CRANIOFACIAL MORPHOLOGY AND THE USE OF NEONATAL NON-INVASIVE VENTILATION THERAPY

by

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Abstract

Objective: A prospective cohort study with the overall objective to characterize the three-dimensional facial morphology of preterm infants over the course of the first 18 months of corrected age, participating in the Neonatal Follow-up Program of B.C. Women's Hospital in Vancouver, BC.

The specific aims of this project are to:

1. Characterize the three-dimensional facial morphology of a cohort of preterm infants at 4, 8 and 18 months of corrected age.
2. Determine the effects of the duration of NIV therapy on facial morphology at 4, 8 and 18 months of corrected age.
3. Evaluate the feasibility, time, adverse events, and minimum effect size to predict an appropriate sample size to improve study design prior to performance of a full scale longitudinal research project.

Methods: To achieve this goal, infants reporting for follow-up at 4, 8 and 18 months of age corrected for prematurity will be screened for defined eligibility and imaged with a 3dMD surface-imaging camera, and facial morphometric parameters will be related to anthropometric data at birth and the specific characteristics of respiratory therapy received during the neonatal period or longer.

Results: The study obtained 43 facial images: 10 images for the four-month cohort; 13 images for the 8-month cohort; 20 images for the 18-month cohort. The mean gestation age is 26 weeks, birth weight is 822 grams, birth length is 32.6 cm, and birth head circumference is 23.8 cm. The mean NIV therapy duration is 45 days and the mean NICU stay is 101 days. There was statistical

significant negative correlation between intercanthal width versus duration of NIV therapy in the 4-month cohort.

Conclusion: There were not any statistical significant correlations between the duration of NIV therapy and the linear distances measured in the transverse, vertical and anterior-posterior plane other than the intercanthal width. The duration of NIV therapy did not have any statistical significant correlation with measured facial angles and facial ratios. This pilot study was however not powered to detect a difference. There is overall positive feasibility for acceptability, demand, implementation, practicality, adaptation, integration and expansion of the research project.

Lay Summary

Babies born preterm often need help breathing earlier on in their life through a mask or nasal prongs. Parents of babies born preterm have often voiced concern whether the constant pressure on their child's face could affect facial growth. Currently, there are a lack of information regarding facial growth in babies born preterm. It is important to study the facial growth and development of preterm babies that have undergone breathing support. In this study, the facial growth and development of preterm babies will be described. The study population will be preterm babies who meet the study conditions and have received breathing support. The study will analyze for possible effects on facial growth of this population having undergone breathing support with a mask or nasal prongs. The researchers will then review the conditions and results of the study to provide recommendations for future research.

Preface

This thesis is an original, unpublished, independent work of the author. Identification and design of this research project were by the author under the direction of his research supervisor, Dr. Benjamin Pliska, Department of Oral Health Sciences, Faculty of Dentistry at the University of British Columbia, Vancouver, Canada. Data collection was conducted by the author with assistance from our clinical research coordinator, Julie Pauwels, and Neonatal Follow-Up program database manager, Arsalan Butt. Dr. Anne Synnes, medical Director of the Neonatal Follow-Up Program, Division of Neonatology, Department of Pediatrics, University of British Columbia, Vancouver, Canada, helped facilitate the collaboration of our research data with the Neonatal Follow-up Program of B.C. Women's Hospital. Dr. Karen Campbell, Chief of Dentistry at B.C. Children's Hospital and Endowed Professor in Dentistry at the University of British Columbia, Vancouver, Canada, helped facilitate the collaboration of our research with the Dentistry department of B.C. Children's Hospital. Dr. Neil K Chadha, Division of Pediatric Otolaryngology, Department of Surgery, Faculty of Medicine, University of British Columbia, Vancouver, Canada, helped provide space for our research software and equipment for data collection and analysis. Data analysis was conducted by the author with the guidance of Jeffrey Bone, statistician. Regular committee meetings were held with the supervisory committee, consisting of Drs. Benjamin Pliska, Neil K Chadha, and Anne Synnes.

Ethical approval for this study was granted by the UBC Children's & Women's Clinical Research Ethics Board [H17-00407]. The online ethics training module Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Course on Research Ethics (TCPS2: CORE) was issued and completed by the author on August 10th, 2015.

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List of Abbreviations

2D – Two dimension

3D – Three dimension

ANCOVA – Analysis of covariance

BCCH – British Columbia Children's Hospital

BCWH – British Columbia Women's Hospital and Health Centre

BPD – Bronchopulmonary dysplasia

CNN – Canadian Neonatal Network

CPAP – Continuous positive airway pressure

FiO2 – Fraction of inspired air

FRC – Functional Residual Capacity

KGH – Kelowna General Hospital

LGH – Lions Gate Hospital

MRN – Medical record number

NCPAP – Nasal continuous positive airway pressure

NICU – Neonatal intensive care unit

NIPPV – Nasal intermittent positive pressure ventilation

NIV – Non-invasive ventilation

NFUP – Neonatal follow-up program

O2 – Oxygen

PaCO2 – Arterial partial pressure of carbon dioxide

PaO2 – Arterial partial pressure of oxygen

PEEP – Positive end expiratory pressure

RDS – Respiratory distress syndrome

RN – Registered nurse

RCH – Royal Columbian Hospital

RRT – Registered respiratory therapist

SMH – Surrey Memorial Hospital

SIDS – Sudden infant death syndrome

WHO – World Health Organization

WOB – Work of breathing

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Dr. Karen Campbell for your encouragement and support for my future endeavors and training to become a successful pediatric dental specialist.

Special thanks to Ashley, my wife, for her unconditional love, strength, patience, support and encouragement throughout my pediatric dentistry training. Finally, my deepest appreciate for my family for their constant support and encouragement throughout my life journey and professional training.

Dedication

I dedicate this thesis to all the parents and families of children with special health care needs that I have encountered over the years during my residency at the British Columbia Children's Hospital. Your strength, perseverance and courage have truly been inspirational.

I would like to dedicate this work to my loving wife, Ashley, and my parents who have supported me unconditionally throughout my education and training.

Chapter 1: Introduction

1.1 Premature Infants

1.1.1 Definition

The World Health Organization (WHO) defines preterm birth as any birth before 37 complete weeks of gestation, or fewer than 259 days since the first day of the woman's last menstrual period (Quinn et al., 2016). Based on gestational age, infants born less than 28 weeks are considered extremely preterm, between 28 to less than 32 weeks are considered very preterm and between 32 to 37 completed weeks of gestation to be moderate or late preterm (Quinn et al., 2016). According to delivery following the onset of the last menstrual period, preterm is considered to be less than 259 days (37 weeks), term to be between 259-293 days (37-41 weeks) and post-term to be between 294 days (42 weeks) or more (Quinn et al., 2016). The weight of an infant at birth correlates well with the index of prematurity (Paulsson, Bondemark, & Soderfeldt, 2004). Premature infants are also classified based on weight: low birth weight (less than 2500 grams), very low birth weight (less than 1500 grams), and extremely low birth weight (less than 1000 grams) (Paulsson et al., 2004). The International Classification of Diseases describes a term birth as optimal timing for a good outcome for the mother and baby (Shapiro-Mendoza et al., 2008). An estimated 15 million infants, with less than 37 weeks of gestation are born every year, representing premature birth rates ranging from 5-18% across 184 countries (Di Fiore, Poets, Gauda, Martin, & MacFarlane, 2016; Parat & Mhanna, 2016; Quinn et al., 2016). In developed countries preterm birth is now the leading cause of perinatal morbidity and mortality (Goldenberg, Culhane, Iams, & Romero, 2008).

1.1.2 General Growth and Development

With improvements in the overall care and management of preterm birth, mortality rates have decreased significantly over the past two decades (Goldenberg et al., 2008). Children born very preterm may show signs of language delay, regulatory and behavioral difficulties, impaired motor function, as well as general and specific neurocognitive difficulties (Woodward et al., 2009). While the life-long neurodevelopmental risk associated with preterm birth are becoming better understood (Woodward et al., 2009), there is also a general decrease in stature (Bracewell, Hennessy, Wolke, & Marlow, 2008). There is considerable and rapid catch-up growth in the first year of life of preterm infants, however at six years of age they remain on mean a full standard deviation lighter and shorter than classroom controls (Bracewell et al., 2008). By 6 years of age, head circumference of extremely preterm children has shown to be smaller than reference data (Bracewell et al., 2008). More recent long-term studies have found that preterm children remain at a height disadvantage compared with full term controls at 18 years of age (Roberts et al., 2013). Emphasizing the need for improved evidenced-based protocols in neonatal care, it has been suggested that medical risk factors including the interventions during the early years may be more important predictors of height than genetic predisposition in preterm children. Medical risk factors are more common in preterm children, compared with term children, and may impair growth in infancy and early childhood. These include, but are not limited to, poor nutrition, respiratory illnesses, increased hospitalization and increased number of medical interventions (Woodward et al., 2009). Premature infants greater than 35 gestational weeks are mature enough to suck and swallow milk but less mature infants will require breast milk supplemented with protein, calories, and minerals through oro- or nasogastric tube (Paulsson et al., 2004). It is known in general that sucking habit may result in dental malocclusion such as a crossbite or

altered palatal morphology (Lindsten, Larsson, & Ogaard, 1996). As a result, the different long term feeding methods may affect craniofacial morphology.

Considerably less is known specifically about facial growth in preterm children and if disturbances are limited to magnitude or if the typical cephalocaudal gradient of development is also affected. Reporting on a cohort of very preterm children from southern Sweden, Paulsson and Bondemark has shown that the craniofacial morphology at 8 to 10 years of age differs significantly from children born at term (Paulsson & Bondemark, 2009). The prematurely born children were found on mean to have a shorter anterior cranial base, less convex profile, and shorter maxillary length (Paulsson & Bondemark, 2009). Clinical investigations have reported conflicting outcomes of preterm birth and malocclusion. Primozic et al. observed no significant differences regarding the prevalence of functional and morphological characteristics of malocclusion in the deciduous dentition phase between prematurely and non-prematurely born subjects (Primozic, Farcnik, Ovsenik, & Primozic, 2014). However, the two groups in this study only differed by a mean of 4 weeks of gestation and were recalled at two years of age, meaning subtle differences in growth effects may not have had time to fully manifest clinically. Paulsson and Harila both reported an increased prevalence of malocclusion in very preterm children, with a tendency towards excess overbite and an increase in mesial molar or Class III relationships (Harila-Kaera, Gron, Heikkinen, & Alvesalo, 2002; Paulsson & Bondemark, 2009; Paulsson, Soderfeldt, & Bondemark, 2008).

The American Academy of Pediatrics have published recommendations that infants sleep in a supine position on a firm sleep surface to decrease the incidence of sudden infant death syndrome (SIDS) (Moon, 2016). However, it was noticed that there was a substantial increase in the prevalence of positional skull deformity (Shweikeh, Nuno, Danielpour, Krieger, & Drazin,

2013). These observations indicate that positioning in the NICU incubators may influence cranial development.

1.1.3 Breathing

Infants born prematurely have an increased risk for morbidity and mortality predominantly due to immature lung development and poor respiratory control, apnea of prematurity, intermittent hypoxemia (HI) and bradycardia (Di Fiore et al., 2016). The major challenges of premature infant care include the stabilization of respiratory control, ventilation and oxygenation. A premature infant's ventilation and oxygenation is difficult to manage, especially between 23 to 27 weeks of gestation because of the immature stage of lung development (Di Fiore et al., 2016).

Poor respiratory control and apnea of prematurity leads to intermittent hypoxemia and apnea (Sateia, 2014). During fetal growth and development, cellular differentiation gives rise to surfactant producing type 2 pneumocytes with increasing capillary growth within the epithelial layer lining the respiratory units (Di Fiore et al., 2016). The initiation of surfactant synthesis and alveolar septation usually occurs between 24 and 28 weeks of gestation (Di Fiore et al., 2016). Surfactant deficiency may lead to atelectasis, respiratory fatigue and secondary apnea (Di Fiore et al., 2016). Additionally, a premature infant's respiration is often unstable due to a highly compliant chest wall (Di Fiore et al., 2016). The highly complaint chest wall often results in a loss of lung volume during apneic episodes reducing the infant's functional residual capacity (Di Fiore et al., 2016). The functional residual capacity is an essential safeguard in both stabilizing oxygenation and reducing the rate of desaturation that may occur during an apneic episode (Di Fiore et al., 2016). With poor pulmonary function and low oxygen reserve, these premature

infants will have episodes of intermittent hypoxemia requiring respiratory support. Without respiratory support, these premature infants are vulnerable to respiratory morbidity due to oxidative stress inflammation (Di Fiore et al., 2016).

1.1.4 Respiratory distress syndrome (RDS)

Respiratory distress syndrome (RDS) is the most common respiratory disorder of premature infants (Esmaeilnia, Nayeri, Taheritafti, Shariat, & Moghimpour-Bijani, 2016; Subramaniam, Ho, & Davis, 2016). Premature infants affected with RDS typically have lungs that are stiff, underdeveloped, surfactant-deficient, fluid-filled, and are likely to develop alveolar atelectasis and airway collapse (Diblasi, 2009). The main risk factors for RDS are low-birth weight and cesarean delivery (Condo et al., 2016). The frequency of RDS decrease with increase gestational age and males are at an increased risk of RDS (Condo et al., 2016). The initial management of RDS in extremely low birth weight infants favors the use of continuous positive airway pressure (CPAP) at delivery. (Parat & Mhanna, 2016).

1.1.5 Bronchopulmonary dysplasia (BPD)

In case of severe respiratory failure, endotracheal intubation and mechanical ventilation are frequently indicated, placing premature infants at greater risk for destabilization and developing severe complications such as bronchopulmonary dysplasia (BPD) (Diblasi, 2009; Mello, Silva, Costa, & Ramos, 2015; Wheeler, Klingenberg, Morley, & Davis, 2011). BPD is a chronic lung disease associated with the use of mechanical ventilation and prolong use of oxygen (Mello et al., 2015). The initial inflammatory response, longer exposure to oxidants during prolong oxygen administration, and continual exposure to ventilator-induced lung injury may

arrest postnatal lung development and pulmonary capillary angiogenesis, increase interstitial fibro-proliferation, cause airway lesions, and decrease surface area for gas exchange (Diblasi, 2009). Premature infants that develop BPD have late development of the lung acinus with abnormal alveoli, deposition of elastin and vascularization (Mello et al., 2015). The lung alterations exhibiting abnormalities in lung function after birth can be lifelong through childhood and beyond (Mello et al., 2015). Although premature infants are commonly managed with strategies to prevent injury to the lungs, such as the use of prenatal steroids, postnatal exogenous surfactants and minimally invasive ventilation strategies, BPD remains the most common respiratory complication of prematurity (Mello et al., 2015).

1.2 Non-invasive ventilation (NIV) therapy

Non-invasive ventilation (NIV) therapy has become the first line of respiratory support for a wide range of respiratory diseases in infants. (Esmaeilnia et al., 2016; Jardine, Inglis, & Davies, 2011; Verder, 2007). NIV assists breathing with delivering positive pressure through an interface outside the airway. There are two types of NIV widely used in respiratory care for premature infants: nasal intermittent positive pressure ventilation (NIPPV) and nasal continuous positive airway pressure (NCPAP) ventilation (Esmaeilnia et al., 2016; Lemyre, Davis, De Paoli, & Kirpalani, 2014). NCPAP is a non-invasive type of respiratory assistance which applies a constant level of pressure during inhalation and exhalation to support spontaneously breathing newborn infants predisposed to developing atelectasis (Diblasi, 2009). NIPPV is a method of augmenting NCPAP by delivering ventilator breaths and increasing minute ventilation and tidal volume in comparison to NCPAP (Esmaeilnia et al., 2016; Lemyre et al., 2014). NIPPV and NCPAP both improve diaphragm function, increase pulmonary compliance, and reduce upper

and lower airway resistance in infants (Esmaeilnia et al., 2016). Premature infants with RDS are frequently supported with NCPAP and NIPPV (Diblasi, 2009; Esmaeilnia et al., 2016; Jardine et al., 2011). NCPAP has also been useful for treating obstructive and central apnea of prematurity, congenital and acquired airway lesions, and other respiratory disorders such as transient tachypnea of the newborn, meconium aspiration syndrome, primary pulmonary hypertension, pulmonary hemorrhage, patent ductus arteriosus and consequent pulmonary edema (Diblasi, 2009). NCPAP and NIPPV are commonly delivered using bi-nasal short prongs or a nasal mask to maintain the functional residual capacity (FRC) of the lungs and support gas exchanges to reduce apnea, work of breathing (WOB) and possible lung injury (Diblasi, 2009). The popularity of NIV has been increasingly evident over the past decade because it is less expensive, easier to operate, poses potentially fewer risks, and requires less training than intubation and subsequently conventional mechanical ventilation (Diblasi, 2009).

1.3 Guidelines for Maintaining Non-Invasive Respiratory Support

Standard policy in the Neonatal Intensive Care Unit (NICU) at BC Women's Hospital (BCWH) is that physicians order non-invasive respiratory supportive care for infants. The routine uses of NCPAP and NIPPV within minutes after birth for all newborns with respiratory distress of various etiologies is encouraged. The standard guidelines in the NICU at BCWH for respiratory care for new born infants involving NIV are specific in the selection of the correct prong size, mask size, hat fitting, and the use of lateral straps (Figure 1). The prong size must be easily placed in nares, have adequate seal without persistent blanching of nares, keeping cannula away from the septum to prevent pressure sores and to monitor nasal septum and upper lip for signs of redness and breakdown. The hat size needs to be snug but not tight, monitored for

pressure points on bridge of nose, on upper lip and at base of nose, and to ensure the mask does not touch the eyes. The hat fitting will cover the forehead just above the eyebrows and the back of the hat extends to the base of the neck. The registered nurse (RN) or registered respiratory therapist (RRT) will ensure the hat fit keeps the nares in a neutral position with no pulling of the nose upwards or sideways and the ears are flat and not folded over. The hat fit is changed to a new appropriate size every 24 hour. The lateral straps will have gentle equal tension to secure prongs with no indentations into cheeks. The placement of the lateral straps should be away from the eyes. The infants were positioned supine, prone or on their sides, but nurses routinely alternate their positions.

During NIV, the caring practitioner will do a physical examination daily assessing appearance, respiratory rate, grunting, nasal flaring, fraction of inspired air (FiO2) requirements, FiO2 saturation trends, heart rate, blood gas results, apnea/bradycardia episodes. An extensive assessment occurs every 4-6 hours, which includes a combined RN and RRT respiratory examination. The exam includes the assessment of skin integrity of nares, lip, nasal septum and bridge, compress tip of nares and note if nares remain symmetrical. Throughout the respiratory care for these premature infants, the same NIV system was used but nasal prongs and masks were often used alternatively, switching the devices every 4-6 hours. The decision made to change the type of interface will be for prevention and management of nasal/facial injury. Every hour, the RN or RRT will be doing skin assessments. During the skin assessment, the RN/RT will gently lift the mask interface and place it back onto the skin (the lift/drop technique). The RN/RT will also pull back the bar on the prongs interface from the septum to keep an approximate space of 2-3mm between the prong and septum. If the skin is red, the mask/prongs are repositioned to change the pressure that the equipment may be placing on the skin. The area

is re-evaluated every 30 minutes to ensure injury has not worsened. Once redness has resolved, the RN/RRT will do skin assessments every hour. A pressure of 5-7 cm H2O is maintained, and oxygen is adjusted. If NIV is insufficient to ventilate and oxygenate the patient, oral intubation and mechanical ventilation is used. When the respiratory distress improves, patients are weaned off mechanical ventilation and are extubated to NIV. The documentation for respiratory care includes the nursing flow sheet, the respiratory flow sheet and the bedside information tool (BIT).

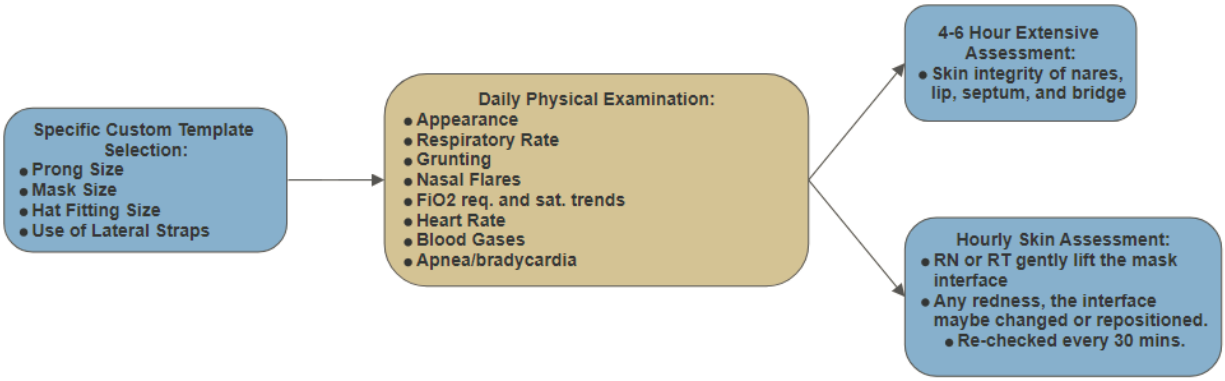

Figure 1 - Standard policy and guidelines for NIV therapy in the NICU at BCCH

1.4 Normal Craniofacial Growth and Development

1.4.1 Normal Cranial Growth

The cranium functions to protect the brain and establishes a platform for craniofacial growth and development. The cranium's morphology is associated with brain development, facial orientation and evolutionary changes (Adams & Moore, 1975; Hou, Liu, Gong, Shao, & Zhang, 2014). During postnatal development of the cranium, substantial changes in size, shape

and proportions of the cranium occurs in all three dimensions: anteroposterior, vertical and transverse dimensions (Meyer-Marcotty et al., 2014). The fastest rate of increase in head circumference was discovered to be during the first year of life and slower growth until three years of age and minimal growth thereafter (Hou et al., 2014). The skull growth index by age six were close to those of adults (Hou et al., 2014). The high growth rate of the cranium in the first year of life suggest disruption of growth and development during this critical period may have long lasting effects on the morphology of the cranium which may lead to unfavorable growth of the facial complex (Meyer-Marcotty et al., 2014).

1.4.2 Normal Maxillary Complex and Mandibular Growth and Development

Anthropometric information regarding normal growth of the craniofacial skeleton and soft tissue is essential for studies to examine pattern of postnatal growth in patients receiving therapy involving the face or with specific craniofacial syndromes. The soft tissue facial tomography can provide useful information on inferencing on the patient's skeletal morphology (Farkas & Posnick, 1992; Farkas, Posnick, & Hreczko, 1992). Farkas et al. examined age-related growth changes using surface measurements from healthy North American Caucasians between one and eighteen years of age (Farkas et al., 1992). Data from birth to one year of age was omitted due to small sample size available and difficulty of obtaining reliable anthropometric measurements in uncooperative infants (Farkas & Posnick, 1992; Farkas et al., 1992).

The facial height is recognized as the vertical projective profile distance measured between the nasion point at the root of the nose and the chin point (gnathion). By age one, the development of the upper facial height (nasion to stomion) is approximately 67% of the eventual adult size in both sexes (Farkas et al., 1992). By one years of age, the mandibular height reached

66% of the eventual adult size in both sexes (Farkas et al., 1992). The heights of the face, upper face and mandible showed the highest relative growth increments until maturity from age one (Farkas et al., 1992).

The facial width is recognized as the bizygomatic diameter of the upper face (right zygion to left zygion) and the mandibular width is recognized as the bigonion diameter (right gonion to left gonion). By age one, the mean development of the facial width approaches 72% of its eventual adult size in both sizes (Farkas et al., 1992). By age one, the mean development of the mandibular width approaches 80% of its eventual adult size (Farkas et al., 1992). The observation of the surface morphology shows that by age one, the width of the face (bizygomatic diameter) and the mandible (bigonion diameter) are further developed in relation to their adult size than the development of facial height (Farkas et al., 1992).

The middle third face depth is the projective distance between the tragion landmark of the ear and the subnasale point localized at the midpoint of the columella base. The lower third face depth is the projective distance between the ear's tragion landmark and the chin point (gnathion). The middle third of the face depth is seen to approach 76% on average of its eventual adult size in both sexes by age one (Farkas et al., 1992). The mean lower third face depth growth approaches 74% of its eventual adult size in both sexes by age one (Farkas et al., 1992). The depth of the maxilla and mandible are further developed by age one than the vertical heights of the facial profile (Farkas et al., 1992).

Overall, it is apparent that the mandibular width exhibited advanced development by age one and grew little to reach its adult size. The vertical facial height continues growth and development after age one and rapid growth is mostly seen between ages one and four (Farkas et

al., 1992). The mandibular height increased the most after one year of age compared to other vertical facial measurements (Farkas et al., 1992).

The results of a systematic scoping search for craniofacial anthropometry data in full-term healthy infants are sparse. Sinha et al. measured craniofacial anthropometry in full-term newborns of Sikkimese origin and found the commissural length is the only craniofacial parameter to vary significantly with sex (Sinha, Tamang, & Chakraborty, 2014). The full-term Sikkimese newborn skulls were observed to be hyper-brachycephalic with no significant difference between sexes (Sinha et al., 2014). However overall, anthropometric parameters are known to be affected by factors related to genetics, environment, geography, sex and age (Sinha et al., 2014).

1.5 Craniofacial Growth and Development in Prematurely Born Children

1.5.1 Craniofacial Morphology in Prematurely Born Children

Studies have shown craniofacial morphology of prematurely born children to be different than children born full-term (Harila-Kaera et al., 2002; Paulsson & Bondemark, 2009; Paulsson et al., 2004; Paulsson et al., 2008). A study comparing full-term children, who were matched for sex, age, nationality and living area, to extremely preterm and very preterm children discovered that extremely preterm children had a significantly shorter anterior cranial base and a less convex skeletal profile than full-term children at age 8 to 10 (Paulsson & Bondemark, 2009). A significantly shorter maxillary length was also seen for extremely and very preterm groups compared to full-term children (Paulsson & Bondemark, 2009). The discovery of a shorter maxillary length and anterior cranial base corresponded with the smaller head circumference also observed in extremely premature children (Paulsson & Bondemark, 2009).

1.5.2 Oral and Dental Morphology in Prematurely Born Children

Studies have shown oral and dental morphology of prematurely born children to be different than children born full-term (Harila-Kaera et al., 2002; Paulsson & Bondemark, 2009; Paulsson et al., 2004; Paulsson et al., 2008). There are higher frequencies of palatal grooving, high-arched palate, malocclusion and palatal asymmetry in extremely and very preterm children compared to children born full-term (Harila-Kaera et al., 2002; Paulsson et al., 2004). Orotracheal or nasotracheal intubation is common during neonatal care for extremely and very preterm infants and can account for these oral defects (Angelos, Smith, Jorgenson, & Sweeney, 1989). The presence and pressure from the oral tube on the palate can result in growth inhibition and remodeling around the oral tube (Angelos et al., 1989; Seow, 1986). When comparing the extremely preterm to the very preterm children at age 8 to 10, the lower incisors were significantly more retroclined and retruded (Paulsson & Bondemark, 2009). The permanent incisors are expected to continuously achieve a more proclined position from 5 to 16 years of age while in the present study, the lower incisors were found to be significantly more retroclined in the extremely preterm group compared to the very preterm group and full-term control group (Paulsson & Bondemark, 2009). Because of early birth, growth and development has possibly been unable to catch-up to the expected chronological age. Deep bite, more than two third of the mandibular incisors were covered by the maxillary incisors, was also a common finding in children born extremely preterm compared to children born full-term (Paulsson et al., 2008). Enamel defects such as quantitative loss of enamel (hypoplasia), qualitative changes in the translucency of enamel (opacity) or combination of both can be recognized in premature infants (Kopra & Davis, 1991; Seow, 1997). These defects are normally located on permanent teeth

which were undergoing mineralization around the time of premature birth (Seow, 1997). The altered palatal morphology can lead to increase in malocclusion such as crossbite, resulting in an increasing need for orthodontic treatment in late childhood which was evident in Paulsson et al. 2008 (Paulsson et al., 2008; Seow, 1997). There was a greater prevalence of crossbite found in two groups of children (ages three to five and seven to ten years old) who had been intubated neonatally and were of low birth-weight compared to same-aged children of average birth weight who were not intubated at birth (Kopra & Davis, 1991). Kopra and Davis findings of localized enamel defects among previously intubated three to five year old children and a greater prevalence of high vaulted palates and palatal grooving among children that were born prematurely and intubated, indicate strong support for intubation as a cause of oral defects among neonatally intubated children (Kopra & Davis, 1991). Other studies have debated this correlation. Seow et al. demonstrated no difference in palatal morphology between intubated and non-intubated two-to-five year old children and Fadavi et al. found no significant prevalence of crossbite in the primary dentition between premature and control groups (Fadavi, Adeni, Dziedzic, Punwani, & Vidyasagar, 1992; Kim Seow, Tudehope, Brown, & O'Callaghan, 1985). However, it is difficult to qualitatively or quantitively standardize the deformity of the palate and confounding factors such as non-nutritive habits such as thumb sucking is not always considered in these retrospective studies. Another confounding variable that is not considered is the development of the dentition (primary or mixed dentition). Studies have demonstrated delay in tooth maturation, development and eruption among premature children, but when corrected age was considered, there was no delay found in tooth maturation, development and eruption (Paulsson et al., 2004; Seow, 1996; Seow, Humphrys, Mahanonda, & Tudehope, 1988).

1.6 Craniofacial Growth and Development and NIV Therapy

1.6.1 Craniofacial Soft Tissue Changes with NIV Therapy

Though an essential life supporting treatment, respiratory therapy is not without side effects. The skin injuries and facial deformities that can occur with NIV therapy have been well documented (Fauroux et al., 2005; Fischer et al., 2010; Hogeling, Fardin, Frieden, & Wargon, 2012; K. K. Li, Riley, & Guilleminault, 2000; Y. Li, Sepulveda, & Buchanan, 2015; Villa et al., 1997; Villa, Pagani, Ambrosio, Ronchetti, & Bernkopf, 2002; Yong, Chen, & Boo, 2005). The current CPAP machines are effective in maintaining positive end expiratory pressure (PEEP) but do so while applying pressure on the nares, nasal septum and forehead leading to decreased skin integrity and injury in neonates (Newnam et al., 2013). Fischer et al. have reported nasal trauma in approximately 42.5% of neonates using NCPAP, with incidence and severity of trauma inversely correlated with gestational age and birth weight (Fischer et al., 2010). It was further noted that neonates less than 32 weeks of gestational age, weighing less than 1500g at birth, treated greater than 5 days by NCPAP or staying greater than 14 days in the NICU were at greater risk for nasal trauma (Fischer et al., 2010). Fauroux et al. found skin injury such as transient or prolonged erythema to occur in approximately 48% of their sample pediatric population, including an 8% incidence of skin necrosis. This same group also subjectively reported global facial flatting in 68% of patients (Fauroux et al., 2005). These incidences may vary depending on the proactive preventative measures taken. There was no correlation observed with age or the type of mask used or the underlying disease but there was an association with prolonged daily use of NIV (Fauroux et al., 2005). Another study characterized nasal deformities seen in adolescent and adult patients who had been admitted to NICU for NCPAP treatment at a mean gestational age of 26 weeks (Y. Li et al., 2015). The nasal soft triangle and columella were

most commonly affected showing notching, soft tissue deficiency, asymmetry scarring or retraction (Y. Li et al., 2015). A change of a commercial mask for a custom-made mask did show an association with reduction of skin injury (Fauroux et al., 2005).

1.6.2 Characteristics of Craniofacial Growth and Development of NIV Therapy

It should be noted that previous studies have not been able to separate the effects of the preterm birth itself from the medical interventions typically implemented in the preterm infants. In other words, it is unclear if the tendency towards midface deficiency or a Class III malocclusion in preterm cohorts is due to alterations in neuromuscular activity, or a direct result of the medical interventions of the perinatal period (Harila-Kaera et al., 2002). The ability of neonatal interventions to impact growth and morphology has been clearly demonstrated with the more invasive oral intubation, which can cause palatal grooving, high-arched palate, dental crossbite, and palatal asymmetry, however less is known about NIV (Macey-Dare, Moles, Evans, & Nixon, 1999; Paulsson et al., 2004). Studies on the facial morphology following NIV have mostly evaluated and characterized findings based on photographs, direct observation, or lateral cephalometric analysis (Fauroux et al., 2005; Fischer et al., 2010; K. K. Li et al., 2000; Y. Li et al., 2015; Tsuda, Almeida, Tsuda, Moritsuchi, & Lowe, 2010; Villa et al., 1997; Villa et al., 2002). Li et al. presented a case report on the development of mid-face hypoplasia in a healthy, non-syndromic, 15-year-old African-American patient with regular use of a face mask interface for NIV therapy over a ten-year period (K. K. Li et al., 2000). The patient displayed a skeletal class III relationship and a lateral cephalometric radiograph confirmed a retrusive maxillary position in relation to the anterior cranial base (K. K. Li et al., 2000), which was considered to extend far beyond population norms (Dean et al., 1998; Talbert, Kau, Christou, Vlachos, &

Souccar, 2014). This case highlights the commonly held belief that it is the constant pressure from a facemask interface on the developing midface which causes impairment of mid-facial growth (K. K. Li et al., 2000; Y. Li et al., 2015; Villa et al., 2002). From the foundation of literature in both orthodontics and facial growth and development, long term NIV treatment using a nasal or facemask likely carries a high risk for facial growth impairment but further evidence is needed (K. K. Li et al., 2000; Y. Li et al., 2015; Villa et al., 2002).

1.7 Stereophotogrammetry

Stereophotogrammetry is a non-invasive technique that permits acquisition of a true representation of the human face without exposure to ionizing radiation on the principle of photographing a 3D object with two pairs of identical cameras at a known base distance (Brons et al., 2013). There is currently a lack of evidence of its use in infancy. 3D surface imaging systems can be simpler and take less time than traditional photography as some machine-vision camera-based stereophotogrammetry systems are so fast that the erratic movements of young children do not effect image acquisition (Lane & Harrell, 2008). The 3D surface imaging system enables extra-oral imaging protocols to be precise and highly accurate at recording facial surface structures for diagnosis, analysis, treatment monitoring, simulation and outcome evaluation (Lane & Harrell, 2008). One such system of 3D photogrammetry is the 3dMDface (3dMD LLC, Atlanta, GA, USA) digital imaging system that covers 180-degree face and neck capture (ear-to-ear) in less than 2 milliseconds (Aldridge, Boyadjiev, Capone, DeLeon, & Richtsmeier, 2005; Tzou et al., 2014). The 3dMD system works by projecting light patterns from an industrial-grade flash system onto the surface of interest, such as the human face, and two statistic modular units with machine vision cameras are synchronized to perform a single capture (Aldridge et al., 2005;

Tzou et al., 2014). Since the synchronized cameras are used to capture a single shot in the same moment in time, the technology removes a potential source of error in post-data capture "stitching" of multiple images when creating a valid 3D representation of the subject (Aldridge et al., 2005). The three-dimensional surface geometry and texture are captured at the time of data acquisition. The 3dMD system is controlled by the investigator at the PC-controller desktop or laptop (Aldridge et al., 2005; Tzou et al., 2014). Algorithms developed by 3dMD integrate the various 3D surface geometry and texture to obtain a single 3D representation of the subject (Aldridge et al., 2005). The investigator can use the 3dMD software on the PC-controller to visualize and analyze the images. Aldridge et al. have demonstrated that images captured by the 3dMD system are highly reliable and that the 3D landmark data can be acquired with a high degree of precision (Aldridge et al., 2005). The error associated with the placement of landmarks on the 3dMD images is sub-millimeter (Table 1) (Aldridge et al., 2005). However, the glabella and gonion landmarks were demonstrated to have markedly decreased precision (error greater than 2mm) (Aldridge et al., 2005). Aldridge et al. have demonstrated both the error due to digitalization and error due to the 3dMD imaging system are very low, less than 1% and 1.5% respectively (Aldridge et al., 2005).

1.8 Craniofacial anthropometry

Craniofacial anthropometry uses a series of measurements and proportions of landmarks on surface features of the head, face and ears to characterize morphology and changes over time. Traditionally, anthropometric measurements are acquired through direct measurements using calipers or metric tape to measure distances between landmarks (Budai, Farkas, Tompson, Katic, & Forrest, 2003). However, the direct collection of quantitative data points from young children

can be challenging and time-consuming for both the child and the investigator (Budai et al., 2003). Traditional lateral and frontal photographs, while quick and simple to perform have well-known limitations associated with accurately recording three-dimensional (3D) geometry on a two-dimensional (2D) plane (Lane & Harrell, 2008). Further limitations of 2D photography include varying distances between camera and subject, camera angle, head position (roll-pitch-yaw orientations), and photography protocol inconsistencies (Lane & Harrell, 2008). The latest technological advances in 3D surface imaging have begun to erode barriers to safely make human 3D data input precise and easy to obtain (Lane & Harrell, 2008). 3D imaging systems have provided solutions to collect 3D coordinate data points directly from humans and digitize an image for 3D analysis (Aldridge et al., 2005).

1.9 The Neonatal Follow-up Program (NFUP)

The Neonatal Follow-up Program (NFUP) at the BCWH was started in 1983 to collect information about the quality of survival of high-risk infants in the province of British Columbia, Canada. The primary goals of the NFUP are to evaluate the short and long-term outcome of perinatal/neonatal intensive care and specific complex therapies by sequential longitudinal neuro-developmental assessment of infants during infancy and early childhood. These assessments provide discoveries to impairment early in this high-risk population to promote early application of interventional techniques to minimize the severity of perinatal acquired disability. The NFUP continues to promote and carry out research to further knowledge of the long-term effects of selected aspects of perinatal and neonatal management. These infants and children are seen for appropriate sequential neurodevelopmental assessments at 4, 8, 18 months, 3 years and 4.5 years corrected age at the BC Woman's and Children's Hospital. Currently, there is

anecdotal evidence from the neonatal department of global facial flattening through craniofacial growth and development of these infants having a history of prolonged NIV therapy. However, the exact impact that NIV therapy may have on both the short and long-term craniofacial growth and development of the child remains to be characterized.

1.10 The Canadian Neonatal Network (CNN)

The Canadian Neonatal Network (CNN) consist of researchers who collaborate on research topics related to neonatal care. The CNN was found in 1995 by Shoo Lee, MBBS, FRCPC, PhD and now includes members from 30 hospitals and 17 universities across Canada. On a national and international scale, CNN maintains a standardized database on neonatal intensive care and provides a unique opportunity for researchers to participate in collaborative projects. The CNN's goal is to establish a national network of multi-disciplinary Canadian researchers interested in neonatal-perinatal research aimed to improve efficiency and efficiency of neonatal care. NICU care is one of the largest components of child health expenditures and exhibits large variations in mortality, morbidity and cost. The CNN establishes and maintains a national neonatal-perinatal database available to facilitate longitudinal studies to determine outcomes and variation in medical care that increases costs but does not improve outcomes.

1.11 Study Purpose

The purpose of this study is to determine whether, using three-dimensional facial morphology in a cohort of preterm infants at 4, 8 and 18 months corrected age treated with NIV show clinically significant effects of NIV therapy on craniofacial growth and development. The minimal expected outcome from this study would be the creation of normative data for 3D facial

morphology of preterm children in the first 18 months of life after corrected for age. Comparison can then be made to current published data on the morphology of infants born at term (Krimmel et al., 2015). Through the integration of medical intervention and morphologic data, the project will take the first steps towards testing the hypothesis that NIV alters facial morphology in children. The long-term extension of these findings will be to inform future respiratory management protocols for prematurely born infants. Perhaps the most interesting, this project will serve to generate further hypotheses on the mechanisms of early facial growth and development by evaluating the effects of early forces placed on facial structures. As evaluating the outcomes of neonatal therapies is the primary goal of the Neonatal Follow-Up Program, this project will serve to develop the role of orthodontics in the interdisciplinary assessment and management of this most fragile of patient populations and improve our understanding of early effects of premature birth on the growth and development of the face.

1.12 Hypothesis Generating

The pilot study will investigate potential exploratory variables and recruitment challenges to generate a hypothesis. The pilot study anticipates early forces placed on facial structures during NIV therapy in healthy prematurely born infants at 4, 8 and 18 months corrected age will show significant impediment on growth and development of craniofacial structures.

1.13 Objective

The objective of this pilot study is to evaluate the use of neonatal non-invasive ventilation (NIV) therapy and its effect on craniofacial morphology in newborn infants undergoing respiratory care in the neonatal intensive care unit (NICU) at the B.C. Women's Hospital and

Health Center (BCWH). We will be exploring whether neonatal NIV therapy may affect the growth and development of the patient's face with the use of 3-dimensional surface imaging. The study aims to:

1. Characterize the three-dimensional facial morphology of a cohort of preterm infants at 4, 8 and 18 months corrected age.
2. Determine the effects of duration of NIV therapy on facial morphology at 4, 8 and 18 months corrected age.
3. Evaluate the feasibility, time, adverse events, and effect size (statistical variability) to predict an appropriate sample size to improve study design prior to performance of a full scale longitudinal research project.

Chapter 2: Methods

2.1 Study Design

This project is a prospective cohort pilot study with the overall objective to characterize the three-dimensional facial morphology of preterm infants over the course of the first 18 months corrected age, participating in the Neonatal Follow-up Program (NFUP) of BCWH in Vancouver, BC. To achieve this goal, infants reporting for follow-up at 4, 8, and 18 months corrected age (+/- 2 weeks) will be imaged with a 3dMD surface-imaging camera, and three-dimensional facial morphometric parameters will be related to anthropometric data at birth and the specific characteristics of respiratory therapy received during the neonatal period.

2.2 Study Sample and Recruitment

A systematic scoping search of the literature did not find any prospective cohort research data specific to the neonatal population for sample size calculation. Our prospective study will evaluate 4, 8 and 18-month corrected age premature (less than 37-week gestation) infants enrolled in the NFUP at the BCWH in Vancouver, BC, Canada. The NFUP enrolled a mean of 55 infants each year into the program from across the province of British Columbia. Anticipating a high rate of enrollment and minimal drop out as has been reported by the NFUP, the target is to image 100 patients at each time point to create a standard reference for facial morphology of prematurely born infants. The narrow 4 to 18-month old corrected age range was selected because there is high growth rate of the cranium in the first year of life that indicates any disruption of developmental processes during this critical period may have long-lasting effects on morphology of the cranium which may lead to permanent unfavorable growth and

development of craniofacial structures (Meyer-Marcotty et al., 2014). The NFUP focuses on infants with birth weight less than or equal to 800 grams, gestational age less than or equal to 25 weeks of gestation, intraparenchymal intracranial hemorrhage, cystic periventricular leukomalacia, severe retinopathy of prematurity, congenital diaphragmatic hernia, treatment with extracorporeal life support at the BCCH, or receiving home oxygen. Patients moving to British Columbia that do not meet the NFUP criteria are only seen once and directed to appropriate services. Very preterm children born at < 29 weeks gestation who don't meet any of the above criteria are seen once at 18 months corrected age.

2.2.1 Recruitment

Prior to patient follow-up at the NFUP at BCWH, an investigator (pediatric dental resident) received a list of patients a month prior to recruitment with the following information from the NFUP data manager: the patient's first and last name, the medical record number (MRN), visit date, visit age (4, 8 or 18 months corrected age) (Appendix A: 'Month' Screening Log). Using the patient's physical medical chart and BCWH PowerChart Solution Software (Cerner, Kansas City, Missouri, USA), the investigator screened the patients for the inclusion and exclusion criteria. The reason for the inclusion or exclusion of patients was documented on the initial given recruitment list of patients.

Patients fitting the inclusion and exclusion criteria were selected and recorded on the study's subject excel log (Appendix A: Subject Log). The investigator then assigned a study identification code (e.g. NIV001) to the selected patients and obtained the patients' contact information from BCWH PowerChart Solution Software (Cerner, Kansas City, Missouri, USA): the name of patient's guardian and relation, the guardian's telephone number, the mailing

address, and e-mail. All patient information identified by a study identification code was written on in the subject excel log. The screening log was sent to the NFUP data manager to organize a template with all the subject's NFUP appointment times for the investigator to access. The investigator used this template to plan time accordingly to acquire subject images. The project's clinical research coordinator then mailed an invitation letter and consent form to the mailing address at least two weeks prior to their scheduled appointment (Appendix A: Invitation Letter). The voluntary invitation letter encompassed a detailed background and description of our research project in characterizing craniofacial changes in their child after the use of NIV therapy. The letter also detailed the purpose of the study, our inclusion and exclusion criteria, total time required for all study visits, potential risks of harm or side effects of participating, optional withdrawal of consent to participate, patient confidentiality, the investigator contact information, and information on reimbursement for additional parking expenses for participating. A participant consent to participate form was attached at the end of the letter for the guardian to have time to read and have an informed understanding of the request for their consent to acquire a 3D surface image of their child's face at their neonatal follow-up appointment (Appendix A: Informed Consent Form). A telephone call was also provided the day prior to their scheduled appointment to ask if the patient's legal guardian has read the invitation letter and whether they are interested in providing consent for their child's participation in the study and whether they have any questions related to the study. Patients with consent from their legal guardian to participate in the study were then seen by the investigator for the 3D surface imaging in the otolaryngology clinic at BC Children's Hospital (same building as the NFUP) right before or after their NFUP appointment. A ten-dollar reimbursement for each study visit (up to three visits) was given to cover the cost of additional parking expenses for participating in the study.

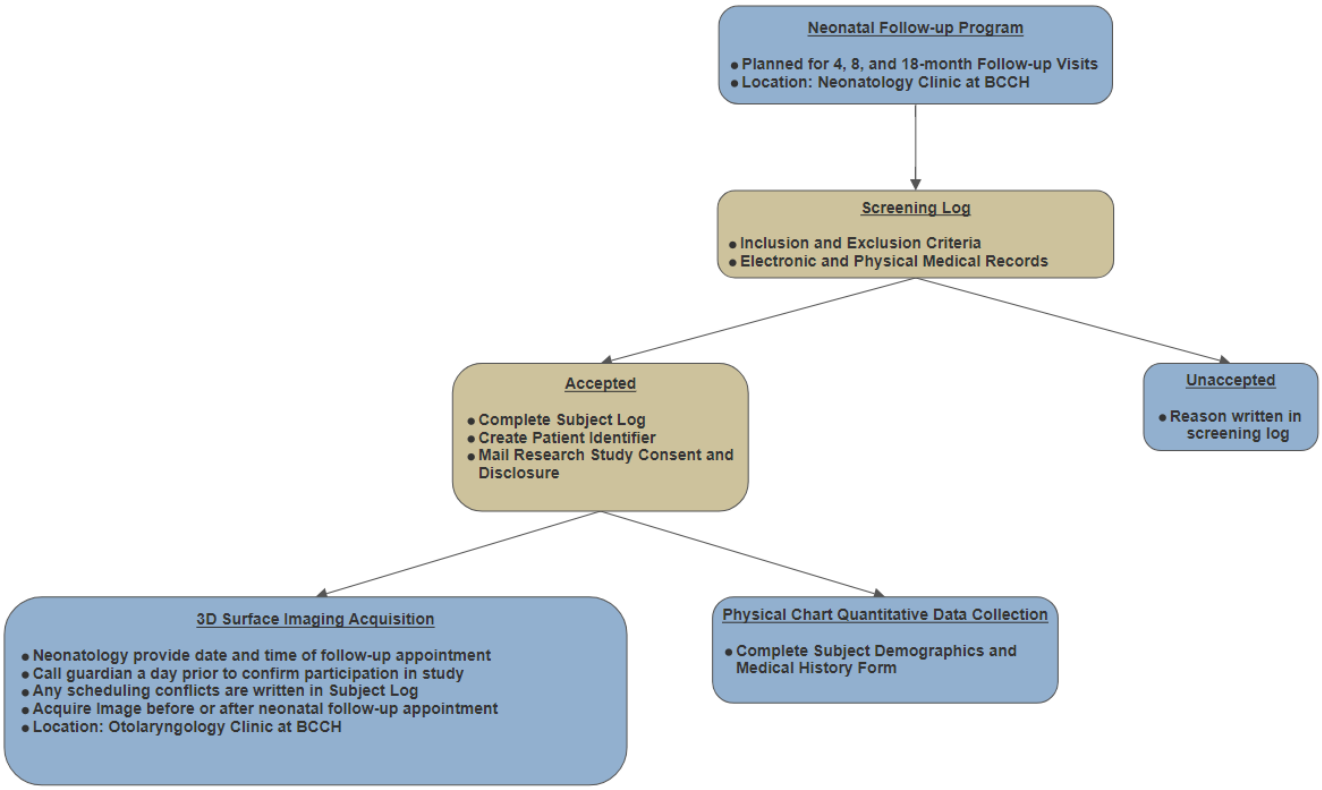

Figure 2 – Recruitment design flow diagram

2.2.2 Inclusion and Exclusion Criteria

The inclusion criteria in our study includes: patients that were (1) using NIV with or without mechanical ventilation and (2) born with gestational age less than 37 weeks. The exclusion criteria in this study are: patients that have (1) a diagnosed syndrome associated with craniofacial abnormalities, or (2) congenital craniofacial abnormalities.

2.2.3 Data Collection

The craniofacial morphology and the use of neonatal non-invasive ventilation therapy data collection form has the subject identification code and the acquisition date (Appendix A:

Subject Demographic and Medical History). The subject's information obtained from the physical NFUP chart, BCWH PowerChart Solution Software (Cerner, Kansas City, Missouri, USA), and the Canadian Neonatal Network (CNN) database was recorded in the data collection spreadsheet which includes patient's sex, ethnicity, gestational age in weeks at birth, birth weight in grams, birth length in centimeters, birth head circumference in centimeters, NIV duration in days, the mode of NIV attachment, the mode of feeding, the number of days in NICU and whether or not long term mechanical ventilation was used (Appendix A: Subject Demographic and Medical History). The subject's legal guardian(s) was asked about the child's ethnicity. The paternal and maternal ethnicity was also found in the patient's medical records. The patient's birth hospital and NICU stay hospital was recorded in the data collection spreadsheet. The process of obtaining the patient's demographic and ventilation therapy information required the investigator to review patient's health records at the BCWH archived record department. The health records could not be removed from the facility. If further information was required, the investigator reviewed the electronic health record using the BCWH PowerChart Solution Software. The investigator also accessed patient documents and read NICU admission summary and NICU discharge narrative word summary to access records on patient's demographics and ventilation treatment. If further data information was missing or questionable, the investigator sought the NICU data manager to access the CNN database.

2.2.4 Participation Incentives

The study provided a ten-dollar monetary imbursement for each voluntary participation by the patient (up to 3 visits) in the study provided consent is given by their legal guardian. The

monetary imbursement was intended to cover the cost of additional parking expenses for participating in this study.

2.2.5 Limitations/Barriers to Recruitment

Some of the main limitations or barriers associated with recruitment in this study included (1) the challenge of contacting the patient's legal guardian to seek voluntary participation the day prior to or the day of the NFUP appointment, (2) parent hesitation to participate due to child's participation in a number of other studies, (3) parent hesitation to participate due to the duration of the NFUP appointment that normally involves physiotherapy and clinical physical examination that typically takes two hours or longer, and (4) scheduling challenges due to multidisciplinary use of the otolaryngology clinic due to cleft palate clinics and craniofacial clinics and investigator hospital duties in the Dentistry clinic and the operating room.

2.3 Three-dimensional Stereophotogrammetric Imaging Acquisition with 3dMDface

Three-dimensional (3D) stereophotogrammetric surface images were acquired using the 3dMDface System (3dMD, Atlanta, GA, USA) at the BC Children's Hospital in the otolaryngology clinic following approved institutional review board protocols. An investigator (a pediatric dental resident or research coordinator) acquired a 3D surface image of each subject in coordinated recall appointments with NFUP at 4, 8 and 18-month assessment periods.

The 3dMDface System (3dMD, Atlanta, GA, USA) has two modular units with vision cameras and flash system mounted on the wall in an enclosed clinical examination room in the otolaryngology clinic at the BCCH (Figure 3). An upright motorized medical chair (Reliance Medical Product, Model 7000L, Mason, Ohio, USA) is situated facing the mounted cameras. An encrypted, offline and password protected desktop computer with appropriate processing capability, random access memory, and video card capability is used to seamlessly operate the 3dMDface System. The computer tower is wall mounted to the side and the computer monitor will be mounted directly in front of the upright motorized medical chair. A wireless keyboard with touchpad capability is used to control the 3dMDface System and image acquisition.

Figure 3 - Three-dimensional stereophotogrammetric imaging acquisition set-up in the otolaryngology clinic at British Columbia Children's Hospital.

Prior to each session, all cameras were calibrated and tested to ensure that the images will be consistent and usable. For each image, the child sits on the lap of a parent. The parent was sitting on the upright motorized medical chair and the investigator moved the chair up or down

until the infant's face is within the cross-hair of the software on the computer monitor directly in front. The investigator stood in front of the patient and parent in the motorized medical chair out of the field of view of the modular units. The investigator typically held a toy or bright object to get the child to hold his/her head up and look at the camera. If necessary, the parent may have to hold and posture the child's back of the head for appropriate facial imaging. Once the patient is comfortable with neutral facial expression including no grimace, no smile, and no raised eyebrows, the investigator acquired the image.

The patient facial characteristics are captured with multiple, precisely synchronized digital cameras configured in two modular units for a 180-degree face capture. The multiple cameras provide a single capture without the need for post-data capture "stitching" of multiple images into a single composite picture. Once the image is acquired, the algorithms developed by 3dMD integrates the multiple images to produce a single 3D image which can be visualized using the 3dMD Vultus software. The investigator acquired three images and reviewed the images in less than a minute to decide whether the images were acceptable. Unacceptable images that contain motion artifacts were deleted and acceptable images were saved as permanent files. The images were stored as proprietary software versions as *.tsb files from the 3dMD files on the encrypted and password protected desktop computer in a secure enclosed room in the otolaryngology clinic at BCCH. The otolaryngology clinic is locked after clinical hours and BCCH security will be patrolling the premise. Later, the 3D models of the faces were analyzed, and soft tissue landmarks identified, and then the 3D coordinates derived. A flow diagram is shown on Figure 4 showing a summary of the steps used to process and characterize the 3D images.

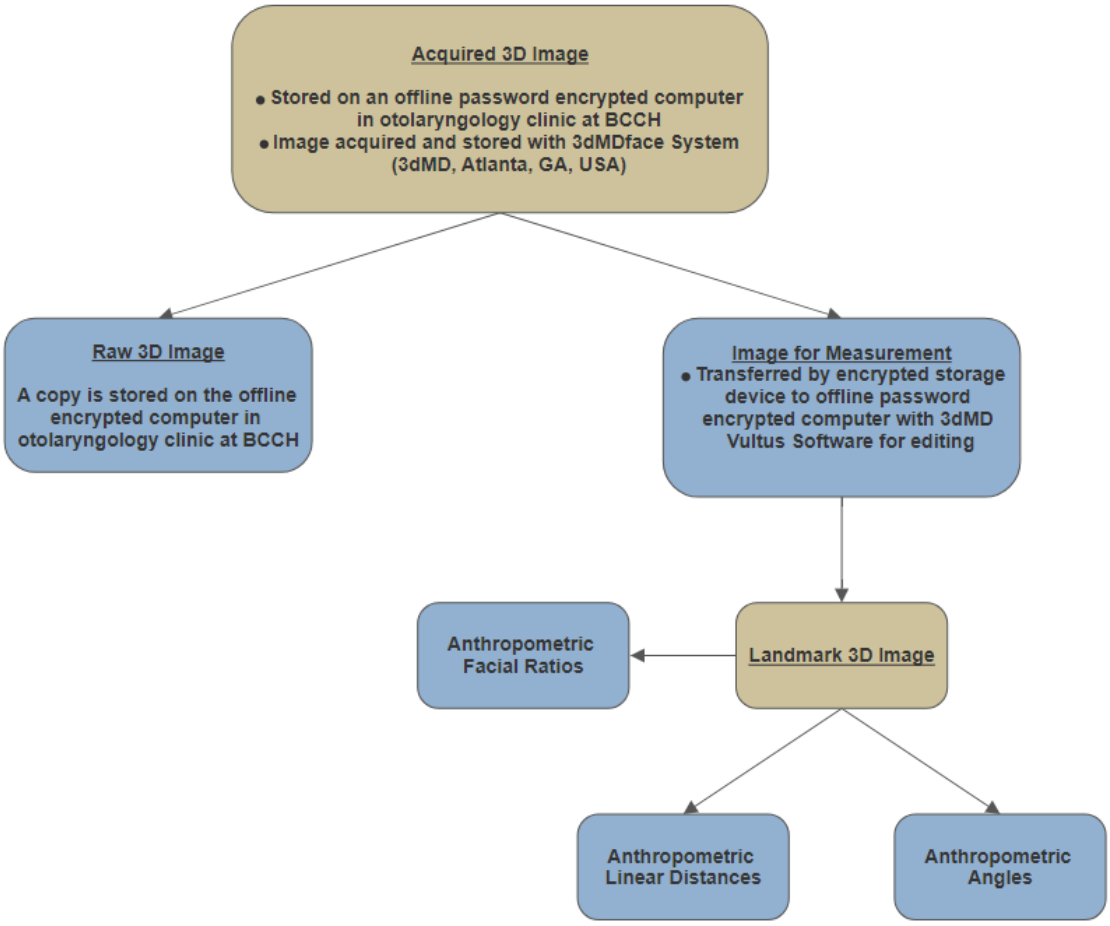

Figure 4 - Flow diagram for use of 3D image after acquisition

2.4 Physical Chart Quantitative Data Collection

Each patient that received 3D craniofacial surface imaging had their demographic and clinical characteristics recorded for statistical analysis. The NFUP will have recorded patient respiratory care data in the physical health records at BCCH. The investigator accessed the centralized health information resources for patients at the BCCH. The following available data including patient's sex, birth weight, birth length, non-corrected gestational age in weeks, NIV duration in days, birth head circumference, mode of feeding upon discharge and whether long

term mechanical ventilation was used was recorded (Appendix A: Subject Demographics and Medical History). Patient's ethnicity was disclosed by patient's parents or guardian.

Patient information that is not available in the patient's physical health records at BCCH was obtained by collaborating with the Canadian Neonatal Network (CNN) database.

2.5 Anthropometric Landmark Data

Anthropometry is the biological science of measuring the size, weight, and proportions of the human body, providing information to characterize phenotypic variation and morphology. Facial anthropometry involves measurements taken between landmarks defined on surface features of the face. The anthropometric landmark coordinate data collected from 3D digital photogrammetric images acquired with the 3dMDface system studied by Aldridge (Aldridge et al., 2005) were shown to be highly repeatable and precise (Figure 5). The 3D landmark coordinate data was collected for 29 landmarks on the 3D images using the 3dMD Vultus software program (Figure 6; Table 2). All landmarks were checked for gross errors prior to analysis. To determine reliability of data collection, an error study was also performed. The coordinate data was converted to all possible linear distances amongst the landmarks. The means, standard deviations and values of standard deviations as percentages of the linear distances were calculated for each image.

An encrypted, password protected and offline desktop computer with appropriate processing capability, random accessing memory and video card processing capability, using the 3dMD Vultus software program, was equipped and installed in the otolaryngology resident room at BCCH for refining and landmarking anthropometric images. A 27-inch high resolution monitor is equipped with the computer to facilitate analysis. Each acquired image was

transferred from the acquisition computer to the analysis computer via an encrypted USB and deleted once transferred. Each acquired image was assigned an identification number (eg. NIV001) that correlates to their data collected information. Unedited acquired images were stored and titled as a raw file. The raw acquired images were then cropped using 3dMD Vultus software tools for facial data that extends to the patient's ears, forehead and neck. Extraneous data such as the patient's clothes or parent's clothes or face incorporated into the image during data capture were cropped and removed. The cropped facial images are stored in a different folder marked as cropped files. The investigator then landmarked the face according to the 29 landmarks in Table 2. Once the facial images are landmarked, the images are stored as landmarked files. Distances between landmarks are then generated by 3dMD analysis and recorded in the Data Collection Spreadsheet (Appendix A: Data Collection Spreadsheet).

The investigator then created an analysis template with the investigated landmark distances and angles. For the facial transverse plane, the skull base width (T_R-T_L), the intercanthal width (EN_R-EN_L), the biocular width (EX_L-EX_R), the morphological nose width (AL_R-AL_L), the anatomical nose width (AC_R-AC_L), the labial fissure length (CH_R-CH_L) and the philtrum width (CPH_R-CPH_L) were analyzed. For the facial vertical plane, the analysis included the morphological face height (N-GN), the upper face height from nasion to stomion superior and upper face height from nasion to subnasale, the lower face height from stomion inferior to gnathion and lower face height from subnasale to gnathion, the nasal bridge length (N-PRN), the nose height (N-SN), the upper lip length (STO_S-SN), the cutaneous upper lip length (SN-LS), the upper vermillion height (LS-STO_S), the lower vermillion height (STO_I-LI), the cutaneous lower lip length (LI-SL) and the lower lip length (STO_I-LI). For the anterior posterior plane, the analysis included the right upper facial third depth (N-T_R), the left

upper facial third depth (N-T_L), the right middle third maxillary depth (SN-T_R), the left middle maxillary third depth (SN-T_L), the right lower facial third mandibular depth (PG-T_R), the lower left facial third mandibular depth (PG-T_L), the right alar depth (PRN-AL_R), the left alar depth (PRN-AL_L), the right alar base depth (PRN-AC_R), the left alar base depth (PRN-AC_L), the nose depth (PRN-SN). For facial angles, the subnasale angle (PRN-SN-LS), the nose protrusion angle (N-PRN-SN), the right upper face angle (N-T_R-SN), the left upper face angle (N-T_L-SN), the right upper and mid-face angle (N-T_R-SL), the left upper and mid-face angle (N-T_L-SL), the right morphometric face angle (N-T_R-GN), the left morphometric face angle (N-T_L-GN), the subnasal protrusion angle (AC_R-SN-AC_L), the alar slope angle (AL_R-PRN-AL_L), the mid-face depth angle (N-SN-SL) were assessed.

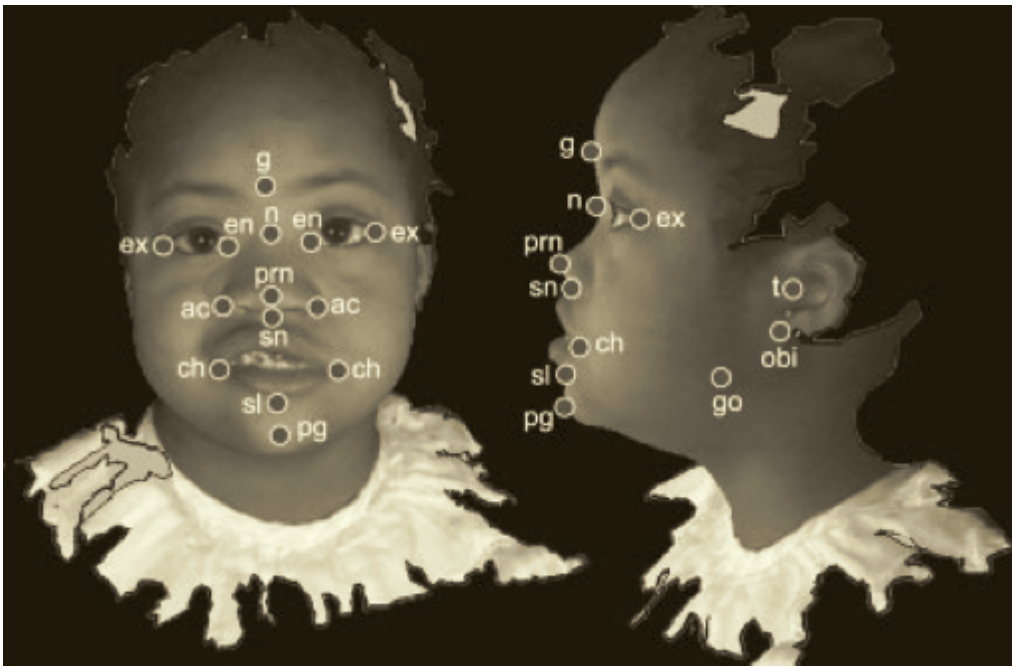

Figure 5. Facial landmarks. Glabella (g), Nasion (n), Pronasale (prn), Subnasale (sn), Sublabiale (sl), Pogonion (pg), Endocanthion left and right (en), Exocanthion left and right (ex), Alar curvature left and right (ac), Chelion left and right (ch), Tragion left and right (t), Otobasion inferius left and right (obi), and Gonion left and right (go). ***Adapted from Aldridge et al. 2005.***

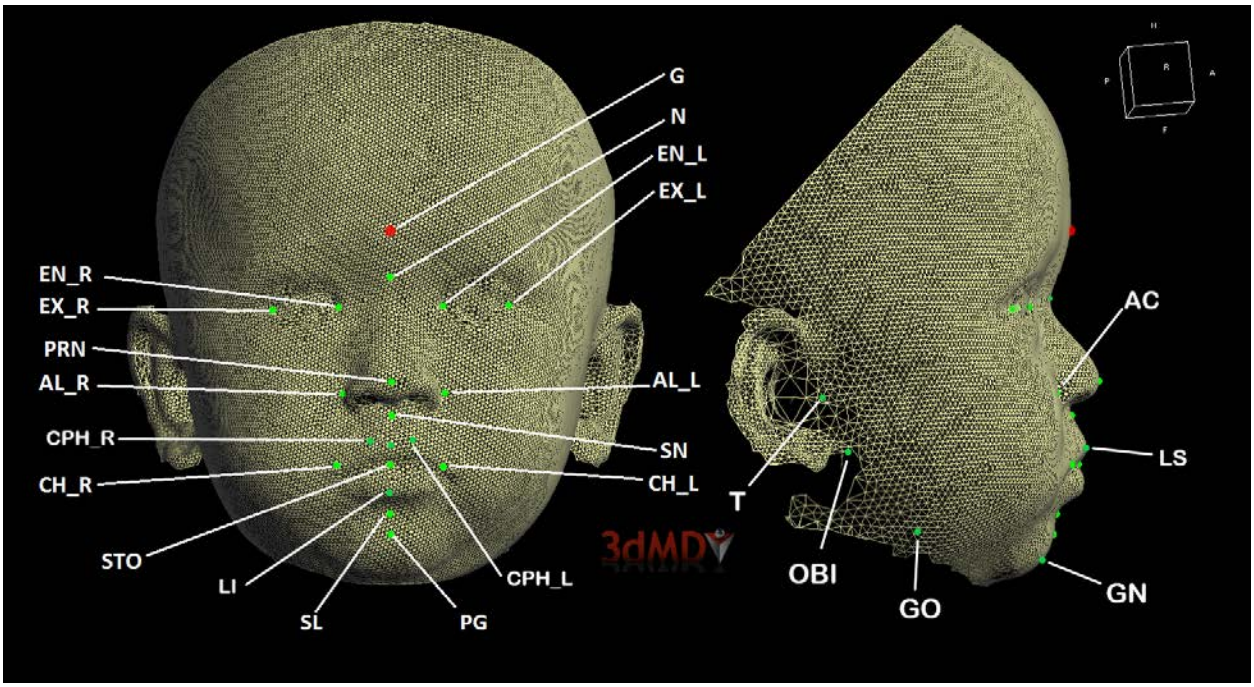

Figure 6 - Facial landmarks used for analysis. Glabella (G), Nasion (N), Endocanthion (EN), Pronasale (PRN), Subnasale (SN), Stomion (STO), Sublabiale (SL), Pogonion (PG), Exocanthion (EX), Alar (AL), Alar Curvature (AC), Labiale Superior (LS), Labiale Inferior (LI), Crista Philtri (CPH), Tragus (T), Gonion (GO), Otobasion Inferius (OBI), Gnathion (GN), and Commissure (CH). Symbols may have added right (_R) or left (_L) to indicate direction

Table 1 – Anthropometric landmark symbols

Anthropometric Landmark	**Symbol**
Alar	AL
Alar Curvature	AC
Commissure	CH
Crista Philtri	CPH
Endocanthion	EN
Exocanthion	EX
Glabella	G
Gonion	GO
Gnathion	GN
Labiale Inferior	LI
Labiale Superior	LS
Pronasale	PRN
Nasion	N
Otobasion Inferius	OBI
Pogonion	PG
Sublabiale	SL
Subnasale	SN
Stomion	STO
Tragus	T

Table 2 - Anthropometric landmarks for analysis with definitions

Landmark Name	**Landmark Label**	**Definition**
Nasion	N	The midpoint on the soft tissue contour of the base of the nasal root
Glabella	G	The most prominent midline between eyebrows
Endocanthion Right	EN_R	The soft tissue point located at the inner commissure of the right eye fissure
Endocanthion Left	EN_L	The soft tissue point located at the inner commissure of the left eye fissure
Pronasale	PRN	The most protruded point of the nasal tip
Subnasale	SN	The midpoint of the angle at the columella base where the lower border of the nasal septum and the surface of the upper lip meet
Stomion Superious	STO_S	The lowest point of the midline of the upper lip
Stomion Inferious	STO_I	The highest point of the midline of the lower lip
Labiale Superior	LS	The midpoint of the vermillion line of the upper lip
Labiale Inferior	LI	The midpoint of the lower vermillion line

Sublabiale	SL	The midpoint of the labiomental sulcus
Pogonion	PG	The most anterior midpoint of the chin
Exocanthion Right	EX_R	The soft tissue point located at the outer commissure of the right eye fissure
Exocanthion Left	EX_L	The soft tissue point located at the outer commissure of the left eye fissure.
Alar Right	AL_R	The most lateral point on the right alar contour
Alar Left	AL_L	The most lateral point on the left alar contour
Alar Curvature Right	AC_R	The most lateral point in the curved baseline of the right ala indicating the facial insertion of the nasal wing-base
Alar Curvature Left	AC_L	The most lateral point in the curved baseline of the left ala indicating the facial insertion of the nasal wing-base
Commissure Right	CH_R	The point located at the right labial commissure
Commissure Left	CH_L	The point located at the left labial commissure
Crista Philtri Right	CPH_R	The point at the right raised margin of the philtrum just above the vermillion line
Crista Philtri Left	CPH_L	The point at the left raised margin of the philtrum just above the vermillion line

Tragus Right	T_R	The most superior aspect of the right tragus where it abuts the face
Tragus Left	T_L	The most superior aspect of the left tragus where it abuts the face
Gonion Right	GO_R	The soft tissue point at the intersection of the right ramus and the right body of the mandible
Gonion Left	GO_L	The soft tissue point at the intersection of the left ramus and the left body of the mandible
Otobasion Inferius Right	OBI_R	The point of attachment of the right ear lobe to the cheek
Otobasion Inferius Left	OBI_L	The point of attachment of the left ear lobe to the cheek
Gnathion	GN	The lowest median landmark on the lower border of the mandible

ANTHROPOMETRIC LANDMARK DISTANCES:

FACE: (ears, nose, eyes, lips, mouth)

Transverse:

Skull Base Width (T_R-T_L)

Intercanthal Width (EN_R-EN_L)

Biocular Width (EX_L-EX_R)

Morphological Nose Width (AL_R-AL_L)

Anatomical Nose Width (AC_R-AC_L)

Labial Fissure Length (CH_R-CH_L)

Philtrum Width (CPH_R-CPH_L)

Vertical:

Morphological Face Height (N-GN)

Upper face height-I (N-STO_S)

Upper face height-II (N-SN)

Lower face height-I (STO_I – GN)

Lower face height-II (SN-GN)

Nasal Bridge Length (N-PRN)

Nose Height (N-SN)

Upper Lip Length (STO_S-SN)

Cutaneous Upper Lip Length (SN-LS)

Upper Vermillion Height (LS-STO_S)

Lower Vermillion Height (STO_I-LI)

Cutaneous Lower Lip Length (LI-SL)

Lower Lip Length (STO_I-LI)

Anterior-Posterior:

Right upper facial third depth (N-T_R)

Left upper facial third depth (N-T_L)

Right Middle third depth (SN-T_R) – Maxillary Depth

Left Middle third depth (SN-T_L) – Maxillary Depth

Right lower facial third depth (PG-T_R) – Mandibular Depth

Left Lower facial third depth (PG-T_L) – Mandibular Depth

Right Alar Depth (PRN-AL_R)

Left Alar Depth (PRN-AL_L)

Right Alar Base Depth (PRN-AC_R)

Left Alar Base Depth (PRN-AC_L)

Nose Depth (PRN-SN)

Angles:

Subnasale Angle (PRN-SN-LS)

Nose Protrusion Angle (N-PRN-SN)

Right Upper Face Angle (N-T_R-SN)

Left Upper Face Angle (N-T_L-SN)

Right Upper and Mid Face Angle (N-T_R-SL)

Left Upper and Mid Face Angle (N-T_L-SL)

Right Morphometric Face Angle (N-T_R-GN)

Left Morphometric Face Angle (N-T_L-GN)

Subnasal Protrusion Angle (AC_R-SN-AC_L)

Alar Slope Angle (AL_R-PRN-AL_L)

Midface Depth Angle (N-SN-SL)

Facial Ratios:

Morphological Face Height (N-GN) to Skull Base Width (T_R-T_L)

Upper Face Height – I (N-STO_S) to Skull Base Width (T_R-T_L)

Upper Face Height – II (N-SN) to Skull Base Width (T_R-T_L)

2.6 Characterization and Analysis of Three-Dimensional Morphometric Data

The investigator characterized the three-dimensional craniofacial morphology of pre-term infants at 4, 8, and 18-month neonatal follow-up visits by determining the average and standard deviation of the linear distances in three facial planes (transverse, vertical and anterior-posterior), facial side-profile angles, and facial ratios.

The investigator assessed the average and standard deviation of the transverse, vertical and anterior-posterior linear distances, facial side-profile angles and facial ratios for the 4, 8 and 18-month cohort separated by patient's sexes. The characterization of morphometric data based on patient's sex provided observational insight on the possible measurement difference between male and female cohorts.

2.7 Statistical Analysis

Pearson's correlation coefficients and univariate linear regression were calculated to determine correlations between NIV duration with linear and angular facial dimensions and facial ratios. Linear model analysis was performed to identify the explanatory variables (gestation age, birth weight, birth length and birth head circumference) that may affect each of the morphological parameters.

To determine the reliability of the investigator anthropometric landmarks, the investigator re-landmarked the same 43 3D facial images initially landmarked. The linear distances in the transverse, vertical and anterior-posterior planes were re-measured on the second landmarked images. The mean difference for each linear distance were then calculated and a 95% confidence interval was determined. The mean linear distance measurements that fall within the 95% confidence interval were deem reliable.

As previously described, coordinate data was converted to the linear distances among the landmarks. The means, standard deviations and values of standard deviations as percentages of the linear distances was calculated for each linear distance. The ranges of the standard deviations were expressed as percentages of linear distance for the linear distances evaluated, and linear distances with standard deviations greater than 5% of the mean were considered less reliable.

2.8 Data Storage and Handling

All participant data, including 3D images, were stored electronically using Vultus Software. All electronic files are password protected and encrypted. Information about study patients and study materials are kept on a password protected computer in the otolaryngology clinic at BCCH. The study records are stored on this computer five year after the study has completed after which they will be permanently erased from the Vultus Software database as well as from the computer, and all paper files will be shredded.

2.9 Study Risks or Limitations

There are no expected risks associated with participating in this study.

Chapter 3: Results

3.1 Description of Recruitment

In this prospective cohort study, 143 patients were screened to fit the study's inclusion and exclusion criteria (Figure 7 – Recruitment flow diagram). A total of 41 patients out of 143 screened were excluded from the study. In summary, 10 patients did not fit our study because they had a congenital craniofacial abnormality, 12 patients did not have a medical record at BCCH due to NICU care at another hospital, 4 patients were not born pre-term, 7 patients did not receive any non-invasive ventilation therapy, and 8 patients had insufficient medical record on respiration. A total of 102 patients out of 143 screened patients were deemed eligible for recruitment for the study. The study successfully imaged 42 patients out of the 102 patients accepted into the study. Two patients did not show to their first appointment but did show up to their first rescheduled appointment and the investigator was able to obtain an image for each patient. There were 4 patients out of the 42 successfully imaged patients returned for their next neonatal follow-up. The investigator was unable to obtain images for 3 patients due to time conflict with the operating time of the cleft palate team use of the needed otolaryngology examination room; an image was successfully captured for one out of the four returning patients. The study successfully acquired a total of 43 images of patients followed up at 4, 8 and 18 months. The study unsuccessfully recruited 60 patients out of 102 patients eligible for the study. In summary, the study was unable to contact 2 patients; the investigator was unavailable to acquire images for 28 patients; 15 patients failed to show up to their appointment; the guardians of 15 patients did not provide consent to participate; and 2 out of 15 patients that did not show up to their initial appointment had rescheduled their appointment. One patient was rescheduled

twice and failed to show. The other patient was rescheduled three times and failed to show. A detailed description of the monthly log of the study recruitment can be found in Appendix A.6.

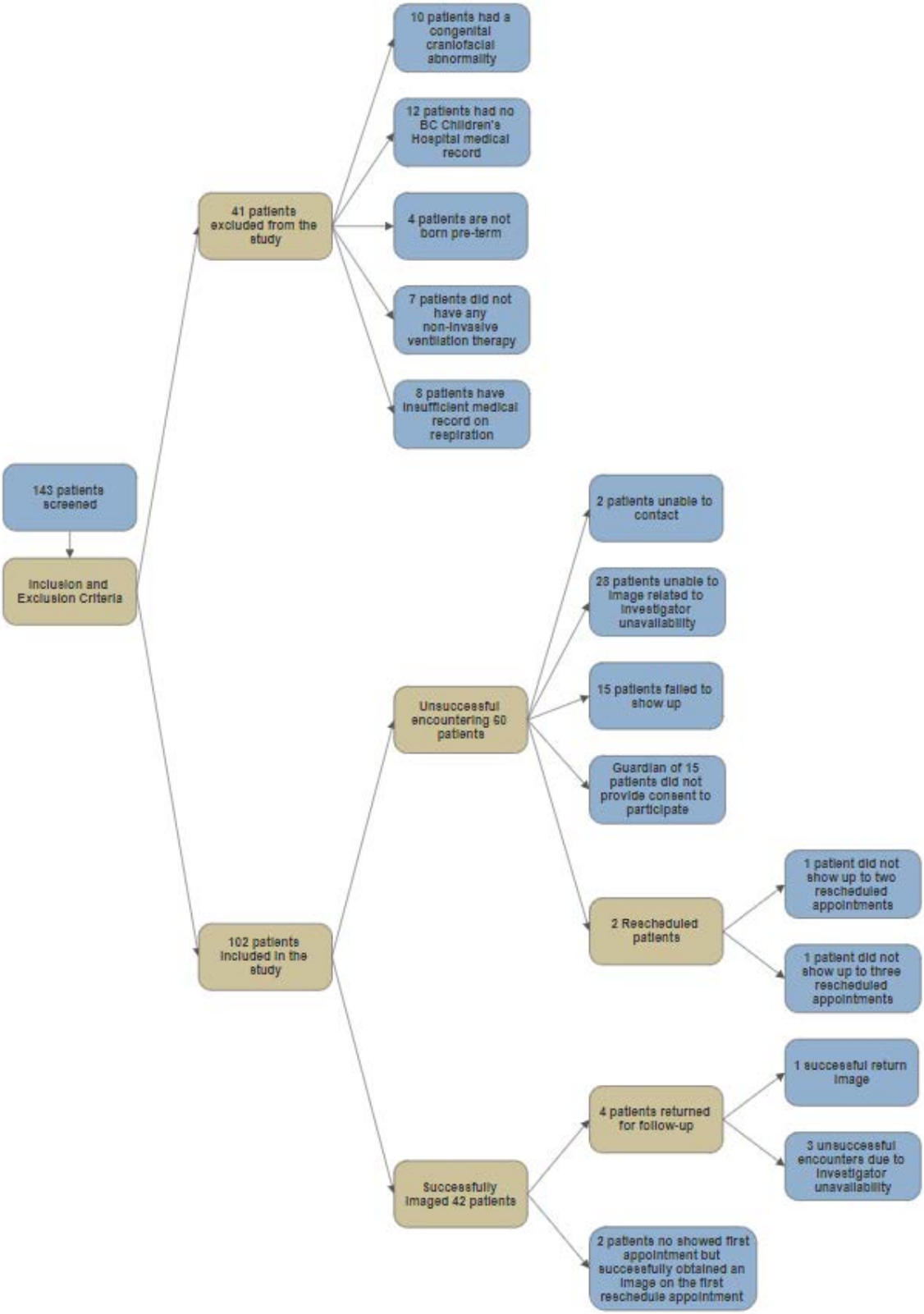

Figure 7 - Recruitment Flow Diagram

3.2 Description of Sample

Our implemented recruitment strategy allocated 42 patients whose legal guardian consented to voluntary patient participation in the study. The study obtained 10 facial images for patients within 4 months of age, 13 facial images for patients within 8 months of age (one image was from a returning patient) and 20 facial images for patients within 18 months of age (Table 3). Two patients were diagnosed with cerebral palsy later in life, but their facial images are still used in the study.

Table 3 - Recruitment number of images and sex distribution in the 4, 8 and 18-month cohorts

	4-Month Cohort	**8-Month Cohort***	**18-Month Cohort**
Number of Images (N=43)	10	13*	20
Number of Males (N=19)	2	3	14
Number of Females (N=23)	8	9	6

*Returning patient for 8-month image was a male

The following demographic parameters were collected: ethnicity, the follow-up visit, sex, gestational age in weeks and days, birth weight in grams, birth length in centimeters, birth head circumference in centimeters, mechanical ventilation duration (greater or less than a day), duration of non-invasive ventilation in days, NICU stay in days, birth hospital and NICU stay

hospital, and mode of feeding. Type of respiratory interface data is not available because of the dynamic interchangeable wear protocol.

The entire cohort consists of multiethnic backgrounds (Table 4). 19 patients had a declared Caucasian background. 5 patients come from a multi-racial background ranging from Caucasian and South East Asian, Scottish and First Nation, First Nation and Caucasian. Two patients had a declared Persian background. Eight patients had a declared East Asian background. Three patients had a declared South Eastern Asian (Philippine) background. One patient had a declared South American background. One patient had a declared African American background. Three patients did not have parents that declared their background.

Table 4 - Recruitment ethnicity summary in the 4, 8 and 18-month cohorts

N = 42	**4-Month Cohort (N=10)**	**8-Month Cohort (N=12)***	**18-Month Cohort (N=20)**
Caucasian	3	7	9
Multi-racial background	1	0	4
Persian	2	0	0
African American	0	0	1
East Asian	4	3	1
South American	0	0	1
South Eastern Asian	0	1	2

*Returning patient in the 8-month cohort is Caucasian

The entirety of the study's cohort consists of 23 female patients and 19 male patients (Table 3). The 4-month cohort consist of 10 patients: 2 males and 8 females. The 8-month cohort consist of 12 patients: 9 females and 3 males. The 18-month cohort consist of 20 patients: 6 females and 14 males.

The location of NIV therapy is shown in Table 5 for the 4, 8 and 18-month cohorts. Thirty patients were born at B.C. Women's Hospital and Health Centre (BCWH). All patients born at BCWH had their neonatal intensive care unit (NICU) stay at B.C. Children's Hospital (BCCH). Five patients were born at the Royal Columbian Hospital (RCH). Two patients born at the RCH had their NICU stay at their birth hospital. The other two patients born at RCH had part NICU stay at their birth hospital and another part at BCCH. The last other patient born at RCH was completely transferred to BCCH for NICU stay. 4 patients were born at the Surrey Memorial Hospital (SMH). Three patients were born at SMH and were cared in NICU at their birth hospital. The other last patient born at SMH was completely transferred to BCCH NICU for care. One patient was born at the Kelowna General Hospital. This patient was completely transferred and had care at BCCH in the NICU.

Table 5 - Recruitment NIV therapy hospital summary in the 4, 8 and 18-month cohorts

NIV Therapy (N=42)	**4-Month Cohort (N=10)**	**8-Month Cohort (N=12)***	**18-Month Cohort (N=20)**
BCCH	8	7	20
RCH	1	1	0
SMH	1	2	0
RCH and BCCH	0	2	0

*Returning patient for 8-month image was born in RCH and had NICU stay at RCH

The mean gestational age is 183 days equivalent to 26 weeks and one day with the standard deviation of 12 days (Table 6). The mean birth weight is 822 grams with the standard deviation of 213 grams. The mean birth length is 32.6 cm and the standard deviation is 3.3 cm. The mean birth head circumference is 23.8 cm with a standard deviation of 2.8 cm.

Table 6 - Recruitment mean anthropometric data for entire cohort

N=42	**Entire Cohort**	
	Mean	S.D.
Gestational Age (days)	183	12
Birth Weight (grams)	822	213
Birth Length (cm)	32.6	3.3
Birth Head Circumference (cm)	23.8	2.8

The mean gestational age is 185 days equivalent to 26 weeks and 3 days with the standard deviation of 12 days in the 4-month cohort; 178 days equivalent to 25 weeks and 3 days with the standard deviation of 13 days for the 8-month cohort; 186 days equivalent to 26 weeks and 4 days with the standard deviation of 12 days in the 18-month cohort (Table 7). The mean birth weight is 813 grams with the standard deviation of 219 grams for the 4-month cohort; 693.8 grams with the standard deviation of 166 grams for the 8-month cohort; 904 grams with the standard deviation of 207 grams for the 18-month cohort. The mean birth length is 33.5 cm with the standard deviation of 3.2 cm for the 4-month cohort; 30 cm with the standard deviation of 3.5 cm for the 8-month cohort; 33.9 cm with the standard deviation of 2.2 for the 18-month cohort. The mean birth head circumference is 23.6 cm with the standard deviation of 2.4 cm for the 4-month cohort; 23.7 cm with the standard deviation of 4.2 cm for the 8-month cohort; 24.0 cm with the standard deviation of 1.5 cm for the 18-month cohort.

Table 7 - Recruitment mean anthropometric data in the 4, 8 and 18-month cohorts

N=42	**4-Month Cohort**		**8-Month Cohort**		**18-Month Cohort**	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Gestational Age (days)	185	12	178	13	186	12
Birth Weight (grams)	813.7	218.9	693.8	165.8	903.5	206.6
Birth Length (cm)	33.5	3.2	30	3.5	33.9	2.2
Birth Head Circumference (cm)	23.6	2.4	23.7	4.2	24.0	1.5

The mean non-invasive ventilation therapy duration is 45 days with a standard deviation of 24 days for the entire cohort; 47 days with the standard deviation of 22 days for the 4-month cohort; 49 days with the standard deviation of 34 days for the 8-month cohort; 43 days with the standard deviation of 22 days for the 18-month cohort (Table 8). The frequency and distribution of duration of NIV therapy can be observed in Figure 8-11. There is a more normally distributed duration of NIV therapy for the 18-month cohort (Figure 10). For the entire cohort, there appears to be a more frequent duration of NIV therapy within the range of 43-49 days and 71-77 days (Figure 11). The mean duration of NICU stay is 101 days with a standard deviation of 40 days for the entire cohort; 99 days with the standard deviation of 33 days for the 4-month cohort; 107 days with the standard deviation of 50 days for the 8-month cohort; 99 days with the standard

deviation of 40 days for the 18-month cohort (Table 8). Ten patients had received mechanical ventilation less than one day before the initiation of their non-invasive ventilation therapy. Thirty-two patients had received mechanical ventilation greater than one day before the initiation of their non-invasive ventilation therapy. At discharge home, 3 patients were exclusively breast fed, 16 patients were combined breast and bottle fed, and 21 patients were fed with only bottle. The information on mode of feeding upon discharge was not available for two patients.

Table 8 – Duration of NIV therapy (days) summary for the 4, 8 and 18-month cohorts

N=42	Entire Cohort		4-Month Cohort		8-Month Cohort		18-Month Cohort	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Duration of NIV therapy (days)	45	24	47	22	49	34	43	22
Duration of NICU stay (days)	101	40	99	33	107	50	99	40

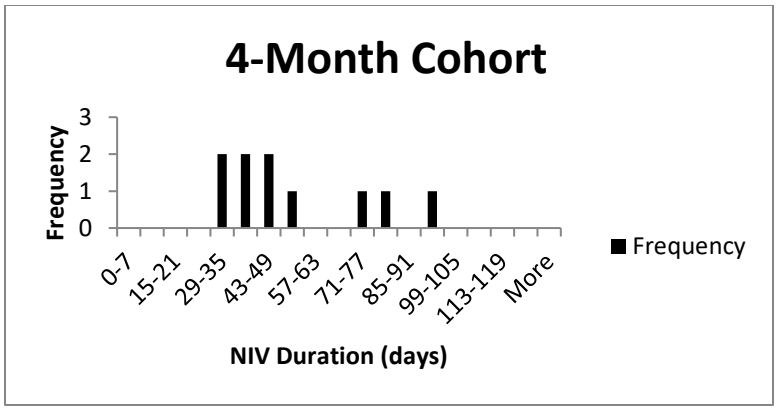

Figure 8 - NIV duration (days) distribution for 4-month cohort

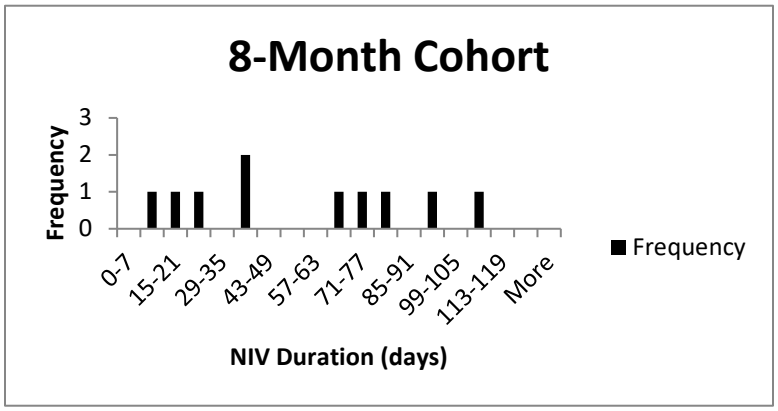

Figure 9 - NIV duration (days) distribution for 8-month cohort

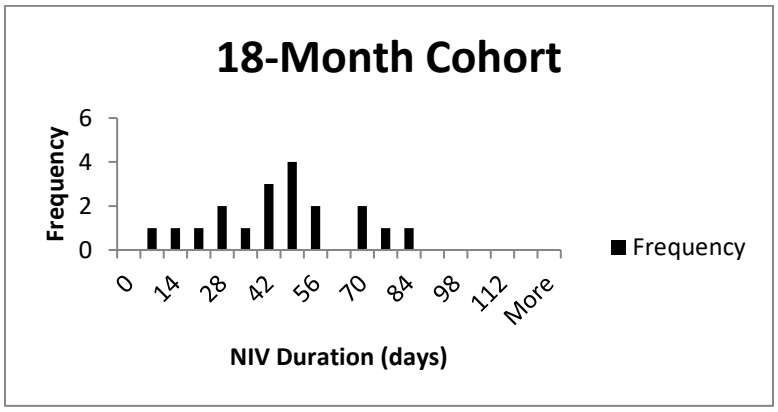

Figure 10 - NIV duration (days) distribution for 18-month cohort

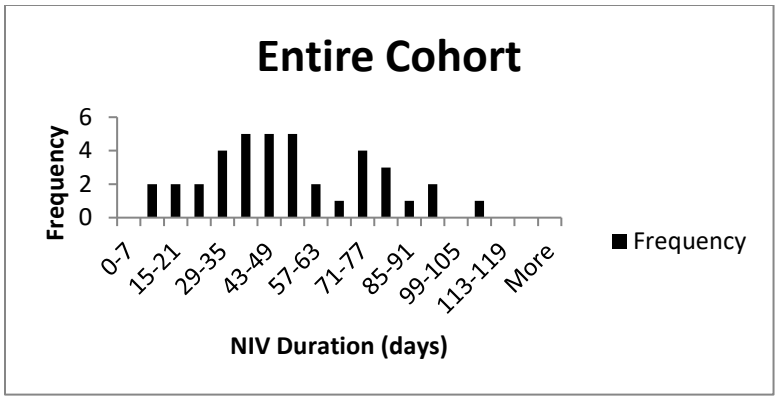

Figure 11- NIV duration (days) distribution for 4, 8 and 18-month cohort

3.3 Anthropometric Distances

The investigator characterized the mean anthropometric linear distance with respective standard deviation for the transverse, vertical and anterior-posterior planes in the 4, 8 and 18-month cohorts. The mean anthropometric linear distance data by follow-up visit for both sexes can be viewed in Table 9. The mean anthropometric linear distance data by follow-up visits for either male or female can be viewed in Appendix A.7.

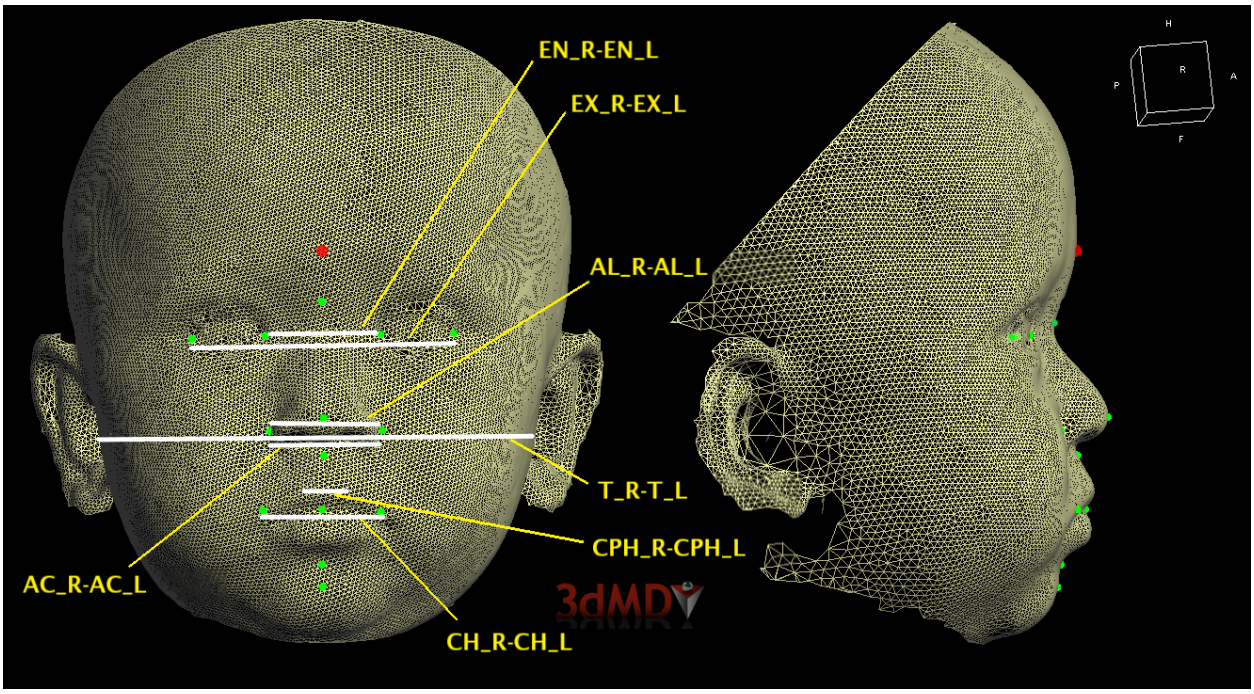

Figure 12 – Diagram of transverse linear distances. Skull base width (T_R-T_L), Intercanthal width (EN_R-EN_L), Biocular width (EX_R-EX_L), Morphological nose width (AL_R-AL_L), Anatomical nose width (AC_R-AC_L), Labial fissure length (CH_R-CH_L), and Philtrum width (CPH_R-CPH_L).

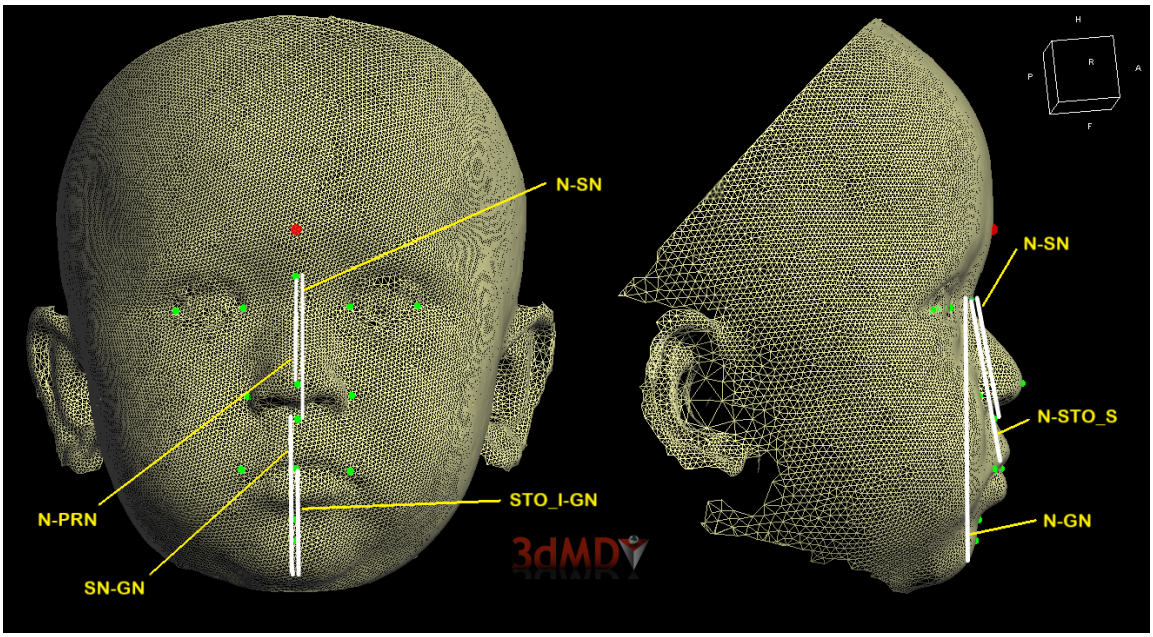

Figure 13 - Diagram of vertical linear distances. Morphological face height (N-GN), Upper face height – I (N-STO_S), Upper face height – II (N-SN), Lower face height – I (STO_I-GN), Lower face height – II (SN-GN), Nasal bridge length (N-PRN), and Nose height (N-SN).

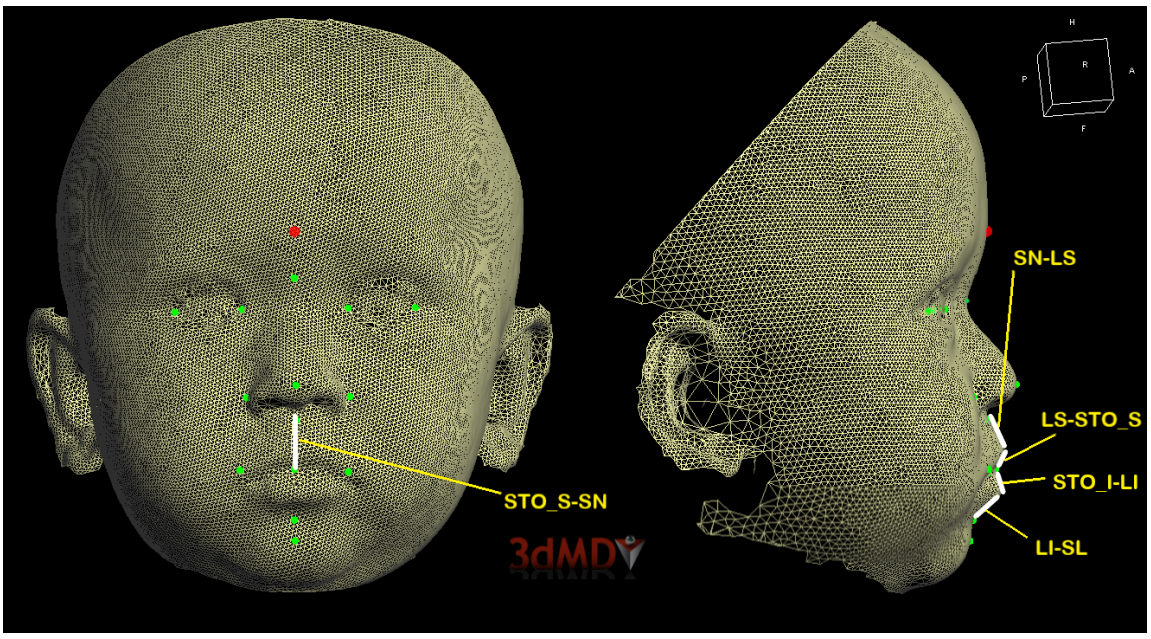

Figure 14 - Diagram of vertical linear distances. Upper lip length (STO_S-SN), Cutaneous upper lip length (SN-LS), Upper vermillion height (LS-STO_S), Lower vermillion height (STO_I-LI), Cutaneous lower lip length (LI-SL), and Lower lip length (STO_I-LI).

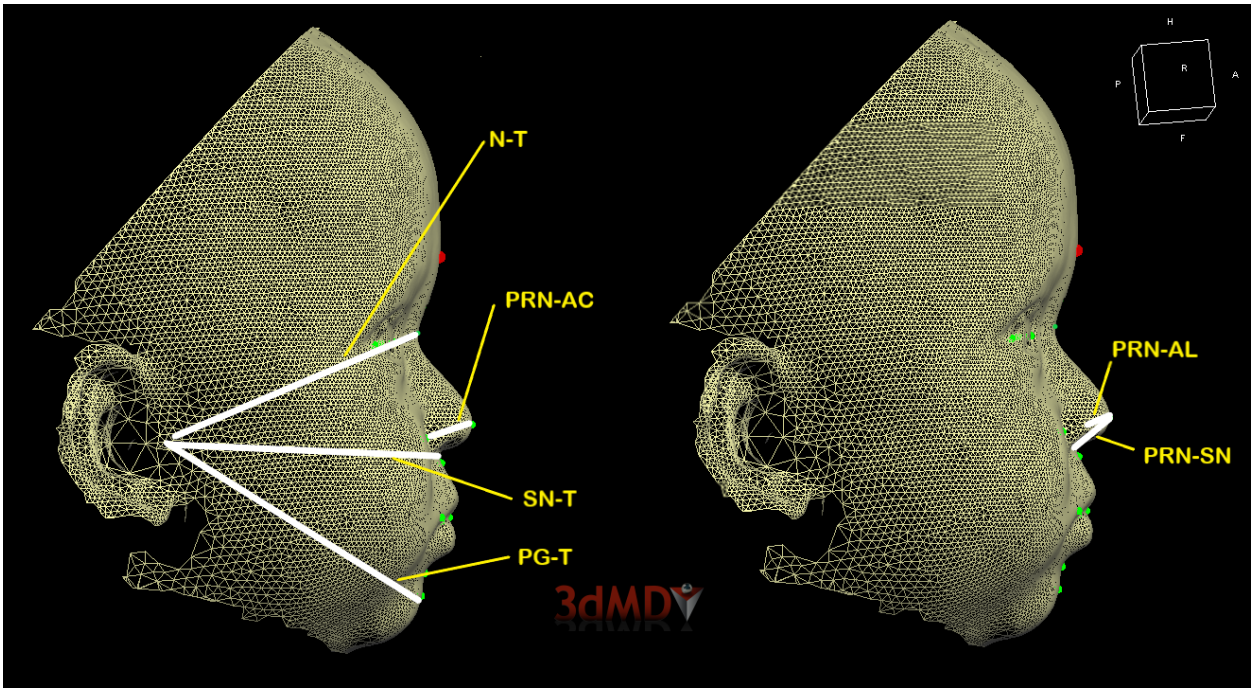

Figure 15 - Diagram of anterior posterior distances. Upper facial third depth (N-T), middle third depth (SN-T), lower facial third depth (PG-T), alar depth (PRN-AL), alar base depth (PRN-AC), nose depth (PRN-SN).

Table 9 – The mean anthropometric distance data by follow-up visit for both sexes

Linear Distance (mm)	4-month visit			8-month visit			18-month visit		
	MEAN	S.D.	S.D. %	MEAN	S.D.	S.D. %	MEAN	S.D.	6.1
Skull Base Width (T_R-T_L)	106.2	2.4	2.3	105.3	4.1	3.9	116.1	7.1	12.2
Intercanthal Width (EN_R-EN_L)	28.1	1.3	4.6	26.5	2.1	7.9	29.5	3.6	8.0
Biocular Width (EX_L-	68.1	3.1	4.6	69.4	3.6	5.2	74.9	6	12.6

EX_R)									
Morphological Nose Width (AL_R-AL_L)	23.9	1.2	5.0	22.8	1.8	7.9	26.1	3.3	12.8
Anatomical Nose Width (AC_R-AC_L)	23.4	2.1	9.0	21.9	2.3	10.5	24.3	3.1	12.2
Labial Fissure Length (CH_R-CH_L)	27.6	2.7	9.8	28.4	2.8	9.9	32.8	4.0	15.6
Philtrum Width (CPH_R-CPH_L)	7.6	0.9	11.8	8.2	1.3	15.9	9.6	1.5	9.4
Morphological Face Height (N-GN)	67.5	6.3	9.3	68.4	4.3	6.3	78.7	7.4	7.5
Upper Face Height – I (N-STO_S)	42.2	3.7	8.8	42.9	2.2	5.1	48.3	3.6	7.8
Upper face Height – II (N-SN)	28.5	2.8	9.8	28.6	1.6	5.6	33.3	2.6	8.2
Lower Face Height – I (STO_I-GN)	23.0	2.4	10.4	23.4	1.5	6.4	26.7	2.2	13.3
Lower Face Height – II (SN-GN)	39.8	5.2	13.1	40.7	3.6	8.9	46.79	6.2	7.7
Nasal Bridge Length (N-PRN)	21.9	2.2	10.1	22.1	1.9	8.6	26.0	2.0	7.8
Nose Height (N-SN)	28.5	2.8	9.8	28.6	1.6	5.6	33.3	2.6	11.9

Upper Lip Length (STO_S-SN)	13.8	1.5	10.9	14.5	1.6	11.0	15.1	1.8	16.5
Cutaneous Upper Lip Length (SN-LS)	10.7	1.6	15.0	11.3	1.7	15.0	10.9	1.8	28.8
Upper Vermillion Height (LS-STO_S)	4.8	0.6	12.5	4.7	1.1	23.4	5.9	1.7	17.2
Lower Vermillion Height (STO_I-LI)	4.6	1.0	21.7	4.4	1.2	27.3	5.8	1.0	14.3
Cutaneous Lower Lip Length (LI-SL)	8.0	1.6	20.0	7.9	1.1	13.9	9.1	1.3	17.2
Lower Lip Length (STO_I-LI)	4.6	1.0	21.7	4.4	1.2	27.3	5.8	1.0	6.0
Right Upper Facial Third Depth (N-T_R)	82.1	4.9	6.0	84.9	4.8	5.7	93.9	5.6	6.0
Left Upper Facial Third Depth (N-T_L)	82.0	4.3	5.2	84.2	3.9	4.6	93.6	5.6	6.0
Right Middle Third Depth (SN-T_R)	81.1	4.3	5.3	83.5	4.4	5.3	93.5	5.5	6.2
Left Middle Third Depth (SN-T_L)	81.0	3.7	4.6	83.7	3.7	4.4	93.8	5.8	6.1
Right Lower Facial Third Depth (PG-T_R)	86.9	4.1	4.7	87.6	4.2	4.8	98.7	6.0	6.3

Left Lower Facial Third Depth (PG-T_L)	86.5	4.0	4.6	88.2	3.7	4.2	99.4	6.3	9.5
Right Alar Depth (PRN-AL_R)	14.8	0.9	6.1	15.2	1.4	9.2	16.9	1.6	10.8
Left Alar Depth (PRN-AL_L)	14.4	0.8	5.6	14.8	1.1	7.4	16.6	1.8	9.9
Right Alar Base Depth (PRN-AC_R)	17.0	1.1	6.5	17.5	1.6	9.1	19.2	1.9	9.6
Left Alar Base Depth (PRN-AC_L)	16.7	0.8	4.8	17.2	1.3	7.6	18.8	1.8	9.8
Nose Depth (PRN-SN)	11.3	1.1	9.7	11.7	0.8	6.8	12.3	1.2	6.1

The transverse plane anthropometric distances obtained pertain to skull base width (T_R-T_L), intercanthal width (EN_R-EN_L), the biocular width (EX_L-EX_R), the morphological nose width (AL_R-AL_L), the anatomical nose width (AC_R-AC_L), the labial fissure length (CH_R-CH_L), and the philtrum width (CPH_R-CPH_L) (Figure 12).

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean skull base width is 106.2 ± 2.4 mm. The mean skull base width for females in the 4-month neonatal follow-up cohort is 106.0 ± 2.6 mm. The mean skull base width for males in the 4-month neonatal follow-up cohort is 107.1 ± 2.0 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean skull base width is 105.3 ± 4.1 mm. The mean skull base width for females in the 8-month neonatal follow-up cohort is 103.1 ± 2.4 mm. The mean skull base width for males in the 8-month neonatal follow-up cohort is 110.2 ± 1.9 mm. For the 18-month

neonatal follow-up cohort, when considering both sexes, the mean skull base width is 116.1 ± 7.1 mm. The mean skull base width for females in the 18-month neonatal follow-up cohort is 111.3 ± 4.3 mm. The mean skull base width for males in the 18-month neonatal follow-up cohort is 118.2 ± 7.2 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean intercanthal width is 28.1 ± 1.3 mm. The mean intercanthal width for females in the 4-month neonatal follow-up cohort is 28.3 ± 1.1 mm. The mean intercanthal width for males in the 4-month neonatal follow-up cohort is 27.1 ± 2.2 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean intercanthal width is 26.5 ± 2.1 mm. The mean intercanthal width for females in the 8-month neonatal follow-up cohort is 25.7 ± 2.0 mm. The mean intercanthal width for males in the 8-month neonatal follow-up cohort is 28.5 ± 0.5 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean intercanthal width is 29.5 ± 3.6 mm. The mean intercanthal width for females in the 18-month neonatal follow-up cohort is 26.9 ± 2.3 mm. The mean intercanthal width for males in the 18-month neonatal follow-up cohort is 30.6 ± 3.5 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean biocular width is 68.1 ± 3.1 mm. The mean biocular width for females in the 4-month neonatal follow-up cohort is 67.8 ± 2.8 mm. The mean biocular width for males in the 4-month neonatal follow-up cohort is 69.2 ± 5.4 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean biocular width is 69.4 ± 3.6 mm. The mean biocular width for females in the 8-month neonatal follow-up cohort is 67.8 ± 2.5 mm. The mean biocular width for males in the 8-month neonatal follow-up cohort is 73.1 ± 3.1 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean biocular width is 74.9 ± 6.0 mm. The

mean biocular width for females in the 18-month neonatal follow-up cohort is 71.0 ± 2.4 mm. The mean biocular width for males in the 18-month neonatal follow-up cohort is 76.6 ± 6.3 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean morphological nose width is 23.9 ± 1.2 mm. The mean morphological nose width for females in the 4-month neonatal follow-up cohort is 23.7 ± 1.3 mm. The mean morphological nose width for males in the 4-month neonatal follow-up cohort is 23.6 ± 0.2 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean morphological nose width is 22.8 ± 1.8 mm. The mean morphological nose width for females in the 8-month neonatal follow-up cohort is 22.3 ± 1.9 mm. The mean morphological nose width for males in the 8-month neonatal follow-up cohort is 24.1 ± 0.7 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean morphological nose is 26.1 ± 3.3 mm. The mean morphological nose width for females in the 18-month neonatal follow-up cohort is 23.9 ± 1.7 mm. The mean morphological nose width for males in the 18-month neonatal follow-up cohort is 27.1 ± 3.4 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean anatomical nose width is 23.4 ± 2.1 mm. The mean anatomical nose width for females in the 4-month neonatal follow-up cohort is 23.1 ± 2.3 mm. The mean anatomical nose width for males in the 4-month neonatal follow-up cohort is 24.5 ± 0.3 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean anatomical nose width is 21.9 ± 2.3 mm. The mean anatomical nose width for females in the 8-month neonatal follow-up cohort is 21.3 ± 2.3 mm. The mean anatomical nose width for males in the 8-month neonatal follow-up cohort is 23.3 ± 1.9 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean anatomical nose width is 24.3 ± 3.1 mm. The mean anatomical nose width for females in the 18-

month neonatal follow-up cohort is 21.8 ± 1.6 mm. The mean anatomical nose width for males in the 18-month neonatal follow-up cohort is 25.3 ± 3.1 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean labial fissure length is 27.6 ± 2.7 mm. The mean labial fissure length for females in the 4-month neonatal follow-up cohort is 26.7 ± 2.3 mm. The mean labial fissure length for males in the 4-month neonatal follow-up cohort is 31.0 ± 0.3 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean labial fissure length is 28.4 ± 2.8 mm. The mean labial fissure length for females in the 8-month neonatal follow-up cohort is 27.1 ± 2.5 mm. The mean labial fissure length for males in the 8-month neonatal follow-up cohort is 31.1 ± 0.5 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean labial fissure length is 32.8 ± 4.0 mm. The mean labial fissure length for females in the 18-month neonatal follow-up cohort is 30.4 ± 2.9 mm. The mean labial fissure length for males in the 18-month neonatal follow-up cohort is 33.8 ± 4.1 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean philtrum width is 7.6 ± 0.9 mm. The mean philtrum width for females in the 4-month neonatal follow-up cohort is 7.4 ± 0.7 mm. The mean philtrum width for males in the 4-month neonatal follow-up cohort is 8.7 ± 0.3 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean philtrum width is 8.2 ± 1.3 mm. The mean philtrum width for females in the 8-month neonatal follow-up cohort is 7.7 ± 1.2 mm. The mean philtrum width for males in the 8-month neonatal follow-up cohort is 9.3 ± 0.7 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean philtrum width is 9.6 ± 1.5 mm. The mean philtrum width for females in the 18-month neonatal follow-up cohort is 8.6 ± 0.4 mm. The mean philtrum width for males in the 18-month neonatal follow-up cohort is 10.1 ± 1.7 mm.

The vertical plane anthropometric distances obtained pertain to the morphological face height (N-GN), the upper face height (N-STO_S), the lower face height (STO_I-GN and SN-GN), the nasal bridge length (N-PRN), the nose height (N-SN), the upper lip length (STO_S-SN), the cutaneous upper lip length (SN-LS), the upper vermillion height (LS-STO_S), the lower vermillion height (STO_I-LI), the cutaneous lower lip length (LI-SL) and the lower lip length (STO_I-LI) (Figure 13-14).

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean morphological face height is 67.5 ± 6.3 mm. The mean morphological face height for females in the 4-month neonatal follow-up cohort is 66.1 ± 6.0 mm. The mean morphological face height for males in the 4-month neonatal follow-up cohort is 73.1 ± 5.3 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean morphological face height is 68.4 ± 4.3 mm. The mean morphological face height for females in the 8-month neonatal follow-up cohort is 67.3 ± 4.1 mm. The mean morphological face height for males in the 8-month neonatal follow-up cohort is 70.7 ± 4.4 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean morphological face height is 78.7 ± 7.4 mm. The mean morphological face height for females in the 18-month neonatal follow-up cohort is 75.1 ± 3.6 mm. The mean morphological face height for males in the 18-month neonatal follow-up cohort is 80.2 ± 8.2 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean upper face height (N-STO_S) is 42.2 ± 3.7 mm. The mean upper face height for females in the 4-month neonatal follow-up cohort is 42.0 ± 4.0 mm. The mean upper face height for males in the 4-month neonatal follow-up cohort is 43.0 ± 3.5 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean upper face height is 42.9 ± 2.2 mm. The mean upper face

height for females in the 8-month neonatal follow-up cohort is 42.3 ± 1.7 mm. The mean upper face height for males in the 8-month neonatal follow-up cohort is 44.2 ± 2.9 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean upper face height is 48.3 ± 3.6 mm. The mean upper face height for females in the 18-month neonatal follow-up cohort is 46.4 ± 2.1 mm. The mean upper face height for males in the 18-month neonatal follow-up cohort is 49.2 ± 3.9 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean lower face height (STO_I-GN and SN-GN, respectively) is 23.0 ± 2.4 mm and 39.8 ± 5.2 mm. The mean lower face height for females in the 4-month neonatal follow-up cohort is 23.2 ± 2.5 mm and 38.7 ± 3.8 mm. The mean lower face height for males in the 4-month neonatal follow-up cohort is 22.5 ± 2.9 mm and 44.0 ± 9.9 mm, respectively. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean lower face height is 23.4 ± 1.5 mm and 40.7 ± 3.6 mm, respectively. The mean lower face height for females in the 8-month neonatal follow-up cohort is 23.0 ± 1.6 mm and 40.0 ± 3.5 mm. The mean lower face height for males in the 8-month neonatal follow-up cohort is 24.4 ± 0.8 mm and 42.4 ± 3.6 mm, respectively. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean lower face height is 26.7 ± 2.2 mm and 46.8 ± 6.2 mm, respectively. The mean lower face height for females in the 18-month neonatal follow-up cohort is 24.9 ± 2.0 mm and 43.8 ± 3.6 mm. The mean lower face height for males in the 18-month neonatal follow-up cohort is 27.4 ± 1.9 and 48.1 ± 6.8 mm, respectively.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean nasal bridge length is 21.9 ± 2.2 mm. The mean nasal bridge length for females in the 4-month neonatal follow-up cohort is 21.6 ± 2.1 mm. The mean nasal bridge length for males in the 4-

month neonatal follow-up cohort is 23.4 ± 2.8 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean nasal bridge length is 22.1 ± 1.9 mm. The mean nasal bridge length for females in the 8-month neonatal follow-up cohort is 21.5 ± 1.7 mm. The mean nasal bridge length for males in the 8-month neonatal follow-up cohort is 23.5 ± 1.9 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean nasal bridge length is 26.0 ± 2.0 mm. The mean nasal bridge length for females in the 18-month neonatal follow-up cohort is 25.9 ± 1.4 mm. The mean nasal bridge length for males in the 18-month neonatal follow-up cohort is 26.1 ± 2.3 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean nose height (N-SN) is 28.5 ± 2.8 mm. The mean nose height for females in the 4-month neonatal follow-up cohort is 28.1 ± 2.6 mm. The mean nose height for males in the 4-month neonatal follow-up cohort is 30.2 ± 3.9 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean nose height is 28.6 ± 1.6 mm. The mean nose height for females in the 8-month neonatal follow-up cohort is 28.2 ± 1.3 mm. The mean nose height for males in the 8-month neonatal follow-up cohort is 29.6 ± 2.1 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean nose height is 33.3 ± 2.6 mm. The mean nose height for females in the 18-month neonatal follow-up cohort is 32.5 ± 1.1 mm. The mean nose height for males in the 18-month neonatal follow-up cohort is 33.6 ± 3.0 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean upper lip length (STO_S-SN) is 13.8 ± 1.5 mm. The mean upper lip length for females in the 4-month neonatal follow-up cohort is 14.0 ± 1.6 mm. The mean upper lip length for males in the 4-month neonatal follow-up cohort is 13.0 ± 0.2 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean upper lip length is 14.5 ± 1.6 mm. The mean upper lip length

for females in the 8-month neonatal follow-up cohort is 14.8 ± 1.9 mm. The mean upper lip length for males in the 8-month neonatal follow-up cohort is 14.9 ± 0.9 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean upper lip length is 15.1 ± 1.8 mm. The mean upper lip length for females in the 18-month neonatal follow-up cohort is 13.9 ± 1.6 mm. The mean upper lip length for males in the 18-month neonatal follow-up cohort is 15.6 ± 1.6 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean cutaneous upper lip length (SN-LS) is 10.7 ± 1.6 mm. The mean cutaneous upper lip length for females in the 4-month neonatal follow-up cohort is 10.9 ± 1.6 mm. The mean cutaneous upper lip length for males in the 4-month neonatal follow-up cohort is 10.0 ± 0.4 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean cutaneous upper lip length is 11.3 ± 1.7 mm. The mean cutaneous upper lip length for females in the 8-month neonatal follow-up cohort is 11.1 ± 2.0 mm. The mean cutaneous upper lip length for males in the 8-month neonatal follow-up cohort is 11.8 ± 1.0 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean cutaneous upper lip length is 10.9 ± 1.8 mm. The mean cutaneous upper lip length for females in the 18-month neonatal follow-up cohort is 10.0 ± 0.9 mm. The mean cutaneous upper lip length for males in the 18-month neonatal follow-up cohort is 11.2 ± 2.0 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean upper vermillion height (LS-STO_S) is 4.8 ± 0.6 mm. The mean upper vermillion height for females in the 4-month neonatal follow-up cohort is 4.9 ± 0.7 mm. The mean upper vermillion height for males in the 4-month neonatal follow-up cohort is 4.5 ± 0.3 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean upper vermillion height is 4.7 ± 1.1

mm. The mean upper vermillion height for females in the 8-month neonatal follow-up cohort is 4.5 ± 0.5 mm. The mean upper vermillion height for males in the 8-month neonatal follow-up cohort is 5.2 ± 2.0 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean upper vermillion height is 5.9 ± 1.7 mm. The mean upper vermillion height for females in the 18-month neonatal follow-up cohort is 5.2 ± 1.3 mm. The mean upper vermillion height for males in the 18-month neonatal follow-up cohort is 6.2 ± 1.7 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean lower vermillion height (STO_I-LI) is 4.6 ± 1.0 mm. The mean lower vermillion height for females in the 4-month neonatal follow-up cohort is 4.6 ± 0.9 mm. The mean lower vermillion height for males in the 4-month neonatal follow-up cohort is 4.8 ± 1.9 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean lower vermillion height is 4.4 ± 1.2 mm. The mean lower vermillion height for females in the 8-month neonatal follow-up cohort is 4.4 ± 1.1 mm. The mean lower vermillion height for males in the 8-month neonatal follow-up cohort is 4.5 ± 1.7 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean lower vermillion height is 5.8 ± 1.0 mm. The mean lower vermillion height for females in the 18-month neonatal follow-up cohort is 5.7 ± 1.1 mm. The mean lower vermillion height for males in the 18-month neonatal follow-up cohort is 5.8 ± 1.0 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean cutaneous lower lip length (LI-SL) is 8.0 ± 1.6 mm. The mean cutaneous lower lip length for females in the 4-month neonatal follow-up cohort is 8.1 ± 1.7 mm. The mean cutaneous lower lip length for males in the 4-month neonatal follow-up cohort is 7.6 ± 1.6 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean cutaneous lower lip length is 7.9 ± 1.1 mm. The mean cutaneous lower lip length for females in the 8-month neonatal follow-

up cohort is 7.5 ± 1.0 mm. The mean cutaneous lower lip length for males in the 8-month neonatal follow-up cohort is 8.9 ± 0.4 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean cutaneous lower lip length is 9.1 ± 1.3 mm. The mean cutaneous lower lip length for females in the 18-month neonatal follow-up cohort is 8.5 ± 1.1 mm. The mean cutaneous lower lip length for males in the 18-month neonatal follow-up cohort is 9.4 ± 1.3 mm.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean lower lip length (STO_I-LI) is 4.6 ± 1.0 mm. The mean lower lip length for females in the 4-month neonatal follow-up cohort is 4.6 ± 0.9 mm. The mean lower lip length for males in the 4-month neonatal follow-up cohort is 4.8 ± 1.9 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean lower lip length is 4.4 ± 1.2 mm. The mean lower lip length for females in the 8-month neonatal follow-up cohort is 4.4 ± 1.1 mm. The mean lower lip length for males in the 8-month neonatal follow-up cohort is 4.5 ± 1.7 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean lower lip length is 5.8 ± 1.0 mm. The mean lower lip length for females in the 18-month neonatal follow-up cohort is 5.7 ± 1.1 mm. The mean lower lip length for males in the 18-month neonatal follow-up cohort is 5.8 ± 1.0 mm.

The anterior-posterior anthropometric distances obtained pertain to the right upper facial third depth (N-T_R), the left upper facial third depth (N-T_L), the right middle third depth (SN-T_R), the left middle third depth (SN-T_L), the right lower facial third depth (PG-T_R), the left lower facial third depth (PG-T_L), the right alar depth (PRN-AL_R), the left alar depth (PRN-AL_L), the right alar base depth (PRN-AC_R), the left alar base depth (PRN-AC_L), and the nose depth (PRN-SN) (Figure 15).

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean the right upper facial third depth (N-T_R) is 82.1 ± 4.9 mm and the average left upper facial third depth (N-T_L) is 82.0 ± 4.3 mm. The mean right and left upper facial third depth for females in the 4-month neonatal follow-up cohort is 81.1 ± 4.9 mm and 81.3 ± 4.5 mm, respectively. The mean right and left upper facial third depth for males in the 4-month neonatal follow-up cohort is 86.4 ± 0.3 mm and 85.1 ± 1.9 mm, respectively. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean right upper facial third depth is 84.9 ± 4.8 mm and the mean left upper facial third depth is 84.2 ± 3.9 mm. The mean right and left upper facial third depth for females in the 8-month neonatal follow-up cohort is 83.1 ± 4.1 mm and 82.6 ± 3.0 mm, respectively. The mean right and left upper facial third depth for males in the 8-month neonatal follow-up cohort is 88.8 ± 3.9 mm and 87.7 ± 3.4 mm, respectively. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean right upper facial third depth is 93.9 ± 5.6 mm and the mean left upper facial third depth is 93.6 ± 5.6 mm. The mean right and left upper facial third depth for females in the 18-month neonatal follow-up cohort is 91.0 ± 3.3 mm and 89.9 ± 2.9 mm, respectively. The mean right and left upper facial third depth for males in the 18-month neonatal follow-up cohort is 95.1 ± 6.1 mm and 95.2 ± 5.8 mm, respectively.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean right middle third depth (SN-T_R) is 81.1 ± 4.3 mm and the mean left middle third depth (SN-T_L) is 81.0 ± 3.7 mm. The mean right and left middle third depth for females in the 4-month neonatal follow-up cohort is 80.2 ± 4.0 mm and 80.5 ± 3.1 mm, respectively. The mean right and left middle third depth for males in the 4-month neonatal follow-up cohort is 85.0 ± 4.6 mm and 82.9 ± 6.7 mm, respectively. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean right middle third depth is 83.5 ± 4.4 mm and the mean left middle third depth is

83.7 ± 3.7 mm. The mean right and left middle third depth for females in the 8-month neonatal follow-up cohort is 81.9 ± 4.0 mm 82.1 ± 2.7 mm, respectively. The mean right and left middle third depth for males in the 8-month neonatal follow-up cohort is 87.3 ± 2.9 mm and 87.2 ± 3.6 mm, respectively. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean right middle third depth is 93.5 ± 5.5 mm and the mean left middle third depth is 93.8 ± 5.8 mm. The mean right and left middle third depth for females in the 18-month neonatal follow-up cohort is 90.7 ± 2.9 mm and 89.9 ± 2.8 mm, respectively. The mean right and left middle third depth for males in the 18-month neonatal follow-up cohort is 94.7 ± 6.1 mm and 95.4 ± 6.0 mm, respectively.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean right lower facial third depth (PG-T_R) is 86.9 ± 4.1 mm and the mean left lower facial third depth (PG-T_L) is 86.5 ± 4.0 mm. The mean right and left lower facial third depth for females in the 4-month neonatal follow-up cohort is 85.8 ± 2.4 mm and 86.1 ± 2.7 mm, respectively. The mean right and left lower facial third depth for males in the 4-month neonatal follow-up cohort is 91.1 ± 8.2 mm and 87.9 ± 9.2 mm, respectively. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean right lower facial third depth is 87.6 ± 4.2 mm and the mean left lower facial third depth is 88.2 ± 3.7 mm. The mean right and left lower facial third depth for females in the 8-month neonatal follow-up cohort is 86.3 ± 3.9 mm 87.3 ± 2.5 mm, respectively. The mean right and left lower facial third depth for males in the 8-month neonatal follow-up cohort is 90.4 ± 3.9 mm and 90.3 ± 5.4 mm, respectively. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean right lower facial third depth is 98.7 ± 6.0 mm and the average left lower facial third depth is 99.4 ± 6.3 mm. The mean right and left lower facial third depth for females in the 18-month neonatal follow-up cohort is 95.2 ± 2.9 mm and

95.5 ± 2.5 mm, respectively. The mean right and left lower facial third depth for males in the 18-month neonatal follow-up cohort is 100.2 ± 6.4 mm and 101.1 ± 6.7 mm, respectively.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean right alar depth (PRN-AL_R) is 14.8 ± 0.9 mm and the mean left alar depth (PRN-AL_L) is 14.4 ± 0.8 mm. The mean right and left alar depth for females in the 4-month neonatal follow-up cohort is 14.6 ± 0.7 mm and 14.1 ± 0.7 mm, respectively. The mean right and left alar depth for males in the 4-month neonatal follow-up cohort is 15.6 ± 1.2 mm and 15.5 ± 0.1 mm, respectively. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean right alar depth is 15.2 ± 1.4 mm and the mean left alar depth is 14.8 ± 1.1 mm. The mean right and left alar depth for females in the 8-month neonatal follow-up cohort is 14.6 ± 1.2 mm 14.5 ± 1.1 mm, respectively. The mean right and left alar depth for males in the 8-month neonatal follow-up cohort is 16.5 ± 0.8 mm and 15.7 ± 0.5 mm, respectively. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean right alar depth is 16.9 ± 1.6 mm and the average left alar depth is 16.6 ± 1.8 mm. The mean right and left alar depth for females in the 18-month neonatal follow-up cohort is 16.2 ± 0.4 mm and 15.6 ± 0.7 mm, respectively. The mean right and left alar depth for males in the 18-month neonatal follow-up cohort is 17.2 ± 1.9 mm and 17.1 ± 2.0 mm, respectively.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean right alar base depth (PRN-AC_R) is 17.0 ± 1.1 mm and the mean left alar base depth (PRN-AC_L) is 16.7 ± 0.8 mm. The mean right and left alar base depth for females in the 4-month neonatal follow-up cohort is 16.8 ± 1.1 mm and 16.5 ± 0.8 mm, respectively. The mean right and left alar base depth for males in the 4-month neonatal follow-up cohort is 17.9 ± 0.7 mm and 17.5 ± 0.2 mm, respectively. For the 8-month neonatal follow-up cohort, when considering both sexes, the

mean right alar base depth is 17.5 ± 1.3 mm and the average left alar base depth is 17.2 ± 1.3 mm. The mean right and left alar base depth for females in the 8-month neonatal follow-up cohort is 16.8 ± 1.3 mm and 16.8 ± 1.3, respectively. The mean right and left alar base depth for males in the 8-month neonatal follow-up cohort is 18.9 ± 1.3 mm and 18.1 ± 0.9 mm, respectively. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean right alar base depth is 19.2 ± 1.9 mm and the mean left alar base depth is 18.8 ± 1.8 mm. The mean right and left alar base depth for females in the 18-month neonatal follow-up cohort is 18.3 ± 0.4 mm and 17.7 ± 1.2 mm, respectively. The mean right and left alar base depth for males in the 18-month neonatal follow-up cohort is 19.6 ± 2.1 mm and 12.3 ± 1.3 mm, respectively.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean nose depth (PRN-SN) is 11.3 ± 1.1 mm. The mean nose depth for females in the 4-month neonatal follow-up cohort is 11.3 ± 1.1 mm. The mean nose depth for males in the 4-month neonatal follow-up cohort is 11.4 ± 1.7 mm. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean nose depth is 11.7 ± 0.8 mm. The mean nose depth for females in the 8-month neonatal follow-up cohort is 11.6 ± 0.9 mm. The mean nose depth for males in the 8-month neonatal follow-up cohort is 11.7 ± 0.4 mm. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean nose depth is 12.3 ± 1.2 mm. The mean nose depth for females in the 18-month neonatal follow-up cohort is 12.2 ± 1.0 mm. The mean nose depth for males in the 18-month neonatal follow-up cohort is 12.3 ± 1.3 mm.

3.4 Anthropometric Angles

The investigator acquired the mean and standard deviation of anthropometric angles in relation to the patient's facial side-profile in the 4, 8 and 18-month cohorts. The mean anthropometric angles by follow-up visit for both sexes can be viewed on Table 10. The mean anthropometric angles by follow-up visit for males and females can be found in Appendix A.8. The following angles were obtained: subnasale angle (PRN-SN-LS), nose protrusion angle (N-PRN-SN), right upper face angle (N-T_R-SN), the left upper face angle (N-T_L-SN), the right upper and mid-face angle (N-T_R-SL), the left upper and mid-face angle (N-T_L-SL), the right morphometric face angle (N-T_R-GN), the left morphometric face angle (N-T_L-GN), the subnasal protrusion angle (AC_R-SN-AC_L), the alar slope angle (AL_R-PRN-AL_L), and the midface depth angle (N-SN-SL).

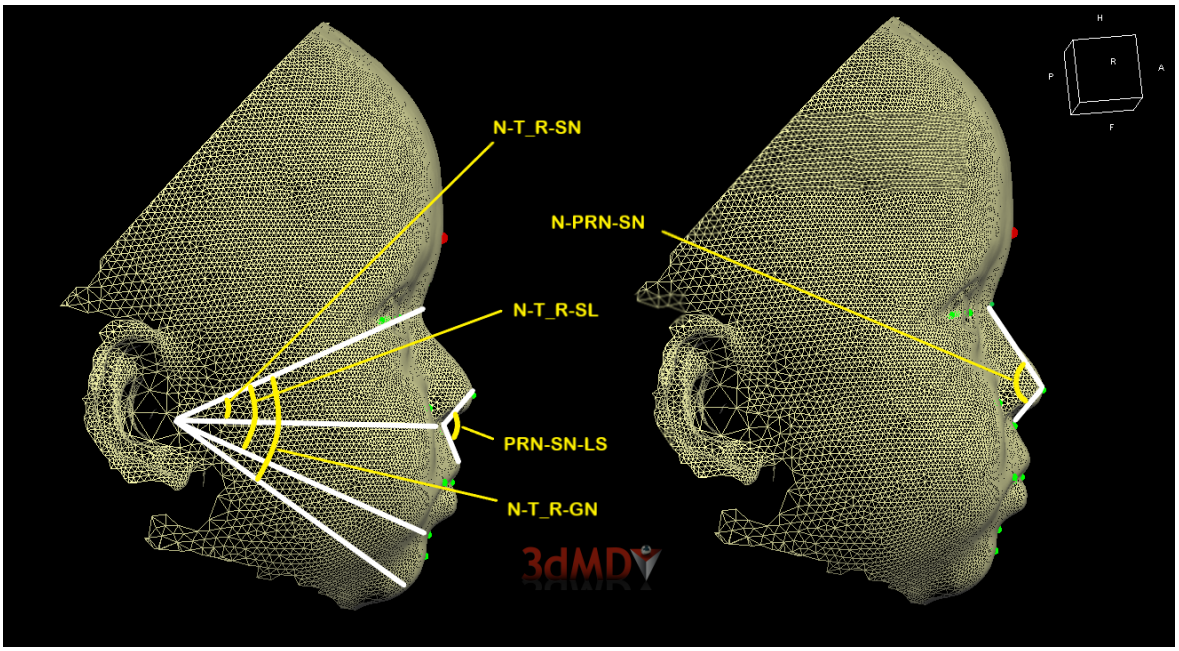

Figure 16 - Diagram of facial angles. Subnasale angle (PRN-SN-LS), Nose protrusion angle (N-PRN-SN), Right upper face angle (N-T_R-SN), Right upper and mid-face angle (N-T_R-SL), and Right morphometric face angle (N-T_R-GN).

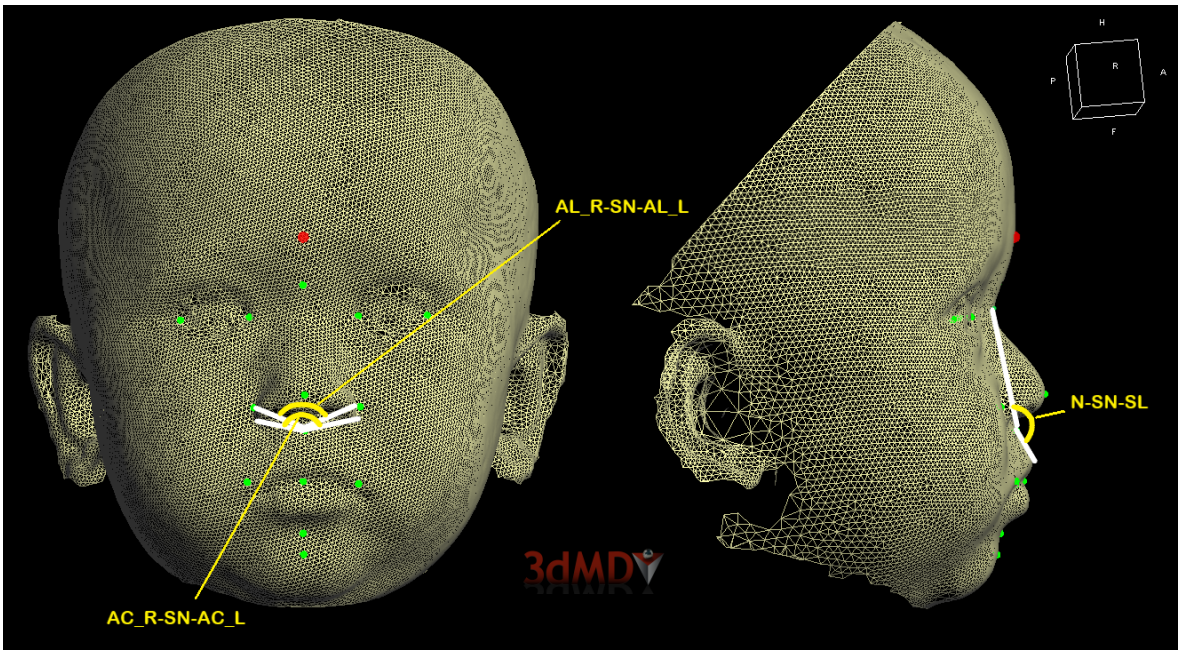

Figure 17 - Diagram of facial angles. Subnasal protrusion angle (AC_R-SN-AC_L), Alar slope angle (AL_R-PRN-AL_L), and Mid-face depth angle (N-SN-SL).

Table 10 - The mean anthropometric angle data by follow-up visit for both sexes

Angles (degrees)	4-month visit			8-month visit			18-month visit		
	MEAN	S.D.	S.D. %	MEAN	S.D.	S.D. %	MEAN	S.D.	S.D. %
Subnasale Angle (PRN-SN-LS)	26.6	3.0	11.3	25.8	4.6	17.8	28.2	3.7	13.1
Nose Protrusion Angle (N-PRN-SN)	65.4	4.8	7.3	67.5	5.0	7.4	63.7	5.0	7.9
Right Upper Face Angle (N-T_R-SN)	78.3	4.9	6.3	77.6	2.3	3.0	79.2	2.6	3.3
Left Upper Face Angle (N-T_L-SN)	78.2	4.8	6.1	79.2	2.0	2.5	80.1	2.6	3.3
Right Upper Mid Face Angle (N-T_R-SL)	71.9	5.0	7.0	70.7	2.1	3.0	71.3	2.8	3.9
Left Upper Mid Face Angle (N-T_L-SL)	71.6	4.6	6.4	71.9	2.4	3.3	72.2	2.5	3.5
Right Morphometric Face Angle (N-T_R-GN)	71.1	4.8	6.8	69.3	2.1	3.0	69.8	2.7	3.9

Left Morphometric Face Angle (N-T_L-GN)	70.7	4.6	6.5	70.4	2.6	3.7	70.5	2.5	3.6
Subnasal Protrusion Angle (AC_R-SN-AC_L)	12.5	5.3	42.4	19.0	4.1	21.6	20.0	4.2	21.0
Alar Slope Angle (AL_R-PRN-AL_L)	34.1	4.5	13.2	39.9	2.7	6.8	38.4	4.2	10.9
Midface Depth Angle (N-SN-SL)	8.9	2.6	29.2	9.4	2.1	22.3	10.2	3.3	32.4

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean subnasale angle (PRN-SN-LS) is 26.6 ± 3.0 degrees. The mean subnasale angle for females in the 4-month neonatal follow-up cohort is 27.4 ± 2.7 degrees. The mean subnasale angle for males in the 4-month neonatal follow-up cohort is 23.8 ± 3.3 degrees. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean subnasale angle is 25.8 ± 4.6 degrees. The mean subnasale angle for females in the 8-month neonatal follow-up cohort is 24.9 ± 5.0 degrees. The mean subnasale angle for males in the 8-month neonatal follow-up cohort is 27.7 ± 3.6 degrees. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean subnasale angle is 28.2 ± 3.7 degrees. The mean subnasale angle for females in the 18-month neonatal follow-up cohort is 27.9 ± 2.8 degrees. The mean subnasale angle for males in the 18-month neonatal follow-up cohort is 28.4 ± 4.0 degrees.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean nose protrusion angle (N-PRN-SN) is 65.4 ± 4.8 degrees. The mean nose protrusion angle for females in the 4-month neonatal follow-up cohort is 65.8 ± 5.3 degrees. The mean nose protrusion angle for males in the 4-month neonatal follow-up cohort is 63.6 ± 0.2 degrees. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean nose protrusion angle is 67.5 ± 5.0 degrees. The mean nose protrusion angle for females in the 8-month neonatal follow-up cohort is 66.4 ± 5.6 degrees. The mean nose protrusion angle for males in the 8-month neonatal follow-up cohort is 70.1 ± 1.7 degrees. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean nose protrusion angle is 63.7 ± 5.0 degrees. The mean nose protrusion angle for females in the 18-month neonatal follow-up cohort is 67.4 ± 2.3 degrees. The mean nose protrusion angle for males in the 18-month neonatal follow-up cohort is 62.1 ± 5.1 degrees.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean right upper face angle (N-T_R-SN) is 78.3 ± 4.9 degrees and the mean left upper face angle (N-T_L-SN) is 78.2 ± 4.8 degrees. The mean right and left upper face angle for females in the 4-month neonatal follow-up cohort is 78.5 ± 4.3 degrees and 78.7 ± 3.7 degrees, respectively. The mean right and left upper face angle for males in the 4-month neonatal follow-up cohort is 77.8 ± 9.4 degrees and 76.2 ± 10.3 degrees, respectively. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean right upper face angle is 77.6 ± 2.3 degrees and the mean left upper face angle is 79.2 ± 2.0 degrees. The mean right and left upper face angle for females in the 8-month neonatal follow-up cohort is 77.7 ± 2.3 degrees and 79.2 ± 2.4 degrees, respectively. The mean right and left upper face angle for males in the 8-month neonatal follow-up cohort is 77.4 ± 2.6 degrees and 79.2 ± 1.1 degrees, respectively. For the 18-month neonatal follow-up

cohort, when considering both sexes, the mean right upper face angle is 79.2 ± 2.6 degrees and the mean left upper face angle is 80.1 ± 2.6 degrees. The mean right and left upper face angle for females in the 18-month neonatal follow-up cohort is 79.2 ± 2.7 degrees and 79.6 ± 3.0 degrees, respectively. The mean right and left upper face angle for males in the 18-month neonatal follow-up cohort is 79.2 ± 2.7 degrees and 80.3 ± 2.4 degrees, respectively.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean right upper mid-face angle (N-T_R-SL) is 71.9 ± 5.0 degrees and the mean left upper mid-face angle (N-T_L-SL) is 71.6 ± 4.6 degrees. The mean right and left upper mid-face angle for females in the 4-month neonatal follow-up cohort is 72.4 ± 4.9 degrees and 72.4 ± 4.2 degrees, respectively. The mean right and left upper mid-face angle for males in the 4-month neonatal follow-up cohort is 69.8 ± 6.6 degrees and 68.2 ± 6.2 degrees, respectively. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean right upper mid-face angle is 70.7 ± 2.1 degrees and the mean left upper mid-face angle is 71.9 ± 2.4 degrees. The mean right and left upper mid-face angle for females in the 8-month neonatal follow-up cohort is 71.5 ± 2.0 degrees and 72.8 ± 2.3 degrees, respectively. The mean right and left upper mid-face angle for males in the 8-month neonatal follow-up cohort is 68.8 ± 1.1 degrees and 69.9 ± 1.2 degrees, respectively. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean right upper mid-face angle is 71.3 ± 2.8 degrees and the mean left upper mid-face angle is 72.2 ± 2.5 degrees. The mean right and left upper mid-face angle for females in the 18-month neonatal follow-up cohort is 71.1 ± 2.4 degrees and 72.3 ± 2.5 degrees, respectively. The mean right and left upper mid-face angle for males in the 18-month neonatal follow-up cohort is 71.5 ± 3.0 degrees and 72.2 ± 2.6 degrees, respectively.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean right morphometric face angle (N-T_R-GN) is 71.1 ± 4.8 degrees and the mean left morphometric face angle (N-T_L-GN) is 70.7 ± 4.6 degrees. The mean right and left morphometric face angle for females in the 4-month neonatal follow-up cohort is 71.5 ± 5.0 degrees and 71.5 ± 4.3 degrees, respectively. The mean right and left morphometric face angle for males in the 4-month neonatal follow-up cohort is 69.5 ± 4.9 degrees and 67.1 ± 5.1 degrees, respectively. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean right morphometric face angle is 69.3 ± 2.1 degrees and the mean left morphometric face angle is 70.4 ± 2.6 degrees. The mean right and left upper morphometric face angle for females in the 8-month neonatal follow-up cohort is 69.8 ± 2.3 degrees and 71.0 ± 2.7 degrees, respectively. The mean right and left morphometric face angle for males in the 8-month neonatal follow-up cohort is 68.2 ± 1.2 degrees and 68.8 ± 1.9 degrees, respectively. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean right morphometric face angle is 69.8 ± 2.7 degrees and the mean left morphometric face angle is 70.5 ± 2.5 degrees. The mean right and left morphometric face angle for females in the 18-month neonatal follow-up cohort is 69.8 ± 2.1 degrees and 70.6 ± 2.1 degrees, respectively. The mean right and left morphometric face angle for males in the 18-month neonatal follow-up cohort is 69.8 ± 2.9 degrees and 70.4 ± 2.7 degrees, respectively.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean subnasal protrusion angle (AC_R-SN-AC_L) is 12.5 ± 5.3 degrees. The mean subnasal protrusion angle for females in the 4-month neonatal follow-up cohort is 10.9 ± 4.1 degrees. The mean subnasal protrusion angle for males in the 4-month neonatal follow-up cohort is 19.2 ± 4.6 degrees. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean subnasal protrusion angle is 19.0 ± 4.1 degrees. The mean subnasal protrusion angle for females

in the 8-month neonatal follow-up cohort is 17.7 ± 2.9 degrees. The mean subnasal protrusion angle for males in the 8-month neonatal follow-up cohort is 22.1 ± 5.1 degrees. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean subnasal protrusion angle is 20.0 ± 4.2 degrees. The mean subnasal protrusion angle for females in the 18-month neonatal follow-up cohort is 21.9 ± 2.2 degrees. The mean subnasal protrusion angle for males in the 18-month neonatal follow-up cohort is 19.3 ± 4.7 degrees.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean alar slope angle (AL_R-PRN-AL_L) is 34.1 ± 4.5 degrees. The mean alar slope angle for females in the 4-month neonatal follow-up cohort is 33.3 ± 4.7 degrees. The mean alar slope angle for males in the 4-month neonatal follow-up cohort is 37.4 ± 0.9 degrees. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean alar slope angle is 39.9 ± 2.7 degrees. The mean alar slope angle for females in the 8-month neonatal follow-up cohort is 39.7 ± 2.8 degrees. The mean alar slope angle for males in the 8-month neonatal follow-up cohort is 40.4 ± 2.8 degrees. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean alar slope angle is 38.4 ± 4.2 degrees. The average alar slope angle for females in the 18-month neonatal follow-up cohort is 40.4 ± 2.8 degrees. The mean alar slope angle for males in the 18-month neonatal follow-up cohort is 37.6 ± 4.5 degrees.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean midface depth angle (N-SN-SL) is 8.9 ± 2.6 degrees. The mean midface depth angle for females in the 4-month neonatal follow-up cohort is 8.4 ± 2.3 degrees. The mean midface depth angle for males in the 4-month neonatal follow-up cohort is 10.6 ± 4.2 degrees. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean midface depth angle is 9.4 ± 2.1 degrees. The mean midface depth angle for females in the 8-month neonatal follow-up cohort is

8.3 ± 1.1 degrees. The mean midface depth angle for males in the 8-month neonatal follow-up cohort is 11.9 ± 1.9 degrees. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean midface depth angle is 10.2 ± 3.3 degrees. The mean midface depth angle for females in the 18-month neonatal follow-up cohort is 10.0 ± 1.3 degrees. The mean midface depth angle for males in the 18-month neonatal follow-up cohort is 10.4 ± 3.9 degrees.

3.5 Anthropometric Facial Ratios

The investigator has obtained the mean and standard deviation for the morphological face height (N-GN) to skull base width (T_R-T_L) ratio, the upper face height (N-STO_S) to skull base width (T_R-T_L) ratio and the second upper face height (N-SN) to skull base width (T_R-T_L) ratio (Figure 18). The mean and standard deviation of the anthropometric facial ratios for both sexes for each cohort can be viewed on Table 11. The mean and standard deviation of the anthropometric facial ratios for females and males can be seen in Appendix A.9.

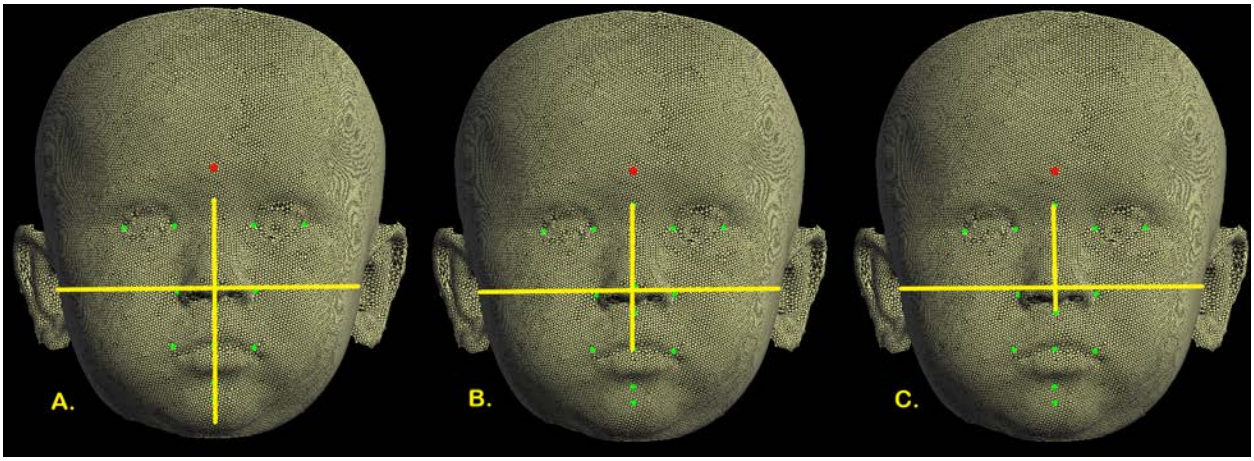

Figure 18 - Diagram of facial ratios. (A) Morphological face height (N-GN) to Skull base width (T_R-T_L), (B) Upper face height – I (N-STO_S) to Skull base width (T_R-T_L), and (C) Upper face height – II (N-SN) to Skull base width (T_R-T_L).

Table 11 - The mean anthropometric angle data by follow-up visit for all sexes

Facial Ratios	4-month visit			8-month visit			18-month visit		
	MEAN	S.D.	S.D. %	MEAN	S.D.	S.D. %	MEAN	S.D.	S.D. %
Morphological Face Height (N-GN) to Skull Base Width (T_R-T_L)	0.63	0.05	7.9	0.65	0.04	6.2	0.68	0.04	5.9
Upper Face Height – I (N-STO_S) to Skull Base Width (T_R-T_L)	0.40	0.03	7.5	0.41	0.02	4.9	0.42	0.02	4.8
Upper Face Height – II (N-SN) to Skull Base Width (T_R-T_L)	0.27	0.02	7.4	0.27	0.02	7.4	0.29	0.01	3.5

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean morphological face height (N-GN) to skull base width (T_R-T_L) ratio is 0.63 ± 0.05. The average morphological face height to skull base width ratio for females in the 4-month neonatal follow-up cohort 0.62 ± 0.04. The mean morphological face height to skull base width ratio for males in the 4-month neonatal follow-up cohort is 0.68 ± 0.04. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean morphological face height to skull base width ratio is 0.65 ± 0.04. The mean morphological face height to skull base width ratio for females in the 8-month neonatal follow-up cohort is 0.65 ± 0.04. The mean morphological face height to

skull base width ratio for males in the 8-month neonatal follow-up cohort is 0.64 ± 0.04. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean morphological face height to skull base width ratio is 0.68 ± 0.04. The mean morphological face height to skull base width ratio for females in the 18-month neonatal follow-up cohort is 0.68 ± 0.03. The mean morphological face height to skull base width ratio for males in the 18-month neonatal follow-up cohort is 0.68 ± 0.05.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean upper face height (N-STO_S) to skull base width (T_R-T_L) ratio is 0.40 ± 0.03. The mean upper face height to skull base width ratio for females in the 4-month neonatal follow-up cohort 0.40 ± 0.03. The mean upper face height to skull base width ratio for males in the 4-month neonatal follow-up cohort is 0.40 ± 0.04. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean upper face height to skull base width ratio is 0.41 ± 0.02. The mean upper face height to skull base width ratio for females in the 8-month neonatal follow-up cohort is 0.41 ± 0.01. The mean upper face height to skull base width ratio for males in the 8-month neonatal follow-up cohort is 0.40 ± 0.03. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean upper face height to skull base width ratio is 0.42 ± 0.02. The mean upper face height to skull base width ratio for females in the 18-month neonatal follow-up cohort is 0.42 ± 0.01. The mean upper face height to skull base width ratio for males in the 18-month neonatal follow-up cohort is 0.42 ± 0.01.

For the 4-month neonatal follow-up cohort, when considering both sexes, the mean second upper face height (N-SN) to skull base width (T_R-T_L) ratio is 0.27 ± 0.02. The mean second upper face height to skull base width ratio for females in the 4-month neonatal follow-up cohort 0.26 ± 0.02. The mean second upper face height to skull base width ratio for males in the

4-month neonatal follow-up cohort is 0.28 ± 0.04. For the 8-month neonatal follow-up cohort, when considering both sexes, the mean second upper face height to skull base width ratio is 0.27 ± 0.02. The mean second upper face height to skull base width ratio for females in the 8-month neonatal follow-up cohort is 0.27 ± 0.02. The mean second upper face height to skull base width ratio for males in the 8-month neonatal follow-up cohort is 0.27 ± 0.02. For the 18-month neonatal follow-up cohort, when considering both sexes, the mean second upper face height to skull base width ratio is 0.29 ± 0.01. The mean second upper face height to skull base width ratio for females in the 18-month neonatal follow-up cohort is 0.29 ± 0.01. The mean second upper face height to skull base width ratio for males in the 18-month neonatal follow-up cohort is 0.28 ± 0.02.

3.6 The Correlation between Craniofacial Morphology and Non-Invasive Ventilation

Correlation and univariate linear regression models have been performed for each facial measurement on a stereo-photometric image taken at the patient's 4, 8 and 18-month follow-up visit and related to the duration of non-invasive ventilation therapy they had received during their NICU encounter. The correlation is judged on the average estimated effect of one day of NIV therapy on a 95% confidence interval. The tables for correlation and univariate linear regression for each facial measurement related to non-invasive ventilation therapy in each cohort can be viewed in Table 12-14.

Table 12 - Correlation and univariate linear regression for each facial measurement versus NIV therapy at 4-months of age

	Correlation	Average estimated effect of 1 day of NIV therapy (95% CI)	p-value
T_R-T_L	0.00	0.001 (-0.09,0.091)	0.99
EN_R-EN_L	-0.72	-0.044 (-0.079,-0.01)	0.019*
EX_L-EX_R	-0.33	-0.047 (-0.158,0.064)	0.355
AL_R-AL_L	0.28	0.016 (-0.028,0.06)	0.434
AC_R-AC_L	0.38	0.037 (-0.036,0.11)	0.276
CH_R-CH_L	0.51	0.064 (-0.024,0.153)	0.133
CPH_R-CPH_L	0.50	0.02 (-0.008,0.049)	0.139
N-GN	0.18	0.054 (-0.181,0.289)	0.611
N-STO_S	0.23	0.04 (-0.099,0.178)	0.528
N-SN	0.45	0.058 (-0.036,0.152)	0.191
STO_I-GN	-0.42	-0.047 (-0.13,0.035)	0.222
SN-GN	-0.05	-0.011 (-0.209,0.186)	0.897
N-PRN	0.40	0.04 (-0.036,0.116)	0.257
STO_S-SN	-0.27	-0.018 (-0.073,0.036)	0.455
SN-LS	-0.13	-0.01 (-0.068,0.049)	0.711
LS-STO_S	-0.25	-0.007 (-0.031,0.016)	0.493
STO_I-LI	-0.39	-0.018 (-0.052,0.016)	0.262

	Correlation	Average estimated effect of 1 day of NIV therapy (95% CI)	p-value
LI-SL	0.10	0.007 (-0.054,0.069)	0.791
N-T_R	0.15	0.034 (-0.149,0.217)	0.678
N-T_L	0.08	0.016 (-0.148,0.179)	0.832
SN-T_R	-0.12	-0.024 (-0.187,0.14)	0.748
SN-T_L	-0.29	-0.051 (-0.185,0.084)	0.408
PG-T_R	-0.16	-0.031 (-0.186,0.123)	0.651
PG-T_L	-0.33	-0.061 (-0.203,0.08)	0.349
PRN-AL_R	0.59	0.024 (-0.002,0.05)	0.07
PRN-AL_L	0.30	0.011 (-0.018,0.041)	0.398
PRN-AC_R	0.44	0.023 (-0.016,0.061)	0.206
PRN-AC_L	0.34	0.013 (-0.016,0.042)	0.338
PRN-SN	0.35	0.019 (-0.022,0.059)	0.32
PRN-SN-LS	-0.30	-0.043 (-0.151,0.066)	0.392
N-PRN-SN	-0.20	-0.045 (-0.223,0.134)	0.579
N-T_R-SN	-0.52	-0.121 (-0.28,0.039)	0.119
N-T_L-SN	-0.61	-0.138 (-0.283,0.007)	0.06
N-T_R-SL	-0.45	-0.105 (-0.274,0.064)	0.191
N-T_L-SL	-0.50	-0.108 (-0.258,0.042)	0.137
N-T_R-GN	-0.34	-0.077 (-0.249,0.095)	0.333

	Correlation	Average estimated effect of 1 day of NIV therapy (95% CI)	p-value
N-T_L-GN	-0.47	-0.1 (-0.253,0.052)	0.168
AC_R-SN-AC_L	0.43	0.105 (-0.076,0.285)	0.218
AL_R-PRN-AL_L	0.15	0.03 (-0.137,0.198)	0.687
N-SN-SL	-0.24	-0.029 (-0.125,0.068)	0.511
N-GN.to.T_R-T_L	0.23	0.001 (-0.001,0.002)	0.524
N-STO_S.to.T_R-T_L	0.27	0 (-0.001,0.001)	0.448
N-SN.to.T_R-T_L	0.51	0.001 (0,0.001)	0.132

Table 13 - Correlation and univariate linear regression for each facial measurement versus NIV therapy at 8-months of age

	Correlation	Average estimated effect of 1 day of NIV therapy (95% CI)	p-value
T_R-T_L	0.10	0.013 (-0.079,0.104)	0.761
EN_R-EN_L	-0.30	-0.018 (-0.062,0.025)	0.363
EX_L-EX_R	-0.11	-0.008 (-0.065,0.048)	0.752
AL_R-AL_L	0.12	0.006 (-0.032,0.045)	0.716
AC_R-AC_L	0.19	0.014 (-0.04,0.068)	0.569
CH_R-CH_L	0.20	0.017 (-0.045,0.078)	0.554

	Correlation	Average estimated effect of 1 day of NIV therapy (95% CI)	p-value
CPH_R-CPH_L	-0.13	-0.005 (-0.034,0.024)	0.706
N-GN	-0.24	-0.031 (-0.129,0.066)	0.486
N-STO_S	0.21	0.014 (-0.036,0.064)	0.531
N-SN	0.01	0 (-0.038,0.038)	0.981
STO_I-GN	0.16	0.007 (-0.028,0.043)	0.648
SN-GN	-0.34	-0.035 (-0.107,0.037)	0.302
N-PRN	0.26	0.015 (-0.027,0.058)	0.434
STO_S-SN	0.38	0.017 (-0.015,0.049)	0.251
SN-LS	0.43	0.019 (-0.011,0.049)	0.19
LS-STO_S	-0.21	-0.008 (-0.034,0.018)	0.527
STO_I-LI	0.03	0.001 (-0.028,0.03)	0.94
LI-SL	0.44	0.014 (-0.008,0.037)	0.178
N-T_R	0.13	0.018 (-0.081,0.116)	0.695
N-T_L	-0.01	-0.001 (-0.082,0.08)	0.974
SN-T_R	0.09	0.012 (-0.081,0.104)	0.782
SN-T_L	-0.02	-0.002 (-0.081,0.076)	0.947
PG-T_R	0.04	0.004 (-0.082,0.091)	0.917
PG-T_L	0.00	0 (-0.081,0.081)	0.999
PRN-AL_R	0.14	0.006 (-0.024,0.035)	0.685

	Correlation	Average estimated effect of 1 day of NIV therapy (95% CI)	p-value
PRN-AL_L	0.21	0.007 (-0.017,0.031)	0.538
PRN-AC_R	0.27	0.012 (-0.022,0.046)	0.429
PRN-AC_L	0.26	0.009 (-0.017,0.036)	0.449
PRN-SN	-0.06	-0.001 (-0.017,0.014)	0.851
PRN-SN-LS	0.14	0.019 (-0.086,0.125)	0.688
N-PRN-SN	0.57	0.089 (-0.008,0.185)	0.068
N-T_R-SN	-0.15	-0.011 (-0.065,0.044)	0.667
N-T_L-SN	-0.05	-0.003 (-0.052,0.045)	0.876
N-T_R-SL	-0.14	-0.009 (-0.057,0.039)	0.686
N-T_L-SL	0.12	0.009 (-0.046,0.064)	0.718
N-T_R-GN	0.06	0.004 (-0.045,0.053)	0.863
N-T_L-GN	0.14	0.011 (-0.051,0.074)	0.689
AC_R-SN-AC_L	0.03	0.003 (-0.091,0.098)	0.935
AL_R-PRN-AL_L	0.16	0.014 (-0.051,0.078)	0.64
N-SN-SL	-0.14	-0.008 (-0.052,0.035)	0.676
N-GN.to.T_R-T_L	-0.30	0 (-0.001,0.001)	0.376
N-STO_S.to.T_R-T_L	0.19	0 (0,0)	0.582
N-SN.to.T_R-T_L	-0.06	0 (0,0)	0.868

Table 14 - Correlation and univariate linear regression for each facial measurement versus NIV therapy at 18-months

	Correlation	Average estimated effect of 1 day of NIV therapy (95% CI)	p-value
T_R-T_L	0.14	0.045 (-0.114,0.204)	0.562
EN_R-EN_L	0.31	0.05 (-0.028,0.128)	0.195
EX_L-EX_R	0.08	0.022 (-0.113,0.157)	0.734
AL_R-AL_L	0.11	0.017 (-0.061,0.094)	0.655
AC_R-AC_L	0.06	0.008 (-0.064,0.08)	0.821
CH_R-CH_L	-0.13	-0.024 (-0.115,0.068)	0.596
CPH_R-CPH_L	0.11	0.007 (-0.026,0.041)	0.646
N-GN	0.14	0.043 (-0.114,0.199)	0.575
N-STO_S	-0.05	-0.008 (-0.084,0.068)	0.836
N-SN	0.01	0.001 (-0.056,0.058)	0.97
STO_I-GN	0.18	0.019 (-0.033,0.071)	0.45
SN-GN	0.11	0.031 (-0.106,0.167)	0.641

	Correlation	Average estimated effect of 1 day of NIV therapy (95% CI)	p-value
N-PRN	-0.07	-0.006 (-0.048,0.037)	0.779
STO_S-SN	-0.13	-0.009 (-0.046,0.028)	0.606
SN-LS	-0.24	-0.018 (-0.057,0.02)	0.327
LS-STO_S	0.23	0.018 (-0.02,0.055)	0.338
STO_I-LI	-0.16	-0.007 (-0.029,0.015)	0.522
LI-SL	-0.08	-0.004 (-0.031,0.023)	0.752
N-T_R	0.11	0.028 (-0.099,0.155)	0.648
N-T_L	0.15	0.038 (-0.087,0.163)	0.535
SN-T_R	0.04	0.009 (-0.118,0.135)	0.885
SN-T_L	0.08	0.02 (-0.113,0.153)	0.756
PG-T_R	0.18	0.045 (-0.078,0.168)	0.451
PG-T_L	0.27	0.072 (-0.06,0.203)	0.266
PRN-AL_R	0.14	0.01 (-0.025,0.044)	0.569
PRN-AL_L	0.09	0.007 (-0.033,0.047)	0.712
PRN-AC_R	0.08	0.006 (-0.034,0.047)	0.75
PRN-AC_L	0.00	0 (-0.041,0.041)	0.999
PRN-SN	-0.04	-0.002 (-0.027,0.023)	0.88
PRN-SN-LS	0.18	0.025 (-0.046,0.097)	0.468

	Correlation	Average estimated effect of 1 day of NIV therapy (95% CI)	p-value
N-PRN-SN	-0.21	-0.049 (-0.162,0.065)	0.377
N-T_R-SN	-0.26	-0.03 (-0.089,0.028)	0.289
N-T_L-SN	-0.23	-0.028 (-0.086,0.031)	0.333
N-T_R-SL	0.06	0.008 (-0.057,0.073)	0.795
N-T_L-SL	0.14	0.016 (-0.041,0.073)	0.566
N-T_R-GN	0.09	0.011 (-0.052,0.074)	0.717
N-T_L-GN	0.20	0.023 (-0.035,0.08)	0.422
AC_R-SN-AC_L	-0.21	-0.039 (-0.13,0.053)	0.387
AL_R-PRN-AL_L	-0.08	-0.015 (-0.116,0.086)	0.758
N-SN-SL	-0.35	-0.054 (-0.127,0.019)	0.139
N-GN.to.T_R-T_L	0.05	0 (-0.001,0.001)	0.845
N-STO_S.to.T_R-T_L	-0.35	0 (-0.001,0)	0.147
N-SN.to.T_R-T_L	-0.17	0 (0,0)	0.49

For the 4-month neonatal follow-up cohort, when considering both sexes, the transverse plane anthropometric distances (the skull base width (T_R-T_L), intercanthal width (EN_R-EN_L), the biocular width (EX_L-EX_R), the morphological nose width (AL_R-AL_L), the anatomical nose width (AC_R-AC_L), the labial fissure length (CH_R-CH_L), and the philtrum width (CPH_R-CPH_L)) showed statistical significant difference in correlation with duration of NIV therapy with the intercanthal width measurement with a p-value of 0.019 (Table 12). For the

8-month neonatal follow-up cohort, when considering both sexes, there were no statistical significant correlation between the transverse plane anthropometric distances with the duration of NIV therapy (Table 13). For the 18-month neonatal follow-up cohort, when considering both sexes, there were no significant difference in correlation between the transverse plane anthropometric distances with the duration of NIV therapy (Table 14).

For the 4-month neonatal follow-up cohort, when considering both sexes, the vertical plane anthropometric distances (The morphological face height (N-GN), the upper face height (N-STO_S), the lower face height (STO_I-GN and SN-GN), the nasal bridge length (N-PRN), the nose height (N-SN), the upper lip length (STO_S-SN), the cutaneous upper lip length (SN-LS), the upper vermillion height (LS-STO_S), the lower vermillion height (STO_I-LI), the cutaneous lower lip length (LI-SL) and the lower lip length (STO_I-LI)), showed no significant correlation with the duration of NIV therapy (Table 12). For the 8-month neonatal follow-up cohort, when considering both sexes, there were no significant correlation between the vertical plane anthropometric distances with the duration of NIV therapy (Table 13). For the 18-month neonatal follow-up cohort, when considering both sexes, there were no significant differences in correlation between the transverse plane anthropometric distances with the duration of NIV therapy (Table 14).

For the 4-month neonatal follow-up cohort, when considering both sexes, the anterior-posterior anthropometric distances obtained that pertain to the right upper facial third depth (N-T_R), the left upper facial third depth (N-T_L), the right middle third depth (SN-T_R), the left middle third depth (SN-T_L), the right lower facial third depth (PG-T_R), the left lower facial third depth (PG-T_L), the right alar depth (PRN-AL_R), the left alar depth (PRN-AL_L), the right alar base depth (PRN-AC_R), the left alar base depth (PRN-AC_L), and the nose depth

(PRN-SN) showed no significant correlation with the duration of NIV therapy (Table 12). For the 8-month neonatal follow-up cohort, when considering both sexes, there were no significant correlation between the anterior-posterior anthropometric distances with the duration of NIV therapy (Table 13). For the 18-month neonatal follow-up cohort, when considering both sexes, there were no significant differences in correlation between the anterior-posterior anthropometric distances with the duration of NIV therapy (Table 14).

The anthropometric angles obtained that pertain to the subnasale angle (PRN-SN-LS), nose protrusion angle (N-PRN-SN), right upper face angle (N-T_R-SN), the left upper face angle (N-T_L-SN), the right upper and mid-face angle (N-T_R-SL), the left upper and mid-face angle (N-T_L-SL), the right morphometric face angle (N-T_R-GN), the left morphometric face angle (N-T_L-GN), the subnasal protrusion angle (AC_R-SN-AC_L), the alar slope angle (AL_R-PRN-AL_L), and the midface depth angle (N-SN-SL) showed no significant correlation with duration of NIV therapy for the 4, 8 and 18-month neonatal follow-up cohorts.

The facial ratios obtained that pertain to the morphological face height (N-GN) to skull base width (T_R-T_L) ratio, the upper face height (N-STO_S) to skull base width (T_R-T_L) ratio and the second upper face height (N-SN) to skull base width (T_R-T_L) ratio showed no significant correlation with the duration of NIV therapy for the 4, 8, and 18-month neonatal follow-up cohorts.

3.7 Exploring Anthropometric Physical Data and Duration of NIV Therapy

The study investigated the correlation between duration of NIV therapy with other variables such as gestational age, birth length, birth weight, and birth head circumference. The correlation between the duration of NIV therapy in relation to the gestational age, birth length,

birth weight and birth head circumference, when considering both sexes, appears to show the expected negative overall correlation in the 4, 8 and 18-month cohorts (Figure 19-22; Table 15-18).

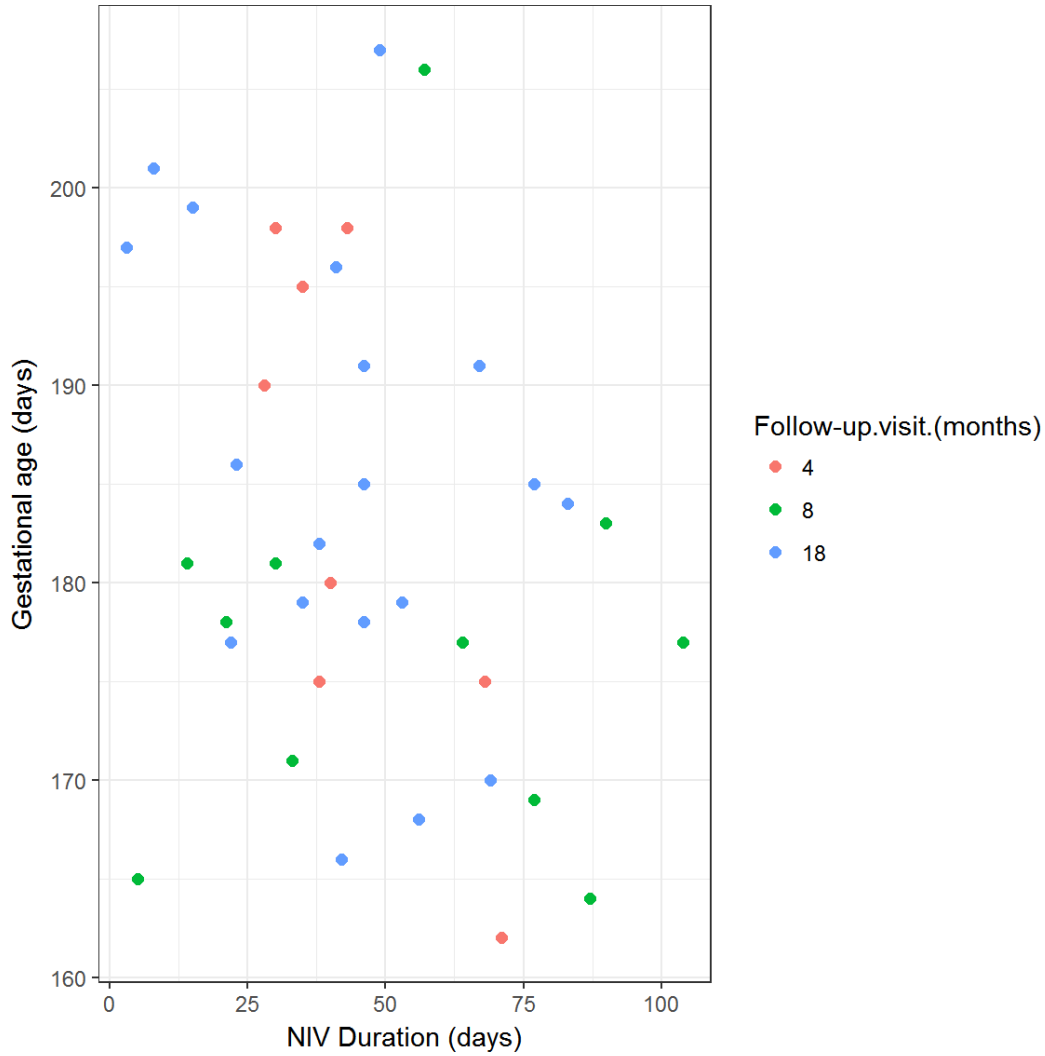

Figure 19 - Scatterplot for duration of NIV therapy versus gestational age for 4, 8 and 18-month cohorts

Table 15 - Correlation between duration of NIV therapy (days) and gestational age (years)

Follow-up visit (months)	Correlation
Overall	-0.29
4	-0.57
8	0.03
18	-0.36

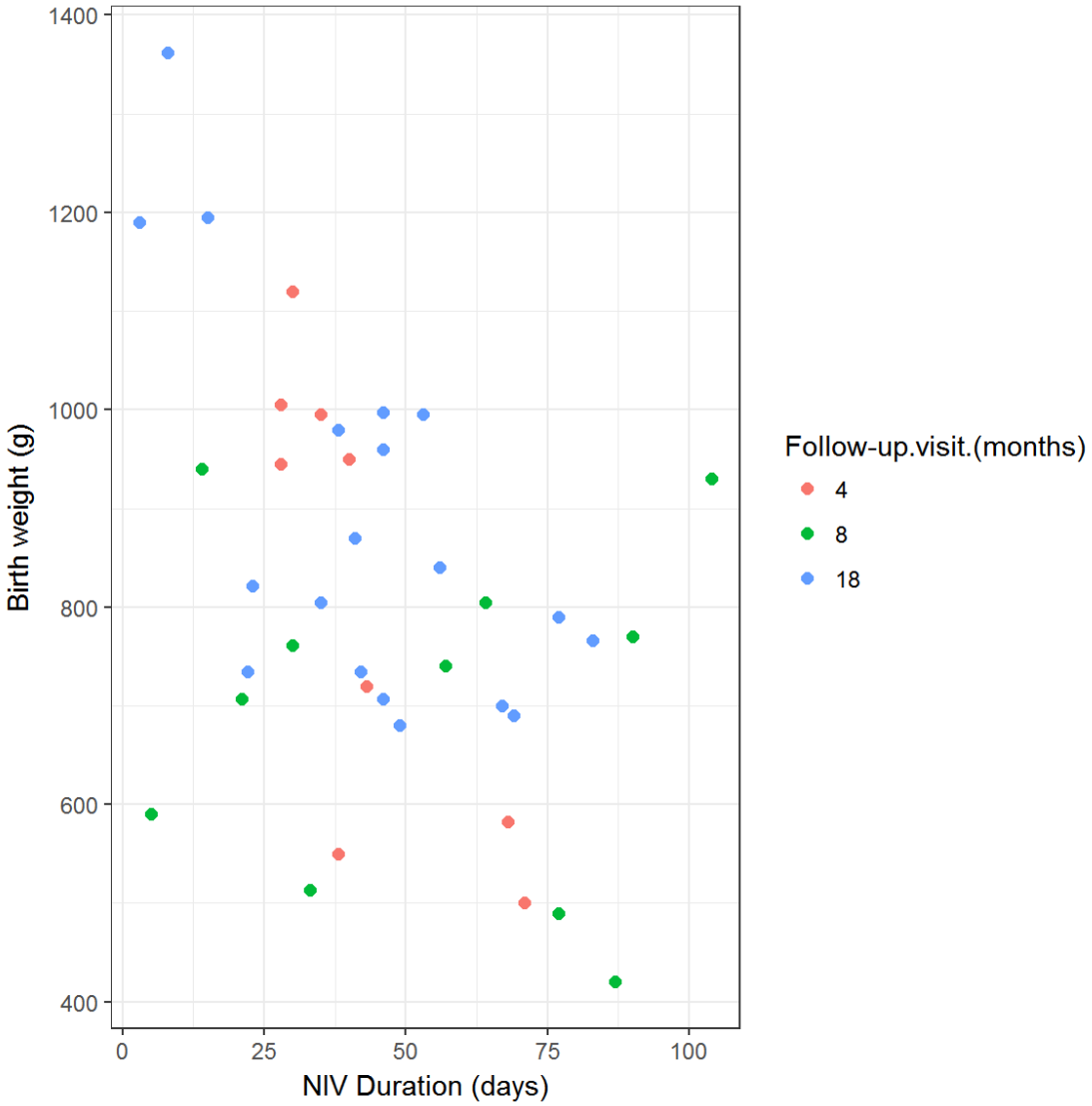

Figure 20 - Scatterplot for duration of NIV therapy versus birth weight for 4, 8 and 18-month cohorts

Table 16 - Correlation between duration of NIV therapy (days) and birth weight (grams)

Follow-up visit (months)	Correlation
Overall	-0.44
4	-0.61
8	-0.02
18	-0.65

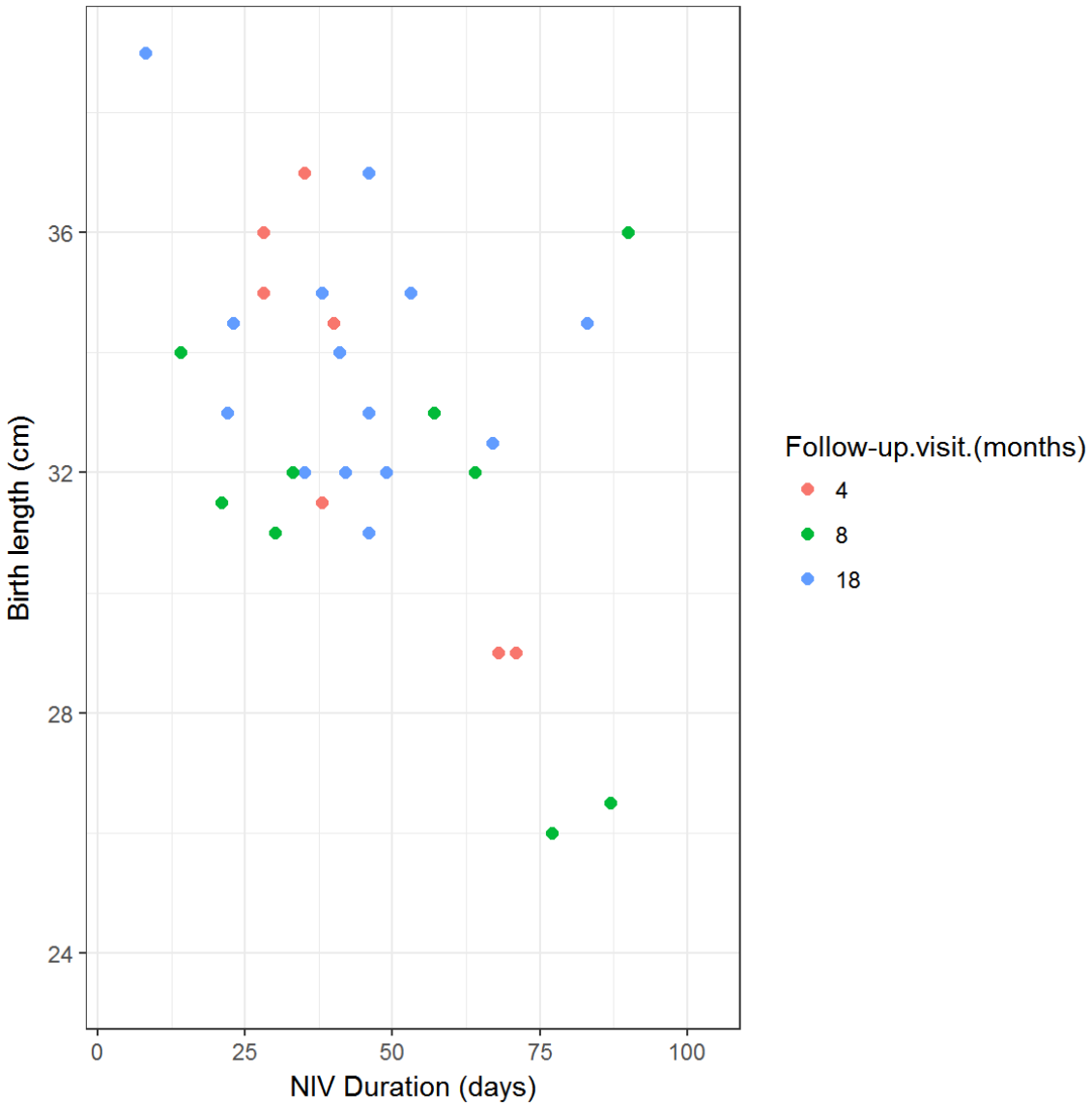

Figure 21 - Scatterplot for duration of NIV therapy versus birth length for 4, 8 and 18-month cohorts

Table 17 - Correlation between duration of NIV therapy (days) and birth length (cm)

Follow-up visit (months)	Correlation
Overall	-0.36
4	-0.38
8	-0.29
18	-0.33

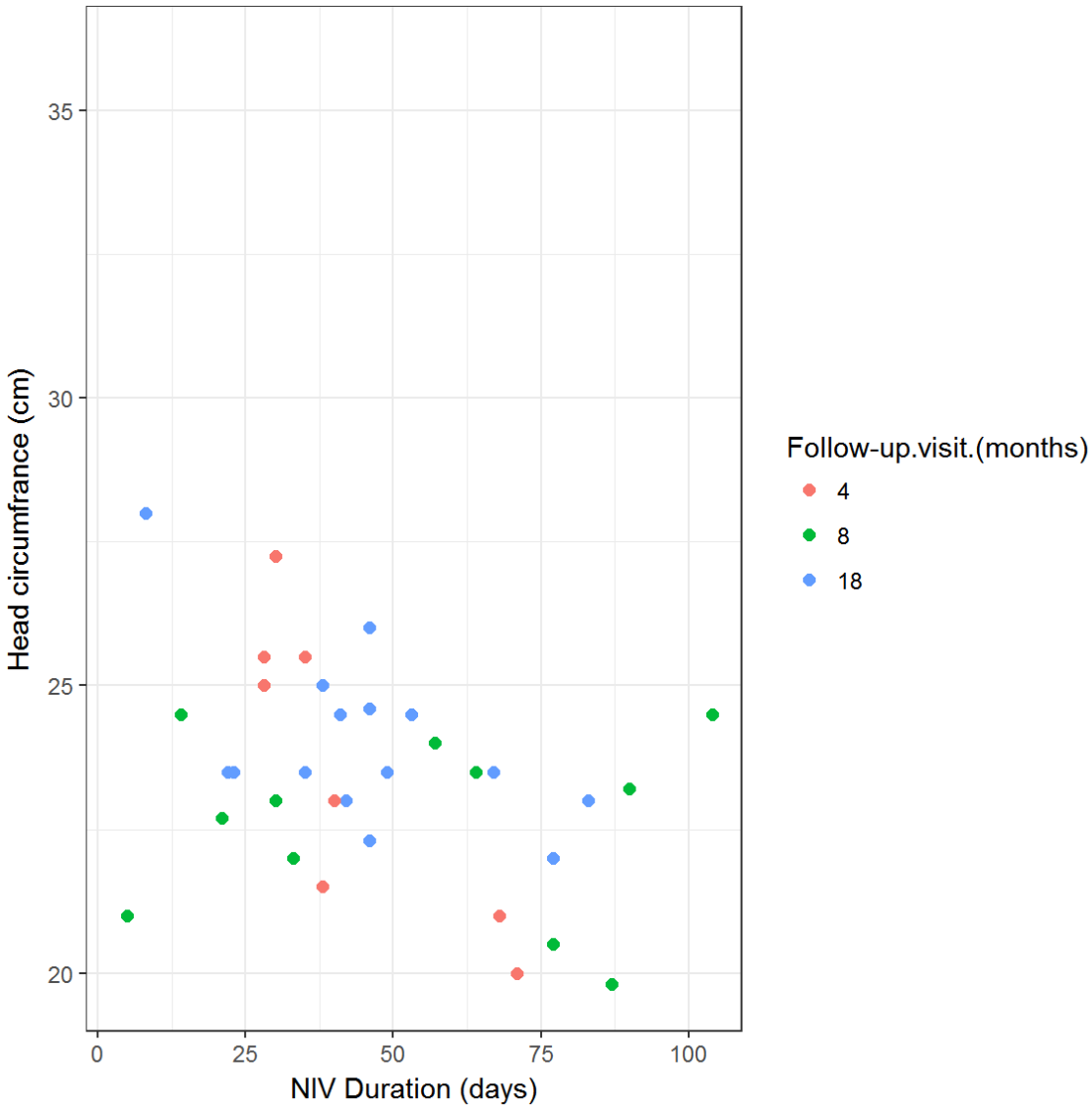

Figure 22 - Scatterplot for duration of NIV therapy (days) versus birth head circumference (cm) for 4, 8 and 18-month cohorts

Table 18 - Correlation between duration of NIV therapy (days) and birth head circumference (cm)

Follow-up visit (months)	Correlation
Overall	-0.37
4	-0.64
8	-0.02
18	-0.56

In the 4-month neonatal follow-up cohort, there is a negative correlation found with the duration of NIV therapy in relation to gestational age, birth weight, birth length and birth head circumference. In the 8-month neonatal follow-up cohort, there is a small positive correlation (0.03) found with the duration of NIV therapy in relation to gestational age. There is a negative correlation between the duration of the NIV therapy and birth length, birth weight and birth head circumference for the 8-month neonatal follow-up cohort. In the 18-month neonatal follow-up cohort, there is a negative correlation found with the duration of NIV therapy in relation to the gestational age, birth weight, birth length and birth head circumference.

3.8 Exploring Anthropometric Physical Data and Duration of NICU Stay

The study investigated the correlation between duration of the NICU stay with other variables such as gestational age, birth length, birth weight, and birth head circumference. The correlation between the duration of the patient's NICU stay in relation to the gestational age, birth length, birth weight and birth head circumference, when considering both sexes, appears to show a negative overall correlation in the 4, 8 and 18-month cohorts (Figure 23-26; Table 19-22).

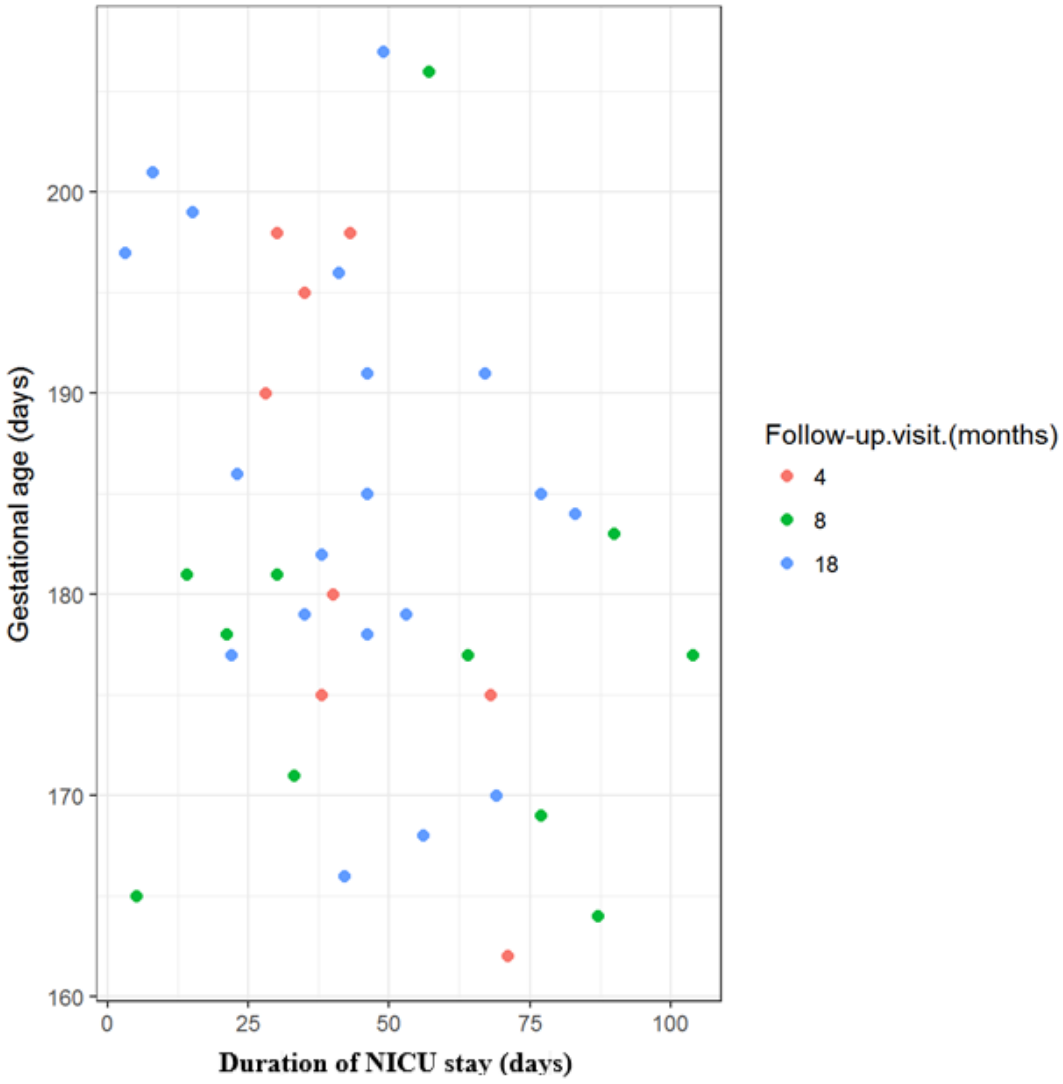

Figure 23 - Scatterplot for duration of NICU stay (days) versus gestational age (years) for 4, 8 and 18-month cohorts

Table 19 - Correlation between duration of NICU stay (days) and gestational age (years)

Follow-up visit (months)	Correlation
Overall	-0.55
4	-0.62
8	-0.24
18	-0.74

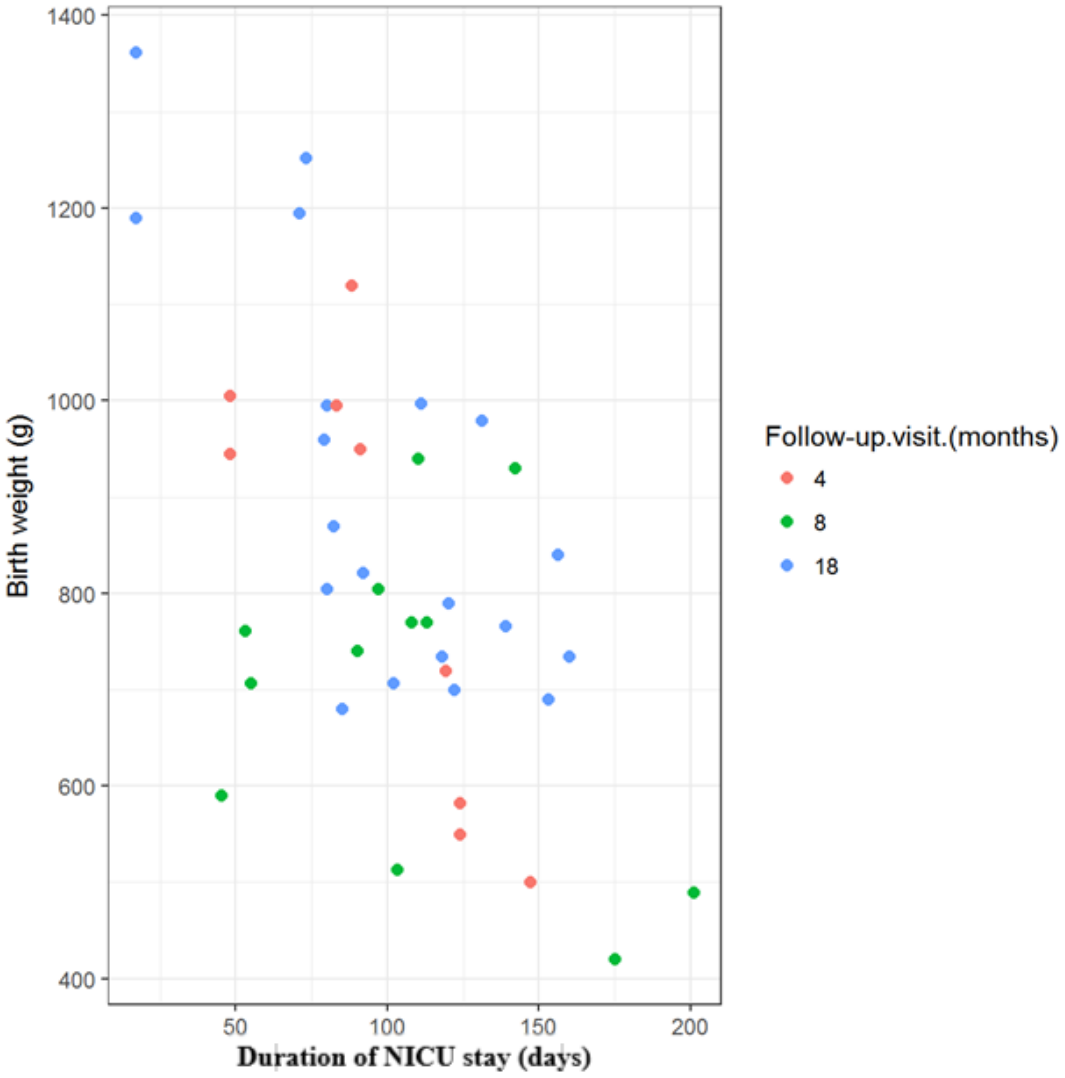

Figure 24 - Scatterplot for duration of NICU stay (days) versus birth weight (cm) for 4, 8 and 18-month cohorts

Table 20 - Correlation between duration of NICU Stay (days) and birth weight (grams)

Follow-up visit (months)	Correlation
Overall	-0.59
4	-0.83
8	-0.32
18	-0.72

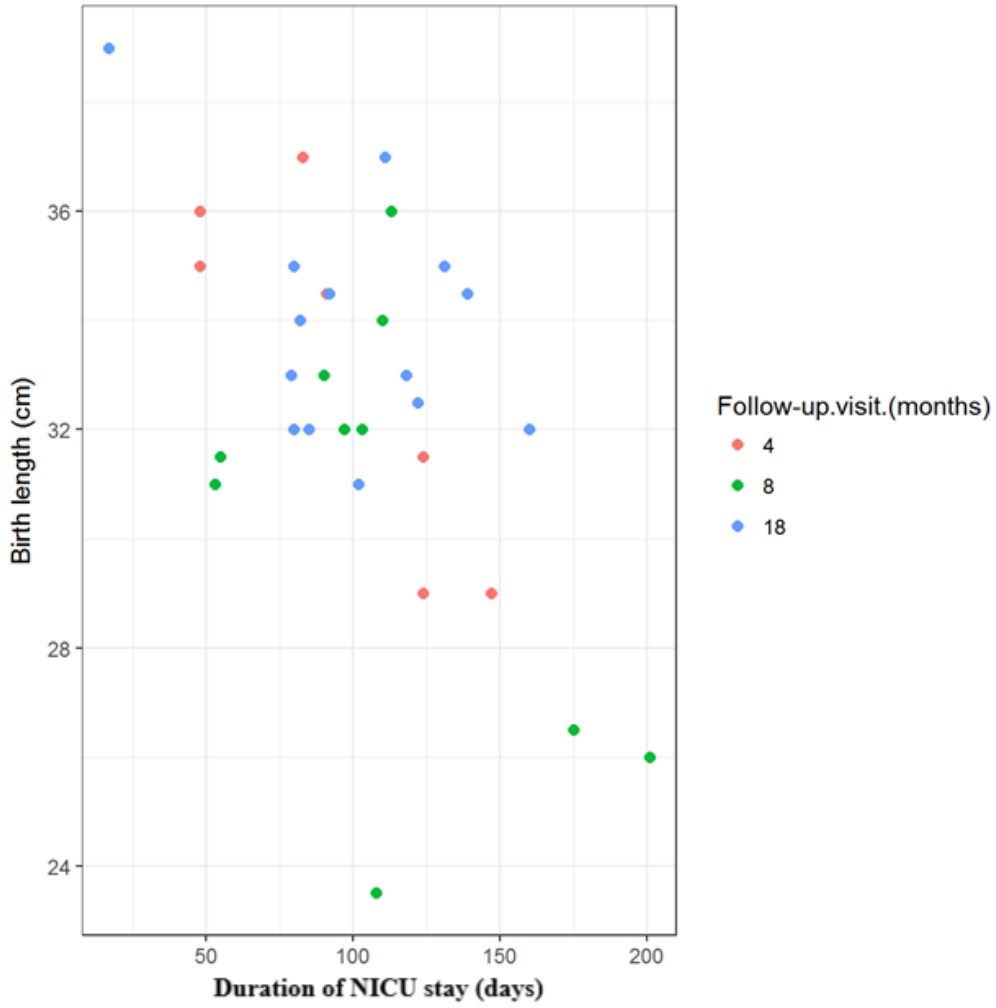

Figure 25 - Scatterplot for duration of NICU stay (days) versus birth length (cm) for 4, 8 and 18-month cohorts

Table 21 - Correlation between duration of NICU Stay (days) and birth length (cm)

Follow-up visit (months)	Correlation
Overall	-0.53
4	-0.75
8	-0.49
18	-0.45

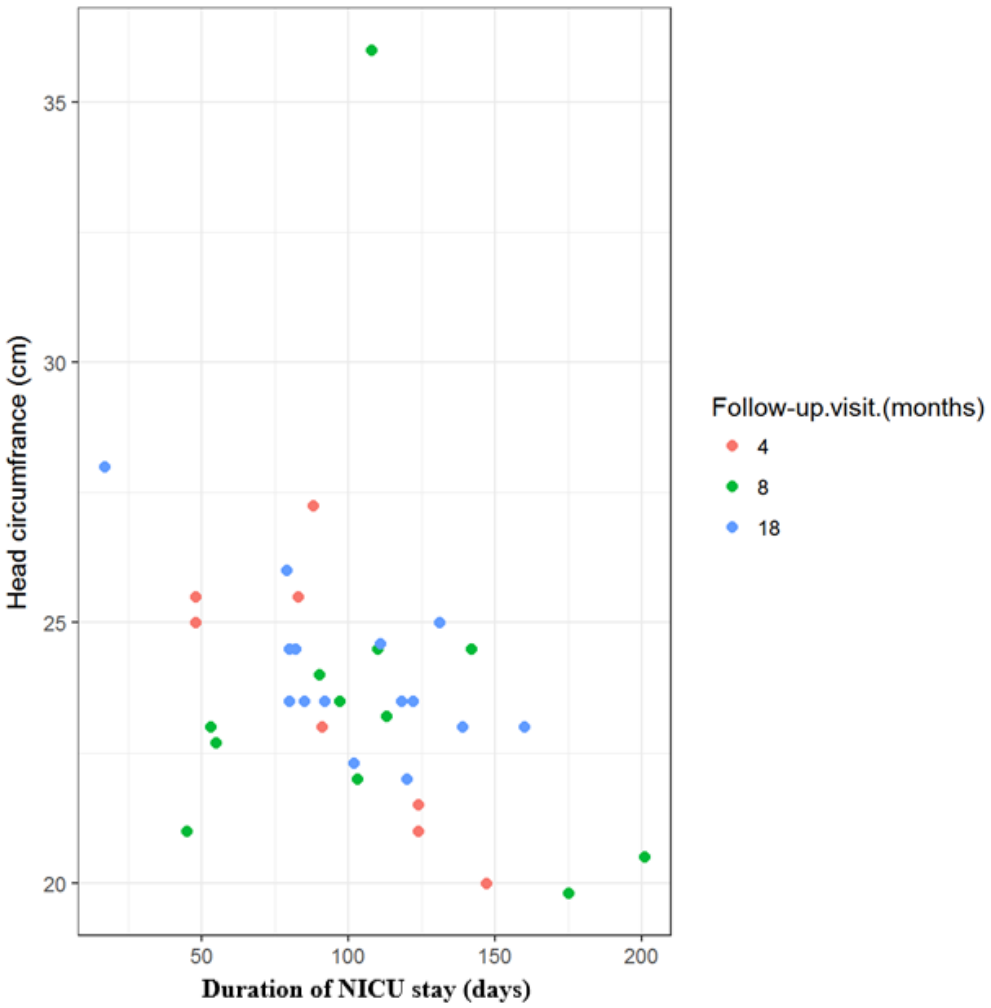

Figure 26 - Scatterplot for duration of NICU stay (days) versus birth length (cm) for 4, 8 and 18-month cohorts

Table 22 - Correlation between duration of NICU Stay (days) and birth head circumference (cm)

Follow-up visit (months)	Correlation
Overall	-0.35
4	-0.80
8	-0.12
18	-0.69

In the 4-month neonatal follow-up cohort, there is a negative correlation found with the duration of the NICU stay in relation to the gestational age, birth weight, birth length and birth head circumference. In the 8-month neonatal follow-up cohort, there is a negative correlation found with the duration of the NICU stay in relation to the gestational age, birth weight, birth length and birth head circumference. In the 18-month neonatal follow-up cohort, there is a negative correlation found with the duration of the NICU stay in relation to the gestational age, birth weight, birth length and birth head circumference.

The study investigated further the correlation between the duration of NIV therapy and duration of NICU stay in days (Figure 27). An overall positive correlation is found with the duration of the NICU stay versus the duration of NIV therapy (Table 23).

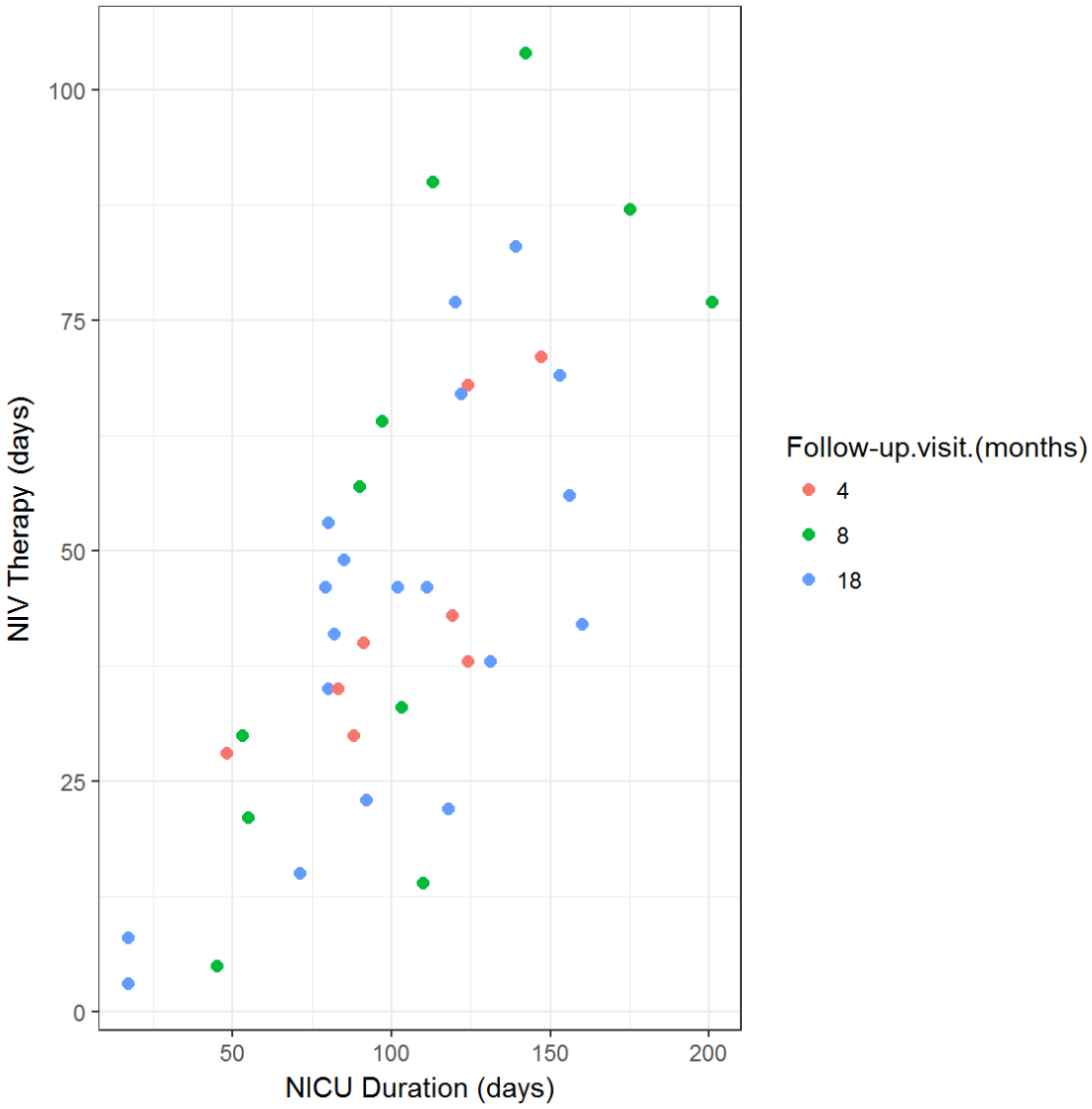

Figure 27- Scatterplot for duration of NIV therapy (days) versus duration of NICU stay (days) for 4, 8 and 18-month cohorts

Table 23 - Correlation between duration of NIV therapy (days) and duration of NICU stay (days)

Follow-up visit (months)	Correlation
Overall	0.70
4	0.68
8	0.72
18	0.70

3.9 Landmarking Reliability Tests

To determine the reliability of the investigator anthropometric landmarks, the investigator re-landmarked the same 43 3D facial images initially landmarked. The linear distances in the transverse, vertical and anterior-posterior planes were re-measured on the second landmarked images. The mean difference for each linear distance were then calculated and a 95% confidence interval was determined.

In the 4-month cohort, the mean difference of all transverse, vertical, and anterior-posterior linear distances between the initial and second landmarked images were within 95% confidence. In the 8-month cohort, the mean difference of all transverse, vertical, and anterior-posterior linear distances between the initial and second landmarked images were within 95% confidence. In the 18-month cohort, the mean difference of all transverse, vertical, and anterior posterior linear distances between the initial and second landmarked images were within 95% confidence.

Table 24 - The reliability test for landmarking images in the 4, 8 and 18-month cohorts

Linear Distances	4-Month Cohort		8-Month Cohort		18-Month Cohort	
N=43	Mean Difference	95% Confidence Interval	Mean Difference	95% Confidence Interval	Mean Difference	95% Confidence Interval
T_R-T_L	-0.066	(-0.22,0.09)	0.32	(0.08,0.57)	0.30	(0,0.6)
EN_R-	0.516	(-0.02,1.05)	-0.20	(-0.63,0.22)	-0.40	(-0.74,-0.05)

EN_L						
EX_L-EX_R	-0.371	(-1.3,0.56)	0.14	(-0.33,0.6)	-0.54	(-1.01,-0.06)
AL_R-AL_L	-0.052	(-0.21,0.11)	0.00	(-0.12,0.13)	0.39	(0.17,0.62)
AC_R-AC_L	0.566	(-0.32,1.45)	0.29	(-0.29,0.87)	0.50	(0.09,0.92)
CH_R-CH_L	1.363	(0.75,1.97)	1.07	(0.37,1.77)	0.64	(0.13,1.14)
CPH_R-CPH_L	0.206	(-0.17,0.59)	0.27	(-0.1,0.63)	0.12	(-0.17,0.4)
N-GN	-0.751	(-1.83,0.33)	-1.33	(-1.92,-0.74)	-1.61	(-2.24,-0.99)
N-STO_S	-0.457	(-1.01,0.09)	-1.19	(-1.66,-0.72)	-1.32	(-1.77,-0.88)
N-SN	-0.309	(-1,0.38)	-1.17	(-1.63,-0.71)	-1.46	(-1.81,-1.12)
STO_I-GN	-0.299	(-0.82,0.23)	-0.10	(-0.69,0.5)	-0.13	(-0.61,0.36)
SN-GN	-0.464	(-0.93,0)	-0.13	(-0.6,0.33)	-0.16	(-0.68,0.37)
N-PRN	-0.494	(-1.05,0.06)	-1.63	(-2.28,-0.97)	-1.25	(-1.74,-0.75)
STO_S-SN	-0.165	(-0.44,0.11)	0.10	(-0.26,0.45)	0.14	(-0.08,0.35)
SN-LS	-0.105	(-0.39,0.18)	0.04	(-0.29,0.36)	-0.14	(-0.47,0.2)
LS-STO_S	-0.093	(-0.57,0.39)	0.12	(-0.18,0.43)	-0.07	(-0.47,0.32)
STO_I-LI	0.148	(-0.29,0.59)	0.11	(-0.19,0.41)	0.56	(0.21,0.9)
LI-SL	-0.063	(-0.28,0.16)	-0.36	(-1.31,0.59)	-0.71	(-1.12,-0.3)
N-T_R	0.392	(-0.3,1.09)	0.72	(-0.02,1.45)	0.43	(0.08,0.79)
N-T_L	0.026	(-0.47,0.53)	-0.29	(-0.87,0.29)	-0.25	(-0.6,0.1)

SN-T_R	0.625	(-0.06,1.31)	0.91	(0.32,1.49)	0.35	(0.02,0.68)
SN-T_L	0.252	(-0.19,0.7)	0.72	(0.42,1.02)	0.37	(-0.07,0.81)
PG-T_R	0.438	(-0.57,1.45)	0.59	(-0.02,1.2)	-0.57	(-0.94,-0.19)
PG-T_L	0.29	(-0.34,0.92)	0.82	(0.43,1.22)	0.33	(-0.1,0.76)
PRN-AL_R	0.198	(-0.12,0.51)	0.54	(0.19,0.89)	0.59	(0.28,0.9)
PRN-AL_L	-0.46	(-0.78,-0.14)	-0.14	(-0.43,0.14)	-0.04	(-0.45,0.37)
PRN-AC_R	0.344	(-0.07,0.76)	0.58	(0.21,0.95)	0.50	(0.22,0.78)
PRN-AC_L	-0.129	(-0.46,0.2)	0.21	(-0.13,0.55)	0.06	(-0.2,0.32)
PRN-SN	0.185	(-0.12,0.49)	0.55	(0.1,1)	-0.07	(-0.41,0.27)

Chapter 4: Discussion

4.1 Characterization of Three-Dimensional Facial Morphology of a Cohort of Preterm Infants at 4, 8 and 18 Months Corrected Age

The first objective of the study was to characterize the three-dimensional facial morphology of a cohort of pre-term infants at 4, 8, and 18-month corrected age that have received non-invasive ventilation with or without mechanical ventilation during their NICU stay. The goal of this first objective is to quantify and establish normative anthropometric facial data values for pre-term newborn infants in their first 18 month of life to help facilitate our understanding of facial growth and development in this vulnerable population.

For the anthropometric distance data for the transverse facial plane, when comparing the 4-month old cohort to the 8-month old cohort there is slight decrease in the skull base width, the intercanthal width, the morphological nose width, and the anatomical nose width. Whereas there is an increase in average transverse facial linear measurements are shown in the bi-ocular width, labial fissure length and the philtrum width at 8 months. Possible reasons for this unexpected decrease include the use of cross sectional data and relatively small sample sizes in both these earliest time points. The mean gestational age, birth weight and birth length are smaller in the 8-month cohort than the 4-month cohort which may explain the decrease in skull base width, the intercanthal width, the morphological nose width, and the anatomical nose width from the 4 to 8-month cross sectional cohorts. There is a general increase in all average transverse facial linear measurements in the 18-month cohort compared to the 4 and 8-month cohorts.

For the anthropometric distance data for the vertical facial plane, when comparing the 4-month and 8-month cohort average vertical linear distances, there a slight increase in morphological face height, nasal bride length, upper lip length, and cutaneous upper lip length.

There are no changes to upper face height, both lower face height (STO_I-GN and SN-GN), nose height, and cutaneous lower lip length. There is a slight decrease in upper vermillion height, lower vermillion height, lower lip length. There is a general increase in all average vertical facial linear measurements in the 18-month cohort when compared to the 4 and 8-month cohorts. However, there appears to be no change in cutaneous upper lip length comparing the 4 and 18-month cohort and a slight decrease in cutaneous lower lip length when comparing the 8 to 18-month cohorts.

For the anthropometric linear distance for the anterior-posterior facial plane, when comparing the 4 and 8-month cohort mean anterior-posterior linear distances, there is an increase in upper facial third depth, right and left middle third depth and lower facial third depth. The alar depth, alar base depth and nose depth appear to be relatively constant. In general, the upper, middle and lower third depth appears to show large linear growth when comparing the 18-month cohort to the 8 and 4-month cohorts. The alar depth and alar base depth average shows a slight increase from the 8 to 18-month cohort. The nose depth average within standard deviation appears to be relatively constant between the 8 and 18-month cohort.

For the anthropometric facial angles, when comparing the 4 and 8-month cohort mean facial angles, the upper, upper mid-face and morphological face angle appear to be relatively unchanged. There is an increase in subnasal protrusion angle and midface depth angle, when comparing facial angles from the 4, 8, and 18-month cohort, respectively. However, the statistical variability (standard deviation) is high for the subnasal protrusion angle and the midface depth angle. Due to small sample size and large standard deviation, the study cannot make a conclusion with the difference in angle measurement between the 4, 8 and 18-month cohorts. The use of cross sectional data and the overlapping average angle values due to large

standard deviation between 4, 8 and 18-month cohorts provide a challenge to confidently state an actual depiction of the angular growth trend. Infants are observed to be easily irritated and parents learning to posture their child correctly is a challenge. The images taken may not be the infants precise resting face due to his or her involuntary facial movements or grunting. There is no remarkable change in direction of vertical growth based on observed facial angles. The use of cross sectional data and high statistical variability due to large standard deviation between the 4, 8 and 18-month cohorts provide a challenge to confidently state an actual depiction of the angular growth trend.

The morphological face height to skull base width ratio and upper face height ratios appear to be constant through the 4, 8 and 18-month cohorts. There is a slight increase in morphological face height to skull base width but there is high statistical variability. There is overall upper face height to skull base width slight increase from 4 to 18-month cross sectional. There is a modest increase in upper part of the upper face height to skull base width from 8 to 18 months. Overall, this characterization shows possible more growth in the vertical direction than transverse direction.

The characterization of craniofacial morphology of preterm infants treated with non-invasive ventilation with or without mechanical ventilation can be influenced by patient's sex, ethnicity, gestational age difference, birth weight, birth length, birth head circumference, duration of mechanical ventilation if any, duration of non-invasive ventilation, duration and location of NICU stay, birth hospital, and mode of feeding. The investigator did not anticipate that some patients had partial or complete treatment at other neonatal intensive care units in British Columbia and were only visiting BCWH for neonatal follow-up. Since ventilation therapy protocols are quite dynamic, the birth hospital and NICU treatment hospital can variably affect

each of the morphological parameters. After dividing the images into 4, 8 and 18-month cohorts and specifically into male and female cohorts, there is a significant small sample size. The small sample size is also unevenly distributed with females and males in each 4, 8 and 18-month cohorts. As a result, the study cannot identify sex specific influences on the craniofacial morphology of our population.

The study tested for normality of the anthropometric linear distances, angles and facial ratios in the 4, 8 and 18-month cohort (Appendix A.10). Due to significantly small sample size, the study cannot provide an accurate conclusion on the nature of sample size distribution.

4.2 The Effects of Duration of NIV therapy on Craniofacial Morphology at 4, 8 and 18 Month Corrected Age

The second objective of the study is to determine the possible effects the duration of NIV therapy may have on craniofacial morphology in a cohort of pre-term infants that have received non-invasive ventilation with or without mechanical ventilation. The goal of the second objective of the study is to determine potential modifying effects of the NIV received by each patient.

When comparing the 4 and 8-month cohort average transverse linear distances, there is a slight decrease in the skull base width, intercanthal width, morphological nose width, and anatomical nose width. The rationale for the short-term slight decrease in the skull base width, intercanthal width, morphological nose width and anatomical nose width could be associated with their ventilation therapy (interface and straps). For the 4-month neonatal follow-up cohort, when considering all genders, showed a negative correlation between intercanthal and bi-ocular width versus duration of NIV therapy. In the 4-month cohort, the negative correlation is statistically significant for the intercanthal width versus the duration of NIV therapy. As a result,

there is a predictable level of significance supporting an increase in duration of NIV is related to a decrease in intercanthal width. There is currently not any published research in early infancy showing a decrease in intercanthal width. Paulsson and Bondemark have discovered children ages 8 to 10 born extremely premature have a shorter maxillary length, anterior cranial base and smaller head circumference but did not investigate intercanthal width (Paulsson & Bondemark, 2009). The possible pathophysiological mechanism may be associated with the compressive pressure from the straps of the interface. Compressive forces are known to demonstrate bone remodeling and inhibiting osteogenic differentiation (Sen, Diercke, Zingler, Lux, & Erber, 2015). The negative correlation found for bi-ocular width versus duration of NIV therapy was not statistically significant. In general, the study observed the duration of NIV therapy may have a negative growth influence on intercanthal width. However, the study cautions the overall interpretation as the sample sizes are small and the gender ratios are unevenly distributed.

When comparing the 4-month and 8-month cohort average vertical linear distances, it is reasonable to see growth in morphological face height, nasal bridge length, upper lip length, and cutaneous upper lip length. However, there appears to be no change to upper face height, both lower face height (STO_I-GN and SN-GN), nose height, and cutaneous lower lip length. This observation could be related to NIV therapy or a result of normal growth and development (Budai et al., 2003; Farkas & Posnick, 1992; Farkas et al., 1992; Meyer-Marcotty et al., 2014; Sinha et al., 2014). There is a slight decrease in averages for upper and lower vermillion height and lower lip length. For the 4-month neonatal follow-up cohort, when considering both sexes, showed a negative correlation for both lower face height (STO_I-GN and SN-GN), upper lip length, cutaneous upper lip length, upper and lower vermillion height. However, none of these negative correlations showed any statistical significance. This interpretation is limited by the

small sample size and uneven sex distribution. The duration of NIV therapy in the 4 and 8-month cohort are unevenly distributed while the distribution is fairly normal for the 18-month cohort (Figure 8-11). Due to the uneven distribution per cohort, there are limitations to conclude our findings associated with duration of NIV therapy. As a result, our preliminary observations showed no clear indication that the duration of NIV therapy has any significant impediment of vertical growth.

When comparing the 4-month and 8-month cohort average anterior-posterior linear distances, there is an increase in upper, middle and lower facial third depth but the alar depth, alar base depth and nose depth appears to be relatively stable. This observation shows that there is no obvious impediment on anterior-posterior craniofacial growth. For the 4-month neonatal follow-up cohort, when considering both sexes, showed a negative correlation for the middle and lower facial third depth. However, none of these negative correlations showed any statistical significance. As a result, our observations showed no clear indication that the duration of NIV therapy has any significant impediment of anterior-posterior growth.

When comparing the 4, 8 and 18-month cohort average anthropometric angles, there are slight changes to all average angles overtime, but the standard deviations are large in value bringing challenges to interpreting the small changes. In the 4-month cohort, when considering both sexes, there is a negative correlation for the subnasale angle, nose protrusion angle, upper face angle, mid-face angle, and morphometric face angle, and mid-face depth angle. However, none of these negative correlations showed any statistical significance. As a result, our observations showed no clear indication that the duration of NIV therapy has any significant impediment of the measured facial angulation of growth.

When comparing the 4, 8 and 18-month cohort facial ratios, the growth appears to be proportional in the transverse and vertical plane. There was no statistical significant negative correlation between the duration of NIV therapy and proportional facial growth in the 4, 8 and 18-month cohort. As a result, our observations showed no clear indication that the duration of NIV therapy has any significant influence on facial symmetry in the growth potential of the transverse and vertical planes.

The craniofacial morphology of neonates undergoing non-invasive ventilation with or without mechanical ventilation during their stay in the neonatal intensive care unit can be affected by multiple confounding variables. The following demographic parameters may skew or affect our interpretation of the craniofacial morphology of our sample population: patient's sex, ethnicity, gestational age difference, birth weight, birth length, birth head circumference, duration of mechanical ventilation if any, duration of non-invasive ventilation, duration of NICU stay, birth hospital, and mode of feeding. Due to the need to reduce facial and skin injuries, the NICU protocol at BCWH require interchanging between different respiratory interfaces. As a result, the effect of interface on craniofacial morphology cannot be evaluated in this sample. Some patients imaged were cared for in NICUs other than BCWH. We included them to obtain normative data but different practices in other NICUs is a confounding factor and limits our ability to evaluate the effect of NIV on our measurements. Multiple logistic regressions analysis has been performed to identify explanatory variables (gestational age, birth weight, birth length, and birth head circumference) that may affect each of the morphological parameters. The correlation and univariate linear regression for each facial measurement versus NIV therapy data can be viewed in Table 12-14. There is an overall negative correlation, in all 4, 8 and 18-month cohorts, associated with gestational age, birth weight, birth length and birth head circumference

versus the duration of NIV therapy. As a result, our observation shows that the longer the duration of NIV therapy, the lower the gestational age, birth weight, birth length and birth head circumference is associated with the pre-term infant. An infant has an increased risk of failure to thrive and overall medical comorbidities when there are lower or smaller gestational age, birth weight, birth length and birth head circumference (Woodward et al., 2009). As a result, we anticipated that preterm infants in the NICU with lower gestational age, birth weight, birth length and birth head circumference to require more and longer medical intervention such as respiratory care. This would logically explain the longer the duration of NIV therapy, the lower the gestational age, birth weight, birth length and birth head circumference. Due to this potential growth impediment factor due to pre-maturity, the patient's overall gestational age, birth weight, birth length, and birth head circumference may influence the infant's craniofacial morphology. Extremely pre-term infants were usually born with multiple system complications which may have an indirect effect on facial growth and development. Most extremely pre-term infants on long term ventilatory support have bronchopulmonary dysplasia and this may affect long-term airway function which may indirectly affect future facial development. Literature have shown that genetics play an important factor in craniofacial growth and development (Battle, Schneider, Magder, & Pae, 2018; C. Li, Cai, Chen, & Chen, 2016). Many genetic conditions and syndromes in infants are not diagnosed until many years later. For example, cerebral palsy may not be diagnosed until many infants reach certain motor milestones. Certain genetic conditions and syndromes may have an influence on long-term craniofacial growth and development. These undiagnosed genetic factors may affect our morphological parameters. The cohorts had a relatively large mixture of different ethnicities. Literatures have shown ethnic differences in facial traits and dentofacial patterns during periods of active growth (Cooke & Wei, 1989;

Thilander, Persson, & Adolfsson, 2005). Because of the large differences in ethnicity and a small sample size, we cannot factor in the variability that ethnicity may influence our morphometric parameters. Some of these pre-term infants may also have been influenced by prenatal alcohol exposure. The literature has shown heavy prenatal alcohol exposure may result in orbit hypertelorism and changes to facial curvature (Suttie et al., 2017). Most patients were intubated in their initial hours to days of life and some were intermittently requiring intubation due to low oxygen saturation or unstable airway. The length of intubation in infants has been shown in the literature to change palatal morphology and may indirectly affect facial morphology (Harila-Kaera et al., 2002; Paulsson et al., 2004). Two patients in the study were later diagnosed with cerebral palsy and were still included in the study. Due to muscle hypotonia or hypertonia, the literature has shown long-term variable changes in facial morphology and the presence of malocclusion (Abanto et al., 2014).

4.3 The Feasibility, Time, Adverse Events, and Effect Size

The third objective of the study is to evaluate the feasibility, time, adverse events, and effect size (statistical variability). The goal of this third objective is to provide appropriate insight and recommendations for future attached projects and an attempt to predict an appropriate sample size to improve study design prior to performance of a full scale longitudinal research project.

The overall acceptability and demand of the research project is positively feasible. There are many pre-term infants visiting the neonatal follow-up program at 4, 8 and 18 months corrected age. During the 9 months of recruitment, there were approximately 39 patients presenting to the neonatal follow-up program for their first 4-month visit. There were 40 patients

returning for their 8-month visit and 65 patients returning for their 18-month visit. As most parents or guardians have voluntarily provided consent for their child to participate in the study, the project had a strong recruitment acceptability from the parents. One hundred and two patients were accepted into the study out of 143 screened patients. Fifteen patients did not consent to participate but 7 out of 15 were due to a temporary halt in recruitment because of ethics certificate expiration in April 2018. The study's ethical certificate was renewed at the end of April 2018 and recruitment started again in May 2018. Parents that did provide consent for their child to participate in the study acknowledged historical concerns about how respiratory intervention in their child's initial days of life in the NICU may have affected their child's facial growth and development.

The overall implementation and practicality of the research project is positively feasible. To improve the success of the study, the investigator consulted neonatology, otolaryngology and dentistry to seek insight into their daily work environment and their approval to integrate the research project into their daily clinics. After appropriate consultation, a draft protocol was designed to understand the work flow of our research project and where specialized equipment will need to be installed. The appropriate administrative leaders from neonatology, otolaryngology and dentistry were contacted and the objective, goals, design of our research were presented. The department of neonatology required the ethics certificate and introduction of all investigators to their department to inform their clinics of our presences and to protect patient confidentiality. The department of otolaryngology recommended our use of one of their examination rooms to install the 3dMDface System (3dMD, Atlanta, GA, USA) and the offline password encrypted computer. The analysis offline password encrypted computer was installed in the otolaryngology resident room. The department of pediatric dentistry recommended that the

investigator, a pediatric dental resident, dedicate priority to dental related hospital duties while coordinating patient recruitment. After obtaining appropriate recommendations, the investigator made the appropriate considerations in the study design and obtained department approval from neonatology, otolaryngology and pediatric dentistry. The final protocol was drafted and granted by the UBC Children's & Women's Clinical Research Ethics Board [H17-00407]. Although there were numerous limitations and challenges, the implementation of the research project was a success. The appropriate equipment was installed in otolaryngology without any damage or conflict of interest. The work flow of the design required a multi-disciplinary approach. Arsalan Butt, the data manager in the Neonatal Follow-Up Program, provided monthly neonatology follow-up appointment information so the investigator could timely screen patients based on the study's inclusion and exclusion criteria. Julie Pauwels, the research coordinator, facilitated recruitment by committing time to communicate with parents of patients participating in the research project and acquiring images when the investigator was not available. The investigator had to coordinate time appropriate to encounter recruited patients because of full-time dedicated dental related hospital duties such as oral rehabilitation under hospital general anesthesia, dental care for special health care needs patients and craniofacial and cleft palate clinics. Overall, the research project is practical. Challenges to patient recruitment included when patients show up late, do not provide notification that they are not showing up, and times when their neonatal follow-up appointment is during time when the investigator is not available (Figure 28). Every Tuesday, otolaryngology runs a full day craniofacial and cleft palate schedule with plastic surgeons, ENT doctors, pediatric dentists, orthodontists, audiologist, speech and language pathologist and pediatricians. As a result, patients booked for neonatal follow-up appointments on Tuesdays couldn't be imaged due to time conflicts and most were not willing to wait after

their neonatal follow-up appointment event with parking incentives. The learning curve to image infants was initially challenging but relatively straight forward after having learnt to image them in a timely fashion with appropriate posturing and positioning.

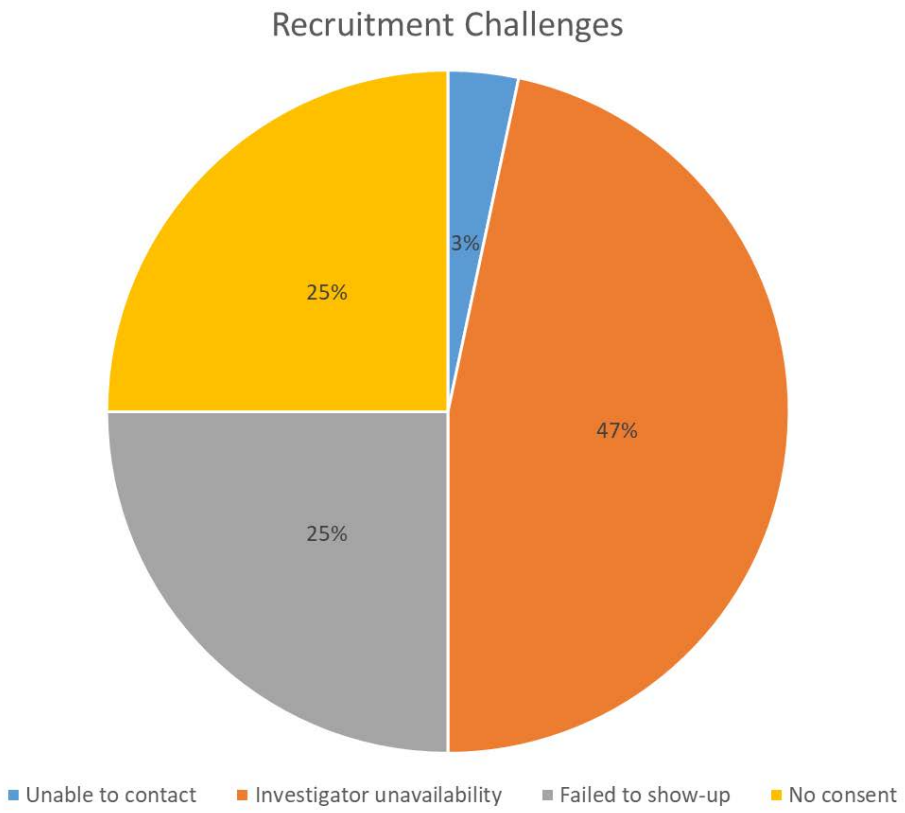

Figure 28 - Recruitment challenges associated with unsuccessful recruitment

The overall adaptation, integration, and expansion of the research project is positively feasible. Throughout the designing and implementation of the research project, the investigator had to ensure the research project adapts to ongoing changes within the hospital, considerations to ongoing recommendations from departments and to appropriately modify and accommodate those changes. The respiratory ventilation protocol in the NICU is relatively dynamic as there are

new consideration for interfaces. The pediatric dentistry department's schedule is quite dynamic as the investigator's hospital duties change weekly but relatively firm schedules are given monthly. As a result, the investigator must improvise, and time manage appropriate to recruit patients. The neonatology, otolaryngology and pediatric dentistry departments have been welcoming of the research project and there have not been any conflicts or adverse events during recruitment and image acquisition associated with the normal operation of department clinics. As a result, the integration of a new program or process associated with the current research project is feasible accounting for appropriate implementation. The expansion of the research project is feasible and has already begun to amplify study sample size, consideration of looking further into tomographic observations of facial changes and extending the screening into the third and four years of life of these patients.

In this study, the investigator's landmarks were deemed reliable within 95% confidence. In the 4, 8 and 18-month cohorts, the mean difference of all transverse, vertical, and anterior-posterior linear distances between the initial and second landmarked images were within 95% confidence. Aldridge et al. have demonstrated both the error due to digitalization and error due to 3dMD imaging system are very low, less than 1% and 1.5% respectively (Aldridge et al., 2005). The investigator did not use the glabella and gonion landmarks because they were demonstrated in a previous study to have markedly decreased precision (error greater than 2mm) (Aldridge et al., 2005).

The research study had limitations regarding interpretation of our data due to small sample size and uneven gender distribution. As a result, to predictably increase sample size in future research related to this project, a limited-efficacy test was performed. To determine the minimum effect size, the difference in linear distance of 1.0 mm was used and a level of

statistical significance of 0.05 under the current linear distance variability with 80% power with a 5% significance level for 1.0 mm difference to be detected between 4, 8 and 18-month cohorts and a 1.0 mm standard deviation, 16 subjects are required per group. The groups would be considered as each 4, 8 and 18-month cohorts. To further describe normal craniofacial growth, a term born control group would be desirable. In the preterm group, the effect of NIV could be better described with more participants with long term NIV use.

4.4 Limitations and Study Challenges

There were numerous limitations that created obstacles and challenges facing implementation and delivery of the research study. The investigator of the project pioneered a protocol with ambiguity in recruitment expectations, a clear understanding of limitations and challenges associated with imaging an infant, challenges facing learning to use the hardware and software programs associated with the study, and challenges facing data collection.

The research study faced many recruitment limitations and challenges. The neonatology department predicts approximately 50 patients accepted into the neonatal follow-up program at BCWH each year. However, there are variations in terms of the number of returning patients for follow-up. As a result, it was challenging to gauge predictably the number of patients that would be screened and accepted into the study for the 8 and 18-month cohorts. The research study did consider recruiting a control group. The neonatology department had provided initial feedback during our study design that we should expect very few or none of the pre-term infants, especially extremely pre-term infants, that would not be on some form of respiratory support. There were a few cases during our screening process where infants returning for neonatal follow-up had not received non-invasive ventilation. These infants were recruited for other indications

than extreme prematurity. The study did contact the parents for these patients, but they were reluctant to participate in the study due to lack of interest. During the screening process, the investigator found vast information in electronic and physical medical records for these patients due to the presence of multiple congenital comorbidities, surgical care and lengthy treatment duration in the neonatal intensive care unit. There was a considerable amount of time dedicated to reading medical records during the screening and data collection process. The study faced unexpected recruitment challenges when screening patients. A few patients were transfer patients from another hospital with different NIV protocols. Other patients were raised by surrogate parents and had neonatal care in the United States. As a result, finding sufficient respiratory information for these patients was difficult and most were rejected from the study. Another recruitment challenge was understanding how infants later diagnosed with cerebral palsy may affect their craniofacial growth and development. Other recruitment challenges include appointment cancellations due to weather or without reason. These patients are difficult to coordinate and follow-up with their next rescheduled neonatal follow-up appointment. Some patients present to the BCWH to see multiple specialists before and after their neonatal follow-up appointment. The patient is typically fatigued by the end of the day. Therefore, it is challenging for these infants to stay longer for the research project. Some infants are anxious or agitated after their neonatal follow-up appointment which affects parent's decision of proceeding with the research project or make it challenging to take the facial image. Other recruitment challenges include investigator availability. Certain unexpected hospital responsibilities occur during normal dental clinic operating times which may conflict coordinating images with parents during their neonatal follow-up appointments. There are other uses of the otolaryngology examination room every Tuesday for craniofacial examinations and cleft lip and palate clinics. As a result,

most neonatal follow-up appointments made on Tuesdays are challenging to coordinate because the craniofacial and cleft lip and palate clinics run for the entire day.

The investigator faced many challenges with imaging infants at 4, 8 and 18-months of age. At 4-months of age, infants are typically starting to have the strength to lift their head up. As a result, it is challenging to image a 4-month-old infant with poor head control. The parent is usually holding the infant in his or her lap while having a hand postured behind their child's head for stability. However, the picture needs to be taken fast or the infant will become agitated and show grimace or make it difficult to take an overall clear image due to repetitive uncontrolled movement. The 8 month of age infants are not as challenging to take images as they have more control of their neck and head movements. However, at 18-months of age, most children at this age are walking and running. The 18-month old patients have a short attention span and may unexpectedly move or want to move out of their parents lap or chair. The investigator has found an area in front and between the two mounted module cameras that are out of the field of view. The investigator would then make sounds or play a children song clip on a mobile device to get the child's attention to the specific focal trough that would give a clear image. With a cordless keyboard with a touchpad, the investigator could control and access when the image can be taken. The examination chair that the parent sits on with the child has the capability of moving up and down. This easily allows the investigator to move the chair up and down so the child is within the focal trough of the cameras. There were initial challenges with learning to organize the raw image data and editing the images to crop out unnecessary background information. However, with dedication and time towards organizing and learning the software, the simplest way to organize and store data is to have the raw files stored on the acquisition computer and edited and measured images on the analysis computer. There is a learning curve to the perceptual

ability to rotate images and deleting 3-dimension excess background information. All images can be landmarked, and the software allows the landmarks to be saved. The investigator can revisit these images and compute the linear distances and angles.

The investigator faced many limitations and challenges associated with data collection. All the pre-term infants treated in the NICU at BCWH have extensive medical record information. The respiratory support information is longitudinally described in physical archived medical records which require authorized access. However, there is a summarized NICU discharge summary that provides sufficient information on patient demographics, and duration of respiratory intervention. The information on the type of interface of ventilation was not adequately documented but the mode of ventilation was clearly explained such as CPAP, high flow (HF) or endotracheal intubation (ETT). The investigator learned over the data collection process to read certain electronic documents that would have information on paternal and maternal ethnicity, duration of respiratory intervention, gestational age, gender, birth weight, birth length, birth head circumference, mode of feeding at discharge, birth hospital and treated or transferred hospital. The investigator was also able to calculate the NICU stay duration by following patient's birth and discharge dates. Any missing information would be accessed through their physical records. Three patients in the entire sample had missing ventilatory support information. To ensure accurate information and to obtain possible missing data, the study accessed the CNN data base.

Chapter 5: Conclusion and Recommendations

5.1 Conclusion and Recommendations

In conclusion, the research study has characterized the three-dimensional facial morphology of a cohort of pre-term infants at 4, 8 and 18 months corrected age, described the effects of the duration of NIV therapy on craniofacial morphology of these pre-term infants, and explored the feasibility, adverse events and effect size to establish appropriate recommendations for future research.

The characterization of the three-dimensional facial morphology of a cohort of pre-term infants at 4, 8, and 18 months corrected age have shown that short-term there is a statistical significant negative correlation between the duration of NIV therapy and the intercanthal width within a 95% confidence interval for one day of NIV therapy. In the transverse plane, there is a decrease in linear distance for intercanthal width, skull base width, nose width between 4 and 8-month cross-sectional cohorts. There was more vertical growth than transverse from 8 to 18-months. In the vertical plane, the upper and lower vermillion height decrease between 4 and 8-month cross-sectional cohorts. There was general increase in vertical growth from 4 to 18-month cohorts. The direction of growth appears to be unchanged from 4 to 18 months. In the anterior-posterior plane, there was a general increase in anterior-posterior growth from the 4 to 18-month cohorts. Anterior-posterior plane of the nose appears to be unchanged from 4 to 18-month cohorts.

Our observation did not show statistically significant correlation between the duration of NIV therapy and the linear distance measured for the transverse, vertical and anterior-posterior plane other than the intercanthal width. Our observations did not show statistical significance correlation between the duration of NIV therapy and side-profile facial angles in the cohort of

pre-term infants at 4, 8 and 18 months. The facial ratio shows that growth is proportional in the transverse to vertical facial plane. There were no statistical significant correlation showing NIV therapy had an influence on facial symmetry in the growth potential of the transverse and vertical planes. This pilot study did not have the sample size and power to detect a statistically significant difference.

There is overall positive feasibility for the acceptability, demand, implementation, practicality, adaptation, integration and expansion of the research project. In addition, the reproduced landmarks by the investigator were within 95% confidence. The recommendations to improve study design would be to amplify study sample size, consideration using facial tomography analysis to view morphometric changes over time and consideration of a future longitudinal study. Using the current research data to test for statistical variability and minimum effect sizes for linear distance, facial angle and ratios, future studies can measure at a level of significance to predict sample size recruitment objectives. The 3dMD Vultus software has the capability of performing superimposition of facial tomographic data at different time periods. This function will allow future studies to view morphometric changes over time. Using tomographic analysis and superimpositions at different time periods to view areas where the respiratory interface rests is a useful tool to observe the possible effects of NIV therapy on the face over time. An implementation of a longitudinal study with these software capabilities can be useful in improving our understanding of facial growth and development.

Premature birth and consequent exceptional adaptation from intra- to extra-uterine life may influence the growth and development of the dental occlusion. As a result, it is recommended to further explore topics on dental abnormalities and malocclusion seen in this vulnerable population as they reach school age. To evaluate whether alterations of dental

abnormalities, malocclusion or craniofacial morphology are permanent or transient, it would have been ideal to longitudinally follow premature and full-term born children. Thus, further well controlled longitudinal studies are needed. These recommendations will improve our understanding of short-term and long-term effects of premature birth on the growth and development of the dentition and face.

Considering possible future research direction, the methodology of being capable of imaging this vulnerable young population opens vast capability to explore patients born with cleft lip and palate. The exploration of craniofacial morphology before intervention, such as naso-alveolar molding techniques and cleft lip and palate surgical repairs, will educate the medical and dental field on how certain biological mechanics and intervention may influence craniofacial growth and development.

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Appendices

Appendix A

A.1 Screening Log

First Name	Last Name	MRN	Visit Date	Check-In Time	ACCEPT (YES/NO)	Type of Ventilation (INTUB/NIV/ BOTH)	Congenital Craniofacial Abnormality (YES/NO)	Congenital Syndrome (YES/NO)	Long Term Intubation (>1 Day)	PRETERM (YES/NO)	NICU STAY HOSPITAL

A.2 Subject Log

Study ID	Last Name	First Name	MRN	Sex	Relations	Phone Number	Mailing Address	Data Collected (N/Y)	Date Letter Sent	Date Called	Comments	Consented (date)	Type of Appointment (4/8/18-month)

A.3 Invitation Letter

BC WOMEN'S HOSPITAL+ HEALTH CENTRE An agency of the Provincial Health Services Authority	**BC Women's Hospital** **Neonatal Follow-up Program** **4480 Oak Street** **Vancouver BC V6H 3V4** **Tel: (604)-875-2854** **Fax: (604)-875-2483**

Date:

Dear Parent/ Legal Guardian,

I am writing to inform you about a research study called "**Craniofacial Morphology and the Use of Neonatal Non-Invasive Ventilation Therapy**". This study is being conducted by myself, Dr. Anne Synnes, in collaboration with Dr. Benjamin Pliska, Dr. Don He, Dr. Fernanda Almeida, and Dr. Neil Chadha at BC Children's Hospital. We are contacting you because your daughter Tru Wende was born prematurely at BC Children's Hospital and received non-invasive ventilation therapy (NIV) shortly after birth to assist her with her breathing. We would like to invite you and your child to take part in our research study, which investigates how NIV and the use of face masks and prongs inserted in the nostrils to provide oxygen can affect later facial structure growth and development in preterm babies.

Participating in this study involves having a 3D image taken of your child's face with a camera at BC Children's Hospital up to 3 times after your clinic visits with the Neonatal Follow-up Program. You will be approached by dentistry resident, Dr. Don He, at your next clinic appointment to participate in this study. This will take only an additional 15 minutes of your time at each visit to take the photo and poses no risks to your child. We will also review your child's hospital chart for medical information. More detailed information about this study and what is involved can be found in the study consent form included in this package.

If you/your child would like to participate in this study or if you wish for further information, please contact the study coordinator, Julie Pauwels at 604-875-2000 ext. 5189 or julie.pauwels@cw.bc.ca. If we have not heard from you by the time you come in for your follow-up visit, a study research assistant may approach you at the clinic to answer any questions or concerns you may have about this study.

Thank you for taking the time to consider this study.

Sincerely,

Dr. Anne Synnes

Clinical Professor

Division of Neonatology

BC Children's Hospital

4480 Oak Street

Vancouver, BC

V6H 3N1

Tel: 604-875-2135

Fax: 604-875-3106

A.4 Informed Consent Form

PARTICIPANT INFORMATION AND CONSENT FORM
For the Parent or Legal Guardian Consenting for the Participant

Title: Craniofacial Morphology and the Use of Neonatal Non-Invasive Ventilation Therapy

Principal Investigator:
Dr. Benjamin Pliska
Assistant Professor
Department of Dentistry
BC Children's Hospital
4480 Oak Street
Vancouver, BC
V6H 3N1
Tel: 604-822-7237
Fax: 604-822-3562

Co- Investigators:
Dr. Don He, Department of Dentistry
Dr. Neil K Chadha, Division of Otolaryngology-Head and Neck Surgery
Dr. Fernanda Almeida, Department of Dentistry
Dr. Anne Synnes. Department of Pediatrics

Study Coordinator:
Ms. Julie Pauwels, Division of Pediatric Otolaryngology-Head and Neck Surgery
Tel: 604-875-2345 ext. 5189

Emergency Telephone Number: 604-875-2133

If you are a parent or legal guardian of a child who may take part in this study, permission from you and the assent (agreement) of your child may be required. When we say "you" or "your" in this consent form, we mean you and/or your child; "we" means the doctors and other staff.

Invitation
You are being invited to take part in a research study that investigates how non-invasive ventilation (NIV) therapy can affect later growth and development of the facial structures in children who were born premature. NIV therapy moves breathable air in and out of the lungs through a facial mask and/or prongs inserted in the nostrils for patients who cannot breathe well enough on their own. Children attending the Neonatal Follow-up Program (NFUP) for their 4-month, 8-month, and 18-month clinic appointments and who received NIV at birth at BC Women's & Children's Hospital are invited to participate in this study.

Participation
Your participation is voluntary. You have the right to refuse to participate in this study. If you decide to participate, you may still choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services to which you are entitled or are presently receiving.

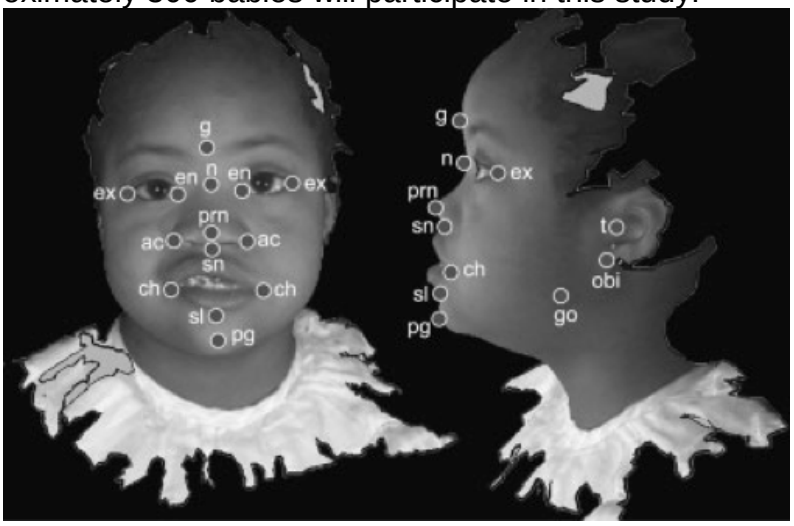
You should be aware that there is a difference for both you and your doctor between being a patient and being a research participant. As a patient all medical procedures and treatments are carried out for your benefit only according to standard accepted practice. As a research participant you and your doctor also must take into account the requirements for the research study. These may include procedures and treatments that are not part of standard practice or are not yet proven. This consent form describes the diagnostic and treatment procedures that are being carried out for research purposes. Please review the consent document carefully when deciding whether or not you wish to be part of the research and sign this consent only if you accept being a research participant.

If you wish to participate in this study, you will be asked to sign this form. Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

Who is Conducting the Study?
This study is being conducted by Dr. Benjamin Pliska, the Principal Investigator.

Background
Difficulties breathing are one of the most common concerns for babies born preterm (born under 37 weeks of age) as the baby's lungs and chest are often not fully developed. Non-invasive respiratory therapy (NIV) is often given to premature babies in order to make sure they are receiving enough oxygen in their lungs and to help them breathe. In NIV therapy, air is delivered to the baby's lungs using a face oxygen mask

and/or tubes inserted in the nostrils. While NIV therapy can save a baby's life, there are risks of side effects such as damage to the skin and structure of the face and around the nose, sometimes causing permanent damage, especially for preterm babies. While these are known risks of NIV, there is very little known about how this type of therapy might affect the development of the face muscles and bones of these children later in life. This study will investigate how the muscles and bones of the faces of preterm babies develop in the first 18-months of life by taking 3D photos of children (see example below) who have received NIV therapy at BC Women's & Children's Hospital. In this study we exam how facial shape measurements from these photos are related to the type and length of NIV therapy that preterm babies received to get a better understanding of how NIV therapy might affect facial growth and development. We expect that approximately 300 babies will participate in this study.



Example of a photo image from the 3D camera.

What is the Purpose of the Study?
The purpose of this study is to evaluate how NIV therapy might affect the later growth and development of facial structures in preterm babies. This information might help doctors in guiding care for babies who require interventions to improve breathing at birth.

Who Can Participate in this Study?
Babies:

- Who were born prematurely at less than 37 weeks
- Who received NIV therapy or a combination of NIV and mechanical ventilation (respiratory therapy requiring intubation) at birth in the Neonatal Intensive Care Unit at BC Women's Hospital
- Who are reporting for their 4-month, 8-month and/or 18-month follow-up appointment at the NFUP clinic

Who Should not Participate in this Study?
Babies:

- Who have congenital (occurring at birth) systemic diseases or syndromic conditions (diseases or conditions that affect a number of different body systems or organs) related to craniofacial abnormalities (deformations of the facial structures such as cleft lip and/or palate)

What Does the Study Involve?
If you agree to participate, your child will have their photo taken with the 3D camera in the Pediatric Otolaryngology Clinic (ENT clinic) at BC Children's Hospital. After your appointment at the NFUP clinic, a research assistant will escort you and your child to the ENT clinic, which is located in the same building as the NFUP. You will be asked to sit in the clinic chair and to hold your child in your lap while the photo is being taken. 2 cameras on opposite sides will scan your child's face to take the photo. The cameras will not touch your child's face and taking this image does not pose any harm to your child's health. The entire photo-taking process takes approximately 5 minutes. If you participate in this study you may be asked to have your child's photo taken on up to 3 occasions: At your child's 4-month, 8-month, and 18-month NFUP appointments depending on when your child was enrolled in the study. For example, if you child was enrolled at their 8-month appointment, they would have their photo taken 2 times, at 8 and 18 months.
We will also collect demographic information about your child such as their gender and age and ethnic background. We would like to collect ethnic background information about your child because research has found people of certain ethnicities have distinct facial shapes and measurements in common. Certain facial shapes may be more affected by the use of NIV therapy as it relates to facial growth and development. Providing information about your race of ethnic origin is voluntary.
We will also collect medical information from your child's hospital chart will including information about their birth (age, weight, height, and head size at birth) and information about their stay in the NICU. We will collect details of your child's NICU stay such as the type and length of the NIV therapy used and medical information about any health conditions your child may have.
Total Time Required for All Study Visits
You will be asked to dedicate a maximum of approximately 1 hour of your time to participate in this study depending at which time point your child was enrolled. The first visit will take approximately 30 minutes and the following visits (up to 2) will take 15 minutes each.

What Are my Responsibilities?
You are responsible for coming with your child to the ENT clinic to have their photo taken.

What Are the Possible Risks of Harm or Side Effects of Participating?
There are no known risks of harm of side effects from having your child's photo taken with the 3D camera. As the camera takes a realistic image similar to a photograph, there is a potential risk to your child's privacy and confidentiality. Please see the "Will

my Participation in this Study be Confidential?" section of this form for more information on the steps that the investigators will take to keep your child's photo confidential.

What Are the Benefits of Participating in the Study?
You may not benefit from participating in this study. However, information learned from this study may help doctors in guiding follow-up care for preterm babies who received NIV therapy at birth.

What if New Information Becomes Available that may Affect My Decision to Participate?
If new information arises during the study that may affect your willingness to remain in the study, you will be advised.

What Happens if I Decide to Withdraw my Consent to Participate?
You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, you have the right to request the withdrawal of your information collected during the study. This request will be respected to the extent possible. Please note however that there may be exceptions where the data will not be able to be withdrawn for example where the data is no longer identifiable (meaning it cannot be linked in any way back to your identity) or where the data has been merged with other data. If you would like to request the withdrawal of your data, please let your study doctor know. If your participation in this study includes enrolling in any optional studies, or long term follow-up, you will be asked whether you wish to withdraw from these as well.

What Happens if Something Goes Wrong?
Signing this consent form in no way limits your legal rights against the investigators or anyone else.

What Happens After the Study is Finished?
Study results will be available publicly when the research project is completed. No identifying information will be made public, only anonymized information. We will post a summary of the results on the Ear, Nose, and Throat Department website. As well, you can ask for the study results through the Principal Investigator (Dr. Pliska) or search for it through the Internet medical libraries. You will continue to be followed in the Pediatric Otolaryngology clinic at BC Children's Hospital with the standard of care on an as needed basis.

What Will the Study Cost me?
We will provide you with $10 for each study visit (up to 3 visits) to cover the cost of additional parking expenses for participating in this study.

Will my Participation in this Study be Confidential?
Your confidentiality will be respected. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his designate by

representatives of Health Canada, and the UBC Children's & Women's Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. We will also collect personally identifying information, including you and your child's name and home address from your child's hospital chart, in order to contact you about this study. The list that matches your name and contact information to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law. Your personally identifiable information will be kept in a separate password protected file and will only be accessed by study team members for the purposes of this study only. Your personal information will be kept confidential and will not be sold or used for future research purposes.

The 3D photos of your child will be kept private and confidential. The photos will be stored electronically on the 3D camera software in a database. This secure database is password-protected and is not connected to the Internet. The photos of your child will not be published or presented in relation to this study and only the study team will have access to the photo database. The photo will not be linked to your child's name and only to the unique study number assigned. Once the study is completed the photos of all participants will be permanently deleted from the software system.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

Who do I Contact if I Have Questions About the Study During my Participation?
If you have any questions or desire further information about the study before or during participation, you can contact Dr. Pliska at 604-822-7237.

Who do I Contact if I Have Any Questions About my Rights and/or Experiences as a Participant?
If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Services by email at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free Number 1-877-822-8598).

PARTICIPANT CONSENT TO PARTICIPATE

Craniofacial Morphology and the Use of Neonatal Non-Invasive Ventilation Therapy

- I have read and understood the participant information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the result will only be used for scientific objectives.
- I understand that my child's participation in this study is voluntary
- I understand that my child and I are completely free at any time to refuse to participate or to withdraw from this study at any time, and that this will not change the quality of care that my child receives.
- I understand that I am not waiving any of my or my child's legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to my child.
- I have read this form and I freely consent to participate in this study.
- I have been told that I will receive a dated and signed copy of this form.

I agree that my child, _____, may take part in this study.

_____	_____	_____
Printed Name of Parent/Legal Guardian	Signature of Parent/Legal Guardian	Date
_____	_____	_____
Printed Name of Person Consenting	Signature of Person Consenting	Date

A.5 Subject Demographics and Medical History

Craniofacial Morphology and the Use of Neonatal Non-Invasive Ventilation Therapy

Subject Demographics and Medical History

SUBJECT ID: _____ DATE: _____

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1) Gender M or F
2) Gestational Age _____ (in weeks)
3) Birth Weight _____ (in grams)
4) Birth Length _____ (in cm)
5) Birth Head Circumference _____ (in cm)
6) NIV/ NCPAP duration _____ (in days)
7) Type of NIV interface _____nasal prongs _____nasal mask
8) Mode of NIV attachment _____hat with lateral staps _____facial tape
9) Mode of feeding _____
10) NICU stay _____ (in days)
11) Was mechanical ventilation used? Y / N

A.6 Monthly Log of Study Recruitment

In September 2017, we screened 16 patients and accepted 13. Three patients did not fit our study because a patient was diagnosed with congenital facial vascular malformation, another one was born not pre-term and the other did not have any medical record information due to being hospital transfers from Winnipeg. 8 patients were successfully imaged. The study was unable to contact two patients and the guardian of the other three did not want to participate in the study.

In October 2017, we screened 11 patients and accepted 7 patients. The four patients did not fit our study because one was diagnosed with abnormal chromosome microarray and complete cleft lip, two had no medical record information due to being hospital transfers from Alberta and one did not receive any form of needed respiratory intervention. Five patients were successfully imaged. The guardian of one patient did not want to participate in the study and the other cancelled their neonatal follow-up appointment in October and did not reschedule.

In November 2017, we screened 14 patients and accepted 13 patients. One patient that did not fit our study was not born pre-term. 5 patients out of 13 were successfully imaged. The guardians of three patients did not want their child to participate in the study. Two patients did not show-up to their appointment, and the investigator was unavailable to image the other three patients.

In December 2017, we screened 15 patients and accepted 11 patients. Two patients previously screened and fitted our study returned for facial imaging at their 8-month visit. The investigator was only able to obtain images for one of the returning patient and not the other due to investigator availability. Four patients were not accepted into the study. One patient had medical record information not authorizable. Two patients did not fit our study because they did

not receive any form of respiratory intervention. One patient did not fit the study because the patient was not born pre-term. 8 images were successfully imaged out of the 11 accepted patients. One patient did not show up to their appointment. The guardians of two patients did not want their child to participate in the study.

In January 2018, we screened 15 patients and accepted 8 patients. Two patients previously screened and fitted out study returned for facial imaging at their 8-month visit. The investigator was unable to obtain the images for the two returning patients because of investigator availability. 7 patients were not accepted into the study. Four patients had medical record information not authorizable. Two patients had congenital craniofacial abnormalities. One patient was not born pre-term. One patient was successfully imaged out of eight accepted patients. Six patients did not show up to their neonatology follow-up appointment. The investigator was unavailable to image one patient.

In February 2018, we screened 22 patients and accepted 14 patients. There were no returning patients in February. 8 patients were not accepted into the study. Two patients had congenital craniofacial abnormalities. Five patients did not have sufficient medical record information about patient respiration due to being planned follow-up visits for another hospital. One patient did not receive non-invasive ventilation therapy. 6 patients were successfully imaged out of 14 patients. 4 patients did not show up to their neonatal follow-up appointment. The investigator was unavailable to image the other four patients.

In March 2018, we screened 16 patients and accepted 10 patients. Two patients have been rescheduled to be seen in March because they did not show up to their previous neonatal follow-up appointment. The study successfully imaged one patient at the reschedule appointment but the other rescheduled patient failed to show up to their appointment. Six patients were not accepted

into the study. Three patients had congenital craniofacial abnormalities. The other three patients did not have sufficient medical record information about patient respiration due to being planned follow-up visits from another hospital. The study successfully imaged two patients out of the accepted 10 patients. The study was unable to obtain pictures for 8 out of 10 accepted patients. Three patients had guardianship not approve their participation in the study. The other three patients did not show up to their neonatal follow-up appointment. The investigator was unable to obtain pictures for the other two patients due to investigator availability.

In April 2018, we screened 13 patients and accepted 9 patients. Three patients have been rescheduled to be seen in April because they did not show up to their previous neonatal follow-up appointment. The study successfully imaged one patient at the reschedule appointment but the other two rescheduled patients failed to show up to their appointment. Four patients were not accepted into the study. Two patients did not have any medical record information because their neonatal care was at another hospital but their planned neonatal follow-up visit was at B.C. Children's Hospital. The other two patients did not have any non-invasive ventilation therapy during their neonatal stay at B.C. Women's Hospital and Health Centre. They study successfully imaged 2 out of 9 patients accepted in the month of April 2018. The investigator was not available to image the other 7 patients.

In May 2018, we screened 21 patients and accepted 17 patients. There were not any returning patients during this month. Four patients did not fit our study. One patient did not require any form of ventilation therapy. Two patients did not have medical record information because neonatal care was at another hospital but their planned neonatal follow-up visit was at B.C. Children's Hospital. One patient was diagnosed with a chromosomal abnormality. The study successfully imaged 3 patients out of 17 patients. The guardians of three patients did not

provide consent for their child to participate in the study. The investigator was unavailable to acquire images for the other 11 patients.

A.7 Anthropometric Distance Data

Table 25 - The average anthropometric distance data by follow-up visit for females

Linear Distance (mm)	4-month visit		8-month visit		18-month visit	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
Skull Base Width (T_R-T_L)	106.0	2.6	103.1	2.4	111.3	4.3
Intercanthal Width (EN_R-EN_L)	28.3	1.1	25.7	2.0	26.9	2.3
Biocular Width (EX_L-EX_R)	67.8	2.8	67.8	2.5	71.0	2.4
Morphological Nose Width (AL_R-AL_L)	23.7	1.3	22.3	1.9	23.9	1.7
Anatomical Nose Width (AC_R-AC_L)	23.1	2.3	21.3	2.3	21.8	1.6
Labial Fissure Length (CH_R-CH_L)	26.7	2.3	27.1	2.5	30.4	2.9
Philtrum Width (CPH_R-CPH_L)	7.4	0.7	7.7	1.2	8.6	0.4
Morphological Face Height (N-GN)	66.1	6.0	67.3	4.1	75.1	3.6
Upper Face Height – I (N-STO_S)	42.0	4.0	42.3	1.7	46.4	2.1
Upper face Height – II (N-SN)	28.1	5.6	28.2	1.3	32.5	1.1
Lower Face Height – I (STO_I-GN)	23.2	2.5	23.0	1.6	24.9	2.0
Lower Face Height – II (SN-GN)	38.7	3.8	40.0	3.5	43.8	3.6
Nasal Bridge Length (N-PRN)	21.6	2.1	21.5	1.7	25.9	1.4
Nose Height (N-SN)	28.1	2.6	28.2	1.3	32.5	1.1

Upper Lip Length (STO_S-SN)	14.0	1.6	14.37	1.9	13.9	1.6
Cutaneous Upper Lip Length (SN-LS)	10.9	1.7	11.1	2.0	10.0	0.9
Upper Vermillion Height (LS-STO_S)	4.9	0.7	4.5	0.5	5.2	1.3
Lower Vermillion Height (STO_I-LI)	4.6	0.9	4.4	1.1	5.7	1.1
Cutaneous Lower Lip Length (LI-SL)	8.1	1.7	7.5	1.0	8.5	1.1
Lower Lip Length (STO_I-LI)	4.6	0.9	4.4	1.1	5.7	1.1
Right Upper Facial Third Depth (N-T_R)	81.1	4.9	83.1	4.1	91.0	3.3
Left Upper Facial Third Depth (N-T_L)	81.3	4.5	82.6	3.0	89.9	2.9
Right Middle Third Depth (SN-T_R)	80.2	4.0	81.9	4.0	90.7	2.9
Left Middle Third Depth (SN-T_L)	80.5	3.1	82.1	2.7	89.9	2.8
Right Lower Facial Third Depth (PG-T_R)	85.8	2.4	86.3	3.9	95.2	2.9
Left Lower Facial Third Depth (PG-T_L)	86.1	2.7	87.3	2.5	95.5	2.5
Right Alar Depth (PRN-AL_R)	14.6	0.7	14.6	1.2	16.2	0.4
Left Alar Depth (PRN-AL_L)	14.1	0.7	14.5	1.1	15.6	0.7
Right Alar Base Depth (PRN-AC_R)	16.8	1.1	16.8	1.3	18.3	0.4
Left Alar Base Depth (PRN-AC_L)	16.5	0.8	16.8	1.3	17.7	1.2
Nose Depth (PRN-SN)	11.3	1.1	11.6	0.9	12.2	1.0

Table 26 - the average anthropometric distance data by follow-up visit for males

Linear Distance (mm)	4-month visit		8-month visit		18-month visit	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.

Skull Base Width (T_R-T_L)	107.1	2.0	110.2	1.9	118.2	7.2
Intercanthal Width (EN_R-EN_L)	27.1	2.2	28.5	0.5	30.6	3.5
Biocular Width (EX_L-EX_R)	69.2	5.4	73.1	3.1	76.6	6.3
Morphological Nose Width (AL_R-AL_L)	23.6	0.2	24.1	0.7	27.1	3.4
Anatomical Nose Width (AC_R-AC_L)	24.5	0.3	23.3	1.9	25.3	3.1
Labial Fissure Length (CH_R-CH_L)	31.0	1.3	31.1	0.5	33.8	4.1
Philtrum Width (CPH_R-CPH_L)	8.7	0.3	9.3	0.7	10.1	1.7
Morphological Face Height (N-GN)	73.1	5.3	70.7	4.4	80.2	8.2
Upper Face Height – I (N-STO_S)	43.0	3.5	44.2	2.9	49.2	3.9
Upper face Height – II (N-SN)	30.2	3.9	29.6	2.1	33.6	3.0
Lower Face Height – I (STO_I-GN)	22.5	2.9	24.4	0.8	27.4	1.9
Lower Face Height – II (SN-GN)	44.0	9.9	42.4	3.6	48.1	6.8
Nasal Bridge Length (N-PRN)	23.4	2.8	23.5	1.9	26.1	2.3
Nose Height (N-SN)	30.2	3.9	29.6	2.1	33.6	3.0
Upper Lip Length (STO_S-SN)	13.0	0.2	14.9	0.9	15.6	1.6
Cutaneous Upper Lip Length (SN-LS)	10.0	0.4	11.8	1.0	11.2	2.0
Upper Vermillion Height (LS-STO_S)	4.5	0.3	5.2	2.0	6.2	1.7
Lower Vermillion Height (STO_I-LI)	4.8	1.9	4.5	1.7	5.8	1.0
Cutaneous Lower Lip Length (LI-SL)	7.6	1.6	8.9	0.4	9.4	1.3
Lower Lip Length (STO_I-LI)	4.8	1.9	4.5	1.7	5.8	1.0
Right Upper Facial Third Depth (N-T_R)	86.4	0.3	88.8	3.9	95.1	6.1
Left Upper Facial Third Depth (N-T_L)	85.1	1.9	87.7	3.4	95.2	5.8

Right Middle Third Depth (SN-T_R)	85.0	4.6	87.3	2.9	94.7	6.1
Left Middle Third Depth (SN-T_L)	82.9	6.7	87.2	3.6	95.4	6.0
Right Lower Facial Third Depth (PG-T_R)	91.1	8.2	90.4	3.9	100.2	6.4
Left Lower Facial Third Depth (PG-T_L)	87.89	9.2	90.3	5.4	101.1	6.7
Right Alar Depth (PRN-AL_R)	15.6	1.2	16.5	0.8	17.2	1.9
Left Alar Depth (PRN-AL_L)	15.5	0.1	15.7	0.5	17.1	2.0
Right Alar Base Depth (PRN-AC_R)	17.9	0.7	18.9	1.3	19.6	2.1
Left Alar Base Depth (PRN-AC_L)	17.5	0.2	18.1	0.9	19.3	1.9
Nose Depth (PRN-SN)	11.4	1.7	11.7	0.4	12.3	1.3

A.8 Anthropometric Angle Data

Table 27 - The average anthropometric angle data by follow-up visit for females

Angles (degrees)	4-month visit		8-month visit		18-month visit	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
Subnasale Angle (PRN-SN-LS)	27.4	2.7	24.9	5.0	27.9	2.8
Nose Protrusion Angle (N-PRN-SN)	65.8	5.3	66.4	5.6	67.4	2.3
Right Upper Face Angle (N-PRN-SN)	78.5	4.3	77.7	2.3	79.2	2.7
Left Upper Face Angle (N-T_R-SN)	78.7	3.7	79.2	2.4	79.6	3.0
Right Upper Mid Face Angle (N-T_R-SL)	72.4	4.9	71.5	2.0	71.1	2.4

Left Upper Mid Face Angle (N-T_L-SL)	72.4	4.2	72.8	2.3	72.3	2.5
Right Morphometric Face Angle (N-T_R-GN)	71.5	5.0	69.8	2.3	69.8	2.1
Left Morphometric Face Angle (N-T_L-GN)	71.5	4.3	71.0	2.7	70.6	2.1
Subnasal Protrusion Angle (AC_R-SN-AC_L)	10.9	4.1	17.7	2.9	21.9	2.2
Alar Slope Angle (AL_R-PRN-AL_L)	33.3	4.7	39.7	2.8	40.4	2.8
Midface Depth Angle (N-SN-SL)	8.4	2.3	8.3	1.1	10.0	1.3

Table 28 - The average anthropometric angle data by follow-up visit for males

Angles (degrees)	4-month visit		8-month visit		18-month visit	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
Subnasale Angle (PRN-SN-LS)	23.8	3.3	27.7	3.6	28.4	4.0
Nose Protrusion Angle (N-PRN-SN)	63.6	0.2	70.1	1.7	62.1	5.1
Right Upper Face Angle (N-PRN-SN)	77.8	9.4	77.4	2.6	79.2	2.7
Left Upper Face Angle (N-T_R-SN)	76.2	10.3	79.2	1.1	80.3	2.4
Right Upper Mid Face Angle (N-T_R-SL)	69.8	6.6	68.8	1.1	71.5	3.0
Left Upper Mid Face Angle	68.2	6.2	69.9	1.2	72.2	2.6

(N-T_L-SL)						
Right Morphometric Face Angle (N-T_R-GN)	69.5	4.9	68.2	1.2	69.8	2.9
Left Morphometric Face Angle (N-T_L-GN)	67.1	5.1	68.8	1.9	70.4	2.7
Subnasal Protrusion Angle (AC_R-SN-AC_L)	19.15	4.6	22.1	5.1	19.3	4.7
Alar Slope Angle (AL_R-PRN-AL_L)	37.4	0.9	40.4	2.8	37.6	4.5
Midface Depth Angle (N-SN-SL)	10.6	4.2	11.9	1.9	10.4	3.9

A.9 Anthropometric Facial Ratios

Table 29 - The average anthropometric facial ratios by follow-up visit for females

Facial Ratios	4-month visit		8-month visit		18-month visit	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
Morphological Face Height (N-GN) to Skull Base Width (T_R-T_L)	0.62	0.04	0.65	0.04	0.68	0.03
Upper Face Height – I (N-STO_S) to Skull Base Width (T_R-T_L)	0.40	0.03	0.41	0.01	0.42	0.01
Upper Face Height – II (N-SN) to Skull Base Width (T_R-T_L)	0.26	0.02	0.27	0.02	0.29	0.01

Table 30 - The average anthropometric facial ratios by follow-up visit for males

Facial Ratios	4-month visit		8-month visit		18-month visit	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
Morphological Face Height (N-GN) to Skull Base Width (T_R-T_L)	0.68	0.04	0.64	0.04	0.68	0.05
Upper Face Height – I (N-STO_S) to Skull Base Width (T_R-T_L)	0.40	0.04	0.40	0.03	0.42	0.01
Upper Face Height – II (N-SN) to Skull Base Width (T_R-T_L)	0.28	0.04	0.27	0.02	0.28	0.02

A.10 Test for Normality

Table 31 - Test for normality of landmark distances, angles and facial Ratios

Measurement	**4**	**8**	**18**
AC_R-AC_L	0.17	0.66	0.07
AC_R-SN-AC_L	0.83	0.02	0.23
AL_R-AL_L	0.02	0.29	0.00
AL_R-PRN-AL_L	0.13	0.63	0.08
CH_R-CH_L	0.84	0.23	0.93
CPH_R-CPH_L	0.20	0.56	0.33
EN_R-EN_L	0.63	0.63	0.34
EX_L-EX_R	0.57	0.20	0.08
LI-SL	0.36	0.11	0.67
LS-STO_S	0.59	0.04	0.13
N-GN	0.90	0.86	0.01
N-GN.to.T_R-T_L	0.98	0.59	0.38
N-PRN	0.78	0.85	0.33
N-PRN-SN	0.62	0.28	0.18
N-SN	0.22	0.58	0.27

Measurement	4	8	18
N-SN-SL	0.86	0.16	0.13
N-SN.to.T_R-T_L	0.10	0.96	0.80
N-STO_S	0.91	0.23	0.08
N-STO_S.to.T_R-T_L	0.46	0.56	0.87
N-T_L	0.04	0.38	0.25
N-T_L-GN	0.44	0.88	0.22
N-T_L-SL	0.77	0.43	0.80
N-T_L-SN	0.51	0.67	0.75
N-T_R	0.03	0.37	0.12
N-T_R-GN	0.24	0.51	0.97
N-T_R-SL	0.80	0.54	0.29
N-T_R-SN	0.33	0.16	0.31
PG-T_L	0.67	0.10	0.32
PG-T_R	0.07	0.56	0.24
PRN-AC_L	0.19	0.42	0.00
PRN-AC_R	0.77	0.64	0.00
PRN-AL_L	0.48	0.61	0.00
PRN-AL_R	0.44	0.97	0.00
PRN-SN	0.29	0.77	0.48
PRN-SN-LS	1.00	0.85	0.14
SN-GN	0.61	0.74	0.10
SN-LS	0.82	0.67	0.92
SN-T_L	0.34	0.04	0.18
SN-T_R	0.97	0.90	0.04
STO_I-GN	0.33	0.26	0.29
STO_I-LI	0.44	0.33	0.98
STO_S-SN	0.65	0.81	0.95
T_R-T_L	0.60	0.88	0.64

A p-value in isolation of less than 0.05 indicates that the data may not be normal. Given the number of comparisons, the significance level of 0.05 should likely be lowered, (for example to 0.05/N, where N is the number of comparisons. Here, N = 43*3 = 129. This is the so called Bonferonni correction).

p-values from Shapiro-wilks test applied to each set of measurements in each follow up group