]

The second survey was conducted in the nine Level-III Swiss perinatal centres with (neuro)developmental units: Geneva, Lausanne, Bern, Basel, Zurich, Luzern, Lausanne, Thurgau, and Munsterlingen, between September 2020 to February 2021. The survey was hosted on *Microsoft Forms*.

The third survey was the consultants' survey in the UK (UK Survey 2). This ran from May to November 2021 and focused primarily on consultants, a group of experienced care

[c] London neonatal network is split into three clinical networks
[ci] https://www.bapm.org/pages/19-neonatal-networks

providers identified in the first survey as the specialist group mainly conducting neurodevelopmental follow-ups of children born preterm in the UK.

A second survey was undertaken during the Covid-19 pandemic to learn how the pandemic had impacted neurodevelopmental follow-up services and which alternatives to face-to-face assessments were considered or offered. In addition, the first survey indicated that (neonatal) consultants are the main cadre of staff who perform the neurodevelopmental assessments. Therefore, the survey sought to understand consultants' views on extending these assessments to all children born preterm, including the MLPTs.

The UK survey 2 was hosted on *Qualtrics* platform.

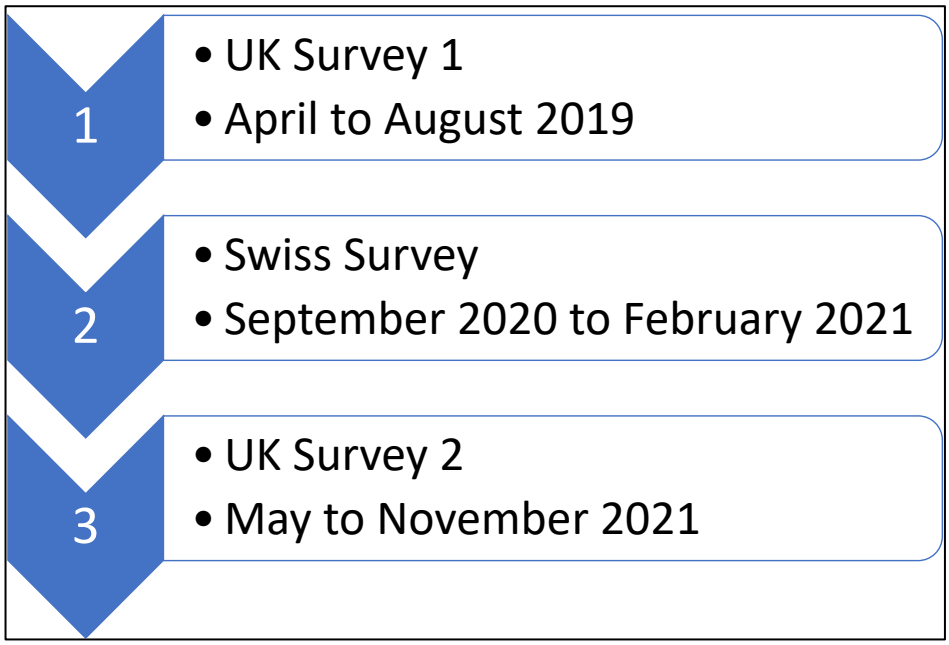



*Figure 42: Survey recruitment cycles for UK and Switzerland*

| Neonatal Networks in the UK |
|---|
| East Midlands |
| East of England |
| North West |
| London: North Central & East |
| London: Northwest |
| London: South |
| Kent Surrey and Sussex |
| Scotland |
| Northern |
| West Midlands |
| South West |
| Northern Ireland |
| Thames Valley and Wessex |
| Wales |
| Yorkshire & Humber |

*Table 24: Neonatal networks invited to participate in the survey*

### 26.1.2 Survey instrument

A set of questions to identify the neurodevelopmental follow-up patterns was designed with input from a team of neonatologists and clinicians familiar with the follow-up pathways for children born preterm in the UK and Switzerland. After the first UK survey (UK survey-I), the questionnaire[cii] was slightly modified to suit the Swiss context (Swiss survey)[ciii] and the consultants' survey (UK survey-II)[civ]. The revisions were aimed at making the questionnaire more targeted and comprehensive in addressing the research questions. It investigated parameters such as the availability of a protocol for NDAs, preferred tools for assessment, eligibility criteria for follow-up, frequency of assessments, and specialities and seniority of staff who perform the assessments.

[cii] UK Survey-I: https://www.surveymonkey.com
[ciii] Swiss survey: https://forms.office.com/Pages/ResponsePage.aspx?id=G96VzPWXk0-0uv5ouFLPkdVdlyto9GRKmJhtauk0JlxUMk9WQkQySVVBMVAyQlpIQ1lKS1Y1NkxFMi4u&wdLOR=cFFE2CF1C-4013-4B44-9165-A5FC965702A5
[civ] UK Survey-II: https://wrh.qualtrics.com/jfe/form/SV_0AujTVHy6k4zqqG

### 26.1.3 Survey pretesting and administration

The questionnaire was designed and pretested between December 2018 and March 2019. In the first round of the survey, the questionnaire was hosted on *SurveyMonkey*[cv] for UK survey-I participants. A survey weblink was obtained from the platform and emailed to all neonatal network leads in the UK. A snowballing approach was adopted so the leads would forward the link to staff involved in neurodevelopmental follow-up.

### 26.1.4 Study preparation: UK and Switzerland recruitment

Several activities were undertaken to prepare for the survey, including internet searches to identify eligible facilities and contacts of staff involved in neurodevelopmental follow-up. In the first survey, the link was shared with neonatal leads to forward to staff who perform neurodevelopmental follow-up, an approach similar to Marcroft et al's (2023) survey of neurodevelopmental follow up in UK neonatal services [365]. To increase the reach of eligible staff for the survey, hospitals were further contacted by phone to identify the neurodevelopmental follow-up leads in order to send an invitation to participate in the survey. The decision to contact hospitals to inquire about the neurodevelopmental follow-up lead or focal person was discussed with my supervisor, Dr Frances O'Brien, a Consultant Neonatologist and the neurodevelopmental follow-up lead at Oxford University Hospitals.

Due to the many person-hours invested and still required to complete a database for the survey, a research assistant was recruited to help retrieve contacts of eligible persons in all participating hospitals in the UK. A study guideline was developed to standardise how facilities should be contacted and streamline recruitment. A data tracking template (snapshot in Figure 43) was designed to collect contact information of hospitals and eligible staff.

[cv] https://www.surveymonkey.com

| DPHIL RESEARCH: UK NEONATAL NETWORK CONTACTS FOR HOSPITAL SURVEY- MARCH 2021 | | | | | | | |
|---|---|---|---|---|---|---|---|
| SNU | | | | | | | |
| Hospital Name | Address with postcode | Direct contact number (from website) | Contact Person (Neonatal lead for neurodevelopmental | Email (to send survey) | Neontal Unit Address (corrected- verified during calls) | Direct contact number (corrected) | Comment/Note |

*Figure 43: Data collection template for hospital information*

The direct one-on-one calls to eligible hospitals to source contacts proved time intensive and less effective in building up the recruitment database. Based on the design of an unrelated study (*Oxygen Targets and Caffeine Use Study*), a new approach was adopted to consult a paid service called *SpecialistInfo.*[cvi] The service is an online medical directory provider with a large database of consultants, GPs, hospitals, and surgeries to source for contacts of prospective participants.

The study's recruitment approach for the UK participants is described in Figure 44.

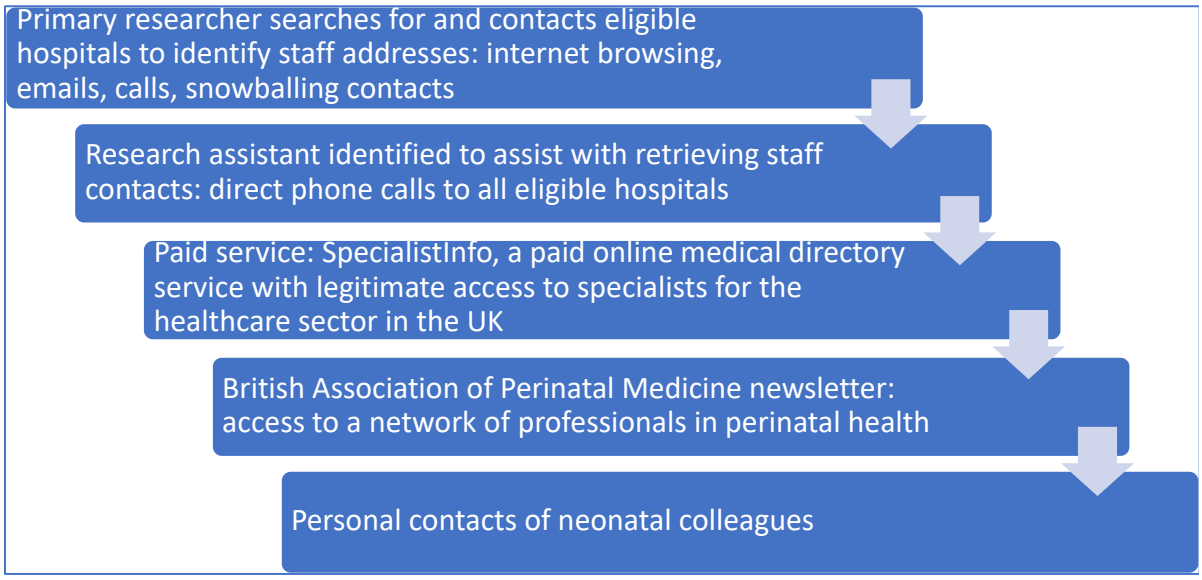



*Figure 44: Approaches to recruiting UK survey participants*

In Switzerland, eligible staff were contacted directly by one of the network members, who acted as a research collaborator.

[cvi] https://www.specialistinfo.com

#### *26.1.4.1 Study preparation*

The survey was extended to neonatal units in the UK and Switzerland, where the DPhil study was carried out to ensure that findings could be corroborated with other aspects of the DPhil research, including the parent survey and interviews and the developmental assessments of the study participants.

### 26.1.5 Ethical considerations

The survey was carried out as a service delivery activity with the neonatal unit at the JRH, and with developmental follow-up centres in Switzerland. Therefore, the surveys did not require ethical approval at either site.

### 26.1.6 Statistical analysis

Survey results pooled from *SurveyMonkey, Microsoft Forms, and Qualtrics* were downloaded for data cleaning into Microsoft Excel *(Version 16.66.1 and* exported into SPPS *(IBM SPSS Statistics Version 28.0.0.0)* for analysis. Descriptive statistics were used to summarise the findings. Qualitative responses were categorised into themes using thematic content analysis [303] and/or incorporated into the quantitative dataset as appropriate.

#### *26.1.6.1 Data cleaning*

The data cleaning protocol for the parent survey in Chapter 3 was adapted for the hospital survey (Appendix VII). The analysis did not include blank survey entries. Entries were considered if the IP addresses were the same, but the staff roles of the respondents were different.

# 27 Results

## 27.1 Respondent characteristics

The UK survey was run at two different time points. The first survey was sent to the neonatal leads in all 15 neonatal networks (Table 24) for the link to be forwarded to all UK neonatal units.[cvii] The second UK survey was sent to neonatal consultants in the UK via email and neonatal personnel through the BAPM newsletter. Neonatal consultants were recruited from the *SpecialistInfo* if their email addresses were registered in the database.

## 27.2 Descriptive results

### 27.2.1 UK Survey-I round 1

At the end of the first survey, 79 responses were recorded and have been used in the UK survey-I analysis.

#### *27.2.1.1 Protocol for follow-up*

All 79 respondents noted that their hospitals offer neurodevelopmental follow-up for children discharged home from their institutions, either directly in their facilities or at another facility. Seventy-four out of the 79 units (93.7%) had a protocol for their follow-up.

#### *27.2.1.2 Neurodevelopmental assessments: criteria for eligibility*

The main criteria for offering a follow-up to a child were based on the GA (76/79 responses, 97.2%), clinical diagnosis (77/79 responses, 97.4%) and birth weight (63/79 responses, 79.7%). A breakdown of the GA groups offered routine follow-up is presented in Figure 45. The VPT group are mostly prioritised for follow-up (76/79), followed by the MPT (33/79) and LPT (11/79) groups.

[cvii] https://www.infantjournal.co.uk/nicu_list.html

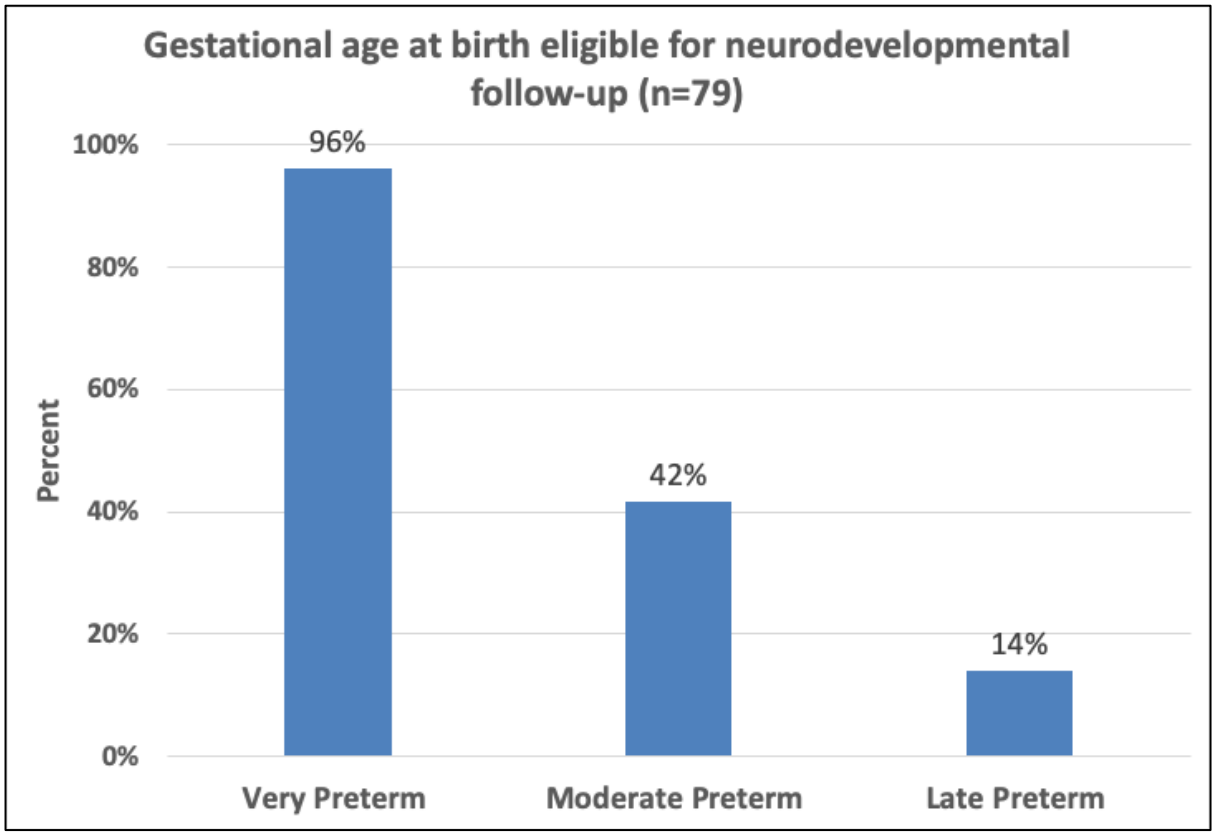



*Figure 45: Eligibility criteria - gestational age (weeks) at birth as a cut-off for neurodevelopmental follow-up in the UK.*[cviii]

#### *27.2.1.3 Tools for neurodevelopmental assessments*

The BSID-III is the most commonly used neurodevelopmental follow-up tool (52/79 responses, 66%). Other tools mentioned include the Ages and Stages Questionnaire, Alberta Infant Motor Scale, Amiel-Tison, Developmental checklist, and Brunet Lezine Scale.

[cviii] Multiple responses were allowed.

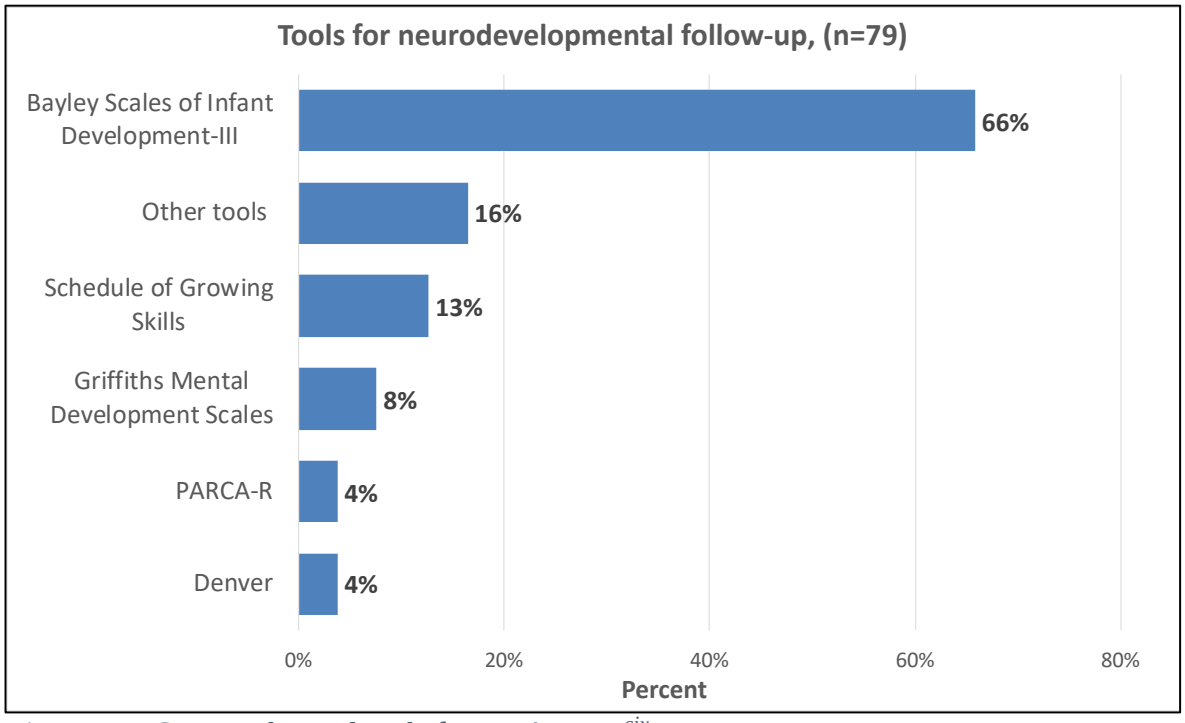



*Figure 46: Commonly used tools for NDAs, UK.*[cix]

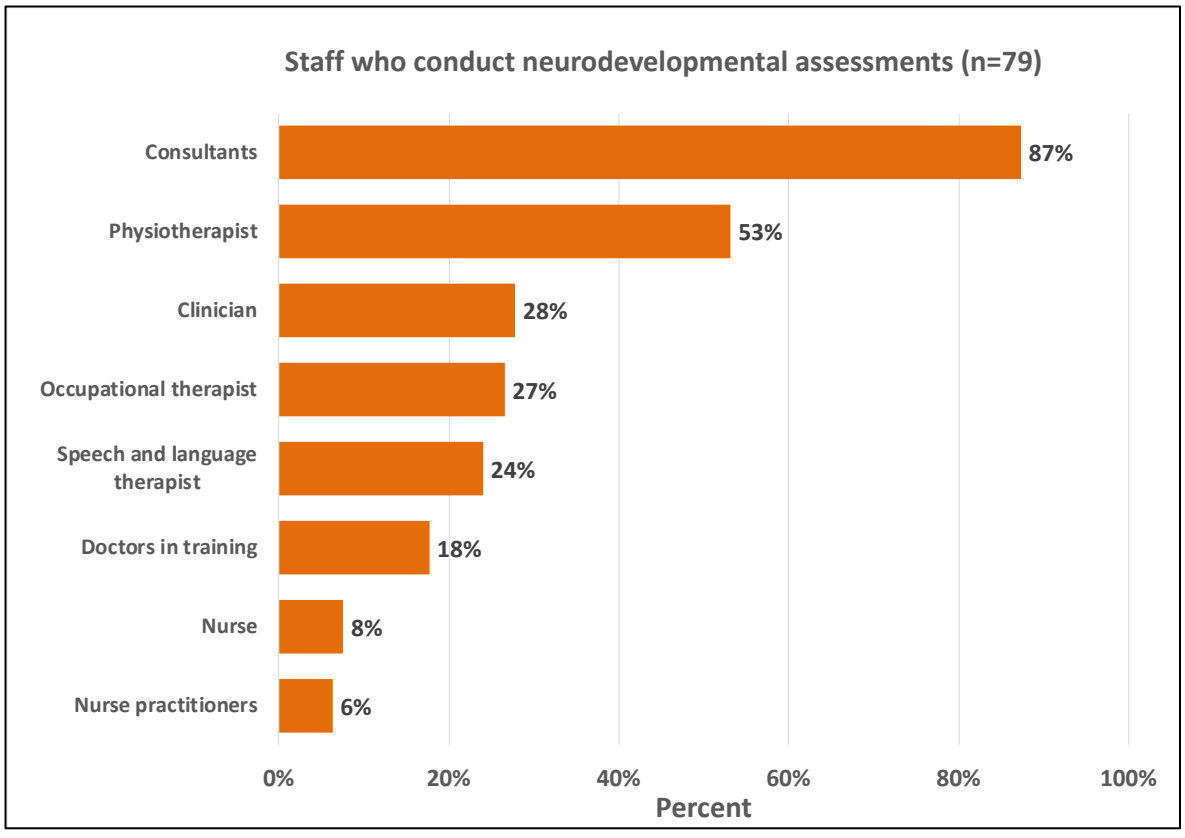



*Figure 47: Staff who conduct NDAs in the UK*[cx]

[cix] Multiple responses were allowed
[cx] Multiple response were allowed

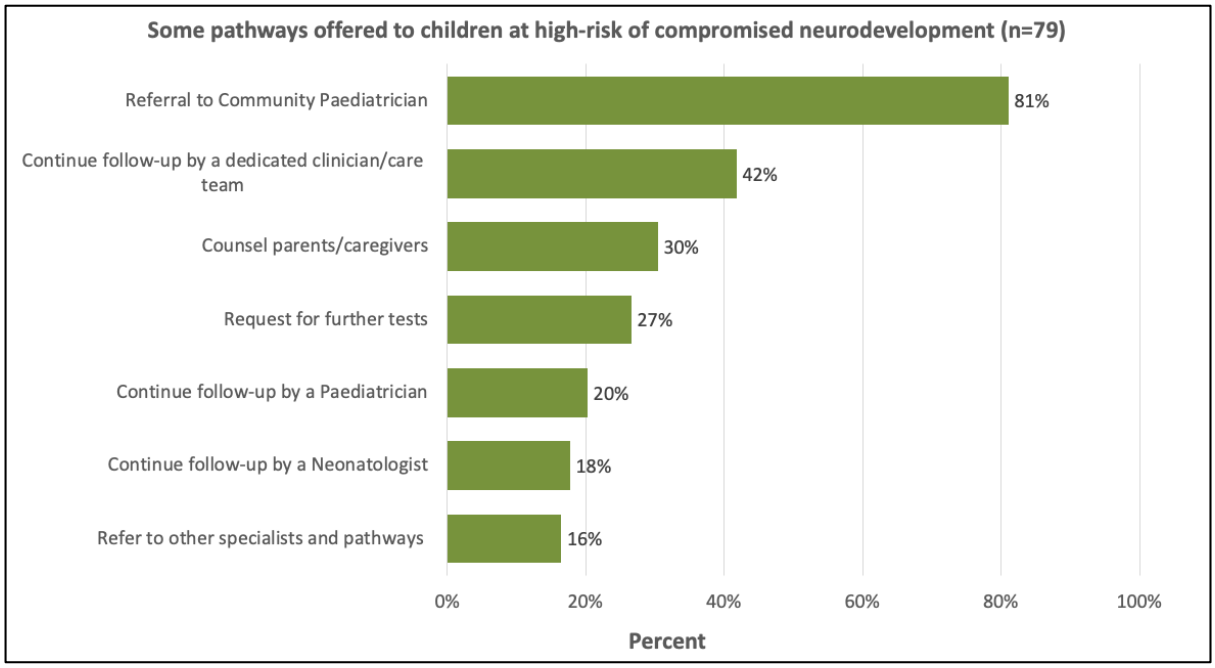



*Figure 48: Referral pathways offered to children at risk of compromised neurodevelopment*[cxi]

[cxi] Multiple responses were allowed

### 27.2.2 UK Survey-II: Consultants

At the end of the survey period in November 2021, 51 responses were recorded in *Qualtrics*, out of which 39 have been included in the analysis. The reason for excluding 12 entries was that the survey was logged without any answers or responses to the survey questions. The survey fields were all empty except for one respondent who provided the basic information about their name, country and role at the hospital (information excluded from analysis).

Out of the 39 responses that have been included in the UK survey-II analysis, (30/39, 77%) answered all questions in the survey (100% completion); (4/39; 10%) completed up to 79% of the survey questions, and (5/39; 10%) of respondents answered 32% of the survey questions.

### 27.2.3 Overview of survey responses

Responses from UK survey-II are presented in two parts: the first section describes the background characteristics of respondents, which includes their completion rate for the survey, the country in which they work, the neonatal level of their facility, and their professional role (Table 25).

The second section (Table 26) gives an overview of the neurodevelopmental practices, which include the criteria of eligibility for neurodevelopmental follow-up staff who conduct NDAs (Figure 49 and Table 27), professionals involved in follow-up referrals and interventions for children identified at high risk of compromised neurodevelopment (Figure 50), tools for assessments (Figure 51), age at which assessments are offered (Figure 52 and Figure 53) and when they are discharged from follow-up.

#### *27.2.3.1 Background characteristics*

Most respondents for UK survey-II (35/39, 90%) were consultant neonatologists or consultant paediatricians who were recruited through the *SpecialistInfo* database and BAPM newsletter. Survey responses have been anonymised; therefore, it is impossible to determine whether the consultants responded via the *SpecialistInfo* database or the BAPM newsletter recruitment drive. The remaining four respondents identified as a Physiotherapist (2/39, 5%), Specialty and Associate Specialist (SAS) doctor (1/39, 3%) or another profession (1/39, 3%).

Neurodevelopmental practices in all four UK countries were reflected in the survey, with England recording the highest representation of health workers (79%) and Wales the least (1/39, 3%). Experiences of all three levels of neonatal care were reported in the survey; the respondents were mainly working in NICUs (21/39, 54%) and a few in a special care baby unit (3/39, 8%).

| UK Survey-II Summary Table | | |
|---|---|---|
| **Hospital Survey: Background Characteristics (n=39)** | | |
| **Countries represented** | **Frequency** | **Percent** |
| England | 31 | 79 |
| Northern Ireland | 4 | 10 |
| Scotland | 3 | 8 |
| Wales | 1 | 3 |
| | | |
| **Neonatal Level** | **Frequency** | **Percent** |
| Level 1 - Special Care Baby Unit – (SCBU) | 3 | 8 |
| Level 2 - Local Neonatal Unit – (LNU) | 15 | 38 |
| Level 3 - Neonatal Intensive Care Unit – (NICU) | 21 | 54 |
| | | |
| **Respondent roles** | **Frequency** | **Percent**[cxii] |
| Consultant Neonatologist | 24 | 62 |
| Consultant Paediatrician | 11 | 28 |
| Other (please specify) | 1 | 3 |
| Physiotherapist | 2 | 5 |
| SAS Doctor | 1 | 3 |

*Table 25: Hospital UK Survey-II: Background Characteristics*

[cxii] Response percentages may exceed 100% due to rounding.

#### *27.2.3.2 Overview of Neurodevelopmental Follow-up*

The decision to offer neurodevelopmental follow-up to a child is based on criteria[cxiii], which aligns with the NICE guideline for enhanced developmental surveillance at 2 years of age [27]: GA at birth, birth weight and/or presenting clinical diagnosis. More than one response could be selected according to the hospital's practices. GA (36/39, 92%) and clinical diagnosis (35/39, 90%) were the predominant reasons for offering neurodevelopmental follow-up. A child could be offered neurodevelopmental follow-up assessment if their birth weight was <1000g (15/39, 38.5%), or <1500g (15/39, 38.5%), or if their weight was in the <10$^{th}$ centile at birth[cxiv] (6/39, 15%).

Clinical diagnoses that inform the decision to offer children neurodevelopmental follow-up include hypoxic ischaemic encephalopathy, neonatal bacterial meningitis, brain lesion (intraventricular haemorrhage) and other major cerebral anomalies. These clinical conditions may interfere with normal brain development.

[cxiii] The survey asked about the general criteria neonatal units apply in offering a follow-up to a child according to birth weight, gestational age and clinical diagnosis. Respondents could select multiple responses. It is unclear if the decision to offer follow-up to a particular child is based on a single or a combination of criterion/a.

[cxiv] Criteria for ascertaining low birth weight was not specific to a particular monitoring chart or tool used.

| Overview of Neurodevelopmental Follow-up Practices in the UK[cxv] (n=39) | | |
|---|---|---|
| **Neurodevelopmental Follow-up** | **Frequency** | **Percent** |
| Hospital offers neurodevelopmental follow-up | 36 | 92 |
| Preschool assessment offered | 2 | 5 |
| | | |
| **Criteria for Neurodevelopmental Follow-up** | **Frequency** | **Percent** |
| GA | 36 | 92 |
| Birth weight | 27 | 69 |
| Clinical diagnosis | 35 | 90 |
| **Gestational ages offered Neurodevelopmental Follow-up** | **Frequency** | **Percent** |
| Very Preterm (<32 weeks' gestation) | 30 | 77 |
| Moderate Preterm (32+0 to 33+6 weeks' gestation) | 8 | 21 |
| Late Preterm (34+0 to 36+6 weeks' gestation) | 2 | 5 |
| Term babies (>37 weeks' gestation) | 2 | 5 |
| **Birthweight groups offered Neurodevelopmental Follow-up** | **Frequency** | **Percent** |
| Extremely Low Birth Weight (ELBW < 1000g) | 15 | 38 |
| Very Low Birth Weight (VLBW < 1500g) | 15 | 38 |
| Low birth weight (<2500g) | 2 | 5 |
| Birth weight (<10$^{th}$ centile for GA) | 6 | 15 |
| **Clinical diagnoses offered Neurodevelopmental Follow-up** | **Frequency** | **Percent** |
| Hypoxic ischaemic encephalopathy | 30 | 77 |
| Neonatal bacterial meningitis | 28 | 72 |
| Brain lesion (e.g., Intraventricular haemorrhage) | 26 | 67 |
| 'Other' major cerebral anomaly | 26 | 67 |
| Other diagnoses | 21 | 54 |

*Table 26: Eligibility criteria for neurodevelopmental follow-up practices, UK Survey-II*

#### *27.2.3.3 Health personnel who provide neurodevelopmental follow-up*

Participants were provided with five options (identified from the first survey) to choose the most common specialist groups that typically perform NDAs. There was an additional option for 'other' to accommodate additional specialist groups. Follow-up is performed mainly by consultant neonatologists and paediatricians (16/31, 52%), occupational therapists and physiotherapists (4/31, 13%) and other cadres (11/31, 35%).

[cxv] Multiple responses were allowed.

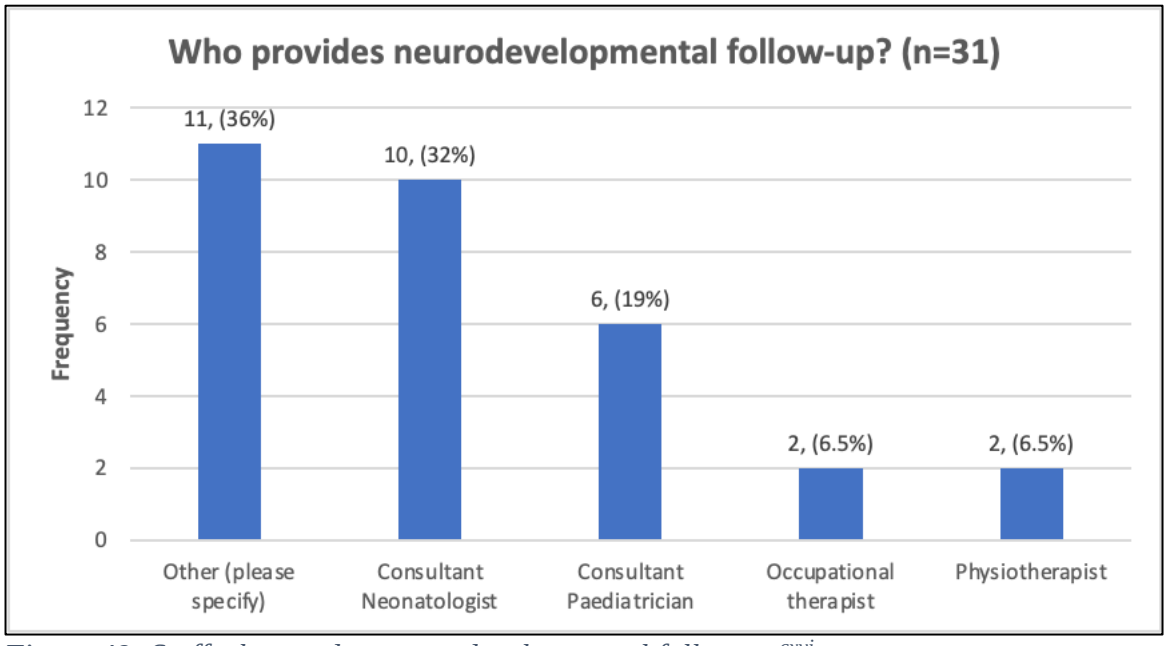



*Figure 49: Staff who conduct neurodevelopmental follow-up*[cxvi]

The 'Other' personnel who conduct NDAs (taken from the narrative information) are shown in the table below:

| |
|---|
| "Associate specialist in neonatology and neurodisability, physiotherapist and speech and language therapist " |
| "Combination of consultant neonatologist, physiotherapist and consultant neonatal neurologist" |
| "Community staff grade" |
| "Consultant paediatrician and physiotherapist" |
| "Joint neonatologist and neonatal physiotherapist" |
| "Multidisciplinary team (MDT) neonatal team including consultants, occupational therapist, physiotherapist and nurses" |
| "MDT of neonatologist, physio, speech language therapist (SLT)" |
| "Neurodevelopmental specialist team plus neonatologist" |
| "Relevant specialty involved" |
| "Speech and language therapist" |
| "We do have one hour per week of physiotherapy review in NICU; our babies who need physiotherapy input following discharge would be referred to as OPD". |

*Table 27: Other personnel who conduct neurodevelopmental follow-up*

[cxvi] Response percentages may not add up to 100% due to rounding.

#### *27.2.3.4 Onward care for children identified as at higher risk of compromised neurodevelopment*

The multidisciplinary team of health workers involved in follow-up and providing interventions for children at risk of compromised neurodevelopment includes those presented in Figure 50

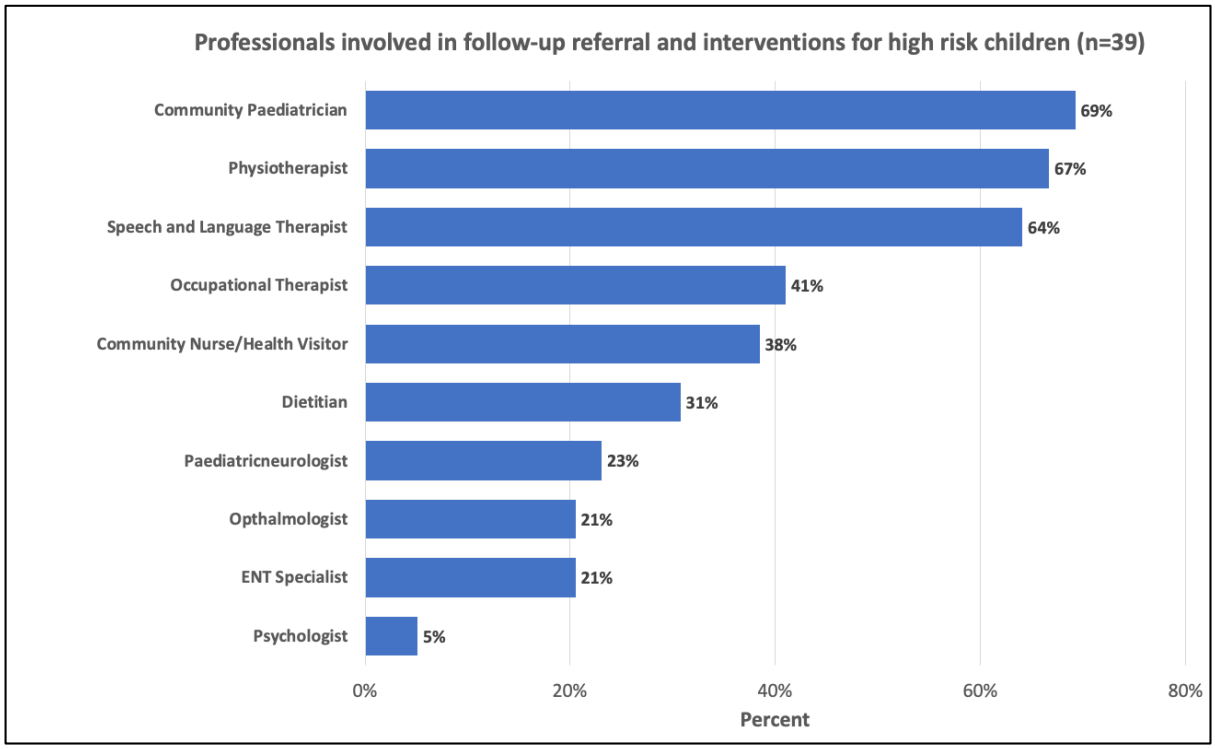



*Figure 50: Professionals involved in follow-up referral and interventions for children at high risk of compromised neurodevelopment*

### 27.2.4 Tools for neurodevelopmental assessment

Several neurodevelopmental follow-up tools are used in the UK. The most commonly used, according to the survey, is the Bayley Scales of Infant Development-III, followed by PARCA-R, and others such as the Schedule of Growing Skills, Developmental Checklist, Ages and Stages, and Griffiths Mental Development Scales.

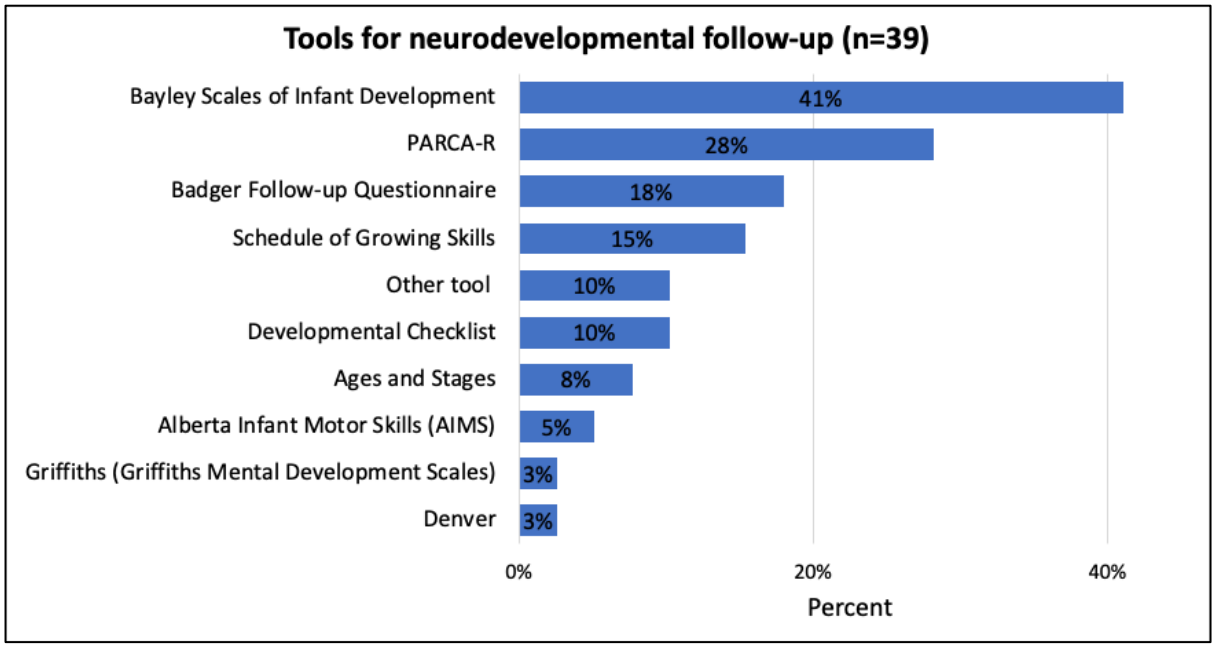



*Figure 51: Commonly used tools for conducting NDAs according to survey-2 respondents*

#### *27.2.4.1 Age of assessment and discharge and frequency of assessments*[cxvii]

NDAs were primarily offered at 24 months (28/39, 72%); during the same period, most children are discharged from the follow-up service (26/29, 90%). Most respondents (22/30, 73%) indicated that their facilities offer assessments more than four times to a child. In contrast, some children receive up to three assessments (3/30, 10%), two assessments (1/30, 3.3% or only one assessment (4/30, 13%).

Figure 52 shows an overview of follow-up assessments chronologically and Figure 53 shows the Pareto of age at which follow-up assessments are prioritised.

[cxvii] Changing denominators reflect the differing response rates to the survey questions.

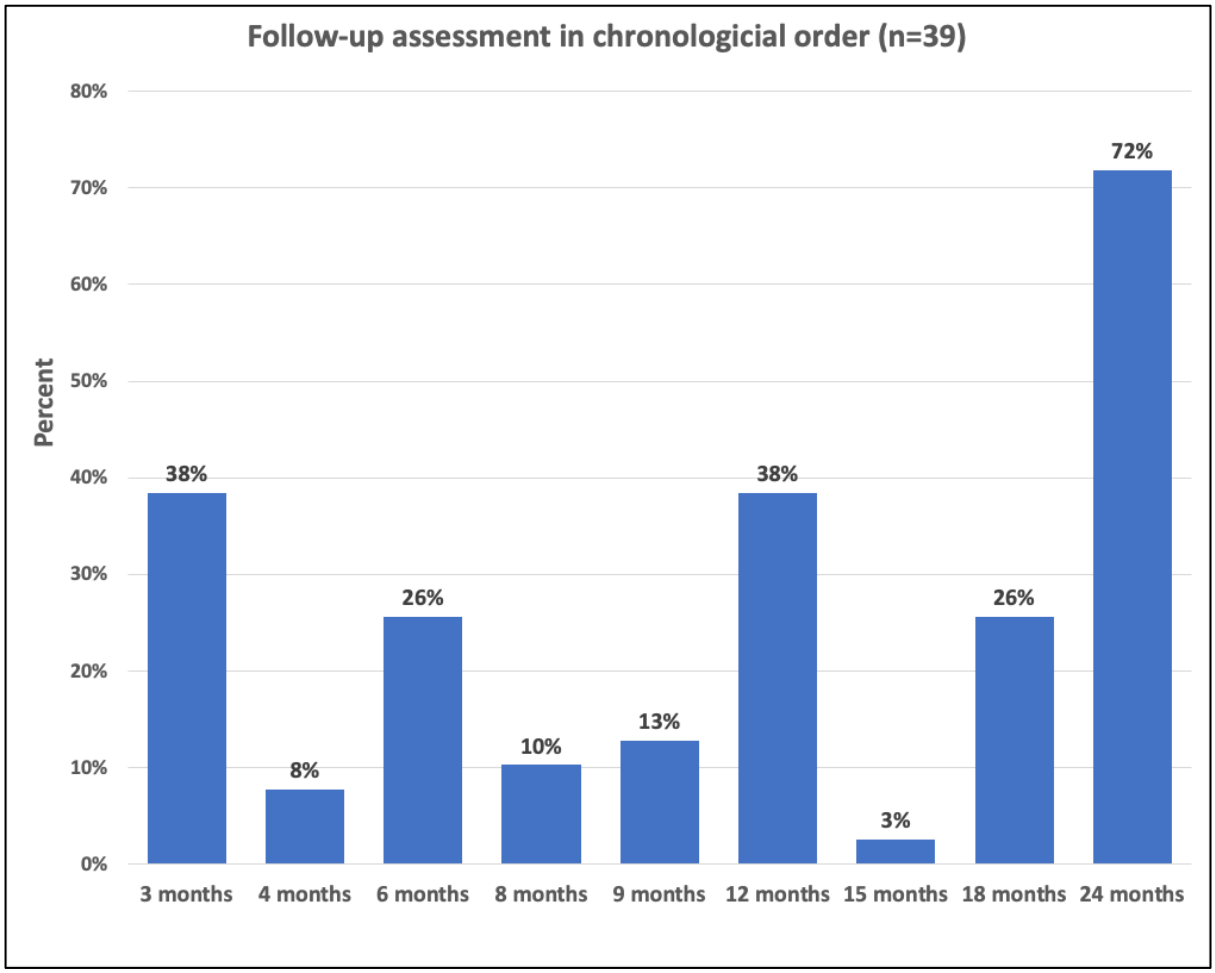



*Figure 52: Follow-up assessment in chronological order*

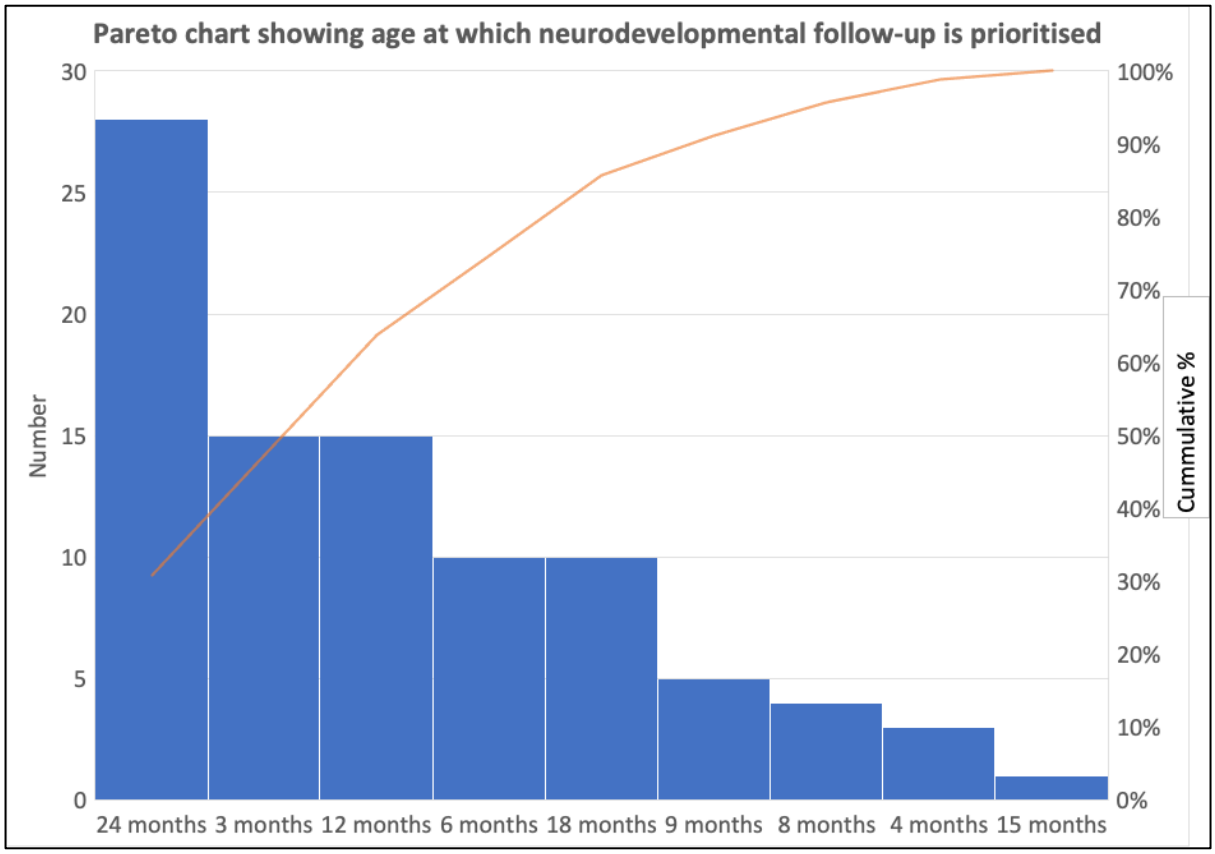



*Figure 53: Age at which neurodevelopmental follow-up is offered*

### 27.2.5 Neurodevelopmental Follow-up for children born MLPT

In the second UK survey-II, the following question was asked: "*Would you recommend that all children born moderate (32+0 – 34+6 weeks) to late preterm (34+0 – 36+6 weeks) be offered routine neurodevelopmental follow-up at 2 years of age?"*. Out of the 39 responses used in the survey-II analysis, five respondents did not answer the question (5/39; 13%), and out of the 34 who did, (27/34; 79%) did not recommend offering MLPT children routine neurodevelopmental follow-up, while (7/34; 21%) responded *'yes'* to the question.

According to the survey, the professional mix of the respondents who did not recommend routine neurodevelopmental follow-up to MLPT children were: consultant neonatologist (16/27), consultant paediatrician (8/27), physiotherapist (2/27) and one *other*, not specified (1/27). The respondents who recommended '*yes'* to extend neurodevelopmental follow-up

to all MLPT children were consultant paediatrician (2/7), consultant neonatologist (4/7) and SAS doctor (1/7) who work in level II and III hospitals in England and Northern Ireland.

### 27.2.6 Impact of Covid-19 on Neurodevelopmental Follow-up

During the peak of the pandemic (May-September 2021), an additional objective was included in the survey to understand the extent of disruption on neurodevelopmental follow-up services. Respondents were asked to express their agreement on a 5-point Likert scale of the extent of any disruption, if applicable, or other follow-up alternatives where face-to-face appointments could not be offered. The survey asked questions about attendance to neurodevelopmental follow-up visits, modalities of remote assessments tried (e.g., via phone or video call), and whether neurodevelopmental follow-up services had been halted due to the pandemic or otherwise.

In summary, the pandemic affected neonatal units differently and their ability to offer neurodevelopmental follow-up services as usual or through alternative approaches. For example, less than a tenth of participants (7%) indicated they *somewhat* agreed to an increase in attendance to neurodevelopmental follow-up, while 93% disagreed or were indifferent to an increase in neurodevelopmental follow-up. Nearly half of the respondents (48%) indicated that neurodevelopmental follow-up attendance had not changed, while about a quarter (24%) (strongly) disagreed; 47% (strongly) agreed that the pandemic had not affected their follow-up services, and 43% (strongly) disagreed to offering neurodevelopmental follow-up appointments as usual, and 10% were indifferent to the pandemic affecting their services. The questions and responses about the impact of the Covid-19 pandemic on neurodevelopmental follow-up are presented in Figure 54 below.

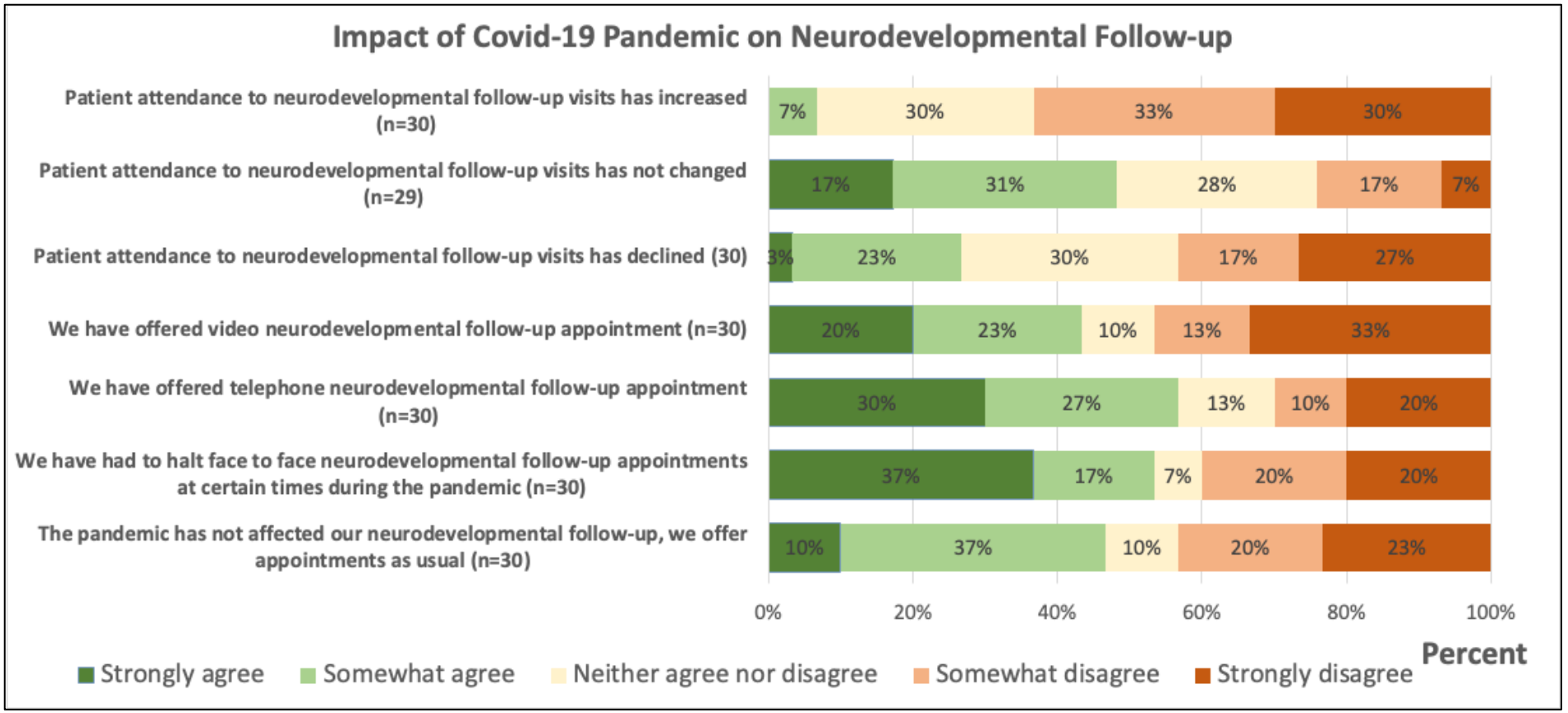



*Figure 54: Impact of Covid-19 pandemic disruptions on neurodevelopmental follow-up*

#### *27.2.6.1 Virtual neurodevelopmental follow-up*

During the pandemic, alternative approaches to providing face-to-face health services were considered by some facilities. Further to identifying the extent of disruption the pandemic had on neurodevelopmental follow-up, the survey also sought to identify opportunities for neurodevelopmental follow-up in the face of challenges the health system was encountering. Therefore, respondents were asked whether virtual assessments were an option for NDA during the pandemic. Almost half of the respondent facilities (49%) were offering some form of virtual assessment or remote support to parents to report the neurodevelopment of their children. Of the other half who were not providing a virtual assessment at the time of the survey, a tenth were considering providing virtual assessments; however, about a third of the respondents indicated that virtual assessment was not an option for NDA during the pandemic.

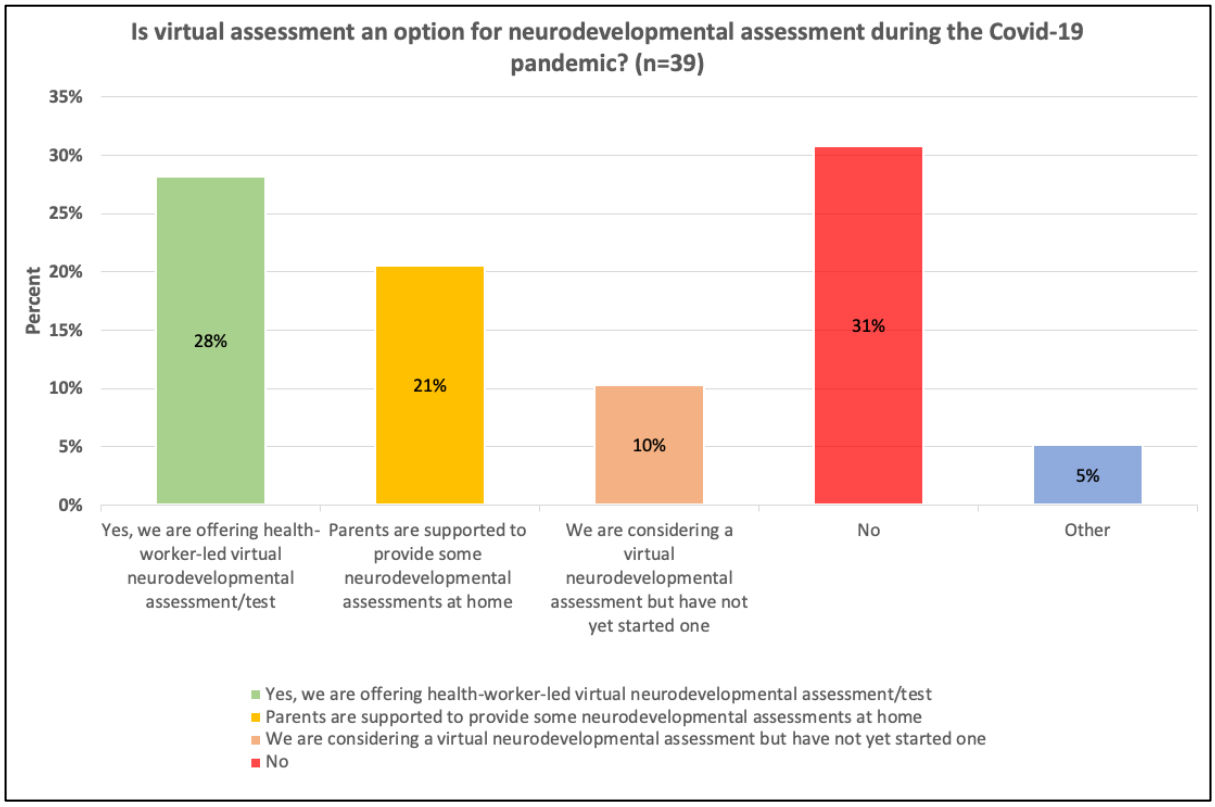



*Figure 55: Virtual NDAs during the Covid-19 pandemic*

The two UK surveys have highlighted the range of neurodevelopmental follow-up practices in the UK, such as tools used for assessments, which children are prioritised for follow-up, similarities and disparities in operations, challenges to and opportunities for neurodevelopmental follow-up services during the pandemic and practices which can be replicated in other settings.

## 27.3 Survey study site 2: Switzerland

### 27.3.1 Main findings

The Swiss survey received eight responses from seven out of the nine (79%) neonatal centres in the country (Geneva, Zurich, Bern, Lucerne, Lausanne, Basel and Munsterlingen). Except for the Zurich site, which recorded two survey responses, the remaining six respondent facilities recorded one response per facility. The denominator for the analysis has been presented according to the seven centres unless otherwise indicated. A summary of the principal survey findings appears below:

The criteria for determining which children receive routine neurodevelopmental follow-up are as follows:

- GA: 7/7 (100%) and the preterm subgroup offered follow-up are the VPTs. The MLPT group are not routinely offered follow-up.
- Clinical diagnosis: 7/7 (100%) including hypoxic-ischaemic encephalopathy, neonatal cerebral stroke or sinovenous thrombosis, psychosocial risk factors, major cardiac malformations, major brain lesions, neurological abnormalities at discharge.
- Birth weight: 3/7 (43%).

Staff who provide neurodevelopmental follow-up are:

- Consultant/specialist clinician: 7/7 hospitals (100%)
- Doctor in training/resident/intern: 4/7 hospitals (57%)

- Other specialist groups include psychologist: 1/7, occupational therapist: 1/7

The follow-up may be performed under the supervision of a consultant in a neuro-paediatric or behavioural and developmental paediatric centre.

Children are offered follow-up assessments at different time points in the various facilities:

- 6 months: 4/7
- 12 months: 5/7
- 18 months: 3/7
- 24 months: 6/7
- 36 months: 1/7
- 48 months: 2/7
- 60 months: 6/7

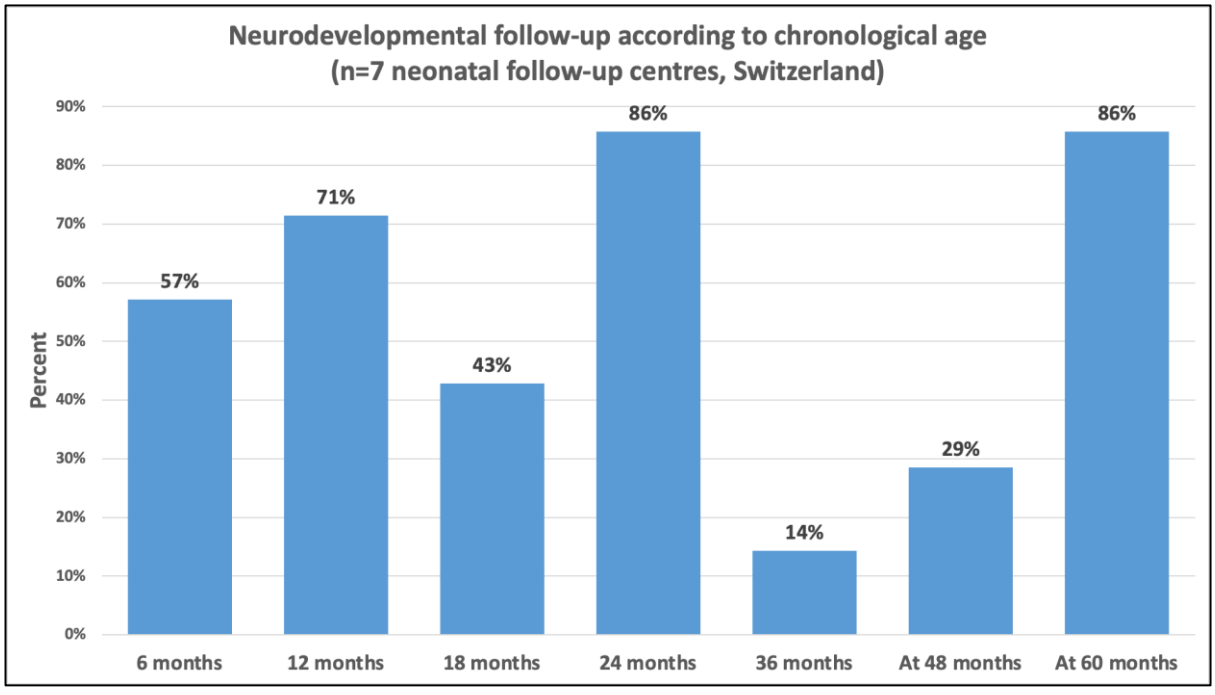



*Figure 56: Follow-up assessment in Switzerland in chronological order*

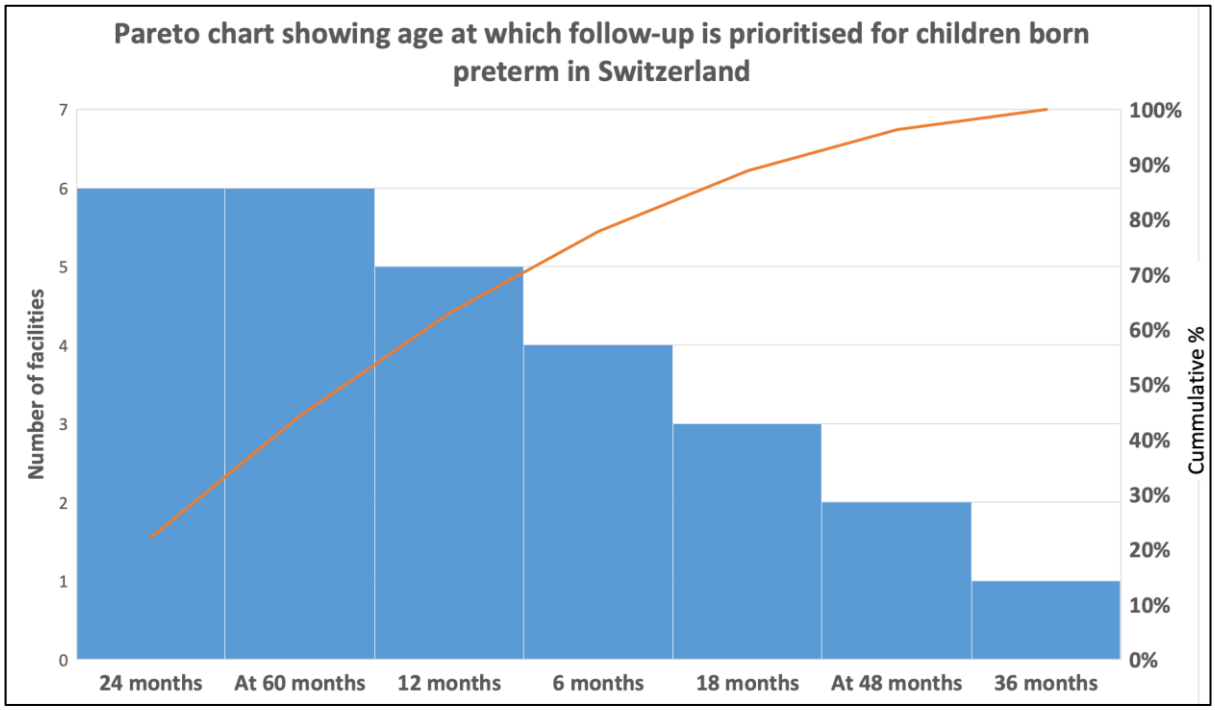



*Figure 57: Age at which follow-up is prioritised for children in Switzerland*

### 27.3.2 Overview of neurodevelopmental follow-up practices in Switzerland

Eligible children for neurodevelopmental follow-up are offered an average of three assessments depending on their underlying risk factors. Survey respondents indicated that eligible children are offered follow-up assessments between three and five times. For example, one respondent wrote: *If normal neurodevelopmental course: at 12 weeks corrected age, 6 months, 12 months, 18-24 months, 4-5 years*. Another facility respondent also indicated: *3-6-12 months (depending on the risk factors).*

Respondents (6/7; 86% of respondent facilities) indicated that follow-up assessments are offered up to 60 months or 48 months (1/7; 14%). However, when asked about the age at which standardised assessment is performed, one respondent mentioned that 72 months is the age at which children are discharged from follow-up in their institution. Extrapolating this observation, it may be the case that although standardised assessments are offered up to 60 months in that institution, an assessment could be extended up to 72 months, depending on a child's need.

The main neurodevelopmental follow-up tool in all participating hospitals is the Bayley Scale of Infant and Toddler Development, 3rd edition (BSID-III), 7/7 (100%); in a few cases, the Griffiths Mental Development Scale, 1/7 (14%) may be used.

The main source of funding for neurodevelopmental follow-up in Switzerland is private health insurance, 7/7 (100%).

Once a child is identified as falling below the threshold for what may be considered normal neurodevelopment under any of the domains assessed, the pathways followed may include:

- Physical therapy

- Continued follow-up by a dedicated neurodevelopmental team, clinician, or paediatrician
- Counselling for parents/caregivers
- A clinician may request further assessments with other tools or qualified personnel to confirm the first test

Pathways are specific to each child's needs and circumstances.

### 27.3.3 Qualitative responses from the survey

In addition to the standard quantitative questionnaire and upon preliminary analysis of the UK survey-I and Swiss surveys, respondents to UK Survey-II were given the opportunity to make additional comments or submissions if they had extra information that informs neurodevelopmental follow-up trends beyond the questionnaire or if they simply wanted to clarify any of their quantitative responses.

Through a thematic content analysis of the qualitative responses, themes were identified deductively and inductively from the free text as:

i. *Barriers to follow-up: staffing*
ii. *Barriers to follow-up: funding*
iii. *Barriers to follow-up: family situations*
iv. *Variations in follow-up practices*
v. *In-person vs virtual assessment*
vi. *Impact of Covid-19 on follow-up*
vii. *Onward care for high-risk infants*
viii. *Criteria for follow-up*
ix. *Recommendations for follow-up*

Barriers to follow-up and recommendations for follow-up (themes i to iv) are emerging themes that complement the original themes in the quantitative survey (themes v to ix). Respondents provided additional context to the existing themes in the survey through their free text (under themes iii to vii). **A selective set of quotes from the free texts are presented below, according to the level and region of the respondent:**

**i. Staffing** was identified as a barrier to NDAs:

*'Neurodevelopmental FU questionnaire-based parents have completed during Covid, and those with concerns have been seen face to face, some limit in Bayley-3 Assessment due to staffing constraints' (Level III facility respondent in England).*

*'< 27w (are) all seen by a consultant for a 2-year follow-up. As from (the) end of June, (the) consultant seeing patients and supervising service retires, and no plan (is) currently made to replace (them)' (Level III respondent in England).*

ii. Although NDAs are covered under the NHS, **funding is a barrier** to offering assessments in some institutions: *'I have tried and failed to develop neurodevelopmental follow-up services in my institution, as no money has been made available for this service' (Level 2 facility in Northern Ireland).*

*'We have no capacity to offer more follow-up - I think an assessment at 4 years would be helpful to detect more issues as I think we miss behavioural and learning issues at the 2-year check – however, this would need to be alongside an expectation that an EHCP would be funded and initiated' (Level 2 facility in England).*

iii. One of the barriers to follow-up is **family situations** as relates to loss to follow-up, either through not showing up for appointments or families moving out of an area (of the jurisdiction of the clinic)

*'There are some difficulties to comply with NNAP, mostly due to DNA (meaning Do Not Arrive) of appointments and moving out of region; I guess most places have similar kinds of difficulties' ((Level III facility respondent in England).*

iv. On **variations in follow-up practices**, respondents indicated:

*'Our organisation has no routine formal NDAs even for babies born <32 weeks' gestation, never mind those born over this' (Level II facility respondent in Northern Ireland).*

*'… There is a wide variety of follow up for late preterm infants; it depends on the family'(Level III facility respondent in England).*

*'We don't offer neurodevelopmental follow-up to our babies currently. We were doing Bayley 3s on all <32 weekers but stopped due to a lack of funding. Some babies will have formal ND follow-ups by local community paediatricians. We complete the 2-year follow-up on BadgerNet, but I wouldn't regard this as formal ND F/U as no named developmental assessment tool is used' (Level III facility respondent in England).*

**v. & vi. In-person vs virtual assessment and impact of Covid-19 on follow-up.**

*'I trialled Bayley assessments simulation via video with very mixed success. Much better to do face-to-face' (Level II facility respondent in England).*

*'Face-to-face has restarted and is working' (Level II respondent in England).*

*'Telephone neurodevelopment assessments are possible but are not as accurate as face-to-face ones, and we will aim to return to face-to-face assessments' (Level II respondent in England).*

**vii. Onward care for high-risk infants.**

*'In our setting, we also have a clear pathway of referral of babies/infants with any signs of neurodevelopmental problems to our early intervention clinic; those referrals are also accepted from paediatricians (all children below 2 years old)' (Level III respondent in England).*

**viii. Criteria for follow-up**

*'Less than 30 weeks get an automatic follow-up. Less than 34 weeks with abnormal USS/ meningitis/ stormy course get followed up. All HIEs are followed up, and all meningitides get followed up.'*

**ix. Recommendations for follow-up**

*'Needs to be a policy in place to offer a developmental follow-up to late prems' (Level II respondent in England).*

*'Follow-up should be in community child health / primary care, not neonatology'(Level III respondent in England).*

## 27.4 Discussion

## 27.5 Trends in neurodevelopmental follow-up from the hospitals' survey: variations and similarities and implications for future care

There is a global consensus about the need to identify at-risk children who will benefit from routine neurodevelopmental follow-up. Risk factors include specific clinical diagnoses such as HIE preterm birth and LBW [27, 342]. There are variations in the implementation of follow-up practices and the identification of high-risk groups in different settings, as seen in the survey results between the UK and Switzerland. Even within the same country, institutions have different practices for follow-up activities, such as which children are offered assessments, the frequency of assessments, the age at which children are discharged from follow-up and the tools used for assessment.

### 27.5.1 Criteria for follow-up

#### *27.5.1.1 GA, birth weight and clinical diagnosis*

The severity of compromised neurodevelopment among VPT children is well documented: up to one-third show neurodevelopmental impairment at age 2 [366]. In accordance with the NICE guideline [27], VPT children were usually offered neurodevelopmental follow-up in the facilities of UK-survey I and II respondents, (96%) (Figure 45) and (77%) (Table 26), respectively. Additionally, some MLPT children and a few children born at term (2%) were offered routine follow-up in the UK (Table 26 and Figure 45). From the survey, the criteria for offering routine neurodevelopmental follow-up did not include term birth. The at-term children who were indicated as receiving neurodevelopmental follow-up may have been prioritised for neurodevelopmental follow-up due to other underlying conditions, which the survey did not probe. From the Swiss survey, however, eligibility for routine NDA based on GA only favoured the VPT group. It may be the case that, similar to the UK, at-term children

with risk factors such as HIE/ brain malformations are offered neurodevelopmental follow-up, however, this was not explicitly indicated in the survey responses.

The national UK and Swiss guidelines both consider LBW and clinical diagnosis as criteria for identifying eligible children for routine follow-up [27, 342]. The birth weight groups prioritised in both countries are the extremely (<1000g) and very low birth weight (<1500g) groups. Actual practices in the two countries reported in the surveys followed the respective national recommendations. The UK respondents' decision to offer follow-up was observed in the first survey to be determined by clinical diagnosis (97%) and GA (97%), and least by birth weight (80%). Similarly in the second UK survey, consultants also rated eligibility criteria for neurodevelopmental follow-up to include clinical diagnosis (92%), GA (90%) and the least important criterion as birth weight (69%). All units that indicated SGA as a criterion for neurodevelopmental follow-up also prioritise VPT. In the Swiss survey results, high-risk children for follow-up were prioritised by equal importance on the basis of GA and clinical diagnosis (100% each) and least by birth weight (43%).

#### *27.5.1.2 Follow-up practices for children born moderate-to-late preterm.*

The literature shows a higher risk of developmental delay among the MLPT group than their term counterparts [15, 51, 367] even though MLPT children are traditionally regarded as low-risk preterm infants in follow-up programmes [368]. Some recent studies report similar developmental trajectories among the VPT and MLPT groups and provide evidence for including the MLPT group in routine surveillance [294, 368]. For example, Dicanio et al., (2022) observed similar neurodevelopmental outcomes between early (28+0 to 33+6 weeks' gestation) and late (34+0 to 36+6 weeks gestation) preterm infants [368].

Children born MLPT were not reflected in the Swiss survey as their GAs were not considered eligible for routine follow-up, nor were they considered as high-risk groups.

High-risk infants were the VPT group or children who developed HIE soon after birth [342]. In the wake of growing evidence of compromised neurodevelopment among the MLPT [15, 51, 367], national guidelines should consider recommendations to include the MLPT group for routine neurodevelopmental follow-up.

In the UK, the NICE guidelines also prioritise VPT infants, similar to the guidance in Switzerland. In both surveys, I and II, the UK survey respondents indicated that some MLPT children are offered routine follow-up assessments. However, it is unclear whether they are offered assessments solely on the basis of GA at birth or if they had underlying conditions that qualified them for routine follow-up. It may also be that some clinical teams in the UK are aligned with the growing literature on the negative consequences of preterm birth among the MLPT [25] and therefore include them in their follow-up surveillance.

#### *27.5.1.3 Specialists offering assessments*

Those involved in NDAs were mostly consultant neonatologists, paediatricians, or specialist clinicians. Other cadres, including doctors in training, residents, or interns, and other specialist groups such as psychologists, occupational therapists, and physiotherapists, are also involved in offering neurodevelopmental follow-up (Table 27 and Figure 49). The VPT group, currently prioritised for follow-up, make up less than 20% of the preterm population. Therefore, to advance the debate on prioritising MLPT children for routine neurodevelopmental follow-up, there would have to be a careful consideration of the human resource capacity to carry out the follow-up for the MLPT group who constitute more than 80% of the preterm population [7].

On a global scale, the prevalence of preterm births is higher in developing country settings [3, 7] where doctor-to-patient ratios are low (for example, patient to doctor ratios of 0.23 to 10,000 in Somalia compared to 75.1 to 10,000 in Monaco). In developed country settings,

the preterm prevalence rate is lower and the doctor-to-patient ratio is much higher, for example, 5.8 per 1,000 in the UK and 4.3 per 1000 in Switzerland [369])[cxviii]. In the UK and Switzerland, the professionals involved in follow-up are specialised staff [196], mostly doctors, as observed in the survey.

As noted in the UK survey, inadequate staffing (*qualitative theme i*) was a barrier to conducting follow-ups for at-risk children. Suppose follow-up were extended to include the MLPT children, deploying highly specialised doctors may not be a sustainable approach to offering NDAs at scale. Task-shifting and effectively managing human resource capacity to accommodate the increasing demand for follow-up services would be required even within systems with good doctor-to-patient ratios [370, 371].

#### *27.5.1.4 Preschool assessments*

NDAs at school age offer the additional benefit of identifying certain skills that are only apparent when complex tasks and executive functions such as mathematics may be identified [343]. The NICE guideline recommends follow-up at age 4 for all EPT infants (born <28 weeks' gestation) and children identified with compromised development during any of their previous follow-up visits [27]. However, from survey II, only 5% of UK respondents' facilities offer preschool assessments.

In Switzerland, the rate of preschool assessments was higher than in the UK survey responses: 29% and 86% of participating facilities offer NDAs at 4 or 5 years, respectively (Figure 53). Additionally, high-risk infants such as VPT children may receive up to five assessments until age 5 in most follow-up centres (and at age 6 in one respondent's institution). Assessments at ages 2 and 5 were the most common times for follow-up

[cxviii] https://www.who.int/data/gho/data/indicators/indicator-details/GHO/medical-doctors-(per-10-000-population)

assessments. The importance of offering assessments at age 2 is that it is the age at which conventionally used assessment tools such as the Bayley Scales of Infant Development show good predictive validity for medium to long-term outcomes. It is also the age at which transient neurological problems of prematurity do not confound with neurodevelopmental problems [201, 372]. Furthermore, age 2 corresponds to the end of Piaget's sensorimotor development, when rapid cognitive development occurs [373].

#### *27.5.1.5 Funding*

The NHS covers health services in the UK for all residents and is funded through taxpayers' money. According to *Statista* Research Department's report in 2020[cxix], about 10% of the UK population purchased supplementary private health insurance in 2019 mainly to access services more promptly where long waiting times exist. The NHS financing principle is based on the need for health care and not the ability of an individual to pay. Therefore, most services are accessible under the scheme. NDAs are consequently covered under the NHS. In Switzerland, developmental follow-up is covered by private health insurance schemes and the choice of insurance service provider is subject to the Swiss Federal Law on Compulsory Health Care.[cxx] Since follow-up is borne by an insurance system in Switzerland, the ability to pay [374] should not be a barrier for families to access follow-up services. This is a good practice that could be encouraged in other settings to take the burden off families.

#### *27.5.1.6 Intervention Pathways*

After NDAs, children identified as having compromised neurodevelopment are referred for further assessments and interventions. Pathways should be specific to a child's needs but the surveys indicate how much variation in practice exists. In the UK, professionals involved in

[cxix] https://www.statista.com/statistics/683451/population-covered-by-public-or-private-health-insurance-in-united-kingdom/
[cxx] https://www.ca-nextbank.ch/en/en/expatriate-switzerland/getting-insurance/how-does-health-insurance-work-in-switzerland.html

therapy or intervention pathways for children with compromised neurodevelopment include consultants, physiotherapists, community paediatricians, occupational therapists, speech and language therapists, nurses and/or nurse practitioners. Similarly, in Switzerland, depending on the domain affected, high-risk children may be referred for physical therapy (motor development) or further assessments with other tools or by qualified personnel for a confirmatory test. As multiple domains of a child's development may be affected, planning and establishing an interdisciplinary team of professionals for follow-up is essential in providing comprehensive care to vulnerable infants [99].

As essential stakeholders in the care of their children, parents are considered an important component of onward care, as identified in the surveys. Parental counselling and education and providing support to families are offered as part of the package extended to the child. Parent-infant interaction has been identified as essential in improving children's outcomes [99, 192].

#### *27.5.1.7 Referral*

Considering the wide range of pathways and professionals involved in caring for at-risk children, an effective communication strategy and referral system are needed to ensure the benefits of the referral are realised. Sometimes, families encounter longer waiting times to secure appointments when referred [375]. The longer the waiting time for interventions, the more likely the condition may deteriorate, warranting more contact time for therapy or minimising the benefit of early interventions [99]. Prompt referral and parental guidance once a child is identified to have compromised neurodevelopment enhances the benefits of early surveillance and follow-up of at-risk infants [376]and according to the *Harvard Center on the Developing Child*, early preventive interventions yield better outcomes compared to remediation later in life [344].

#### *27.5.1.8 Standardised tests and tools for assessments*

The BSID-III is the most common tool used for NDAs in the UK and Switzerland. Other tools being used include the PARCA-R, the Schedule of Growing Skills, Developmental Checklist, Ages and Stages, and Griffiths Mental Development Scales Griffiths Mental Development Scale.

Each of these tools may be used for a specific domain of neurodevelopment [40]. The disadvantage of this wide range of tools for assessment is that comparing outcomes is difficult when the tools measure different domains. Only by standardising them against the gold standard, the BSID-III, might reliable comparisons be feasible.

It must be noted that tools are often used for different tasks. A screening tool to identify high-risk infants or one to establish a definitive diagnosis may not accurately predict developmental compromise during early follow-up assessments. To optimise the follow-up process, tools should remain relevant over the early years of life up to 3 years of age [368]. It is also essential that teams evaluate the pros and cons of the tool they choose and complement it, if necessary [196].

### 27.5.2 Methodologies for addressing the hospitals' survey objectives

#### *27.5.2.1 Survey design and recruitment approaches*

The UK survey-I involved a mix of professionals involved in the neurodevelopmental follow-up of children born preterm in the UK. The UK survey-II focused on consultants identified in the UK survey-I as the largest group of professionals offering neurodevelopmental follow-up to understand their perspectives on the trends in the field. An interesting observation from the consultants' responses in survey II was that most consultants (79%) recommended not extending routine neurodevelopmental follow-up to the MLPT group. Further studies are required to explain the reasons for this observation and

to ascertain if a larger pool of consultant respondents would yield similar responses. Also, the timing of future surveys post-pandemic might influence responses considering that this survey was carried out during the peak of the Covid-19 pandemic when the health system was overly stretched.

Running the UK survey a second time allowed the opportunity to adjust and streamline the survey tool to address the research objectives and enhance the analysis process. For example, in the first survey, respondents were asked to write their facility names. This option made it tedious to analyse the data as respondents named their facility differently. Sometimes, it took time to identify some of the hospital names that were not on the UK's standard list of neonatal units. In the second survey, therefore, the standard list of hospitals was provided as a checklist with an option for an additional field as *'other'* to accommodate facilities that may not have been included on the standard list. In addition, the second survey focused on understanding the perspective of consultants, who are more specialised and senior care providers, in the developmental follow-up of at-risk infants.

In Switzerland, developmental follow-up of at-risk children is carried out at the level three (tertiary) level of care to complement the usual developmental follow-up all children receive with their paediatricians. Therefore, the survey was only extended to the level 3 hospitals that offer follow-up assessments to children born preterm, the population of interest in this study.

#### *27.5.2.2 Neurodevelopmental follow-up practices through a qualitative lens*

The hospital survey was designed to solicit responses quantitatively. Learning from the earlier two surveys in the UK and Switzerland, the third survey, UK survey-II, provided an option to solicit qualitative responses through free text. The themes deductively identified from the free text, such as **perspectives on in-person and virtual NDAs, the impact of the**

**Covid-19 pandemic on follow-up,** and **onward care for high-risk infants**, were similar to the themes included in the survey questions. However, the qualitative approach allowed respondents to provide further insights into some previously structured questions. In addition, emerging themes were summarised from the free text through an inductive approach [283, 377], including the **barriers to offering neurodevelopmental follow-up** and sub-themes **on staffing, finance and family situations**. Further insights shed light on the **variations in follow-up practices** and **recommendations to improve follow-up.**

These qualitative themes have provided insights into neurodevelopmental follow-up practices beyond those provided by the structured survey. Using a mixed methods approach, as in Chapter 3, where an in-depth qualitative study complemented parent views obtained through the parent survey, the free text option in this hospital survey has answered questions that the quantitative questionnaire did not address [297, 298].

Using a qualitative approach, a research group based in Liverpool identified inconsistency in follow-up and screening processes as barriers to neurodevelopmental follow-up for at-risk children [283]. Identifying barriers to quality of care may be best explored through a qualitative approach. Therefore, extrapolating from this survey and the literature, future studies to understand the scope of follow-up assessments should include an option for providers' opinions beyond a defined structured questionnaire to gain a deeper understanding of the barriers to the successful implementation of follow-up practices.

### 27.6 Survey secondary aim

The secondary aim of the hospitals' survey was to understand the extent of Covid-19-related disruptions or opportunities for neurodevelopmental follow-up in the UK and Switzerland.

### 27.6.1 Impact of Covid-19 pandemic on neurodevelopmental follow-up

The second UK survey coincided with the period of the Covid-19 pandemic and allowed questions to be asked about the impact of the pandemic on NDAs. The pandemic disrupted follow-up activities when in-person assessments were impossible, appointments were cancelled or postponed, and alternative approaches to assessments, which were sometimes not familiar to parents and children, had to be considered or adopted. At the same time, the pandemic presented opportunities for alternative assessments, such as telemedicine which bridges access gaps to in-person assessments.

From the survey, respondents indicated that the pandemic had not increased attendance (only 7% thought it had), almost half of respondents (48%) indicated that attendance had not changed, 47% stated that they were offering appointments as usual, and 43% indicated otherwise. More than half of respondent facilities (54%) had halted follow-up appointments at some point during the pandemic; 57% of respondent facilities had tried a virtual assessment through either a video or telephone follow-up.

Overall, the trends observed with the impact of Covid-19 on NDAs, according to the survey, were fairly neutral. Facilities' ability to offer appointments and parents' attendance at appointments may not have been greatly affected by the pandemic in these participating facilities. Due to the small number of respondents in this section of the survey (30), no generalisable conclusion regarding the state of NDAs in the UK can be deduced. The data should therefore be interpreted with caution especially as the questionnaire was general to the entire period of the Covid-19 pandemic and not specific to any particular periods or waves.

The health uncertainties caused by the pandemic increased patient anxieties about their children's development, as reported in the parent interviews (Chapter 3). Therefore, the opportunity for their children to be assessed may have motivated those who made time to attend their appointments. Facilities recording a decline in attendance (34%) may have been during periods of the pandemic when parents were more apprehensive about being exposed to the virus during a hospital visit and, therefore, declining face-to-face assessments in the facility. Although generally, the UK faced massive strain on the NHS during the pandemic [352], it may be inferred from the survey responses (47% offering assessments as usual) that some facilities may have been affected disproportionately by the pandemic with different severity of Covid-19 cases seen among staff or patient loads, level of stress and staff absenteeism, and the reallocation of the workforce involved in follow-up assessments.

Notably, the pandemic provided facilities with the opportunity to consider alternative approaches through telemedicine. Some facilities could offer virtual assessments: 28% were offering virtual health-worker-led NDAs, and 10% were considering virtual assessments but had not yet started one, while 31% did not think virtual assessments were an option for NDAs. Parents were also supported to assess their children at home (through questionnaires).

## 28 Conclusion

The hospital survey described in this chapter aimed to understand the spectrum of neurodevelopmental follow-up practices in neonatal units in the UK and Switzerland. By highlighting follow-up practices that have worked well and areas for improvement in conducting neurodevelopmental follow-ups in these two countries, findings from the survey can inform healthcare priorities for improving services for children born preterm in these two countries and other settings. A secondary aim was to understand the extent of Covid-19-related disruptions, changes in practices or opportunities for neurodevelopmental follow-up in the UK and Switzerland.

The thesis has highlighted the spectrum of neurodevelopmental follow-up practices in neonatal units in the UK and Switzerland as it relates to the following:

- Tools (for neurodevelopmental assessments)
- Staffing
- Eligibility criteria for follow-up
- Referral pathways (when a child is identified as having neurodevelopmental delays)
- Funding options,
- Barriers to follow-up, and
- Impact of Covid-19 on follow-up.

For the secondary aim of the hospital survey, the study found that Covid-19 impacted follow-up care for children born preterm, for example, through cancellation or postponement of appointments, and some children missing the opportunity to be assessed altogether. However, the pandemic also allowed neonatal facilities to adopt telemedicine more quickly and provide remote support for neurodevelopmental assessments. This chapter also shares

findings from the survey that can inform healthcare priorities for improving services for children born preterm in the two countries and other settings.

Further work is required to understand whether the barriers, changes and opportunities for neurodevelopmental follow-up of children born preterm during the pandemic has been long lived post-pandemic or was temporal, and the extent to which the health system has recovered from these disruptions or sustained the opportunities observed. It will also be interesting to know how the digital approach to caring for preterm and vulnerable infants has been improved or abandoned.

## 28.1 Main findings

The survey findings are consistent with some of the generally known neurodevelopmental follow-up practices in the UK and Switzerland. Additionally, the survey has revealed insightful observations about patterns of neurodevelopmental follow-up of children born preterm in the UK and Switzerland and their implications for policy, research, and future care. Learning points from this survey are relevant for healthcare settings in developed and developing countries.

### 28.1.1 Tools

- The BSID-III is considered the gold standard tool for NDAs of children born preterm
- In the UK and Switzerland, the BSID-III is the most popular tool for conducting assessments.
- In the UK, nevertheless, hospitals use a range of different NDA tools.
- In Switzerland, the survey did not find that many different tools are used, as in UK hospitals.

### 28.1.2 Staffing

- Neurodevelopmental follow-up is usually conducted by highly specialised staff, primarily consultants.

### 28.1.3 Eligibility

- Among the preterm population, children born VPT are considered high-risk and therefore prioritised for routine follow-up.
- A high-risk child may receive up to five assessments in Switzerland, and follow-up may continue until 6 years of age (72 months).
- In the UK, only a few (5% of respondents' facilities) can comply with the NICE guideline to offer assessments to high-risk children at preschool age (at 4 years). Most neurodevelopmental follow-ups in the UK happen at the age of 2 years and it can begin as early as at 3 months.

### 28.1.4 Referral pathways

- Children who fall below the threshold of normality are referred for further assessment or specialist care. Due to the different domains of neurodevelopment that may be affected, a multidisciplinary team may be involved in interventions and care for at-risk children.
- Effective communication and linkages are needed to ensure that once a child is identified with developmental deficits, they can promptly be linked to the next level of care, including providing support and counselling to the child's parent(s).

### 28.1.5 Funding

- Follow-up services are covered by the NHS in the UK and by private insurance in Switzerland.

### 28.1.6 Impact of Covid-19 on follow-up

- The pandemic presented challenges to neurodevelopmental follow-up: some appointments had to be cancelled, postponed or alternative methods were considered, such as parents filling in child development questionnaires at home.
- The pandemic also allowed facilities to adopt telemedicine and remote support to offer NDAs (mainly through phone calls).

### 28.1.7 Barriers to follow-up

- Funding and staffing were identified as barriers to neurodevelopmental follow-up, even to eligible at-risk children (in the UK).

### 28.1.8 Learning points from the UK and Switzerland surveys:

- In the UK, some MLPT children are offered neurodevelopmental follow-up.
- In Switzerland, only VPT children are considered for routine follow-up.
- Considering that preterm birth can impact the neurodevelopment of children born MLPT, there may be value in extending routine neurodevelopmental follow-up assessments to include these children. However, further studies are needed to explore the health system requirements to accommodate such undertaking and the potential benefits this could be for MLPTs and to the health system, if any.
- The survey was run first with a general professional population in the UK and then with consultants to zoom in on their experiences with neurodevelopmental follow-up practices. Most of the observations in the UK survey-I were consistent with the consultants' (UK survey-II).

## 28.2 Study Methodology

Future studies exploring healthcare practice patterns may benefit from a mixed methods approach of quantitative and qualitative approaches instead of employing one method alone.

### 28.2.1 Triangulation of results with parent interviews

- Parents were explicit in the survey and interviews (Chapter 3) that they would like to have continued support for their children born preterm post-hospital discharge. The parents of the MLPT children indicated that they would like NDAs extended to their children (generally considered low-risk preterm infants).
- Most consultants who responded to the survey were adamant about extending assessments to the MLPT. The scope of this study did not explore further the reason for their position. It will be necessary for future studies to explore in much greater depth their views on extending routine neurodevelopmental follow-up to all children born preterm, considering the growing evidence of compromised neurodevelopment MLPT children may face during school age or later in adulthood.
- In Switzerland, the model of private health financing may be a solution to the barrier of funding for neurodevelopmental follow-up that was recorded in the UK. Other countries could learn this model where private insurance schemes absorb the cost of follow-up, so it is not a burden on the parents or the central health system. Early interventions may even be a long-term benefit to insurance companies if they could invest in early screening and interventions for children born preterm.

### 28.2.2 Virtual assessment

During the Covid-19 pandemic, facilities adopted different assessment approaches, including virtual assessment. Chapter 2 presented a detailed look at the feasibility of virtual

neuro-developmental assessments during the pandemic and the implications for the future care of children born preterm.

## 28.3 Implications of findings on research, advocacy, and quality of care for children born preterm

In the UK, most units (96%) have protocols in place for follow-up. In line with the NICE guideline, criteria for offering neurodevelopmental follow-up are based on lower GA at birth (usually <30 weeks' gestation as recommended by NICE although some units like Oxford extend this to include children who were born at <32 weeks' gestation), specific clinical diagnoses such as HIE, and risk factors such as birth weight less than the 10$^{th}$ percentile for GA (or very low birth weight of <1500g). The implementation of the NICE guideline is heterogenous across neonatal units. Most hospitals can offer a routine follow-up to the VPT children, and a few hospitals were able to include some MLPT children as well. At the same time, some hospitals noted that they were struggling with offering assessments to even the high-risk VPT children due to funding and staffing issues.

Facilities struggling to provide follow-up could call on support from within their neonatal networks to ensure that their high-risk infants in need of NDAs can access care.

The Swiss design of conducting neurodevelopmental follow-up in highly specialised level-III centres presents opportunities to ensure that specialists see the most vulnerable infants. At the same time, this may present a barrier to access to families who have to travel far to access care.

To bridge the missing gap in follow-up for children born MLPT, alternative human resource management approaches could be considered to accommodate the increased follow-up demands which would arise. Similarly, follow-up practices should be customised in

resource-limited settings to factor in the doctor-to-patient ratio, delegation of duties, and capacity building of allied health staff to support follow-up activities.

To streamline services, national guidelines are essential to guide how follow-up practices should be carried out. Notably, there should be continuous monitoring of how facilities implement guidelines to inform continuous quality improvement in service delivery. Streamlining neurodevelopmental practices across units and countries allows for effective global comparison of long-term outcomes among children born preterm. Also, effective data management with follow-up and the big data generated from longitudinal follow-up across borders can generate important observations on causality and correlations to improve care for all children born preterm.

Elements to consider for follow-up include staffing needs, funding, standardised assessment tools, good data management systems for data monitoring and close collaboration with parents as essential support in the care of children born preterm.

## 28.4 Limitations

The survey was open to all professionals involved in the neurodevelopmental follow-up of children born preterm. The ideal recruitment strategy for the professionals' survey in UK survey-I at the time of the survey was to snowball contacts through the neonatal leads and to source data from a paid service provider. Eligible staff may only have had the chance to participate in the survey if they received the survey from their leads or if their contacts were updated on the *SpecialistInfo* page at the time of recruitment.

# PART D

# GENERAL CONCLUSION

# 29 General conclusion

## 29.1 Contributions to the field

In this thesis, I set out to answer four main research objectives with sub-objectives presented in four content chapters. The overarching aim of this DPhil research was to identify solutions to improving outcomes of children born preterm, thereby contributing to the global agenda of supporting every child to thrive.

In Chapter 1 of the thesis, I conducted a systematic review of interventions to improve the neurodevelopmental outcomes of children born MLPT. The specific objectives were to identify early interventions offered to MLPT children and to evaluate their effects on the neurodevelopmental outcomes until 18 years of age. The systematic review highlighted the paucity of data on MLPT children and the fact that no study or literature met the inclusion criteria for the review on interventions that target the neurodevelopmental outcomes of MLPT children alone. Research culminated in an empty review and highlighted the need for further studies to better understand the range of interventions that can improve the neurodevelopment of MLPT infants and their effectiveness. The chapter also highlighted the need for a regional balance in research for children born preterm globally. A learning point from the review is the dearth of data and publications on intervention studies involving preterm infants in developing country contexts. Considering the higher burden of preterm birth in these settings, policymakers, researchers and clinicians should increase efforts at including preterm infants in these settings in intervention studies for all children born preterm.

In Chapter 2, I focused on a virtual approach and the applicability of the INTER-NDA for children born preterm. The objectives were to test the feasibility of a virtual platform in conducting NDAs of children born preterm and to estimate the usefulness of the INTER-

NDA as an NDA tool for children born preterm. During the peak of the pandemic, when face-to-face NDAs were not possible, I devised a novel approach to virtual NDAs of children born preterm to bridge the access barrier to care seeking. The study has demonstrated the feasibility of successfully assessing young children remotely through telemedicine. To complement the virtual assessments, I conducted a parent feedback survey on the assessments to identify parents' satisfaction with the remote assessments and collect their feedback to improve the method. Parents' responses showed acceptability and reasonable satisfaction with the virtual assessments.

Further, the parent feedback highlighted elements to consider in virtual assessments, such as the availability and ease of use of the technology involved. The virtual vision assessment had limited use among children who had speech problems and or cognitive delays. Future work is required to improve the methodology of virtual vision assessments for children with language and speech problems or those with cognitive impairment. The INTER-NDA proved to be a useful NDA tool among children born preterm in identifying those at risk of moderate-to-severe impairment in the domains tested: cognition, gross motor, language, and positive and negative behaviour. None of the children tested showed signs of impaired development in fine motor skills. Considering the suitability of the INTER-NDA for large-scale screening and its adaptability to virtual testing, it could address the resource implications of extending neurodevelopmental follow-up for all children born preterm. Beyond the feasibility study, future work is planned to validate the virtual assessments with in-person INTER-NDA assessments among the same sample population and to validate the INTER-NDA against the Bayley for preterm population.

Chapter 3 discussed parental views on neurodevelopmental follow-up of children born preterm (including the MLPTs) using a mixed methods approach. With very little known

about the opinions of parents of children born preterm (especially for the MLPTs) regarding neurodevelopmental follow-up, I undertook this study to evaluate the satisfaction among parents and caregivers with the current standard of care and their views of neurodevelopmental follow-up. Secondary to that, parents' knowledge about neurodevelopmental outcomes for children born preterm and their experiences, satisfaction and recommendations for neurodevelopmental follow-up have been described. Adopting both quantitative and qualitative methods, parent views were triangulated (also with NDA results in Chapter 2) to validate the findings in both approaches—the quantitative survey allowed as many parents as possible to express their opinions about neurodevelopmental follow-up. Findings from the survey corroborate with the qualitative studies where further insights were obtained from parents' experiences more intimately.

Parents, especially of MLPT children expressed their need for a contact link to the health system post-discharge to receive support. In doing so, parents also remarked the need for moderated information sharing through diversified approaches so they are not overwhelmed with the information they receive during what may be a difficult time as "preterm parents". Health visitors were identified generally as a support system for parents. However, parents felt that health visitors have inadequate knowledge about the care for children born preterm and, therefore, may not be well placed to better support parents of preterm children. This observation has been noted in similar studies about parents perceptions and experiences of health visitors in the UK [78]. There was a call from parents in this study, to build the capacity of health visitors who are seen as the first point of contact for home-based care for children. Other recommendations from parents included the need for developmental benchmarking for children born preterm so they can estimate when their children may be growing as expected or falling behind in any domains. Finally, parents expressed their vulnerability to stress and anxiety in having and experiencing preterm birth and the need for

mental health services to support them. Some fathers felt left behind in such support systems and expressed their desire to be represented more in research studies.

This study has implications for policy and research. It advocates for parents' involvement and consideration of their opinions in follow-up study designs. Parent recommendations have highlighted significant findings to improve care for children born preterm and to better support other parents with children born preterm.

Finally, in Chapter 4, I performed a cross-sectional survey of hospitals to look at the patterns of NDAs of children born preterm in the UK and Switzerland. The study aimed to understand the spectrum of neurodevelopmental follow-up practices in their neonatal units and to inform healthcare priorities for improving services for children born preterm in the two countries. The study highlighted follow-up practices that have worked well and areas for improvement in other settings.

Findings from the survey were consistent with generally known practices with neurodevelopmental follow-up services. Insights from the study revealed that the BSID-III is considered the gold standard tool for neurodevelopmental follow-up. A range of tools are used in the UK for neurodevelopmental follow-up, with fewer in Switzerland. Staff involved in neurodevelopmental follow-up in both countries are highly specialised and primarily neonatal consultants. The VPT infants are the preterm group prioritised for follow-up in both countries. The criteria for assessment were mainly GA at birth and specific clinical diagnoses, and sometimes LBW. Neurodevelopmental follow-up can be offered from 3 months until age 5; however, age 2 is when most follow-ups occur. The follow-up frequency varies from 1 to 5 visits until age 5. And, only 5% of respondent hospitals in the UK acknowledged offering neurodevelopmental follow-up at age 4 in accordance with the NICE guideline. Switzerland offers more follow-up visits up to age 5. Children identified as having

moderate-to-late impairment are referred for further care in both countries. Neurodevelopmental follow-up services are covered by the NHS in the UK and by private health insurance in Switzerland.

These findings have policy implications for improving and extending neurodevelopmental follow-up to all children born preterm, including the MLPT. This thesis acknowledges the potential challenges to scaling up follow-up services to include all preterm children and therefore recommends future research on the feasibility and efficacy of extending neurodevelopmental follow-up to include the MLPT group, identifying potential early interventions that can improve their neurodevelopment once deficits are found, uptake of follow-up services by parents, and the cost implications that may be involved in surveillance and early interventions for all preterm infants.

Findings from the study contribute to improving care for children born preterm, including the MLPT group. It further provides knowledge to complement the growing body of evidence to strengthen neurodevelopmental follow-up services for all children born preterm. It also presents learning points that could be replicated in other settings, including in developed and developing countries.

## 29.2 Status of research objectives and direction for future work

This section summarises how the various hypotheses and research objectives have been delivered in the thesis and re-emphasises the direction for future work.

### Chapter 1

The specific objectives of the systematic review were to:

a) Identify which early interventions (from birth until 4 years of age) are being offered to MLPT children (32+0 to 36+6 weeks' gestation) and
b) Evaluate the effects of those interventions on neurodevelopmental outcomes (cognitive, neurobehavioural and motor) up until 18 years of age.

The systematic review did not identify any early intervention (from birth until 4 years of age that are being offered to MLPT children (32+ 0 to < 37+0 weeks' gestation as defined in the systematic review protocol. Hence, objective 2 could not be carried out to evaluate the effects of any identified interventions on neurodevelopmental outcomes (cognitive, neurobehavioural and motor) up until 18 years of age.

Future studies are, however, required to understand which early interventions will most efficiently target the cognitive, motor behaviour and other neurodevelopmental domains of MLPT children. It will be important to know whether MLPT infants and their families require different interventions to those offered to VPT children in terms of dose, frequency and mechanism of action. As early follow-up and interventions at scale may be resource intensive, it will also be important to appreciate the investments required for early interventions of preterm subgroups and the implications for large-scale implementation.

For hypotheses 1 and 2, future work is required to validate the virtual assessments against in-person INTER-NDA (or other suitable neurodevelopmental assessment tools) before it is ready for clinical use.

**Hypothesis 1: Conducting virtual NDAs of children born preterm can be a valuable approach to bridging access where barriers to in-person assessments exist.**

The virtual assessments allowed children born preterm to be offered neurodevelopmental assessments during the Covid-19 pandemic. This way, the virtual approach provided a valuable approach to bridging access barriers to in-person assessments *(valuable here refers to added importance or esteemed characteristics or qualities)*. Additionally, other complementary research activities, such as the parent interviews and survey originally planned to be carried out in person, were successfully offered online, which otherwise would not have happened during the pandemic when in-person research activities were not possible. The virtual tests have provided learning points regarding what worked well and areas which could be improved to enhance future virtual assessments and digital healthcare for children and people with neurodevelopmental disturbances.

**Hypothesis 2: It is feasible to offer a virtual NDA to infants between the ages of 2 & 3.**

All eligible children for the NDAs completed the virtual test; therefore it is feasible to offer virtual ND to infants between the ages of 2 and 3 (using the INTER-NDA tool as explored in this study. The virtual vision test was also generally successful but had limited use among children with cognitive and speech and language delays.

**Hypothesis 3: The INTER-NDA is a suitable tool for assessing the neurodevelopment of children born preterm.**

All eligible children for the neurodevelopmental assessments completed the virtual test.

However, the original EveryPrem study objectives of validating the INTER-NDA tool against the standard, BSID-III, could not be realised. It remains to be seen whether the INTER-NDA can replace the BSID-III (potentially the BSID IV) as a neurodevelopmental assessment tool for clinical use for children born preterm.

**Hypothesis 4: Parents may accept virtual approaches as suitable alternatives for assessing the neurodevelopment of their young children.**

Parents expressed a satisfaction rate of more than 70% for the virtual assessments, which is indicative of their acceptability with the virtual approach.

Further research among a larger parent population with similar or different experiences and in other settings will be useful in determining parents' acceptability of virtual approaches to assessing the neurodevelopment of young children. With the Covid-19 pandemic over, the proliferation of digital health options now available, and the lessons gained in the telehealth space, exploring parents' acceptability of telehealth for young children and neurodevelopmental services will be beneficial in advancing telehealth practices and complementing follow-up services for young children and people at risk of neurodevelopmental disturbances.

**Chapter 3**

The specific objectives of this study were to:

- Evaluate satisfaction among parents (carers) with the current standard of care and their opinions on neurodevelopmental follow-up.
- Understand parents' knowledge about neurodevelopmental outcomes for children born preterm.
- Describe parents' experiences, satisfaction, and recommendations for neurodevelopmental follow-up of children born preterm.

The survey and interviews have highlighted that there is room for improvement in neurodevelopmental follow-up for all children born preterm and support for parents in Oxfordshire. Further research is required to ascertain how these observations may be similar or otherwise across the UK and elsewhere. The contribution of this study (parent interviews) is the generation of new constructs that can be tested in a quantitative setting to determine the generalisability of these constructs among a broader population of parents of children born preterm (in the elsewhere). The hypothesis generated from the study is: *considering the parents' voice in the care of children born preterm provides rich insights for improving the care and follow-up of children born preterm.* Future studies will be required to explore how parents' voices can contribute to improving the care and follow-up of children born preterm in a wider population.

**Chapter 4**

The hospital survey described in this chapter aimed to understand the spectrum of neurodevelopmental follow-up practices in neonatal units in the UK and Switzerland. By highlighting follow-up practices that have worked well and areas for improvement in conducting neurodevelopmental follow-ups in these two countries, findings from the survey can inform healthcare priorities for improving services for children born preterm in these two countries and other settings.

A secondary aim was to understand the extent of Covid-19-related disruptions, changes in practices or opportunities for neurodevelopmental follow-up in the UK and Switzerland.

The thesis has highlighted the spectrum of neurodevelopmental follow-up practices in neonatal units in the UK and Switzerland as it relates to:

- Tools (for neurodevelopmental assessments)
- Staffing
- Eligibility criteria for follow-up
- Referral pathways (when a child is identified as having neurodevelopmental delays)
- Funding options
- Barriers to follow-up, and
- Impact of Covid-19 on follow-up.

For the secondary aim of the hospital survey, the study found that Covid-19 impacted follow-up care for children born preterm, for example through cancellation or postponement of appointments, and some children missing the opportunity to be assessed altogether. However, the pandemic also allowed neonatal facilities to adopt telemedicine more quickly and provide remote support for neurodevelopmental assessments.

Further work is required to understand whether the barriers, changes and opportunities for neurodevelopmental follow-up of children born preterm during the pandemic have been long-lived post-pandemic or were temporal, and the extent to which the health system has recovered from these disruptions or sustained the opportunities observed. It will also be interesting to know how the digital approach to caring for preterm and vulnerable infants has been improved or abandoned.

# PART E

## APPENDICES

## &

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[cxxi] The English version of the INTER-NDA manual can be downloaded from: http://www.inter-nda.com

## 31.1 Appendix I: British Association of Perinatal Medicine (BAPM) award recognition for virtual neurodevelopmental assessment




**BAPM Gopi Menon Awards**

**Celebrating excellence, making a difference**

This is to certify that

**Josephine Agyeman-Duah, John Radcliffe Hospital, Oxford**

was shortlisted for a BAPM award for Excellence in Research or Innovation on 5 October 2021

Helen Mactier

**Dr Helen Mactier**
BAPM President

BAPM, 5-11 Theobalds Road, London, WC1X 8SH Registered Charity 285357

## 31.2 Appendix II: German version, INTER-NDA assessment form



# Das INTERGROWTH-21st Projekt Neuroentwicklungspaket Im EveryPrem-Projekt The

*Contributed by EveryPrem Zurich Team: Josephine Agyeman-Duah, Piroska Herpai, Giancarlo Natalucci (and research assistants)*

Name des Kindes: _____ Geburtsdatum: __ /__ / _____ Untersuchungsdatum: __ /__ / _____

Geschlecht des Kindes: Männlich / Weiblich Ort der Untersuchung: _____

Name des Untersucher/ins 1: _____ Name des Untersucher/ins 2:_____

**Cardiff Schärfetestkarte:** **LogMAR:**

**Cardiff-Kontrast-Testkarte:** **%:**

| **Das INTER-NDA** | | | | | | |
|---|---|---|---|---|---|---|
| **Nr.** | Element | Beobachtete Leistungsfähigkeit | | | | |
| 1 | **Baut einen Turm aus 5 Würfeln** *(Versuche=3, Demonstration=3)* | 5 Würfel | 3-4 Würfel | 2 Würfel | Kein Versuch | Nicht beurteilbar |
| 2 | **Auf Aufforderung 4 Farben benennen** *(Versuche=1, Demonstration=0)* | Benennt 4 Farben | Benennt 3 Farben | Benennt 1 oder 2 Farben | Benennt keine Farbe | Nicht beurteilbar |
| 3 | **Auf Aufforderung 3 gleichfarbige Würfel zusammenstellen** (Versuche=1, Demonstration=1 von einer Farbe) | 3 Farben übereinstimmend | 2 Farben übereinstimmend | 1 Farbe übereinstimmend | keine Farben stimmen überein | Nicht beurteilbar |
| 4 | **Das Kind übergibt dem Prüfer einen Würfel, wenn es dazu aufgefordert wird (Der Prüfer sagt: "Bitte geb mir einen Würfel" und hält die Handfläche 5 Sekunden lang offen, nachdem das Kind einen Würfel übergeben hat.)** | Gibt nur einen Block innerhalb von 5 Sekunden ab | Gibt nur einen Block in mehr als 5 Sekunden ab | Gibt zwei oder mehr Blöcke ab | Gibt keinen Block ab / Kein Versuch | Nicht beurteilbar |

| | | | | | | |
|---|---|---|---|---|---|---|
| | *(Versuche=1, Demonstration=0)* | | | | | |
| 5 | **Stellt den Löffel in die Tasse rein, wenn sie/er aufgefordert wird**<br>*(Versuche=5, Demonstration=0)* | Stellt den Löffel in ≤3 Versuchen in die Tasse rein | Stellt den Löffel in 4-5 Versuchen in die Tasse rein | Nimmt den Löffel oder die Tasse, führt die Handlung aber nicht zu Ende | Kein Versuch | Nicht beurteilbar |
| 6 | **Stellt Formen auf dem Brett zusammen**<br>*(Versuche=5, Demonstration=teilweise - nur Entfernung)* | Alle Formen in ≤3 Versuchen | Alle Formen mit wiederholter Demonstration, d.h. 4-5 Versuche | Eine oder zwei Formen in 4-5 Versuchen | Kein Versuch | Nicht beurteilbar |
| 7 | **Stellt Formen auf einem gedrehten Brett zusammen**<br>*(Versuche=5, Demonstration=teilweise - nur Entfernung)* | Alle Formen in ≤3 Versuchen | Alle Formen mit wiederholter Demonstration, d.h. 4-5 Versuche | Eine oder zwei Formen in 4-5 Versuchen | Kein Versuch | Nicht beurteilbar |
| 8 | **Zeigt richtig, wenn sie/er gefragt wird: "Wo ist die Tür/der Eingang zum Zimmer?"**<br>*(Versuche=5, Demonstration=0)* | Identifiziert die Tür in ≤3 Versuchen richtig | Identifiziert die Tür in 4-5 Versuchen richtig | Versucht, die Tür zu identifizieren, gelingt aber nicht | Kein Versuch | Nicht beurteilbar |
| 9 | **Steckt eine Rosine genau in eine kleine Öffnung einer Flasche**<br>*(Versuche=1, Demonstration=1, Test mit beiden Händen)* | Präzise Abgabe der Rosine in die Flasche mit beiden Händen | Ungeschicktes Auslösen, Rosine fällt mit einer oder beiden Händen aus der Flasche | Versuchte, aber erfolglose Befreiung mit einer oder beiden Händen | Kein Versuch | Nicht beurteilbar |
| 10 | **Trinkt Wasser aus Becher/Flasche/Sippy Cup, wenn es vor dem Kind platziert wird**<br>*(Versuche=1, Demonstration=0; mütterlicher Rückruf, wenn Beobachtung nicht möglich)* | Trinkt Wasser aus einer Tasse/einem Becher, ohne zu kleckern | Trinkt ungeschickt und verschüttet | Versucht, aber erfolglos | Kein Versuch | Nicht beurteilbar |
| 11 | **Schaut auf einen Gegenstand am anderen Ende des Raumes, wenn der Prüfer darauf zeigt**<br>(Versuche=5) | Sieht oder zeigt auf das Objekt in ≤3 Versuchen | Sieht oder zeigt auf ein Objekt in 4-5 Versuchen | Sieht das falsche Objekt an oder versucht, das Objekt | Kein Versuch | Nicht beurteilbar |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | zu identifizieren, kann es aber nicht. | | |
| 12 | **Tut so, als würde sie/er aus einem Spielzeugbecher trinken, wenn er vor dem Kind platziert wird** *(Versuche=2, Demonstration=1, wenn nicht spontan beim ersten Versuch)* | Spontan | Nach 1 Demonstration | Teilweiser Versuch nach 1 Demonstration | Kein Versuch | Nicht beurteilbar |
| 13 | **Ist in der Lage, mit dem Spielzeug-Teeservice eine Tasse Tee zuzubereiten, wenn sie/er vom Prüfer dazu aufgefordert wird (Prüfer sagt: "Kannst du eine Tasse Tee machen?")** *(Versuche=2, Demonstration=1, wenn nicht spontan beim ersten Versuch)* | Spontan, mit einer fliessenden Bewegung | Nach 1 Demonstration | Teilweiser Versuch nach 1 Demonstration | Kein Versuch | Nicht beurteilbar |
| 14 | **Füttert die Puppe, wenn sie/er darum gebeten wird (der Prüfer sagt: "Kannst du der Puppe etwas Tee geben?")** *(Versuche=2, Demonstration=1, wenn nicht spontan beim ersten Versuch)* | Spontan | Nach 1 Demonstration | Teilweiser Versuch nach 1 Demonstration | Kein Versuch | Nicht beurteilbar |
| 15 | **Imitiert gerades horizontales Gekritzel** *(Versuche=5, Demonstration=5)* | ≤3 Versuche | 4-5 Versuche; mit Schwierigkeiten | Versuche (Buntstift halten) | Kann Buntstift nicht halten | Nicht beurteilbar |
| 16 | **Identifiziert das Glitzerarmband unter dem richtigen Waschlappen** *(Versuche=5, Demonstration=0, Test beiderseitig)* | Findet das Armband korrekt in ≤2 Versuchen auf beiden Seiten | Finde das Armband in 3 Versuchen oder auf nur einer Seite richtig | Finde das Armband in 4-5 Versuchen oder auf nur einer Seite richtig | Findet das Armband nicht oder kein Versuch | Nicht beurteilbar |
| 17 | **Objektgruppen unter Verwendung von Pluralformen richtig identifiziert** *(gleichzeitige Beobachtung)* | Verwendet 5 Pluralformen | Verwendet 3-4 Pluralformen | Verwendet 1-2 Pluralformen | Verwendet keine Pluralformen | Nicht beurteilbar |
| 18 | **Fragt mit Gesten oder verbal nach der Toilette** *(Mütterliche Rückruf)* | Guter Abwurf | Ungleichmässiger Abwurf | Teilweise (nur bei Stuhlgang) | Niemals | Nicht beurteilbar |
| 19 | **Läuft** *(Mütterliche Rückruf)* | Läuft gleichmäßig | Versucht | Nur Spaziergänge | Spaziergänge mit Unterstützung | Nicht beurteilbar |

| | | | | | | |
|---|---|---|---|---|---|---|
| 20 | **Wirft den Ball ganz nah**<br>*(Versuche=1, Demonstration=1; beide Hände testen)* | Good release | Gute Freigabe | Versucht | Kein Versuch | Nicht beurteilbar |
| 21 | **Schiesst den Ball**<br>*(Mütterliche Rückruf)* | Schiesst den Ball mit gebeugtem Knie | Läuft dem Ball nach und versucht ihn zu schießen | Läuft und berührt den Ball mit dem Fuss | Kein Versuch | Nicht beurteilbar |
| 22 | **Klettert die Treppe hinauf, indem sie/er sich am Geländer festhält, 2 Fuss/Treppe oder in der Art eines Erwachsenen**<br>*(Mütterliche Rückruf)* | Steigt die Treppe allein und gleichmässig hinauf | Steigt die Treppe allein ungleichmässig hinauf | Steigt die Treppe mit Hilfe hinauf (benutzt das Geländer, hält sich an der Hand des Erwachsenen) | Kein Versuch | Nicht beurteilbar |
| 23 | **Verwendet 2-4-silbiges Geplapper, wie z.B. Dada, Mama, aber nicht speziell auf etwas oder eine Person bezogen**<br>*(gleichzeitige Beobachtung)* | Spontan | Imitiert | 1 Silbengeplapper z. B. ba, ma, da | Keine | Nicht beurteilbar |
| 24 | **Verwendet zwei Wörter zusammen verwenden**<br>*(gleichzeitige Beobachtung)* | Zwei Worte, angemessene Verwendung | Zwei Worte: unangemessene Verwendung | Ein Wort, angemessene Verwendung | Kein Versuch | Nicht beurteilbar |
| 25 | **Zeigt durch Gesten an, dass sie/er nein sagt**<br>*(gleichzeitige Beobachtung oder mütterlicher Rückruf)* | zeigt immer verbal oder durch eindeutige Gesten an | Zeigt manchmal verbal oder durch eindeutige Gesten an | Versucht, aber unvollständige Gesten | Kein Versuch | Nicht beurteilbar |
| 26 | **Verwendung eines Pronomens, z. B. ich, mein, sie, er, es, ich**<br>*(Mütterliche Rückruf)* | ≥1 Pronomen im richtigen Kontext | ≥1 Pronomen, falsche Verwendung | Verwendung von Namen, aber nicht von Pronomen | Keine Verwendung | Nicht beurteilbar |
| 27 | **Wie viele Wörter verwendet das Kind während der Untersuchung außer Mama/Dada noch?**<br>*(gleichzeitige Beobachtung)* | ≥8 Wörter | 6-7 Wörter | 4-5 Wörter | ≤3 Wörter | Nicht beurteilbar |
| 28 | **Wie viele Sätze mit 3 oder mehr Wörtern verwendet das Kind während der Untersuchung?**<br>*(gleichzeitige Beobachtung)* | ≥2 | 1 | ≥1 Zwei-Wort-Äusserung | Keine | Nicht beurteilbar |

| | | | | | | |
|---|---|---|---|---|---|---|
| 29 | **In wie vielen Fällen folgt das Kind einem Gesprächsthema und trägt neue Informationen bei?** *(gleichzeitige Beobachtung)* | Mindestens ein Fall, verwendet ≥ 2 Wörtern, die die richtigen Informationen enthalten. | Mindestens ein fall, verwendet einzelne Wörter, enthält korrekte Informationen | Verwendet eine beliebige Anzahl von Wörtern, enthält falsche Informationen | Folgt Gesprächen nicht | Nicht beurteilbar |
| 30 | **Kombiniert Wort und Geste, wenn sie/er gefragt wird** *( Nicht demonstrieren, Versuche=3, anderes Beispiel verwenden, wenn die Mutter sagt, dass das Kind das, was Sie fragen, nicht kennt)* | Kombiniert Wort und Geste vollständig und angemessen | Kombiniert Wort und Geste vollständig, aber unangemessen | Kombiniert Wort und Geste unvollständig und unangemessen | Kombiniert weder Wörter noch Gesten | Nicht beurteilbar |

Was ist die Muttersprache (Erstsprache) des Kindes? _____
In welcher Sprache wird die Untersuchung durchgeführt? _____
Spricht/versteht das Kind andere Sprachen außer seiner Muttersprache (Erstsprache)? _____

| **Wie häufig traten die folgenden Verhaltensweisen bei dem Kind während der Bewertung auf?** | | | | |
|---|---|---|---|---|
| 31 | **Positiver Affekt** | Nie oder selten | Einige Male | Die meiste Zeit |
| 32 | **Exploration** | Nie oder selten | Einige Male | Die meiste Zeit |
| 33 | **Einfaches Engagement** | Nie oder selten | Einige Male | Die meiste Zeit |
| 34 | **Kooperationsfähigkeit** | Nie oder selten | Einige Male | Die meiste Zeit |
| 35 | **Anpassungsfähigkeit an den Veränderungen** | Nie oder selten | Einige Male | Die meiste Zeit |
| 36 | **Ablenkbarkeit** | Nie oder selten | Einige Male | Die meiste Zeit |
| 37 | **Negativer Affekt** | Nie oder selten | Einige Male | Die meiste Zeit |

Zusätzliche Informationen:

## 31.3 Appendix III: Virtual assessment assessor instruction manual



# The INTERGROWTH-21st Project Neurodevelopment Package In the EveryPrem Project (Virtual Assessment Instruction Manual)

**In the mailed test kit, you will find labelled packs with corresponding numbers for each activity. Refer the parent to the relevant pack prior to each activity. Use the INTER-NDA manual for the face-to-face assessment for the virtual assessment, following the instructions below to adapt to a virtual assessment setting. At all times, ensure that the parent's camera is positioned such that you can see the child and working surface fully.**

**Be vigilant throughout the assessment, documenting any activities of interest on the assessment scoring sheet as you proceed, for example, how many words the child may speak, behaviours, etc.**

What is the child's native (first) language? _____

What is the language in which the assessment is being conducted? A parent *may interpret the instructions in the child's native language if needed*__

Does the child speak/understand languages other than their native (first) language? _____

| No. | Activity | Pack No. | Instructions<br>***Follow instructions in INTER-NDA manual for all activities, adapting to virtual sessions as follows*** | Comments |
|---|---|---|---|---|
| 1 | Builds a tower of 5 cubes | 1 | Ask the parent to:<br>- place 5 blocks on the table/floor in front of the child.<br>- build a tower with 5 blocks and say to the child, 'look at my tower'<br>- offer the child one block at a time and ask the child to build a tower like the parents'<br>(follow the instructions in the INTER-NDA) | 1. Ensure that this activity is done on a hard surface, if the floor is preferred, advise the parent to do it on the smooth floor (not on a woolen carpet) or to use a hardcover book on the floor<br>2. Where a child can follow your instructions, speak directly with the child, asking the parent to offer the play item when needed while you observe and score. Under certain circumstances like when the child prefers to engage directly with the parent, is shy or does not want to watch the screen, give instructions to parents to instruct the child on what to do. Be sure the parent understands your instruction before carrying out the activity. Intervene immediately if a parent does not give exact instruction as relayed |
| 2 | Names four colours | 1 | Follow instructions in INTER-NDA manual, asking parent to select 4 different colours for this activity. | Remember to prompt the parent not to mention the name of the colours which invalidates the test |

| No. | Activity | Pack No. | Instructions<br>***Follow instructions in INTER-NDA manual for all activities, adapting to virtual sessions as follows*** | Comments |
|---|---|---|---|---|
| 3 | Matches 3 cubes/blocks of same colour when requested to do so | 1 | Follow instructions in INTER-NDA manual, asking parent to demonstrate activity with one block (the red) | Here, prompt the parent to maintain a neutral face and not to give any bodily or facial indications to where the matching block is. |
| 4 | Hands the parent one block when asked to do so | 1 | Follow instructions in INTER-NDA manual for this activity.<br><br>After this activity, ask the parent to pack the blocks away into pack 1, the child may find it interesting to help parent 'clean up' | Here, prompt the parent to maintain a neutral face and not to give any bodily indications or assistance in finding a block. Emphasise to the parent not to repeat or to stress on 'ONE block' (for example parent should not say, I said one block, look one block). |
| 5 | Puts the spoon in the cup when asked to do so | 2 | Ask the parent to line up all 5 items in pack 2 in front of the child and follow instructions in the INTER-NDA manual.<br><br>After this activity, ask the parent to pack the items away into pack 2, the child may find it interesting to help parent 'clean up' | Here, prompt the parent to maintain a neutral face and not to give any bodily indications or assistance in finding the spoon or the cup.<br>Parent should not break down the instruction, *for example by saying take the spoon and put it in the cup*. |

| No. | Activity | Pack No. | Instructions<br>***Follow instructions in INTER-NDA manual for all activities, adapting to virtual sessions as follows*** | Comments |
|---|---|---|---|---|
| 6 | Matches shapes on board | 3 | Follow instructions in INTER-NDA manual, asking parent to do partial demonstration only | Here, prompt the parent to maintain a neutral face and not to give any bodily indications or assistance in finding a puzzle piece. |
| 7 | Matches shapes on rotated board | 3 | Follow instructions in INTER-NDA manual, NO DEMONSTRATION of activity<br><br>After this activity, ask the parent to pack the items away into pack 3, the child may find it interesting to help parent 'clean up' | Here, prompt the parent to maintain a neutral face and not to give any bodily indications or assistance in finding a puzzle piece. |
| 8 | **Points correctly when asked "Where is the door/entrance to the room?"**<br>*(trials=5, demonstration=0)* | N/A | Follow instructions in INTER-NDA manual, NO DEMONSTRATION of activity | Here, prompt the parent to maintain a neutral face and not to give any bodily indications or assistance in finding the door. |
| 9 | **Puts a raisin precisely inside a small opening in a bottle**<br>*(trials=1, demonstration=1, test both hands)* | 4 | Follow instructions in INTER-NDA manual, ask parent to demonstrate activity once.<br><br>After this activity, ask the parent to pack the items away into pack 4, the child may find it interesting to help parent 'clean up' | Prompt the parent to offer a raisin at a time as the child may be distracted if there are more raisins on the activity table.<br>Note, children sometimes eat the raisins, be flexible to accommodate this and have a few more raisins in pack 4 during assembling |

| No. | Activity | Pack No. | Instructions<br>***Follow instructions in INTER-NDA manual for all activities, adapting to virtual sessions as follows*** | Comments |
|---|---|---|---|---|
| 10 | **Drinks water from cup/bottle/sippy cup when placed in front of child**<br>*(trials=1, demonstration=0; maternal recall if observation not possible)* | 2 | Follow instructions in INTER-NDA manual, ask parent to use one of the cups in pack 2 for this activity.<br><br>After this activity, ask the parent to pack the items away into pack 2, the child may find it interesting to help parent 'clean up' | Skip this activity if you already observed child demonstrating the action during the course of the assessment. |
| 11 | **Looks towards an object located across the room when pointed at by the examiner**<br>(trials=5) | N/A | Follow instructions in INTER-NDA manual, ask the parent to point to an object from *across* where the child is seated, calling the child's name/attention to the direction of the parent's hand | Encourage the parent to point to an object away from the direction of the child's attention |
| 12 | **Pretends to drink from a toy cup when placed in front of him/her**<br>*(trials=2, demonstration=1 if not spontaneous on first attempt)* | 2 | Follow instructions in INTER-NDA manual, ask parent to use one of the cups in pack 2 for this activity.<br><br>After this activity, ask the parent to pack the items away into pack 2, the child may find it interesting to help parent 'clean up', | Parent can demonstrate with one of the two cups in pack 2 and offer the other cup to the child for this activity.<br>*Alternatively, you may ask the parent to carry out this activity with the tea cups in pack 5 during the next activity* |

| No. | Activity | Pack No. | Instructions<br>***Follow instructions in INTER-NDA manual for all activities, adapting to virtual sessions as follows*** | Comments |
|---|---|---|---|---|
| 13 | **Able to make a cup of tea with the toy tea set when requested by examiner (Examiner says "Can you make a cup of tea?")**<br>*(trials=2, demonstration=1 if not spontaneous on first attempt)* | 5 | Follow instructions in INTER-NDA manual, ask parent to use one of the cups in pack 5 for this activity. | |
| 14 | **Feeds doll when requested to (Examiner says "Can you give the dolly some tea?")**<br>*(trials=2, demonstration=1 if not spontaneous on first attempt)* | 5 | Follow instructions in INTER-NDA manual, ask parent to use one of the cups in pack 5 for this activity.<br>After this activity, ask the parent to pack the items away into pack 5, the child may find it interesting to help parent 'clean up', | |
| 15 | **Imitates straight horizontal scribble**<br>*(trials=5, demonstration=5)* | 6 | Follow instructions in INTER-NDA manual, ask parent to use one of the cups in pack 5 for this activity.<br>After this activity, ask the parent to pack the items away into pack 5, the child may find it interesting to help parent 'clean up', | |
| 16 | **Identifies glitter bracelet under correct washcloth**<br>*(trials=5, demonstration=0, test both sides)* | 7 | Follow instructions in INTER-NDA manual, NO demonstration of activity to the child. | Some parents may find the verbal instruction enough to carry out this activity instruction to the child. Where needed, demonstrate the activity (placing of the |

| No. | Activity | Pack No. | Instructions<br>***Follow instructions in INTER-NDA manual for all activities, adapting to virtual sessions as follows*** | Comments |
|---|---|---|---|---|
| | | | After this activity, ask the parent to pack the items away into pack 7, the child may find it interesting to help parent 'clean up', | washcloth and hiding of bracelet) to the parent via the online platform, using two sheets of paper and a pen, for example |
| 17 | **Correctly identifies object groups using plurals**<br>*(concurrent observation)* | N/A | Follow instructions in INTER-NDA manual, NO demonstration of activity | Encourage the parent to engage in a conversation with the child while you observe and score items under language domain |
| 18 | **Asks for toilet by gesture or verbally**<br>*(maternal recall)* | N/A | Parental recall | |
| 19 | **Runs**<br>*(maternal recall)* | N/A | Parental recall | |
| 20 | **Throws a ball very near**<br>*(trials=1, demonstration=1; test both hands)* | 8 | Follow instructions in INTER-NDA manual, | Prompt parent to set camera in an angle where you can see the child release the ball and see the direction of throw |
| 21 | **Kicks ball**<br>*(maternal recall)* | N/A | Parental recall | Some parents may not have observed this activity with the child and may ask to demonstrate it (with their own ball) during the virtual assessment. |
| 22 | **Climbs upstairs holding rail, 2 feet/stair or in adult fashion**<br>*(maternal recall)* | N/A | Parental recall | |

| No. | Activity | Pack No. | Instructions<br>*Follow instructions in INTER-NDA manual for all activities, adapting to virtual sessions as follows* | Comments |
|---|---|---|---|---|
| 23 | **Uses 2-4 syllable babble such as dada, mama but not specifically to anything or any person**<br>*(concurrent observation)* | N/A | | Encourage the parent to engage in a conversation with the child (during the assessment) while you observe and score items under language domain |
| 24 | **Use two words together**<br>*(concurrent observation)* | N/A | | Encourage the parent to engage in a conversation with the child (during the assessment) while you observe and score items under language domain |
| 25 | **Indicates by gesture to say no**<br>*(concurrent observation or maternal recall)* | N/A | Parental recall or observe during the assessment | Encourage the parent to engage in a conversation with the child (during the assessment) while you observe and score items under language domain |
| 26 | **Use of a pronoun e.g. me, my, she, he, it, I**<br>*(concurrent observation)* | N/A | Parental rec | Encourage the parent to engage in a conversation with the child (during the assessment) while you observe and score items under language domain |
| 27 | **How many words does the child use during the assessment other than mama/dada**<br>*(concurrent observation)* | N/A | Parental recall or observe during the assessment | Encourage the parent to engage in a conversation with the child (during the assessment) while you observe and score items under language domain |
| 28 | **How many sentences of 3 words or more does the child use during the assessment?**<br>*(concurrent observation)* | N/A | Parental recall or observe during the assessment | Encourage the parent to engage in a conversation with the child (during the assessment) while you observe and score items under language domain |

| No. | Activity | Pack No. | Instructions<br>***Follow instructions in INTER-NDA manual for all activities, adapting to virtual sessions as follows*** | Comments |
|---|---|---|---|---|
| 29 | **In how many instances does the child follow on a topic of conversation providing new information?**<br>*(concurrent observation)* | N/A | Parental recall or observe during the assessment | Encourage the parent to engage in a conversation with the child (during the assessment) while you observe and score items under language domain |
| 30 | **Combines word and gesture when asked**<br>*(Do not demonstrate, trials=3, use different example if mother says child does not know the one you are asking)* | N/A | Parental recall or observe during the assessment | Encourage the parent to engage in a conversation with the child (during the assessment) while you observe and score items under language domain |
| **Behaviour domains (assessor observed)**<br>*Observation of behaviours are scored as follows: Never or rarely = 1; Some of the time = 2; Most of the time =3* | | | | |
| 31 | **Positive Affect** | | For example: smiling, laughing, making sounds that are perceived as expression of excitement, happiness or pleasure | Observe and look out for behaviour throughout the assessment |
| 32 | **Exploration** | | For example, curiosity about play items objects and persons (e.g. assessor on the video call), exploring environment, touching objects; attracted towards objects placed away from the child, asking questions | Observe and look out for behaviour throughout the assessment |
| 33 | **Ease of engagement** | | Easy to attract the child's attention to the play items/activities like the doll or tea set | Observe and look out for behaviour throughout the assessment |

| No. | Activity | Pack No. | Instructions<br>***Follow instructions in INTER-NDA manual for all activities, adapting to virtual sessions as follows*** | Comments |
|---|---|---|---|---|
| 34 | **Cooperativeness** | | For example: willingness of the child to respond to requests without fussing and performing tasks when requested | Observe and look out for behaviour throughout the assessment |
| 35 | **Adaptability to change** | | For example: Comfortably plays with new toys; not distressed by new stimuli e.g. new games, new tasks | Observe and look out for behaviour throughout the assessment |
| 36 | **Distractibility** | | For example, poor attention to tasks, easily distracted, leaves tasks incomplete | As part of pre-assessment instructions to parents, indicate that the space for the assessment be with items that would distract the child's attention, for example ask other siblings to excuse themselves, move away toys and keep a plain table or floor surface |
| 37 | **Negative Affect** | | Observe behaviours such as: fussing, pouting, whining, crying, frowning, shouting angrily, aggressive behaviour, tantrums | Observe and look out for behaviour throughout the assessment |

## 31.4 Appendix IV: Standard operating procedure for virtual assessments

**Standard Operating Procedure for Virtual Neurodevelopmental and Vision Assessments**

**Before the assessment**

1. Respond to parents' expression of interest to participate in EveryPrem Study, offering an appointment for the virtual assessment (Email or phone as preferred by a parent).
2. Send instructions to parents on how the virtual session (vision and INTER-NDA) will be organised, including a calendar invite for the session (See email templates for details).
    a. Include the iPad access code and instructions on how to log in to the iPad, where applicable.
3. Arrange for the test kit to be posted to the parent's residential address.
    a. See the flow map on the virtual assessment logistics flow chart for details.
4. Send Study iPad to families without a laptop computer or larger screen for the virtual vision assessment.
    a. Arrange for a courier service to deliver and return the iPad to the Study team.

**On the day of the assessment**

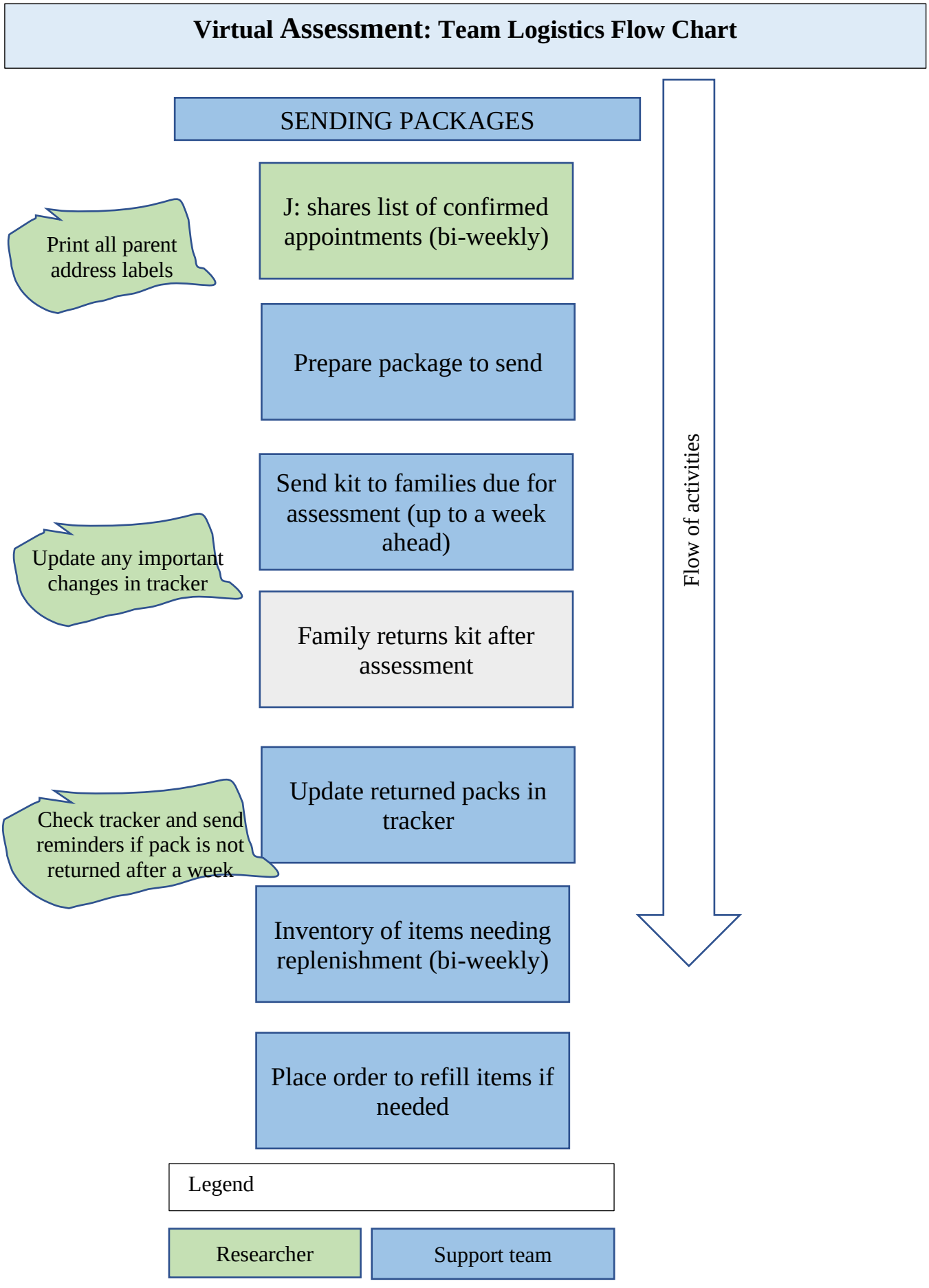
1. Sign in to the virtual platform a few minutes before the session begins
2. Ensure that the iPad is charged and ready for the vision assessment
3. Have the Study forms ready: INTER-NDA assessment form, caregiver behaviour form, parent in-depth interview, and child and parent verbal consent forms (electronic version)
4. Familiarise yourself with the child's records on the reply slip- e.g. name, date of birth, gestational age, etc. before the session starts
5. Welcome the parent(s) and child(ren) to the session (remember to call the child(ren) by name). You may give a complement to the child as an ice breaker, for example, *what a lovely shirt/dress you are wearing*; *I like your dolly; what's her name* or smile at the child
6. Introduce yourself as the assessor and talk briefly about the Study and what the session will entail
7. Ask the parent(s) if they have any questions about the Study or would need any further clarification.
8. Take verbal consent
9. Load the iSight app
10. Confirm with the parent that the child is 1.5m away from the screen and that the parent is using a screen larger than a phone screen for the vision assessment (e.g. iPad or laptop computer)
11. Start the vision assessment.
12. Record the vision score in the iSight app to conclude the vision assessment
13. Start the INTER-NDA assessment (refer to the inventory list to guide parents on which item pack number to use for each stage of the assessment)
14. Follow the instructions in the INTER-NDA manual to perform the neurodevelopmental assessment.
15. For virtual assessments, prompt the parent to offer the test item to the child, reminding parents not to interfere with the child's activities unless asked to demonstrate the activity to the child.

16. As the assessor, for each activity in the INTER-NDA, give instructions to the parents to tell the child how to perform each activity. Where demonstrations are required, such as hiding a bracelet under a cloth, be sure to give clear instructions to g https://www.google.com/url?sa=i&url=https%3A%2F%2Fpeltiertech.com%2Ftext-labels-on-horizontal-axis-in-excel-bar-chart%2F&psig=AOvVaw3r-3kgIxrxEo8KFvyF672g&ust=1672781697786000&source=images&cd=vfe&ved=2ahUKEwj0gavI66n8AhVTxQIHHZ2GD3AQr4kDegQIARBXuide the parent to demonstrate the activity to the child.
17. Observe and document how the child performs each activity and score on a hard copy of the INTER-NDA manual as usual
18. Throughout the assessment, observe and record the number of words a child would speak during the assessment (if any) and take notes of any behaviours as applicable (see behaviour activities 31 to 38 of INTER-NDA assessment sheet)
19. Proceed with the in-depth interview if parents are selected and consent to the interviews.
20. Switch off the video before commencing the interviews. With the parent's permission, remember to record the session for transcription.

**After the assessment**

1. Before the virtual session ends, thank the parent(s) and remind them about the postage stamps and orange slip inside the test kit sent to them.
2. Send a thank you email after the session ends with the following information (see thank you email template for details)
    a. Verbal consent forms for the child's assessment, parent survey and, where applicable, for the in-depth interview
    b. Link to the parent survey (hosted on Qualtrics)
    c. Reminder to return test kit on time
3. Enter the recruitment details onto *Siteline*: participant IDs for parent(s) and child(ren) and date of the assessment
4. Enter the child and parent's details in the master sheet for safe storage
5. Compute INTER-NDA scores and enter data into the data collection sheet
6. Identify children who fall below the threshold as indicated in the INTER-NDA manual
7. Where applicable, discuss the child's results with the neonatologist to initiate the referral process
    a. Complete the relevant portions of the Oxfordshire Referral form (SPORFI) and email parents the form to seek consent for referral
    b. Transmit NY relevant information to the neonatologist to continue the referral process
    c. Send reminders to parents who do not respond to the referral email
    d. Do not contact parents if they decline or do not wish to proceed with the referral.
    e. Treat non-response as a declined referral and inform the neonatologist accordingly.
8. In-depth interviews: safely store the audio recordings and arrange for transcription accordingly.
9. Arrange for the iPad to be couriered back to the Study team.

## 31.5 Appendix V: EveryPrem virtual assessment logistics flow chart



## 31.6 Appendix VI: EveryPrem Study – INTER-NDA test kit inventory

Oxford University Hospitals NHS
NHS Foundation Trust

UNIVERSITY OF OXFORD

# EveryPrem Study

## INTER-NDA Test Kit Inventory for Virtual Assessment

THE EVERYPREM PROJECT

| Packs | Content | Remarks |
|---|---|---|
| Pack 1 | Building blocks<br>• 5 cubes of red<br>• 3 cubes of blue<br>• 3 cubes of green<br>• 3 cubes of yellow | Items to be returned to the EveryPrem Study |
| Pack 2 | • 1 spoon<br>• 1 cup<br>• 1 comb<br>• 1 shoe<br>• 1 toothbrush (*not provided*)<br>• 1 car | Please use the child's usual toothbrush |
| Pack 3 | • Board puzzle with 3 pieces (circle, square and triangle shapes) | Items to be returned to the EveryPrem Study |
| Pack 4 | • A few raisins*<br>• rectangular box with a hole | *Raisins not to be returned |
| Pack 5 | • teapot<br>• 2 teacups and 2 spoons<br>• doll | Items to be returned to the EveryPrem Study |
| Pack 6 | • 2 sheets of A4 paper*<br>• 1 stick of crayon (can choose from red, green, blue or black colour)<br>• Scotch transparent tape | *Sheets of paper not to be returned.<br><br>Crayon and scotch to be returned to the EveryPrem Study.<br><br>*Scotch: for sealing parcel and attaching label* |
| Pack 7 | • 1 bracelet/rubber band<br>• 2 wash cloths | Items to be returned to the EveryPrem Study |
| Pack 8 | • 1 tennis ball | Item to be returned to the EveryPrem Study |

*1. Please return test items with the same postage box using the included address label, orange slip and postage stamps to:* ***The EveryPrem Study, c/o Dr. Frances O'Brien, Nuffield Dept of Women's & Reproductive Health, John Radcliffe Hospital, Level 3, Women's Centre, Oxford, OX3 9DU****.*

*2. Kindly peel off one bar code from the orange slip and keep for your record.*

*3. Please indicate your name on the box so we can track returned items appropriately.*

*For any questions, please contact EveryPrem Study at josephine.agyeman-duah@nhs.net OR ouh-tr.everyprem@nhs.net. Thank you.*

## 31.7 Appendix VII: Survey data cleaning protocol

Criteria for cleaning parent survey data

- Check for unique IP addresses for all entries.
- Interrogate entries where there are multiple responses with the same IP addresses.
- Delete any uncompleted submissions among multiple entries of the same IP address if responses overlap with a completed submission.
    - Select the most complete entry among multiple entries with the same IP address.
- Do not delete two entries with the same IP address if responses are different; the assumption is that both parents may have responded to the survey. The gestational age, in this case, is most likely to be the same.
- Delete an entry of two entries with the same IP address if the responses are the same. The assumption is that a parent completed the survey twice.
- Do not delete entries with the same IP address, even if one is an uncompleted entry with different information from similar entries on the same IP address.
- Do not delete entries with the same IP address if GAs and responses are different (the researcher entered four survey responses from parents who used the hard copy version during the few in-person visits prior to converting the survey to an online platform (i.e., during Covid-19 interruptions to in-person visits).
- Delete blank entries if no question was answered, including the gestational age (an assumption that this is an invalid entry)
- Keep an entry if the gestational age was answered, but all other questions were unanswered. Assume that a blank entry is a valid response from a parent in this case.
- Delete an entry from identical IP addresses if the status is marked as ‘spam’ in Qualtrics and if it has overlapping responses as the other entries under the same IP address.
- Delete an entry that has the status *‘survey preview’* in Qualtrics.

## 31.8 Appendix VIII: Parent in-depth interview guide

**Parent experience, satisfaction and expectations of neurodevelopmental assessments for children born preterm**

Thank you for agreeing to participate in this in-depth interview to share your experience and satisfaction with the care children born preterm receive (including your child) and your expectations for their neurodevelopmental follow-up in the future. Your responses will give us meaningful insights as a valued partner in shaping the health care for your child and other children who were born preterm.

⇒ *Neurodevelopment refers to vision, hearing, cognitive skills, sleep patterns and behaviour.*
⇒ *Preterm refers to all births at less than 37 completed weeks of pregnancy.*

I. Interviewee identifier number:
II. Parent: Father….. OR Mother …..
III. Sex of child: male …..OR female …..
IV. At what gestational age was your child enrolled in this study born?
   - Less than 32 weeks
   - 32 weeks to 33 weeks and 6 days
   - 34 weeks to 36 weeks and 6 days

**A. Parent knowledge about neurodevelopmental patterns for children born preterm**
What is your view about neurodevelopmental patterns and outcomes among children born preterm? How much of this knowledge did you have when your child was born?

**B. Communication with the NHS**
What has been your experience with the NHS regarding information sharing on the neurodevelopmental outcomes among children born preterm? Please share some examples of such information you received and from whom – e.g. your child's GP or neonatal care team, etc.

**C. Neurodevelopmental assessments**
What is your personal experience of neurodevelopmental assessments for children born preterm?

**D. Satisfaction**
How will you describe your satisfaction with the neurodevelopmental follow-up for children born preterm here in the UK?

**E. Expectations for universal neurodevelopmental assessments**
If you had the chance to make any recommendations about neurodevelopmental assessments for children born preterm, what would those be, and to whom would you like to make these recommendations?

## 31.9 Appendix IX: Feedback on Virtual Assessments for Children

*Thank you for your child's participation in the EveryPrem Child Assessment. We would like to receive feedback on your impressions about a virtual assessment compared with a face-to-face assessment for children born preterm.*

Q1 What type of virtual assessment did your child receive through the EveryPrem Study?

- Virtual vision assessment only
- Neurodevelopmental assessment including a vision assessment

Q2 Please rank your satisfaction with the virtual neurodevelopmental assessment your child/children underwent through the EveryPrem Study.

- Very satisfied
- Somewhat satisfied
- Neither satisfied nor dissatisfied
- Somewhat dissatisfied
- Strongly dissatisfied

Q3 How will you rank your satisfaction with a virtual vision assessment (like your child received through the EveryPrem Study)

- Very satisfied
- Somewhat satisfied
- Neither satisfied nor dissatisfied
- Somewhat dissatisfied
- Strongly dissatisfied

Q4 Please state your opinion about the concept of virtual neurodevelopmental assessment for children.

- Good idea
- Neutral
- Bad idea

Q5 Which type of neurodevelopmental assessment would you prefer? (you can click more than one option)

- Face to face
- Virtual
- Don't mind

Q6 Any further comments about a face-to-face follow-up compared with a virtual follow-up for children?

## 31.10 Appendix X: Publications, conference abstracts and awards during DPhil

### Thesis-related

1. Agyeman-Duah J, Kennedy S, O'Brien F and Natalucci G. Interventions to improve neurodevelopmental outcomes of children born moderate to late preterm: a systematic review protocol [version 2; peer review: 2 approved]. Gates Open Res 2021, **5**:78 (https://doi.org/10.12688/gatesopenres.13246.2)

### Conference abstracts

1. Agyeman-Duah J, Kennedy S, O'Brien F. 876 A snapshot of neurodevelopmental follow-up services for children born preterm in the UK: opportunities for improvement Archives of Disease in Childhood 2023;108:A164-A165.

2. Josephine Agyeman-Duah, Stephen Kennedy, Frances O'Brien. Utilising digital health to improve the care of children born preterm, what do parents say. International Society for Quality in Healthcare, South Korea, August 2023.

3. Josephine Agyeman-Duah, Stephen Kennedy, Frances O'Brien. Amplifying Fathers' Voices in Paediatric Qualitative Research. British Association of Perinatal Medicine, Spring Meeting, Edinburgh, April 2023.

4. Agyeman-Duah J, Appiah A, Asibey J, et al. 316 Before scaling-up, speak with the stakeholders: lessons from a preterm project. BMJ Paediatrics Open 2021;5:doi: 10.1136/bmjpo-2021-RCPCH.175

5. Agyeman-Duah, J., S. Kennedy, and F. O'Brien, 1674 Parental views on neurodevelopmental follow-up of children born preterm. Archives of Disease in Childhood, 2021. 106(Suppl 1): p. A453.

6. Josephine Agyeman-Duah, Stephen Kennedy, Frances O'Brien. Improving care for vulnerable children during a pandemic. Global Health Mini-Symposium, Oxford, March 2022

7. Josephine Agyeman-Duah, Stephen Kennedy, Frances O'Brien. Improving care for vulnerable children during a pandemic. International Forum on Quality and Safety in Healthcare, Gothenburg, June 2022

8. Josephine Agyeman-Duah, Michelle Fernandes, Jean Yong, Charles Roehr, Stephen Kennedy, Frances O'Brien. Is standardised neurodevelopmental screening at 2 years of age for all children born preterm feasible?

9. Josephine Agyeman-Duah, Dr Jean Yong, Prof. Charles Roehr, Prof Stephen Kennedy, Dr Frances O'Brien. Neurodevelopmental Assessments of Children Born Moderate to Late Preterm- a survey of Follow-up practices within the UK

10. Josephine Agyeman-Duah, Anita Appiah, Jacqueline Asibey, Ernest Asiedu, Stephen Kennedy, Jose Villar. Providing the right start today for a better tomorrow. BMJ Leaders in Healthcare Conference. October 2020.

11. Adapting clinical care to improve survival, growth and development of preterm infants. Institute for Healthcare Improvement Africa Forum **on Quality and Safety in Healthcare. February 2020.**

**Non-thesis-related publications during DPhil**

1. Effects of prenatal exposure to maternal COVID-19 and perinatal care on the neonatal outcome: results from the INTERCOVID Multinational Cohort Study (https://doi.org/10.1016/j.ajog.2022.04.019)

2. Diabetes mellitus, maternal adiposity, and insulin-dependent gestational diabetes are associated with COVID-19 in pregnancy: the INTERCOVID study (https://doi.org/10.1016/j.ajog.2021.12.032)

3. Kavita Singh, Ilene Speizer, Pierre M Barker, Josephine Nana Afrakoma Agyeman-Duah, et al., (2019), Evaluating the impact of a hospital scale-up phase of a quality improvement intervention in Ghana on mortality for children under five, International Journal for Quality in Health Care, mzz073, (https://doi.org/10.1093/intqhc/mzz073)

**Contributions**

4. Villar J, Ariff S, Gunier RB, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. JAMA Pediatr.2021;175(8):817–826. doi:10.1001/jamapediatrics.2021.1050

5. Papageorghiou AT, Deruelle P, Gunier RB, et al. Preeclampsia and COVID-19: results from the INTERCOVID prospective longitudinal study. Am J Obstet Gyneco 2021;225:289.e1-17

**Unpublished manuscripts from the thesis**

1. Interventions to Improve Neurodevelopmental Outcomes of Children Born Moderate-to-Late Preterm: A Systematic Review.

2. A Virtual Approach and the Applicability of the INTER-NDA for Children Born Preterm

3. Parental Views on Neurodevelopmental Follow-Up of Children Born Preterm: A Mixed Methods Study

4. Patterns of Neurodevelopmental Assessments for Children Born Preterm in the UK and Switzerland: A Cross-Sectional Survey of Hospitals

**Selected awards during DPhil**

1. 2024: Exceptional Women Portraiture at Green Templeton College, University of Oxford New portraits revealed for International Women's Day | Green Templeton College (ox.ac.uk)

2. 2022: PhD Student of the Year, UK
   https://www.ox.ac.uk/news/2022-06-29-oxford-student-wins-phd-student-year-award

3. 2022: Race Equality Award, Oxford Students Union
   https://www.oxfordsu.org/activities/studentawards/

4. 2022: Highly Commended, Green Templeton College Nautilus Citizenship Award

5. 2021: Vice Chancellor's Award, University of Oxford
   https://www.gtc.ox.ac.uk/news-and-events/news/josephine-agyeman-duah-vc-innovation-award/

6. 2021: Excellence in Research or Innovation Gopi Menon Award, British Association of Perinatal Medicine, 2021 (Shortlisted)

7. 2020: Green Templeton College Nautilus Academic Award, 2020
   https://www.wrh.ox.ac.uk/news/nautilus-award-jossey-agyeman-duah

## 31.11 Appendix XI: Checklist for Reporting Results of Internet E-Surveys (CHERRIES)

*This checklist has been adapted to EveryPrem Parent Survey write-up.*

| ***Checklist Item*** | ***Explanation*** | ***Page Number*** |
|---|---|---|
| Describe survey design | Describe target population, sample frame. Is the sample a convenience sample? (In "open" surveys this is most likely.) | 207 |
| IRB approval | Mention whether the study has been approved by an IRB. | 207 |
| Informed consent | Describe the informed consent process. Where were the participants told the length of time of the survey, which data were stored and where and for how long, who the investigator was, and the purpose of the study? | 207 |
| Data protection | If any personal information was collected or stored, describe what mechanisms were used to protect unauthorized access. | 207 |
| Development and testing | State how the survey was developed, including whether the usability and technical functionality of the electronic questionnaire had been tested before fielding the questionnaire. | 208 |
| Open survey versus closed survey | An "open survey" is a survey open for each visitor of a site, while a closed survey is only open to a sample which the investigator knows (password-protected survey). | 208 |
| Contact mode | Indicate whether or not the initial contact with the potential participants was made on the Internet. (Investigators may also send out questionnaires by mail and allow for Web-based data entry.) | 208/9 |
| Advertising the survey | How/where was the survey announced or advertised? Some examples are offline media (newspapers), or online (mailing lists – If yes, which ones?) or banner ads (Where were these banner ads posted and what did they look like?). It is important to know the wording of the announcement as it will heavily influence who chooses to participate. Ideally the survey announcement should be published as an appendix. | N/A |
| Web/E-mail | State the type of e-survey (eg, one posted on a Web site, or one sent out through e-mail). If it is an e-mail survey, were the responses entered manually into a database, or was there an automatic method for capturing responses? | 208/9 |
| Context | Describe the Web site (for mailing list/newsgroup) in which the survey was posted. What is the Web site about, who is visiting it, what are visitors normally looking for? Discuss to what degree the content of the Web site could pre-select the sample or influence the results. For example, a survey about vaccination on a anti-immunization Web site will have different results from a Web survey conducted on a government Web site | 208/9 |

| | | |
|---|---|---|
| Mandatory/voluntary | Was it a mandatory survey to be filled in by every visitor who wanted to enter the Web site, or was it a voluntary survey? | 209 |
| Incentives | Were any incentives offered (eg, monetary, prizes, or non-monetary incentives such as an offer to provide the survey results)? | 209 |
| Time/Date | In what timeframe were the data collected? | 208 |
| Randomization of items or questionnaires | To prevent biases items can be randomized or alternated. | N/A Adaptive questioning rather used |
| Adaptive questioning | Use adaptive questioning (certain items, or only conditionally displayed based on responses to other items) to reduce number and complexity of the questions. | 209 |
| Number of Items | What was the number of questionnaire items per page? The number of items is an important factor for the completion rate. | 210 |
| Number of screens (pages) | Over how many pages was the questionnaire distributed? The number of items is an important factor for the completion rate. | |
| Completeness check | It is technically possible to do consistency or completeness checks before the questionnaire is submitted. Was this done, and if “yes”, how (usually JAVAScript)? An alternative is to check for completeness after the questionnaire has been submitted (and highlight mandatory items). If this has been done, it should be reported. All items should provide a non-response option such as “not applicable” or “rather not say”, and selection of one response option should be enforced. | 209 |
| Review step | State whether respondents were able to review and change their answers (eg, through a Back button or a Review step which displays a summary of the responses and asks the respondents if they are correct). | 209 |
| Unique site visitor | If you provide view rates or participation rates, you need to define how you determined a unique visitor. There are different techniques available, based on IP addresses or cookies or both. | 210 |
| View rate (Ratio of unique survey visitors/unique site visitors) | Requires counting unique visitors to the first page of the survey, divided by the number of unique site visitors (not page views!). It is not unusual to have view rates of less than 0.1 % if the survey is voluntary. | N/A |
| Participation rate (Ratio of unique visitors who agreed | Count the unique number of people who filled in the first survey page (or agreed to participate, for example by checking a checkbox), divided by visitors who visit the first page of the survey (or the informed consents page, if present). This can also be called “recruitment” rate. | 216 |

| | | |
|---|---|---|
| to participate/unique first survey page visitors) | | |
| Completion rate (Ratio of users who finished the survey/users who agreed to participate) | The number of people submitting the last questionnaire page, divided by the number of people who agreed to participate (or submitted the first survey page). This is only relevant if there is a separate "informed consent" page or if the survey goes over several pages. This is a measure for attrition. Note that "completion" can involve leaving questionnaire items blank. This is not a measure for how completely questionnaires were filled in. (If you need a measure for this, use the word "completeness rate".) | 216 |
| Cookies used | Indicate whether cookies were used to assign a unique user identifier to each client computer. If so, mention the page on which the cookie was set and read, and how long the cookie was valid. Were duplicate entries avoided by preventing users access to the survey twice; or were duplicate database entries having the same user ID eliminated before analysis? In the latter case, which entries were kept for analysis (eg, the first entry or the most recent)? | N/A |
| IP check | Indicate whether the IP address of the client computer was used to identify potential duplicate entries from the same user. If so, mention the period of time for which no two entries from the same IP address were allowed (eg, 24 hours). Were duplicate entries avoided by preventing users with the same IP address access to the survey twice; or were duplicate database entries having the same IP address within a given period of time eliminated before analysis? If the latter, which entries were kept for analysis (eg, the first entry or the most recent)? | 216 |
| Log file analysis | Indicate whether other techniques to analyze the log file for identification of multiple entries were used. If so, please describe. | N/A |
| Registration | In "closed" (non-open) surveys, users need to login first and it is easier to prevent duplicate entries from the same user. Describe how this was done. For example, was the survey never displayed a second time once the user had filled it in, or was the username stored together with the survey results and later eliminated? If the latter, which entries were kept for analysis (eg, the first entry or the most recent)? | N/A |
| Handling of incomplete questionnaires | Were only completed questionnaires analyzed? Were questionnaires which terminated early (where, for example, users did not go through all questionnaire pages) also analyzed? | 217 |

| | | |
|---|---|---|
| Questionnaires submitted with an atypical timestamp | Some investigators may measure the time people needed to fill in a questionnaire and exclude questionnaires that were submitted too soon. Specify the timeframe that was used as a cut-off point, and describe how this point was determined. | N/A |
| Statistical correction | Indicate whether any methods such as weighting of items or propensity scores have been used to adjust for the non-representative sample; if so, please describe the methods. | N/A |

This checklist has been modified from Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res. 2004 Sep 29;6(3):e34 [erratum in J Med Internet Res. 2012; 14(1): e8.]. Article available at https://www.jmir.org/2004/3/e34/; erratum available https://www.jmir.org/2012/1/e8/. Copyright ©Gunther Eysenbach. Originally published in the Journal of Medical Internet Research, 29.9.2004 and 04.01.2012.
This is an open-access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/2.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in the Journal of Medical Internet Research, is properly cited.

## 31.12 Appendix XII: Comments from PPI Representatives on Study Protocol

Comment 1: *"I only have positive feedback. Given that these types of documents are not familiar to me I found your proposal easy to read and well written. The content is incredibly interesting, particularly the background and the supporting statistics. I am stunned at the association between pre-term birth and the increased potential of suffering a mental health condition in later life. I believe what you are proposing will add considerable value to many children and their families, in addition to the considerable cost savings too.*

*I can see the many benefits of your proposal for the following reason which is personal to myself. My three children were born between 32-37 weeks' gestation so none were fortunate enough to have received and tests/checks prior to their 2 year health visitor checks. My now ten year old son was born at 32 +3 and it was not 'officially' recognised that his speech and language was delayed and that he needed professional assistance until his 2 year check. Had we have been consulted with on a more regular basis as a result of him being born pre term I do believe this is something that could have been managed, recognised earlier and potentially avoided. I believe as a result of this it has affected his confidence and development.*

*It is clear from reading your proposal that a great amount of time, effort and thought has gone into collating and presenting this information. I can only commend your work and wish you all the very best with your proposal."*

Comment 2: *"I think your project is brilliant. It is very strong, research based and offering to fill a gap in care for premature babies. I am trained in Bayleys and I find it costly, lengthy for parents and child and I am pretty none of the parents had a full understand of the reports I have provided after my assessments. As a mum, I found very difficult to read about the risks of*

*my two children having mental health problems in their future. As you pointed, pre terms 32-37 weekers have been left with no support and very little information about the risks of health mental problems in their future. When my children were in NICU and were discharged, there was no mention of any risks. They did not have any follow ups after discharge and no assessment at 2 years old. As mum, I am sure there loads of other mothers in the same situation. As our children were not "very premature", we were reassured they should be fine.''*

Comment 3: *''I think a developmental screening programme would be invaluable and is something we probably would have benefited from with our boys. It's interesting that babies born 32-37 weeks are often almost ignored by the medical profession etc. This has been our experience mostly.*

*Very few medical professionals take much notice when we say the boys were born 34 and 36 weeks respectively - the usual comments are "that's not very early or preterm". Then I have to tell them they were also growth restricted and very poorly at birth and that sometimes changes their perspective.*

*However, these factors are often still not taken into account as being relevant to their later health. Perhaps recognised checks such as the ones you are proposing would raise red flags earlier which medical professionals would take more seriously. We can only hope.''*