24 – hour oxygen saturation recordings at discharge in preterm infants

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Abstract

Preterm infants have an immature respiratory system and therefore experience an increased number of respiratory pauses and oxygen desaturations. There is now advanced pulse oximetry technology that can record oxygen saturations every two seconds for extended periods of time. There has been insufficient literature that reports the incidence of intermittent hypoxia at time of discharge home from the neonatal unit in preterm infants using new generation oximeters. These respiratory events preterm infants experience have been shown to have some effect on neurodevelopment, but their effect on growth has not been investigated before. The primary aim of this study was to determine the prevalence of intermittent hypoxia in preterm infants at time of discharge home from the neonatal unit. The study also addresses the issue of artefact within oximetry recordings and compares results from automatically edited, manually edited and unedited oximetry data, as well as determining whether overnight 12-hour recordings are of equal value to full 24-hour recordings. The secondary aim of this study was to determine whether intermittent hypoxia at discharge has any effect on post discharge growth and to determine changes in amount of intermittent hypoxia from discharge oximetry to oximetry one-month post discharge.

We recruited preterm infants from the Wellington neonatal intensive care unit. A 24-hour pulse oximetry recording was performed immediately prior to the infant’s discharge home. These oximetry recordings were analysed and median values for measures reported from oximetry recordings were determined. Rules to manually edit oximetry data were created and applied to oximetry recordings. These manually edited reports were then compared with automatically edited and unedited reports. Each recording was also edited to resemble a 12-hour overnight recording and this was compared to the full 24-hour recording. Infants born less than 32 weeks gestational age were further followed up with weekly growth measurements for one-month. A repeat 24-hour oximetry recording was performed at one-month post discharge for these infants and compared to their discharge recording.

We report high rates of intermittent hypoxia in preterm infants at time of discharge home from the neonatal unit. For example the median 4% oxygen desaturation index (DSI 4%) was 57.9 events per hour. The incidence of these events decreased with advancing post-menstrual age. Rates of intermittent hypoxia one month post discharge were greatly
decreased from discharge with improvements of 42% - 57% seen, with DSI 4% reducing to 25.5 events per hour. This study did not show a significant association between intermittent hypoxia and post-discharge growth, possibly because of the small sample size in this study subgroup.

There were few clinically relevant differences on reports edited manually compared with automatically edited reports, with some difference when compared to unedited reports. We recommend automatically editing oximetry reports as this gives similar results to manual editing for the majority of measures, however the nadir of the fall in oxygen saturation is often artefact, and even after automatic editing is the one measure that may remain false. The 24-hour oximetry reports were clinically similar to 12-hour recordings and therefore we suggest 12-hour oximetry studies are sufficient.
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<thead>
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<th>Description</th>
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<tbody>
<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
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<tr>
<td>ALTE</td>
<td>Apparent life threatening event</td>
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<td>ANZNN</td>
<td>Australia and New Zealand Neonatal Network</td>
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<td>AOP</td>
<td>Apnoea of prematurity</td>
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<td>AS</td>
<td>Active sleep</td>
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<tr>
<td>BPD</td>
<td>Bronchopulmonary dysplasia</td>
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<td>BPM</td>
<td>Beats per minute</td>
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<td>BW</td>
<td>Birth weight</td>
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<td>CCH</td>
<td>Chronic constant hypoxia</td>
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<td>CCHD</td>
<td>Critical congenital heart disease</td>
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<td>CCHS</td>
<td>Congenital central hypoventilation syndrome</td>
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<tr>
<td>CIH</td>
<td>Chronic intermittent hypoxia</td>
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<tr>
<td>CLD</td>
<td>Chronic lung disease</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CP</td>
<td>Cerebral palsy</td>
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<td>CO₂</td>
<td>Carbon dioxide</td>
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<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<td>CSF</td>
<td>Cerebral spinal fluid</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>GA</td>
<td>Gestational age</td>
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<td>GOR</td>
<td>Gastro-oesophageal reflux</td>
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<tr>
<td>HIE</td>
<td>Hypoxic-ischemic encephalopathy</td>
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<td>HR</td>
<td>Heart rate</td>
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<td>IH</td>
<td>Intermittent hypoxia</td>
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<tr>
<td>IVH</td>
<td>Intraventricular haemorrhage</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>NEC</td>
<td>Necrotising enterocolitis</td>
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<td>NG</td>
<td>Nasogastric tube</td>
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<td>NICU</td>
<td>Neonatal intensive care unit</td>
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<td>NZ</td>
<td>New Zealand</td>
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<td>MDI</td>
<td>Mental developmental index</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>O₂</td>
<td>Oxygen</td>
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<td>OSA</td>
<td>Obstructive sleep apnoea</td>
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<td>PB</td>
<td>Periodic breathing</td>
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<td>PDA</td>
<td>Patent ductus arteriosus</td>
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<td>PDI</td>
<td>Psychomotor developmental index</td>
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<tr>
<td>PEEP</td>
<td>Positive end expiratory pressure</td>
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<tr>
<td>PIP</td>
<td>Positive inspiratory pressure</td>
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<td>PMA</td>
<td>Postmenstrual age</td>
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<td>PPHN</td>
<td>Persistent pulmonary hypertension of the newborn</td>
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<td>PSG</td>
<td>Polysomnography</td>
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<td>PVL</td>
<td>Periventricular leukomalacia</td>
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<td>RBC</td>
<td>Red blood cell</td>
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<td>RDS</td>
<td>Respiratory distress syndrome</td>
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<td>REM</td>
<td>Rapid eye movement</td>
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<td>ROP</td>
<td>Retinopathy of prematurity</td>
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<td>ROS</td>
<td>Reactive oxygen species.</td>
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<td>s</td>
<td>Seconds</td>
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<td>SaO₂</td>
<td>Arterial oxygen saturation</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SDB</td>
<td>Sleep disordered breathing</td>
</tr>
<tr>
<td>SEE</td>
<td>Energy expenditure during sleep</td>
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<tr>
<td>SET</td>
<td>Signal extraction technology</td>
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<tr>
<td>SGA</td>
<td>Small for gestational age</td>
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<tr>
<td>SIDS</td>
<td>Sudden infant death syndrome</td>
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<tr>
<td>SpO₂</td>
<td>Arterial oxygen saturation as measured by pulse oximetry</td>
</tr>
<tr>
<td>SUDI</td>
<td>Sudden unexpected death in infancy</td>
</tr>
<tr>
<td>TEE</td>
<td>Total energy expenditure</td>
</tr>
<tr>
<td>TOI</td>
<td>Tissue oxygen index</td>
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<tr>
<td>TST</td>
<td>Total sleep time</td>
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<tr>
<td>VLBW</td>
<td>Very low birth weight</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<td>QS</td>
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Chapter 1

Introduction

Preterm infants experience many complications as a result of being born with immature physiological systems. One of these is an immature respiratory centre and lungs which leads to vulnerability with regard to pauses in breathing and hypoxia.

This thesis investigates the incidence of intermittent hypoxic episodes on oxygen saturation recordings in preterm infants at their time of discharge from the neonatal unit. It also examines whether intermittent hypoxia at discharge can predict growth rates in these preterm infants in the first month post discharge.

During the progression of this thesis, the concern of how artefact affects oxygen saturation recordings, and exactly how to best edit this artefact became an issue. It was apparent after talking with experts in this field that the issue of artefact in oxygen saturation recordings has not been well addressed previously and there were no clear guidelines on how to edit these recordings or how editing of reports would affect any values reported. Therefore, this thesis evolved to also investigate methods of editing oxygen saturation recordings and the overall effect this has on measures reported. The question was also raised as to whether there was any benefit of performing a full 24-hour oxygen saturation recording over an overnight 12-hour recording, therefore this thesis also determines whether there are any differences between 24-hour oxygen saturation recordings and 12-hour overnight recordings.
Chapter 2

Background

2.1 The problem of prematurity

Preterm birth is defined by the World Health Organisation (WHO) as the birth of an infant at less than 37 weeks gestational age (GA). There are a total of 15 million preterm infants born worldwide each year (1). In New Zealand (NZ) the proportion of infants born preterm was 7.4% in 2014, which remains unchanged from 2011(2).

There are many reasons an infant may be born prematurely, with 75% of preterm births occurring spontaneously (3). This may be the result of premature rupture of membranes and or preterm labour due to maternal complications such as infection, incompetent cervix or placenta praevia. Fetal medical conditions such as congenital abnormalities or growth restriction as well as pre-eclampsia may indicate the need for an induction of labour prematurely. Other risk factors for preterm birth include smoking, recreational drug use, multiple gestation, pregnancy in woman <18 or >40 years and maternal medical conditions such as diabetes and hypertension (3).

Being born prematurely places an infant at a significantly increased risk of a number of serious morbidities and mortality. The earlier GA an infant is born, the greater the risk of complications occurring. Preterm infants can be grouped according to level of maturity: extremely preterm (less than 28 weeks GA), very preterm (28 to 32 weeks GA) and moderate to late preterm (32 to 37 weeks GA). Data from the Australian and New Zealand Neonatal Network's (ANZNN) 2013 report show that survival rates to discharge from the neonatal intensive care unit (NICU) for infants born ≤ 24 weeks GA is 56.9%, and increases with each week gestation to 97.4% for infants born at 30 weeks GA (4).

All body systems are immature when an infant is born premature, therefore all systems are vulnerable to complications. The brain is at risk of intraventricular haemorrhage (IVH) and the eyes at risk of developing retinopathy of prematurity (ROP). The heart is more likely to have a persistent patent ductus arteriosus (PDA) and necrotising enterocolitis (NEC) is more much more common in preterm infants. However perhaps the most common system
with which preterm infants experience complications is the respiratory system. Respiratory distress syndrome (RDS) is primarily caused by a deficiency of surfactant (a substance that reduces surface tension and prevents lung collapse), and results in respiratory insufficiency. It is very common in very preterm infants with its rate of occurrence inversely related to increasing GA, with 100% of infants born less than 26 weeks GA, 57% of infants born less than 32 weeks GA, and only 3.7% of infants at 36 weeks GA experiencing RDS (5). Steroids are given antenatally when a mother is likely to deliver prematurely to help reduce the incidence and severity of RDS and infants receive exogenous surfactant after birth for treatment if they are symptomatic.

Preterm infants often require addition inspired oxygen and ventilatory assistance to support their respiratory effort and maintain their arterial oxygen saturations ($\text{SaO}_2$) in the desired range. Continuous positive airway pressure (CPAP) is commonly used in the NICU, and for some very preterm or sick infants, endotracheal intubation and ventilation is required. Some preterm infants can develop bronchopulmonary dysplasia (BPD) (also known as chronic lung disease (CLD)), which is generally defined as the ongoing need for additional inspired oxygen at 36 weeks postmenstrual age (PMA) with an abnormal chest x-ray.

Although not all preterm infants experience these more serious respiratory complications, it has been recognised that all preterm infants do experience a greater number of apnoea (broadly defined as a pause in breathing) and oxygen desaturations compared to term infants (6, 7). If there is no clear underlying cause for these respiratory events, they are usually termed Apnoea of Prematurity (AOP). It is the issue of the episodic intermittent oxygen desaturation that is associated with these short respiratory pauses, in particular the presence of these events prior to preterm infants discharge home, that this thesis focuses on.

Neonatal units have a responsibility to provide these vulnerable infants with expert care and treatment. An infant born at 26 weeks GA may spend their first three months of life in NICU. As preterm infants age, their respiratory centre matures and they can slowly be weaned off ventilation and additional inspired oxygen. During the final weeks in NICU they learn to suck and swallow safely and feed by breast or bottle rather than being fed by nasogastric (NG) tube. An infant is ready for discharge home when they can maintain their $\text{SpO}_2$ in the normal range, regulate their temperature, and are feeding and growing satisfactory. For extremely preterm infants this may be at a PMA of 39-42 weeks. A
moderate to late preterm infant may only spend one week or two in NICU and some are discharged home at a PMA of 36-37 weeks, providing they are able to reach the milestones as listed above. The American Academy of Pediatrics (AAP) 2008 policy statement on Hospital Discharge of the High-Risk Neonate states that the three physiologically competencies that should be met before discharge home are “oral feeding sufficient to support appropriate growth, the ability to maintain normal body temperature in a home environment, and sufficiently mature respiratory control”. They do not mention specifically how an infant’s respiratory control should be measured to determine its ‘maturity’ however they do recommend all high-risk infants have a car seat evaluation for physiological stability prior to discharge home (8).

As well as the complications of prematurity seen in NICU patients there is also an increased risk of long-term complications after discharge. Severe disabilities such as blindness, deafness, and cerebral palsy (CP) are becoming less common, but remain a common complication for extremely preterm infants. Data on CP rates from a 2008 meta-analysis reported that 14.6% of extremely preterm infants, 6.2% of very preterm infants and 0.7% of infants born older than 34 weeks GA develop CP (9). Local NZ and Australian data indicate that 8% of extremely preterm infants develop CP (4). Cognitive impairment (IQ<70) is also more common in preterm infants compared with term infants. Overseas data indicate that approximately one third of all preterm infants have some cognitive impairment, while local ANZNN data indicate that 14.6% of infants have some cognitive impairment (4, 10). Preterm infants are more likely to be smaller than term infants long term with local ANZNN data reporting that 19.1% of very preterm infant weights are <3rd percentile at 2-3 years corrected age (4). Preterm infants also have more long-term cardiorespiratory problems, with twice as many cardiovascular malformations than term infants (11). The reason for this is both due to consequences of preterm birth and due to cardiac malformations causing premature birth. However, despite these serious complications many preterm infants do very well.

Preterm infants are likely to need ongoing medical and developmental care and follow up. This means they have a continuing cost to the medical system, as well as having a large impact emotionally on the patient and their family. There has been considerable improvement in the area of preterm infant mortality and severe morbidity over recent years and research efforts are now focusing on further understanding mild morbidity and thereby
further improving long-term outcomes; therefore, this thesis focuses on intermittent hypoxia in the presence of normal mean oxygen saturations.

2.2 Respiratory pauses, bradycardia, and oxygen desaturation in preterm infants

Respiratory pauses, bradycardia, and episodic oxygen desaturation are common issues encountered in the neonatal unit. They are closely interlinked, with a respiratory pause often causing a decrease in SaO2. Bradycardia is commonly defined in preterm infants as a heart rate of less than 100 beats per minute (bpm) or a drop of greater than one third of baseline heart rate (12, 13). Bradycardia is frequently seen in association with respiratory pauses and oxygen desaturation. The bradycardia component has been shown to typically occur after the oxygen desaturation, most likely because of reflex bradycardia mediated via the carotid chemoreceptors (12, 14).

The rate at which SaO2 falls and the SaO2 nadir for each oxygen desaturation event varies between infants and depends on multiple factors including: baseline oxygen saturation, lung volume, metabolic rate, haemoglobin concentration, blood volume, and the presence of intrapulmonary shunting (13, 15). As preterm infants have a small lung volume, higher metabolic rate and a small blood volume, a relatively short pause in breathing (a few seconds) may be followed by a significant drop in SaO2 particularly if the infant is further compromised by CLD. Extremely premature infants often experience many of these respiratory events, however more mature infants with CLD also experience these events, right through to well, late preterm infants that are close to being discharged home and less commonly, term infants (16).

Previously, respiratory pauses have been the focus of research, however now there is more refined technology to measure oxygenation the interest has shifted to the associated episodic oxygen desaturations. Elder et al. compared respiratory recordings of preterm infants with clinical concern for apnoea to those without and found that the differences lay in the degree of episodic oxygen desaturation rather than the type or duration of apnoea and noted that monitoring of oxygen saturation is likely to give a better indication of
clinically significant respiratory events than monitoring breathing movements alone in preterm infants that are about to be discharged home (17).

### 2.2.1 Control of respiration and respiratory variability in preterm infants

The respiratory ‘centre’ lies in the brainstem. The central pattern generator for respiratory rhythm has been shown, by isolating brainstem sections, to be an area called the pre-bötzinger complex in the ventrolateral medulla (18-20). Although the pre-bötzinger complex is the ‘centre’, there are many mechanisms that integrate into the respiratory centre that can alter the generated natural rhythm as well as influence the rate and tidal volume. Central and peripheral chemoreceptors detect carbon dioxide (CO$_2$) and oxygen (O$_2$) blood concentrations and feed back to alter minute ventilation (respiratory rate multiplied by tidal volume). Pulmonary stretch receptors in the lung also provide feedback to the respiratory centre. Higher central nervous system centres can override the respiratory centre, such as the consequences of emotion via the limbic system and sensory input. Temperature, sleep state and feeding also all affect respiration. Some of these mechanisms will be discussed in detail below, with particular reference to the preterm infant.

#### i. Chemoreceptors

The main peripheral chemoreceptors lie in the carotid and aortic bodies and primarily detect changes in O$_2$, accounting for 90% of the ventilator response to hypoxaemia (21). At birth, peripheral chemoreceptors do not initially play a role in regulating respiration, as shown by an infant’s respiratory rate not reducing as expected when exposed to hyperoxia (13). This is thought to be because of the sudden increase in SaO$_2$ at birth that ‘stuns’ the peripheral chemoreceptors. The peripheral chemoreceptors take 48-hours to reset, with their sensitivity gradually increasing (22). After this initial 48-hour resetting process, infants rely on peripheral chemoreceptor sensitivity over central chemoreceptor activity more than adults (21). Infants exhibit a biphasic ventilatory response to hypoxia, which is characterised by an initial increase in ventilation, followed by a decline to or below initial baseline ventilation levels. This biphasic response is more pronounced in preterm infants than term infants and gradually develops into the normal sustained ventilatory response to hypoxia as they mature (13).

The main central chemoreceptors involved in respiratory control are situated on the ventral medulla and respond primarily to changes in CO$_2$, mediated by changes in pH in the
cerebrospinal fluid (CSF). This hypercapnic ventilatory response is reduced in infants compared to adults, and also reduced in preterm infants compared to term infants with sensitivity increasing with advancing PMA (22). The CO₂ threshold for initiating apnoea in preterm infants is very close to their baseline CO₂, being only 1 – 1.3mmHg above baseline CO₂. The CO₂ threshold in term infants and adults is much higher (23, 24).

**ii. Influence of Sleep state**

Sleep state has a significant impact on respiratory variables in infants. Infant sleep states can be broadly classified into active sleep (AS) (similar to rapid eye movement (REM)) or quiet sleep (QS) (equivalent of non-REM). There is also a smaller proportion of sleep that cannot be categorised into either state, and is therefore termed intermediate sleep. Term infants spend a large proportion of their total sleep time in active and intermediate sleep. This proportion decreases with PMA, therefore the amount of time in QS increases with advancing age (25). Preterm infants spend an even greater proportion of total sleep time (TST) in AS, with a 31 week GA infant spending 90% in AS compared to a term infant who on average spends 50% of TST in AS (26, 27). In AS the tonic activity of respiratory muscles is absent and upper airway muscles are also more relaxed. There is irregular respiration and a higher rate of respiration in AS, compared to QS during which respiration is more regular (21). These are likely reasons why an infant experiences more overt apnoea and oxygen desaturation during AS compared to QS.

**iii. Influence of feeding**

Preterm infants initially have poor coordination between their suck, swallow and breathing pattern. This often resolves by term corrected age (13). The laryngeal chemo-reflex in term infants is a normal protective reflex where breathing ceases when fluid hits the pharynx or larynx to protect the airway, however in a preterm infant this response is exaggerated and this can lead to prolonged apnoea during feeding (28). It has been previously thought that infants with gastro-oesophageal reflux (GOR) are at increased risk for apnoea, however many studies have now shown that the temporal timeline does not fit, as the drop in pH associated with GOR occurs after the initiation of apnoea (29). Further adding to the argument of there being no association is that treatment of GOR does not reduce the incidence of apnoea (24, 30-32).
iv. Influence of sleep position

Some neonatal units nurse infants prone as early studies suggested this improves oxygenation and lung function for preterm infants, especially those with residual respiratory disease (33-35). More recent literature however suggests that these earlier studies did not control for sleep state, and when sleep state is controlled for, differences in lung function between prone and supine positioning disappear (36-38). It is now widely accepted that the recommended sleeping position for any preterm infant once at home is the supine sleeping position as it decreases the risk of sudden unexplained death in infancy (SUDI) and this should be modeled prior to discharge (39, 40).

v. Summary

Table 2-1 Main physiological factors influencing respiration in preterm infants

| Decreased chemo-sensitivity to both O₂ and CO₂ |
| Biphasic hypoxic response curve |
| Baseline CO₂ that is close to apnoea threshold |
| Exaggerated laryngeal response |
| Increased time in Active Sleep |
| Less muscle and smaller lung volume |

2.2.2 Apnoea

Apnoea can be used generally to mean cessation of breathing, however ‘apnoea’ when referred to as clinically significant is often defined by a minimum respiratory pause length and this clinical definition is problematic as it can differ considerably. The AAP define apnoea in infants as a sudden cessation of breathing that lasts at least 20 seconds (s), or less if is accompanied by bradycardia or oxygen desaturation (41). The degree of bradycardia or oxygen desaturation that would be of concern is not specified. There are also many other definitions for apnoea in this context. A review by Elder et al. of 93 papers studying infant apnoea found that definitions of apnoea length varied widely from ≥2 s to ≥20 s (42). Mathew et al. also reported the definition for required length varies from ≥5 to ≥20 s (13).

Although there is widespread debate and uncertainty about the length of a respiratory pause that is of sufficient clinical relevance to be termed an ‘apnoea’, clinicians do commonly use the definition of a pause of ≥20 s and apnoea alarms both in the NICU and
those used at home after discharge are often set to alarm after no breathing is detected for 15 – 20 seconds (42). For the remainder of this thesis the term ‘apnoea’ will be used to refer generally to pauses in breathing that are thought to be clinically significant.

i. Types of apnoea

Apnoea can be classified into three subtypes:

Central apnoea is where there is no inspiratory effort, therefore no chest wall movement and no airflow at the nose and mouth.

Obstructive apnoea is where there is inspiratory effort and chest wall movement but there is no resultant airflow due to an obstruction of the upper airway (normally soft tissue).

Mixed apnoea is where there is a central apnoea followed by inspiratory effort, but no airflow throughout.

In preterm infants >50% of apnoea are mixed, 40% are central and only 10% are purely obstructive (28, 43). In older children, it is normally obstruction from soft tissue (e.g. Adenoids/tonsils) that causes apnoea.

ii. Periodic Breathing

Periodic breathing (PB) is a breathing pattern defined as consisting of at least three consecutive apnoea that last three to ten seconds, with periods of up to 20 seconds of normal respiration separating them (44). The respiratory rate is normally high in the normal respiration periods and PB occurs more commonly in AS, however still occurs in QS and wakefulness (25, 26).

Periodic breathing is extremely common in otherwise well preterm infants with nearly all experiencing some PB if monitored over 24 hours (45). The incidence decreases with advancing PMA, however it is still seen in >80% of preterm infants when they are at term equivalent age (46, 47), and also in term infants to a lesser degree (61%) (46). Periodic breathing decreases greatly by 6 months of age (44, 48).
Although PB is usually considered non-pathological, it can cause significant oxygen desaturation. When a desaturation was defined as a drop in arterial oxygenation measured by pulse oximeter (SpO$_2$) to $<80\%$ for $>4$s, two studies found that over 50\% of infants that exhibited PB had an associated desaturation to this level (45, 49). Horne et al. studied PB in relation to brain tissue oxygenation index (TOI) and found that while for most episodes of PB there was no effect on brain TOI, some infants did experience individually significant drops in SaO$_2$ and brain TOI (47).

The cause of PB is unknown but it is thought to be due to immaturity of the brainstem or an increased sensitivity of peripheral chemoreceptors (21, 28). It is self-resolving and no treatment is indicated, and is not thought to be a precursor to significant apnoea (22, 28, 43, 44).

**iii. Apnoea of prematurity**

Apnoea of prematurity is the diagnostic label applied to infants born less than 37 weeks GA that experience repetitive apnoea that is deemed clinically significant. It is a consequence of physiological immaturity rather than an underlying pathology and therefore the many other pathologies (see 2.2.2 iv) that can cause or contribute to apnoea must be ruled out before a diagnosis of AOP can be made. Although again contentious, the common definition for apnoea used in this setting is a pause in breathing $\geq 20$ seconds, or less if associated with a significant bradycardia or desaturation. ‘Apnoea’ of prematurity is misleading, as often short, respiratory pauses result in clinically significant bradycardia or oxygen desaturation with no consensus on the degree of desaturation or bradycardia required before it is considered to be ‘significant’.

Apnoea of prematurity is an extremely common diagnosis in preterm infants. Its prevalence is inversely related to GA and it is found in over 50\% of all preterm infants and almost all those with a birth weight $<1000g$ (50). It usually resolves by 37-40 weeks PMA, but can continue past term corrected age up to 44 weeks in very preterm infants (51, 52).

The pathogenesis of AOP is still not well understood. Normal infant respiration physiology was discussed in section 2.2.1. Table 2.2 lists the likely physiological contributors to AOP.
Table 2-2 Likely physiological contributors to AOP

| Immature central and peripheral nervous system chemoreceptors |
| Reduced hypercapnic response (not only preterm infants less than term, infants with apnoea less than infants without apnoea) |
| Repetitive hypoxic events may increase sensitivity of peripheral chemoreceptors and therefore lead to more unstable control and more apnoea |
| Hypoxic ventilator depression (from the biphasic curve) |
| Infants are very close to pCO₂ threshold for apnoea |
| Functional obstruction of upper airway due to decreased tone in preterm infants |
| Exaggerated response of the laryngeal chemo reflex |
| Impaired pulmonary function due to small lung volumes and reduced muscle |
| Predomination of active sleep in preterm infants |

More recent research has implicated the role of genetics in AOP (24). Gaultier et al. reported de novo mutations in congenital central hypoventilation syndrome (CCHS) which implicates the role of genetics in AOP (53). Bloch-Salisbury et al. published a retrospective twin study that report the heritability of AOP amongst same gender twins was 87% (54).

**iv. Clinical conditions associated with apnoea in preterm infants**

As discussed, AOP is a diagnosis of exclusion. A number of clinical conditions can be associated with increasing apnoeic events such as infection, NEC, intracranial abnormality or haemorrhage, anaemia, metabolic disorders, sedatives, and thermal instability (28). Obstructive apnoea can be caused by congenital malformations such as Pierre Robin sequence. There was previously thought to be a link between apnoea and SUDI, but more recent research has clarified that there is no link between central apnoea and risk of SUDI, however there is an increased risk with mild obstructive apnoea as well as preterm infants being at increased risk of SUDI. Screening infants for apnoea at discharge with polysomnography does not predict risk of SUDI (21, 55-58)
2.2.3 Intermittent Hypoxia

Intermittent hypoxia (IH) is the term used to describe the episodic drops in oxygen saturation and subsequent re-oxygenation that result from recurrent apnoea/AOP. Oxygen desaturations can occur as a result of a respiratory pause, while feeding, or in association with an arousal from sleep. They are often not apparent clinically as the duration of the desaturation may be too short to result in apparent cyanosis. The prevalence of IH in preterm infants is becoming increasingly recognised, as new SpO2 monitoring technology with extended memory storage and short two second averaging times can now accurately document these events.

Yet again, there is no set definition for what constitutes a pathological desaturation, but a fall to less than 90% or 85% SpO2 for ≥3 or ≥5 seconds is common (13). Di Fore et al. used the definition of ≤80% for ≥10 seconds and recorded SpO2 for eight weeks continuously for 79 preterm infants 24 to 28 weeks GA. They report the incidence of IH increased from one to four weeks postnatal age, and then steadily decreased. At the peak of four weeks postnatal age, these infants were having an average of 90 episodes of desaturation per day based on this definition (59).

Studies in animals have shown that IH, compared with sustained hypoxia is pro inflammatory which could have adverse effects on cardiovascular function, growth, ROP, and neurological function (60). Studies have also suggested that pro-inflammatory stimuli inhibit central respiratory output, meaning that if IH increased pro-inflammatory mechanisms, these will in themselves reduce respiratory function, further increasing pro inflammatory processes and creating an ongoing worsening cycle for IH (60).

Research in this area is limited as the extent of IH in preterm infants is just becoming recognised as new technology that can detect it is developed. It is this phenomenon of IH in preterm infants rather than sustained hypoxia that this thesis focuses on.
2.3 Cardiorespiratory monitoring in the neonatal unit

2.3.1 Continuous cardiorespiratory monitoring in neonatal unit

Monitoring infant cardiorespiratory status is important in order to be able to identify any apnoea, oxygen desaturation or bradycardia and therefore the potential need for additional respiratory support. This is particularly important in NICU where, as discussed, infants commonly have apnoea and oxygen desaturation.

Preterm infants admitted to NICU are monitored continuously from birth until they are considered to be free from significant respiratory pauses and are maintaining an adequate baseline SpO₂. The three main continuously measured cardiorespiratory variables are electrocardiogram (ECG), breathing movement, and oxygen saturation. Technological advancements mean clinicians no longer have to rely on observation alone (e.g. the infant becoming cyanosed) to recognise respiratory events in infants; rather the continuous monitoring is set to alarm at certain user defined limits, which can alert carers that the infant may be in difficulty. The type and quantity of respiratory events that are recognised in NICU depends on the specific alarm limits that are set, and how the alarms are responded to. These variables are user set and are therefore often inconsistent between units.

i. Monitoring of breathing movement

In NICU, breathing movement is most commonly monitored by impedance monitoring, where leads are placed on the infant chest (one above and below the diaphragm). As well as measuring ECG signals, the leads use electrical impedance to measure changes in lung volume and provide a trace of breathing movements. Impedance monitoring can distinguish between normal breathing patterns and central apnoea, but cannot accurately distinguish obstructive apnoea or measure tidal volume (61). There are other ways of monitoring breathing movement that are sometimes used, such as apnoea mats and flow sensing devices (e.g. nasal flow cannulas).

ii. Oxygenation monitoring

It is important to be able to accurately estimate SaO₂ levels in preterm infants. The most accurate way to do this is by arterial blood samples, through an indwelling umbilical or
peripheral arterial catheter. However, this is very invasive and only practical when a preterm infant is very young or unstable with a current indwelling catheter. When there is no indwelling catheter, arterial blood gases are limited to spot checks of blood gases, which again is invasive. Therefore, more commonly, less invasive methods are used to estimate $\text{SaO}_2$ readings such as pulse oximetry. This enables continuous oxygen saturation monitoring to be performed.

Continuous monitoring needs to be non-invasive yet accurate. The mainstay of continuous oxygen saturation monitoring in the NICU currently is pulse oximetry. As this is the method used in this research, this will be discussed in detail below. Other non-invasive methods that are occasionally used include transcutaneous oxygen and carbon dioxide monitoring, where an electrode that is separated from the skin by a semipermeable membrane heats the skin to provide partial pressure of oxygen measurements. Disadvantages of this are the need for regular repositioning and re-calibration. The use of these devices has essentially been superseded by pulse oximetry.

### 2.3.2 Monitoring of infants when weaning off supplemental oxygen

An important time for an infant to be closely monitored in NICU is when they are being weaned off supplementary oxygen. This is generally due to the infant having CLD, which has meant the infant has been on supplemental oxygen for a long time and they are now being weaned to a lower flow rate or completely off supplemental oxygen. Infants will often have a 'room air trial' where they are placed off additional oxygen and into room air (21% oxygen) and monitored. In Wellington NICU this is done by a continuous pulse oximetry recording over a 24-hour period, which is then downloaded and a report printed. In Wellington NICU, there are no written guidelines for when a report is considered satisfactory enough that the infant can stay off oxygen, but often a threshold of $>95\%$ mean $\text{SpO}_2$ and $<5\%$ of time spent at $<90\%$ $\text{SpO}_2$ is used to determine a 'pass' of this test.

### 2.3.3 Monitoring of infants for discharge planning

Before a preterm infant can be discharged home from the neonatal unit they need to be able to take all their feeds orally and gain weight, maintain adequate body temperature, and be physiologically stable from a cardiorespiratory perspective. There are various ways to assess an infant for cardiorespiratory stability before discharge including: documenting an 'apnoea free period' while the infant is on impedance monitoring or oximetry monitoring.
alone, a car seat challenge, 24-hour pulse oximetry, or general overall clinical assessment. In Wellington NICU, current practice is to monitor an infant for five days after discontinuing caffeine, and if no significant apnoea are documented, they are deemed to be stable from a cardiorespiratory perspective. As previously discussed, the AAP recommends an infant can be considered for discharge if they are 'physiologically mature and stable cardiorespiratory function has been documented for a sufficient duration', however no details on how to assess this are specified (8).

**i. Apnoea free period**

Perhaps most frequently used is what is known as an 'apnoea free period', where an infant must be determined to be free of apnoea for a certain number of days before being discharged. Darnall et al. showed that guidelines for the required number of 'apnoea free days' vary across centres from one to ten days, most commonly five to seven days (62). They attempted to define a minimal safe apnoea free period and established that apnoea (defined in this study as a pause in breathing of >20 seconds, or a shorter pause in breathing if accompanied by bradycardia or colour change) may occur up to 8 days apart, suggesting that the generally accepted five to seven day period may be too short (62). Oxygen saturation is not always monitored at this stage and if breathing movement monitors alone are used to record apnoic events, obstructive apnoea is not detected. Nurses usually document apnoea by recording when the monitor alarms; however, studies have shown that using nurse observation alone to document apnoea is unreliable and can miss many events (63, 64). It would appear therefore that this frequently used method for assessment of cardiorespiratory stability pre-discharge has no clear evidence base and may overlook potentially significant pauses in breathing less than 20 seconds and persistent IH.

**ii. Car seat challenge**

Pre-discharge 'car seat challenges' are also common when assessing a preterm infant for discharge from the neonatal unit. Continuous oxygen saturation monitoring (oximetry) is performed for one to two hours while the infant is seated in a car seat to assess their cardiorespiratory stability. The length of time the infant is monitored varies from 30 to 120 minutes. Studies have shown that 12-24 hour polysomnography (PSG), which includes oximetry, identifies a greater number of infants with clinically concerning events such as apnoea and desaturations than the car seat challenge does, indicating the car seat challenge may give false reassurances of an infant's cardiorespiratory stability (65, 66). It has been
suggested that reasons for this could be the length of the study (24 hours vs one to two hours) and being able to always capture both sleep and wake states in the 24-hour study. These studies suggest that 24-hour oximetry monitoring may be of more value than the above methods as a pre-discharge tool for assessing cardiorespiratory stability.

**iii. 24-hour pulse oximetry**

Extended (six to 24 hour) pulse oximetry recordings are becoming more frequently utilised worldwide, and are sometimes used to assess a preterm infant's readiness for discharge. In Wellington NICU, only infants where there is clinical concern about apnoea near the time of discharge would be considered for a 24-hour pulse oximetry recording.

**2.3.4 Pulse oximetry**

**i Technology**

Pulse oximetry is a non-invasive technique that uses the detection of pulsatile blood flow and the differing absorption spectra of oxy-haemoglobin and deoxy-haemoglobin to calculate SpO₂. SpO₂ is the estimate of arterial haemoglobin oxygen saturation (SaO₂) by a pulse oximeter. Two light emitting diodes (LED) which transmit red and infrared light are placed on one side of an infant’s foot or hand, or an adult’s finger, and a photoreceptor sensor is placed 5 – 10mm away, directly opposite the LEDs. As deoxy-haemoglobin absorbs much more red light and oxy-haemoglobin absorbs more infrared light, the ratios of absorption can be compared against stored data and algorithms to determine SpO₂.

![Figure 2-1 Pulse oximetry (Pal Oyvind 2012)](67)
**ii. Limitations**

Pulse oximetry is generally considered to give accurate estimates of SaO\(_2\). There are certain conditions that can affect the accuracy of pulse oximeters; these are listed in table 2-3.

### Table 2-3 Sources of inaccuracy when using pulse oximeters

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor perfusion</td>
<td>Lower SpO(_2) readings</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Lower SpO(_2) readings</td>
</tr>
<tr>
<td>Motion artefact</td>
<td>Lower SpO(_2) readings</td>
</tr>
<tr>
<td>Fetal/other types of Hb</td>
<td>Lower/higher depending on Hb</td>
</tr>
<tr>
<td>Inaccurate stored 'normal' data</td>
<td>Lower/higher depending on data</td>
</tr>
<tr>
<td>Light interference/skin pigmentation</td>
<td>Lower SpO(_2) readings</td>
</tr>
</tbody>
</table>

Pulse oximetry relies on detecting only pulsatile blood flow in order to estimate arterial rather than venous oxygenation, therefore background noise from other motion creates noise and artefact. Newer pulse oximeters such as the Masimo; (Masimo corporation, Irvine, California) have signal extraction technology (SET) designed to reduce this artefact. The other main limitation of pulse oximeters is that they rely on algorithms to calculate SpO\(_2\) that are derived from 'normal' volunteers. Each brand of pulse oximetry generally uses their own set of stored data, and therefore there may be inconsistencies between oximeters. The accuracy of SpO\(_2\) decreases with decreasing SpO\(_2\), as normal data for SpO\(_2\) at low oxygen saturations are limited because it is unsafe to subject normal volunteers to such low oxygen levels. Bilirubin does not affect SpO\(_2\) as it is a different spectrum of light, however dark skin has in some cases been thought to influence SpO\(_2\) (68).

**iii. Measures reported from recordings of pulse oximetry monitoring**

Data from pulse oximetry monitoring can now be recorded and saved and reports generated from the data to be interpreted by clinicians. There are many programmes that can download this saved data and generate a variety of reports which include different measures. In NZ and Australia, the main software package used is PROFOX Associates, Inc (69). In this software a variety of measures are calculated and reported, and different data reports can be chosen before printing out a summary of the data collected. Examples
of such reports are included in Appendix A. Common measures that software packages report are mean SpO$_2$, time spent below certain SpO$_2$ values e.g. $<90\%$, $<85\%$ etc, heart rate, and number of desaturation 'events', which vary in definition, e.g $\leq 80\%$ for $\geq 4$ seconds. The desaturation index (DSI) is a measure of desaturations per hour, for example DSI 4% is the average number of desaturations of at least 4% SpO$_2$ per hour. Lee et al suggests that the variability of oxygen saturation measured by the standard deviation (SD), which is reported in PRFOX for each patient, is a more useful measure when compared to mean SpO$_2$ for predicting oxygen saturation instability in premature infants (70).

iv. Use of pulse oximetry in paediatrics

Pulse oximetry is commonly used in NICU as a way of continuously monitoring oxygen saturation in infants, assessing infants during oxygen weaning, and sometimes for discharge planning. Other uses for pulse oximetry in the paediatric population include use when assessing a newborn during resuscitation in the delivery room, as a screening procedure to assess severity of obstructive sleep apnoea (OSA) in children, and a screening tool for critical congenital heart disease (CCHD). The use of pulse oximetry as a screening tool for CCHD in newborns is now validated, although as yet there is no mandated national screening program in New Zealand (71). The screening test for CCHD is performed $>24$ hours after an infant is born but prior to going home and involves a spot check (connected until the perfusion signal is adequate and a reading can be taken, approximately 1 minute) of both pre and post ductal oxygen saturations. The AAP guidelines recommend that a screen be considered negative if pulse oximetry is $\geq 95\%$ in right hand or either foot with $\leq 3\%$ absolute difference in oxygen saturation between right hand and foot (72). This type of screening does not monitor the infant continuously over an extended period of time and therefore only assesses mean SpO$_2$ rather than assessing IH.

v. Current oximetry guidelines for extended recordings in infants

Oximeters and their analysis software are advancing in technology. Despite this there are no clear guidelines on performing these recordings, nor on how to analyse and interpret the data they generate. In NZ there are guidelines from Auckland's Starship hospital from 2009 on performing and interpreting paediatric oximetry. They provide clear guidance on which settings are best, including recommending a short averaging time of two to four seconds and recording time more than six hours. However, the indications and data interpretation are specific to diagnosing sleep problems in children, and do not mention pre-discharge
oximetry for preterm infants (73). The 2009 British thoracic society guidelines are specific to the issue of when home supplemental oxygen is needed for infants (74). They recommend that if an infant has a mean SpO₂ >93%, time spent <90% of <5% and desaturations are 'not frequent or excessive' then there is no need for supplemental oxygen. These guidelines are based on limited evidence, and more information is needed to be able to accurately define 'frequent or excessive' desaturations, as the available guidelines are insufficient.

**vi. Extended oximetry in preterm infants: normal values**

There is some available literature on normal values for a range of different infant populations such as: oxygen saturation values for the first 24-hours after birth, spot checks for term infants at 24 to 48 hours of age, normal oxygenation at different altitudes, and oxygen saturations at different ages through childhood (75-79). As this thesis will report measures from 24-hour oximetry at discharge in preterm infants, the review of this literature is focussed on this age group. Table 2-4 and 2-5 summarise all studies to our knowledge that report on normal values for pre-discharge, extended (more than six hours) oximetry in preterm infants.
<table>
<thead>
<tr>
<th>Authors (year published)</th>
<th>N</th>
<th>GA (wks)</th>
<th>Exclusion criteria</th>
<th>Age at time of study</th>
<th>Recording time (hs)</th>
<th>Oximeter used</th>
<th>Averaging time (seconds)</th>
<th>Sampling rate</th>
<th>Software used</th>
<th>Artefact editing</th>
<th>Control group</th>
</tr>
</thead>
</table>
| Rath et al. (2015)      | 15 | <28      | • Not on any respiratory support for 48hs  
• Congenital abnormalities, anaemia, IVH 3 or more, growth restricted  
• Received caffeine in last 7 days | >37wks GA and ready for d/c home | 12                  | Masimo Rad-7      | Not described | 2 Hz          | Not described | AUTO          | Term infants  |
| Rhein et al. (2014)     | 53 | ≤32      | • Current supplemental O₂  
• Grade 3 or 4 IVH  
• Congenital or genetic disorder | • 1 day after discontinuing caffeine  
• AND >33 weeks PMA | Masimo Rad-8 | 2               | Not described | PROFOX AUTO | Infants that received intervention of prolonged caffeine treatment |
| Shah et al. (2014)      | 20 | 35-36    | • Respiratory resuscitation at birth (e.g CPAP)  
• SGA  
• Congenital malformations | 12 - 48 hs of age | Nellcor OximMax N-600X | 2-3               | Not described | PROFOX Manual | Term infants (assessed at 12-48 hs of age) |
| Pugalenthi et al. (2013) | 49 | <31      | None               | 35-36 wks PMA | PSG with pulse oximetry (Oximeter not specified) | Not described | Not described | Labchart software None described None |
| Rhein et al. (2012)     | 52 | ≤32      | • Supplemental O₂ in 7 days before oximetry  
• >35 wks PMA and within 2 wks of d/c | > 6 hours (overnight) | Masimo Rad-7 | 2               | 1 Hz         | PROFOX AUTO and Manual | Term infants (assessed by 48 hs of age) |
<p>| Lee et al. (2011)       | 31 | &lt;36      | • Mechanical | 36 wks PMA | Masimo Rad-7 | 2             | Not          | Not Manual | None |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Ventilation Description</th>
<th>Days of Age</th>
<th>Oximeter Type</th>
<th>Calibration</th>
<th>Use</th>
<th>Mechanical Ventilation</th>
<th>Supplemental O₂ Time</th>
<th>Supplemental O₂ Duration</th>
<th>Other Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harigopal et al. (2011)</td>
<td>Mechanical ventilation</td>
<td>CPAP &gt;12 hours, Major surgery, Congenital malformations, Currently on supplemental O₂</td>
<td>2 wks of age</td>
<td>Nellcor N 595</td>
<td>2-3</td>
<td>Not</td>
<td>Not described</td>
<td>&gt;48 hours</td>
<td>Not described</td>
<td>Described in methods; Actual: 2-28 days (median 14)</td>
</tr>
<tr>
<td>Beresford et al. (2005)</td>
<td>Mechanical ventilation</td>
<td>Mechanical ventilation for &gt;6 hours, Supplemental O₂ &gt;48 hours</td>
<td>1 wk of age</td>
<td>Ohmeda Biox 3700 E Pulse Oximeter</td>
<td>3</td>
<td>Not</td>
<td>Not described</td>
<td>4 hours (post feed)</td>
<td>Not described</td>
<td>Term infants (assessed 48 hs post delivery)</td>
</tr>
<tr>
<td>Ng et al. (1998)</td>
<td>Mechanical ventilation</td>
<td>Mechanical ventilation for &gt;6 hours, Supplemental O₂ &gt;48 hours</td>
<td>4 hours (post feed)</td>
<td>Ohmeda Biox 3700 E Pulse Oximeter</td>
<td>3</td>
<td>Not</td>
<td>Not described</td>
<td>4 hours (post feed)</td>
<td>2 Hz</td>
<td>None</td>
</tr>
<tr>
<td>Richard et al. (1993)</td>
<td>Any respiratory support</td>
<td>Any respiratory support &gt;24 hours, Major congenital defects</td>
<td>12 hours</td>
<td>Nellcor N200 (and breathing movements)</td>
<td>Not described</td>
<td>Not</td>
<td>Not described</td>
<td>Not described</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Spear et al. (1992)</td>
<td>Supplemental O₂</td>
<td>Supplemental O₂ &gt;48 hours, Grade 3/4 IVH, Cardiac disease, Current infection, Treatment with methylxanthines</td>
<td>6 hours</td>
<td>In channel PSG with Nellcor oximetry</td>
<td>Not described</td>
<td>Not</td>
<td>Not described</td>
<td>Not described</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Poets et al. (1991)</td>
<td>Unlikely to survive</td>
<td>Unlikely to survive, Within 3 days of d/c, AND &gt;37wks PMA</td>
<td>12 hours (overnight)</td>
<td>Nellcor N100 (new software equivalent to N200)</td>
<td>Not described</td>
<td>Not</td>
<td>Not described</td>
<td>Not described</td>
<td>Term infants (reported in a separate paper) and preterm infants 6 weeks later</td>
<td></td>
</tr>
<tr>
<td>Author (year)</td>
<td>Mean SpO₂</td>
<td>Time spent &lt;90% SpO₂</td>
<td>Time spent &lt;85% SpO₂</td>
<td>DSI 4%</td>
<td>Number of desats &lt; 80%</td>
<td>No. Desats &lt; 90%</td>
<td>HR</td>
<td>Other oximetry measures reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rath et al. (2015)</td>
<td>Median: 97</td>
<td>Median (IQR) 3 (1-14.5)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhein et al. (2014)</td>
<td>Not reported</td>
<td>Seconds per hour, Mean (SD)</td>
<td>Seconds per hour, Mean (SD)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>≥ 5 seconds and deviated from baseline ≥ 5%. No. per hour, mean 35PMA 8.4 (8.4) 36PMA 8.2 (11.5) 37PMA 5.2 (6.8) 38PMA 4.7 (6.1) 39PMA 3 (3.3)</td>
<td>Not reported</td>
<td>Time spent &lt;80% SpO₂ S⁻¹ hour, Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shah et al. (2014)</td>
<td>Not reported</td>
<td>Mean 6.9% (5.1) 5th centiles 87.0, 99.0</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pugalenthi et al. (2013)</td>
<td>Mean 95.3 (5th, 95th centiles 87.0, 99.0)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Mean 158 (5th, 95th centiles 130, 186)</td>
<td>Cumulative frequency curves for time spent below each SpO₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhein et al. (2012)</td>
<td>Mean 98.8 (1.4) 5th centiles 95-100</td>
<td>Mean 3.2% (3.3) Median 2.2% (0-14.6)</td>
<td>Not reported</td>
<td>Events that were &gt;10s &amp; &lt;3 min, per h of recording Mean 11.8 (8.1) Median 10.2 (0.3-31.5)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>• SpO₂ infant spent 5 &amp; 10% of time below • % time below 91-95% • DSI4 &amp; DSI10 &gt;3 mins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Mean (SD) or Median (IQR)</td>
<td>SpO2 ≥ 4 seconds</td>
<td>SpO2 ≥ 6 seconds</td>
<td>SpO2 ≥ 6 seconds (6 hours recording time) Mean</td>
<td>Duration of longest desaturation</td>
<td>No. per hour with at least one episode ≥ 4 secs Mean (95% CI)</td>
<td>Total seconds (6 hours recording time) Mean (95% CI)</td>
<td>Cumulative frequency curves for time spent at each SpO2</td>
<td>Cumulative frequency curves for time spent below each SpO2</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
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<td>--------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2011) (70)</td>
<td>Mean 96.9 (3.6) Median 98 (96-99 IQR)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Harigopal et al. (2011) (84)</td>
<td>Median 95 (92-99) Median 4% (no range given)</td>
<td>Median 1% (1-4)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Median 150 (116-168)</td>
<td>Cumulative frequency curves for time spent below each SpO2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beresford et al. (2005) (85)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Ng et al. (1998) (86)</td>
<td>Median 97 (92-100) Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Cumulative frequency curves for time spent at each SpO2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richard et al. (1993) (87)</td>
<td>Median 99.4 (90.7 - 100) Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Episodes ≥ 4 seconds Found in only 18% of infants</td>
<td>Not reported</td>
<td>Not reported</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spear et al. (1992) (88)</td>
<td>Not reported</td>
<td>Total seconds (6 hours recording time) Mean 93.1 (122.7)</td>
<td>Not reported</td>
<td>≥6secs, Total seconds (6 hours recording time) Mean 7.41 (no SD)</td>
<td>≥6secs, Total seconds (6 hours recording time) Mean 15.1 (18.33)</td>
<td>Not reported</td>
<td>Brady &gt; 5 seconds (n)</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poets et al. (1991) (89)</td>
<td>Median 99.4 (88.9-100) Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>No. per hour with at least one episode ≥ 4 secs Median 5.4 (0-156.5)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>• Mean duration of desaturation • Duration of longest desaturation</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

All median (range) and mean (SD) unless stated
Table 2-4 illustrates the large variation in how studies were performed. This makes it difficult to compare any of the results from studies, presented in table 2-5. Each study had different exclusion criteria, ranging from no exclusion criteria to excluding any infant that had any form of respiratory resuscitation at birth. The GA of the infants in each study also varied, from including only very premature infants <31 weeks GA, to only late preterm infants with a GA of 35-36 weeks, or including all preterm infants <37 weeks. Other important features of oximetry recording that can affect the results are the type of oximeter used, averaging time, sampling rate, and how artefact was edited. These factors varied significantly between studies. The type of oximeter used influences the values produced, and as Masimo oximeters are now the main oximeter used in the NICU, the four studies that use new Masimo oximeters are most relevant (69, 70, 80, 81, 83). Six of the twelve studies reported a short averaging time of less than four seconds; the other six studies did not describe the averaging time used so it is difficult to interpret the reported 'number of desaturations' in these studies, as different averaging times have different effects on the overall results. There were only three studies that performed the pulse oximetry recordings 'at discharge', and again they had different exclusion and GA criteria (80, 83, 89).

Table 2-5 lists the average values of the oximetry measures that were reported from each study. There is a large variation in which measures are reported, and which definitions of ‘desaturation’ are used, which is problematic when trying to compare studies. There were four studies that used new technology Masimo (Masimo Corp., Irvine, CA, USA) oximeters (70, 81, 83). Even though two of these studies are comparable in the way they were conducted (both studied infants with a GA <32 weeks, who had no recent supplemental O2 use and had oximetry at a PMA of 37 weeks) none of the reported measures are the same (81, 83). The mean SpO2 is reported in 8/12 studies and varies from 95.3-99%, and median SpO2 95-99.4%, with no clear pattern between studies that included very preterm compared to late preterm infants. The second most frequently reported measure was time spent <90% SpO2. The mean reported was 3.2 % and 6.9% (2 studies (6, 83)), median 2.2 - 5.6% (4 studies (6, 80, 83, 84)) Two studies reported the mean time spent at <90% SpO2 over the total recording (6 hours) which was 1.5 minutes in one study and 25 minutes in another, which is a large difference (6, 88).

The four studies that compared preterm infants with a control group of term infants consistently found significant differences between the groups (6, 80, 83, 85, 89). Shah et
al. reported a significant difference in percentage time with SpO\textsubscript{2} <90% between late-preterm infants (7%) and term infants (4%) p = 0.002 (6). Rhein et al. found that while mean SpO\textsubscript{2} and time spent below 90% SpO\textsubscript{2} were comparable between the two groups, DSI 4% (events/h) differed significantly (preterm 11.8 ± 8.1 and term 9.6 ± 5.4 p = 0.0001) (83).

Poets et al. performed oximetry on preterm infants at discharge and again six weeks later and reported that the median (range) number of oxygen desaturation to ≤80% SpO\textsubscript{2} for ≥4 seconds per recording decreased significantly, from 3 (0-355) to 0 (0-17) p <0.0001 (90)

In summary, studies that report normal preterm infant extended oximetry values vary widely in the way they are performed, making them difficult to compare. There is a lack of recent studies using new technology Masimo oximeters. There is also a lack of studies that perform the oximetry recordings at the time of discharge from NICU. Research is needed in this area to be able to generate normal values so that reports generated from pre-discharge oximetry recordings have reference values to compare with.

### 2.4 Consequences of respiratory events in preterm infants

Previous sections have discussed the physiology, monitoring, and current knowledge of normative values for respiratory events in preterm infants. A clinician’s decision on the level of monitoring required, extent of medical treatment needed, and when an infant can be considered ‘stable’ for discharge from a cardiorespiratory perspective depends fundamentally on knowledge about the quantity and severity of respiratory events that can be tolerated without causing any short or long term adverse consequences. In particular, knowledge about the accepted parameters that define the length of pause in breathing, level of oxygen desaturation, and amount of intermittent hypoxia, that is no longer considered normal respiratory variability but pathological and of possible clinical significance, is necessary for clinical decision-making.

It is biologically plausible that frequent pauses in breathing and the subsequent possible oxygen desaturations may cause damage to the developing brain, and therefore have long term consequences on development and growth. Serious morbidity can be associated with hypoxic – ischemic encephalopathy (HIE). This clinical presentation occurs when there
has been a significant period of cerebral hypo-perfusion associated with low oxygen saturations in relation to an asphyxia event during the perinatal period. The likelihood of brain damage and long-term disability after such an event depends on the severity of the event. Respiratory pauses and bradycardia in preterm infants have been demonstrated to cause cerebral hypo-perfusion and a decrease in cerebral oxygenation (91-93). Within a respiratory event, simultaneous bradycardia and hypoxaemia cause the greatest decrease in cerebral oxygenation, compared to either occurring alone (94). Periodic breathing, which is generally thought to be benign and to cause no long term consequence, has also been shown to cause cyclic deoxygenation and reoxygenation of cerebral blood flow (95, 96).

Apnoea and IH are commonly seen and even considered ‘normal’ in preterm infants, however we must remember that preterm infants are in fact not ‘normal’, in the sense that they have been brought into this world prior to when they were intended to be born and this premature birth has been for a variety of clinically significant reasons. These events that may be considered ‘normal’ in preterm infants may still have detrimental effects on the developing infant brain and research into this area is therefore crucial.

The following section will discuss current knowledge on adverse outcomes associated with apnoea during infancy (in term and preterm infants), knowledge on the association between recurrent apnoea and growth, oxygen saturation targets in the NICU, and finally adverse effects of intermittent hypoxia in particular.

### 2.4.1 Consequences of apnoea in full term and preterm infants

Research has focused on outcomes of cardiorespiratory events and apnoea during infancy, which, as discussed in section 2.2.2 is not consistently defined, however is often described as a pause in breathing for more than 20 s. Most literature focuses on the effect of these respiratory events on neurodevelopmental outcomes, often using the Bayley Scales of Infant Development or The Griffiths Mental Development Scales, in combination with a neurological assessment by a paediatrician.

#### i. Full term infants

Black et al. published a paper in 1979 that suggested that increased respiratory instability in full term infants negatively impacted on neurodevelopment (97). They assessed 122 full term, healthy infants using a one hour nap polygram recording during their first week of life and again at four weeks of age. The relative frequency and average duration of apnoea
were used to develop a score of respiratory instability. Infants with increased respiratory instability in their first week of life, averaged significantly lower in both mental and psychomotor development on the Bayley scale at nine months of age (p < 0.0001); furthermore, infants with increased respiratory instability at four weeks scored even lower on the Bayley scale.

Consequent studies during the 1980’s investigated full term infants with reported apnoea as an infant and found that there were no differences in their neurodevelopmental outcomes (IQ, behaviour scores, neurological assessment) when compared to controls (98, 99). The only significant finding (in a small study of 14 apnoeic infants) was impairment in gross motor scores when compared to siblings (98). The small numbers in the study may have affected the study outcomes. Timing of neurodevelopmental testing in these studies ranged from two to ten years of age, which is another limitation of the study.

**ii. Preterm Infants**

Tudehope et al. published a paper in 1986 that followed very low birth weight (VLBW) infants and similarly reported that after adjusting for confounders (Low birth weight, need for assisted ventilation and presence of CLD), apnoea (defined as a pause for >10 s) was not a predictor for adverse neurodevelopmental outcomes as assessed by the Griffiths scale at 2 years of age (100).

Another study published in 1993 studied 60 premature infants with ‘AOP’, defined as an apnoea or bradycardia requiring stimulation by a nurse, confirmed by an abnormal 12-hour pneumocardiogram (abnormal defined as an apnoea lasting > 20 s or PB for >5% total recording time or a bradycardia to less than two thirds of resting heart rate (HR) for >10 s) (101). These infants were matched for GA and severity of neonatal illness to controls and both underwent neurodevelopmental testing at 12-24 months. Again, there were no significant differences in neurodevelopmental outcomes (Bayley mental and motor scores) between groups. The only difference seen was a greater number of infants with AOP in the ‘mild motor delay’ range compared to controls.

These earlier studies suggest that after correcting for GA and neonatal morbidity, there are no significant adverse neurodevelopmental outcomes for infants that experience apnoea. More recent studies however have suggested that apnoea during early infancy in preterm infants is associated with adverse outcomes. Two large studies looked at the ability of ‘pre-
discharge’ 24-hour monitoring (using 4 channel pneumograms) of preterm/VLBW infants to predict adverse outcomes post-discharge (102, 103). Cheung et al. used mean bradycardia, mean oxygen desaturation and frequency of ‘apnoea’ (defined as >12 seconds with associated desaturation or bradycardia) as their pre-discharge measures and assessed infant neurodevelopment at 2 and 3 years of age. They found that the pre-discharge study was an independent predictor in the high risk group of infants (IVH grade 3 or 4) of the Bayley mental and motor scores at 2 years of age, however infants in the low risk group (no IVH or IVH grade II or III only) showed no association. They concluded that pre-discharge respiratory recording is a useful tool to predict neurodevelopmental outcomes for high-risk VLBW infants (103). Subhani et al. defined a ‘normal’ pre-discharge recording as one where there were no apnoea for > 20 s or no HR to <80 bpm for >5 s. The abnormal group was compared with the normal group for rates of apnoea related hospital readmission, apparent life threatening events (ALTE) or death. Four of the abnormal group (n=32) had post-discharge complications whereas none of the 74 in the normal group had any of the documented post-discharge events. The two groups were of no difference in terms of GA or severity of neonatal course. This research suggested that a ‘normal’ pre-discharge respiratory recording can predict infants with a low risk of serious adverse outcomes (102).

In three recently published studies, researchers recruited preterm infants and used frequency of apnoea during NICU stay as a measure of exposure to respiratory instability. Nurse documentation of machine alarms was used to define frequency of apnoea in all studies (104-106). All three studies report that increased frequency of apnoea during the NICU stay is associated with worse neurodevelopmental outcomes. Janvier et al. studied 175 preterm infants (< 32 weeks GA or <1250g BW) and recorded number of days during hospitalisation that the infant had a least one nurse documented ‘apnoea’ (machines normally set to alarm < 84% SpO₂ or <100 bpm). They assessed infant neurodevelopment at three years of age and found that, after correcting for multiple factors (IVH/GA/use of antenatal steroids), the total number of apnoea days was significantly associated with neurodevelopmental impairment (defined as a Bayleys mental/psychomotor developmental index (MDI/PDI) <70), CP or blindness)(104). Pillekamp et al. studied the frequency of apnoea during the NICU stay of 83 VLBW infants (Machines alarmed at <86% SpO₂ or <80 bpm (for infants <35wks GA) or <100 bpm (infants >35wks GA), and also documented the severity of each apnoea. They found that after correcting for GA, only the
‘adjusted daily apnoea score’ (calculated as frequency of apnoea multiplied by severity) from 31-37 weeks PMA was predictive of neurodevelopmental outcomes at 13 months of age (<69 MDI/PDI) (105). Greene et al. studied 98 infants <1000g BW and again used nurse documentation of ‘cardiorespiratory events’ (CRE), which were defined simply as a HR <80bpm. They reported that more frequent CRE was associated with worse language scores on the Bayley III at 8 months (P < 0.05), and more severe CRE (measured by lowest HR during each event) was associated with receptive language delay at 20 months (106).

iii. Comparing preterm with term infants

The Collaborative Home Infant Monitoring Evaluation (CHIME) is one of the largest studies looking at cardiorespiratory events on home monitors. This large study consisted of 1079 infants including; healthy full term infants, infants with a history of ALTE, infants with a history of sudden infant death syndrome (SIDS) in a sibling and preterm infants ≤ 34 weeks and BW <1750g. The CHIME study included 256 infants (138 full term and 118 preterm) that also completed neurodevelopmental testing at one year of age. For this study published in 2004, infants were classed as having 0, 1-4 or 5+ events over the 180 days of home monitoring (minimum of 175 hours total recording)(107). Events were defined as an apnoea > 20 s or HR <60bpm for at least 5 s or <80bpm for at least 15 s if aged >44 weeks PMA. They reported that both term and preterm infants in the 5+ events group had lower mental (MDI) and motor (PDI) Bayleys scores when compared with the 0 events group; however, after adjusting for confounders, only MDI was significantly different (p = 0.03 term infants, p = 0.04 preterm infants).

iv. Summary

From the studies reviewed, current evidence on the consequences of apnoea is conflicting. Some studies report no association between the presence of recurrent neonatal apnoea and adverse developmental outcomes (98, 99), or report associations that disappear after controlling for confounders (100, 101, 107). Some report an association only in already high-risk infants (103), and some studies do report that neonatal apnoea is an independent predictor of adverse consequences (97, 102, 104-107).

When considering adverse outcomes associated with ‘apnoea’ in preterm infants, possible confounders need to be considered. Poor neurodevelopment and more frequent apnoea are both independently correlated with many primary sources, such as GA, IVH, or other brain
insults in the early neonatal period. Therefore, it may be that apnoea is purely a marker of a more severe neonatal course or brain injury, which in itself leads to worse neurodevelopmental outcomes. Intervention studies are needed to establish whether a decrease in apnoea causes an improvement in outcomes, which would determine whether treatment of the respiratory instability would be indicated.

Most studies simply compared infants with apnoea to infants without, with the definitions of apnoea varying, which results in inconsistent definition of an already crude exposure, and does not focus on the differing severity or duration of the events. Studies also often used the non-objective measure of nurse documentation to assess apnoea prevalence, rather than analysis of data from continuous monitoring. Nurse documentation has been shown to be unreliable (108). Studies commonly used length of a respiratory pause to identify infants with worse apnoea, rather than focusing on the consequence (and likely pathological component) of the respiratory pause, such as a decreased heart rate or degree of oxygen desaturation. No study used measures such as a desaturation index (DSI), which would identify the frequency of intermittent hypoxia, quantifying exactly how much respiratory variability there is rather than simply looking at infants with ‘apnoea’ or no apnoea. It is possible that with more precise measures, research may start to report a more consistent picture of adverse outcome associated with respiratory instability. The current study uses continuous oximetry monitoring over 24 hours, with a range of measures of intermittent hypoxia reported.

2.4.2 Association between respiratory stability and growth

It is known that children with severe OSA have an increased rate of failure to thrive and studies consistently report an increase in weight gain velocity for children after surgical treatment (tonsillectomy and adenoidectomy) (109-116). Adults with OSA have also been shown to gain weight after treatment with CPAP. One large recent (2015) meta-analysis that included 25 high quality papers found that there is a significant increase in BMI after treatment of OSA with CPAP (117).

The cause of this growth restriction in children and adults with OSA has been suggested to be a combination of increased energy expenditure and an imbalance in growth hormones. In obstructive respiratory events, there is increased breathing effort, and therefore an anticipated increase in energy expenditure. Marcus et al. found that after children had been
treated surgically for OSA they did indeed have less energy expenditure during sleep and more weight gain compared to before treatment (115). However, Bland et al. reported no difference in total energy expenditure (TEE) between children with OSA and controls, and found no significant difference in TEE after surgical treatment in the OSA subjects. Nieminen et al. reported insulin-like growth factor 1 (IGF-1) secretion is impaired in children with OSA, and returns to normal after surgical treatment (113). Bar et al. similarly reported an increase in IGF-1 after surgical treatment for OSA in children, suggesting growth hormone impairment is an important contributor to the phenomenon of decreased weight gain in children with OSA (112).

There have been few studies that evaluate the association between respiratory stability and growth in infants, however the few reported studies indicate a positive association (118-121). Riordan et al. studied 99 healthy full term infants and reported that the presence of PB was inversely correlated with percentage weight gain in the first two months of life (118). The three studies that do report on growth as an outcome for preterm infants report only on those preterm infants with CLD. They report a general decrease in growth for infants with CLD and an association between oxygen administration and increased growth rates (119-121).

Farahani et al. examined rat pup growth, comparing controls to animals exposed to chronic constant hypoxia (CCH), and chronic intermittent hypoxia (CIH) in the first four weeks of life (122). They reported a decrease in weight velocity for both CIH and CCH groups compared to controls, with the CCH group more severely affected than the CIH group. CCH is consistent with CLD (although there would be somewhat less CCH if the infant is treated with oxygen), whereas CIH would be more comparable to infants with AOP or PB. Pozo et al. also studied growth in rat pups by exposing two groups to different patterns of repetitive IH and comparing with a control group (123). They found both IH patterns resulted in growth restriction when compared to controls, with pups displaying a catch up growth pattern when the IH exposure was stopped.

As can be seen from the animal, child, adult, and limited infant studies discussed, it is plausible that increased respiratory instability, including increased respiratory pauses and more frequent IH, could be associated with decreased growth rates in preterm infants. The likely pathophysiology appears to be a combination of increased energy expenditure and
decreased growth hormone production. The exposure to hypoxia itself may be a contributory factor. Adequate growth in preterm infants is important, as postnatal weight gain in preterm infants is associated with neurodevelopmental outcomes, as reported recently in a systematic review (124). Despite this theoretical conclusion, to our knowledge there are no published studies that investigate the association between increased respiratory instability and growth rates in preterm infants without CLD. The current study examined growth rates in the one month post discharge from NICU.

2.4.3 Oxygen targets in the neonatal unit

The majority of previous research on oxygenation in preterm infants has been focussed on baseline oxygen levels rather than intermittent hypoxia. A number of large multi-centre studies have tried to define a ‘safe’ baseline oxygen saturation target for preterm infants (125-130). These studies were driven by the realisation that ROP can be caused by hyperoxia. Studies are conflicting, but generally report that although there is a lower rate of ROP at the target range of a SpO₂ of 85-90%, the mortality rate is higher than when baseline oxygen saturation targets are 90-95% (125-128). A further study has suggested a SpO₂ target of 90-95% is preferable to 95-100% (129). It has also been reported that infants in the lower target ranges have higher rates of intermittent hypoxia (130). The BOOST (Benefits Of Oxygen Saturation Targeting) study was a large study that recruited 2448 preterm infants from the United Kingdom, Australia and NZ (131). Infants were randomised into a 85-89% SpO₂ target group or a 91-95% SpO₂ target group. The study was stopped early as infants in the lower oxygen saturation target group were found to have significantly higher mortality rates (23.1% vs 15.9%). Infants in the lower oxygen saturation target group had lower rates of ROP but higher rates of NEC.

2.4.4 Consequences of intermittent hypoxia

Intermittent hypoxia has been discussed previously in section 2.2.3 and is the most important component of a respiratory event, as it is the severity and frequency of oxygen desaturation and resaturation that is thought to be harmful, rather than simply the length of respiratory pause. Most studies discussed so far require a minimum length of pause to classify ‘apnoea’, however even very short pauses, or simply bradycardia, may result in hypoxia. Hypoxia can also be associated with movement and arousal from sleep.
Studies investigating the specific association between IH and adverse outcomes in preterm infants are lacking. However, there are a large number of recent studies looking at the consequences of IH in adults with OSA (132-135). These studies suggest that the cyclic deoxygenation and reoxygenation that occurs with OSA associated IH induces excessive reactive oxygen species (ROS) and activates proinflammatory transcription factors, which result in various pathologies; mainly cardiac, neurological, and metabolic dysfunction.

There have also been many rodent studies published that investigate the effect of IH on rodent physiology. These studies indicate that exposure to IH can cause cardiorespiratory dysfunction and neurodevelopmental delay (136-138), as well as impaired growth. In contrast one rodent study reported that mild exposure to IH was in fact neuroprotective (139).

Bass et al. conducted a large review of the evidence regarding the effect of chronic and intermittent hypoxia on childhood cognition (140). The review included papers that reported on clinical conditions associated with chronic hypoxia such as congenital heart disease (CHD) and conditions associated with IH, such as sleep disordered breathing (SDB). They reported that 31 (83.8%) of the 37 controlled studies that qualified for the review reported an adverse effect on childhood cognition. Sleep disordered breathing, which is associated with IH, was one of two clinical conditions that after review of the evidence, satisfied the Evidence Based Paediatrics and Child Health criteria for causation of adverse childhood cognition. Bass et al. also concluded that “Because adverse effects have been noted at even mild levels of oxygen desaturation, future research should include precisely defined data on exposure to all levels of desaturation”.

Poets et al. published a paper in 2015 that, as part of the Canadian Oxygen Trial (COT) study, reported on the association between episodes of hypoxemia (pulse oximeter oxygen saturation <80%) or bradycardia (pulse rate <80/min for 10 s or longer) and serious morbidity or mortality in preterm infants. They found there was an association between prolonged hypoxemia (episodes lasting longer than one minute) and serious morbidity or mortality at 18 months (relative risk, 1.66; 95% CI, 1.35-2.05), with no significant association for episodes shorter than this (141). A recent review discusses potential morbidity caused by IH in preterm infants (60). This review concluded that there is evidence that IH is a contributing cause, alongside hyperoxia, of ROP (59) with limited
evidence that IH may be contributing to broader outcomes such as growth, cardiovascular
dysfunction and neurodevelopmental outcomes. The authors called for more research into
the area. Many other authors also call for research to be focused on the extent of the
oxygen desaturation and quantity of IH rather than apnoea, and state the need for future
studies on the effects of IH in preterm infants (24, 45, 142, 143).

With recent advances in technology, including advanced oximetry algorithms and shorter
averaging times that improve the accuracy of oximeters, the extent to which IH occurs in
preterm infants is now able to be accurately documented and the magnitude of IH in
preterm infants is becoming recognised. The current study investigates IH in preterm
infants and specifically how measures of IH on oximetry, such as DSI, correlate to growth
in the first month of life post discharge.

2.5 Respiratory support and treatment options for apnoea in preterm
infants

Preterm infants often require respiratory support at birth and sometimes require continued
support until they have matured sufficiently to be able to effectively ventilate their own
lungs and maintain an adequate SaO$_2$ as well as be free from prolonged pauses in
breathing and oxygen desaturation. Apnoea associated with RDS, a common respiratory
condition in very premature infants (discussed in section 2.1), is treated by ventilation and
administration of exogenous surfactant via an endotracheal tube. As well as surfactant
administration, premature infants often need additional assistance over time such as with
CPAP, additional inspired oxygen, and drugs such as caffeine. New treatment options for
apnoea and intermittent hypoxia are also being investigated.

2.5.1 Current treatment

i. Assisted Ventilation

When an infant is born extremely premature (< 26 weeks GA), they may initially have no
breathing effort at all and require invasive ventilation (intubation with an endotracheal
tube) in order to mechanically inflate and oxygenate their lungs. These infants are often
given intermittent positive pressure ventilation (IPPV), which delivers set positive
inspiratory and end expiratory pressures (PIP and PEEP), which effectively ventilate the infant they cannot initiate or maintain breathing.

Once infants mature and can maintain respiration on their own they can be extubated and less invasive measures such as nasal prongs or a nasal mask are used with a continuous flow of positive airway pressure (CPAP), which helps to keep the infant's alveoli open, ensuring successful oxygenation of their lungs. Non-invasive CPAP ventilation is very common in the NICU and is often the only form of assisted ventilation a premature infant requires. Some infants only need CPAP support at birth for a few hours while some may require CPAP support for a few weeks. In the ANZNN 2013 report, 82% of infants 32-36 weeks GA required CPAP for at least 4 hours (4). Often CPAP is achieved by the infant wearing nasopharyngeal prongs (nasal CPAP); alternatively, a high flow nasal cannula (HFNC) that is set at a flow of >2L can also deliver effective respiratory support (145). Non-invasive CPAP can be used to treat obstructive and mixed apnoea by splinting the upper airway open, but will not always treat central apnoea (where there is no respiratory effort) sufficiently (146).

All assisted ventilation options can use either air (21% O₂), or a mixture of air and oxygen to deliver addition inspired oxygen (>21%O₂). For some infants, positive pressure support is enough to maintain their SaO₂, whereas other infants need additional inspired oxygen to maintain SaO₂. Because oxygen toxicity has now been recognised, clinicians aim to have an infant on the lowest amount of supplemental O₂ possible.

**ii. Pharmacotherapy (caffeine)**

Methylxanthines (caffeine/theophylline/aminophylline) are the main treatment used for infants with recurring apnoea. They are a non-selective antagonist of adenosine receptors and are though to act as a respiratory stimulant by increasing the neural respiratory drive, increasing minute ventilation, increasing CO₂ sensitivity, as well as increasing the strength of diaphragm contractility, however the exact mechanism of how methylxanthines work is unknown (147-149).

Caffeine is now the preferred drug over other methylxanthines. Compared to theophylline, caffeine is just as effective but has a better safety profile (150). It has a longer half-life, meaning it can be given just once a day in preterm infants and it has a higher therapeutic
index, therefore less side effects (such as feed intolerance, hyperactivity, and seizures with theophylline), and no requirement for monitoring by blood tests. Caffeine can still have some side effects however, the most common being tachycardia.

Methylxanthines have been shown to be effective compared to placebo in reducing rates of apnoea short-term, as well as lower rates of death and CLD in the short term (up until discharge from the NICU (151, 152). The long-term effects of caffeine have also been shown to be beneficial. A large multi-centre study: Caffeine therapy for Apnoea of Prematurity (CAP); reported on survival and neurodevelopment at 18-21 months for preterm infants who were randomised to receive either caffeine or placebo for treatment of their AOP while in NICU. In the caffeine group 40.2% of infants died or survived with a neurodevelopmental disability compared with 46.2% in the placebo group (OR 0.77, CI 0.64 to 0.93; \( p = 0.008 \)) (153). Doyle et al. published a study that randomised very preterm infants to receive caffeine or placebo and then analysed magnetic resonance imaging (MRI) performed at one year of age. They found no significant differences between the groups in the amount of white or gray matter abnormality, or in global or regional brain volumes; however, significant differences in diffusion changes were seen that were consistent with improved white matter microstructural development in the group that received caffeine (154).

Very preterm infants (born <32 weeks GA) are often started on caffeine prophylactically soon after birth, while preterm infants born at a later GA may only be started on caffeine if they are noticed to be having apnoea that is thought to be clinically significant. Premature infants generally continue taking caffeine until they are 34-35 weeks PMA. In Wellington NICU, if there are no concerns, an infant would be taken off caffeine at 35 weeks PMA and then routinely monitored for an extra five days. If there are no events documented during these five days they will be taken off monitoring and considered stable from a respiratory perspective.

Doxapram is a respiratory stimulant and is sometimes used to treat refractory apnoea that does not respond to caffeine treatment. There is currently insufficient evidence on its efficacy and safety and advice is that it should be used with caution (155).
2.5.2 Future directions for treatment of apnoea / IH

i. Extended use of caffeine

Rhein et al. investigated the use of extended treatment with caffeine (continued after routine discontinuation of caffeine) for preterm infants (81). Infants were randomised into a routine care group or extended caffeine group. The incidence of IH (defined as time spent <90% SpO\textsubscript{2}) was significantly lower in the extended caffeine group compared to controls until 36 weeks PMA, with no significant differences between groups after infants reached 36 weeks PMA. It is suggested the difference in groups was not seen past 36 weeks GA due to insufficient dosing. This could be due to the study not accounting for the changing caffeine citrate half-life, as its half-life has been shown to decrease with advancing PMA and so more frequent dosing is required (81, 156).

ii. Blood transfusions

Haemoglobin levels in preterm infants can influence the severity of IH in premature infants (15, 157). Red blood cell (RBC) transfusions as treatment for apnoea have been considered for some time, and results from studies have shown reduced rates of apnoea (157-159). Abu Jawdeh et al. published a study in 2014 that accurately recorded IH before and after RBC transfusions in premature infants and found that the frequency and severity of IH was significantly reduced for up to 48 hours after a RBC transfusion in premature infants more than one week old. This study is limited by the short follow up monitoring period of 48 hours and does not assess the more long-term impact of blood transfusions on IH (160).

iii. Kinaesthetic treatments

Physical stimulation is often used to treat individual episodes of apnoea. Other tactile stimulation methods such as oscillating waterbeds have been trialled to reduce the incidence of apnoea and IH. There is no good evidence to date on the efficacy of these methods (161). Bloch-Salisbury et al. recently reported that the use of stochastic mechanosensory stimulation (vibrotactile stimulation from actuators embedded in a mattress) stabilised premature infant respiratory patterns, with a significant decrease in incidence of apnoea and time spent <85% SpO\textsubscript{2} (162).
2.6 Preliminary research

Prior to this study commencing, a pilot study investigating the current use of extended oximetry for premature infants at discharge across New Zealand and Australian NICU’s was undertaken as a summer student project (69).

The study was performed by creating an online survey on the use of pre-discharge oximetry and this was sent to all level three neonatal units in NZ and Australia as well as all level two units in NZ (N = 46). A total of 27 units responded (59%).

Considerable variation was found in how preterm infants are screened by oximetry studies prior to discharge across Australasia and also in how studies are performed and reported. No unit reported routinely performing oximetry at discharge for all preterm infants, and one fifth of units surveyed never perform specific oximetry at discharge. The groups of infants for which units do undertake pre-discharge oximetry varies, with infants discharged on supplemental oxygen the only group routinely receiving pre-discharge oximetry in those units using this test.

The most common brand of oximeter used was Masimo® with PROFOX Associates, Inc. the most common oximetry analysis software. Most oximetry reports generated appeared to be PROFOX Associates, Inc.'s default 'Summary Report', with most units keeping the software’s default settings including the default desaturation definition ('a drop in saturation by 4 or more'). Only 20% of units surveyed manually removed artefact from their recordings. Measures on oximetry reports that quantitate intermittent hypoxia, such as number of desaturation events to SpO₂ of <95% or number of drops in oxygen saturation per hour by 2% or 3% (DSI 2%/3%) were less frequently used compared to mean SpO₂ and time spent <90% SpO₂.

This preliminary research study highlighted areas to focus on such as the editing of oximetry reports. It reported on which groups of infants neonatal units are currently utilising extended oximetry at discharge and also gave insight into which models of oximeters are currently being used as well as how units configure their oximeters and edit their oximetry reports.
2.7 Summary

The pathophysiology of apnoea in premature infants is fundamentally an immature respiratory central nervous system, combined with immature and suboptimal lung function. The clinically concerning part of any ‘apnoea’ or respiratory event is the oxygen desaturation rather than the length of the pause, however the degree or frequency of oxygen desaturation that should be of clinical concern is unknown. There has been some research into the consequences of apnoea in infancy, with limited research into intermittent hypoxia specifically; this research does indicate a correlation with neurodevelopmental outcomes. There have been no reported studies that investigate the effect of these intermittent hypoxic episodes on growth in preterm infants, however theoretically IH may cause increased energy expenditure in combination with a decrease in growth factors which could effect growth. Adult and rat studies have also indicated a possible association. Pulse oximetry is a safe and effective way of continuously measuring oxygen saturations and is now refined with two second averaging times that detect brief drops in oxygen saturations. Some neonatal units in Australasia are utilising this tool to assess preterm infants in anticipation of discharge, however the way these reports are edited and the settings used to perform these recordings varies widely. This current study investigates the incidence of IH at discharge in preterm infants and also looks at the effect of IH on growth rates post-discharge.

2.8 Aims and hypotheses

2.8.1 Aims

This study had two parts, the primary study and a smaller follow up study. For the primary study, all preterm infants were recruited to have a 24-hour oximetry recording performed just prior to their discharge home from the neonatal unit. The primary aim of this study was:

1. To determine normative ranges for measures reported from an ‘at discharge’ 24-hour oximetry study

As the thesis developed, additional factors were considered and two new aims developed:
1. To determine whether there is a clinical difference in raw, automatically edited, and manually edited reports.

2. To determine whether there is any clinical difference in 12-hour ‘overnight’ recordings compared to full 24-hour recordings.

The follow up study included only the very preterm infants (< 32 weeks GA) from the primary study group. Its purposes were:

1. To determine whether intermittent hypoxia, measured by measures reported from 24-hour pre-discharge oximetry recordings (number of > 4% SpO\textsubscript{2} desaturations per hour (DSI 4%), DSI 3%, DSI 4% > 10 seconds and time spent <90% SpO\textsubscript{2}), had an impact on infant post-discharge growth as measured by weight Z-scores.

2. To determine the difference in intermittent hypoxia at one month post-discharge compared to prior to discharge.

This was achieved by following these very preterm infants for one month after discharge to record weekly growth measurements, and performing a repeat 24-hour oximetry recording at home at one-month post discharge.

### 2.8.2 Hypotheses

1. All preterm infants will have high rates of intermittent hypoxia (as measured by DSI 3% and DSI 4%) when discharged home from the neonatal unit and infants born at an earlier GA or discharged at an earlier CGA would have more severe intermittent hypoxia.

2. Very preterm infants with greater intermittent hypoxia at discharge will have a slower rate of growth in the first month post discharge.

3. Levels of intermittent hypoxia in very preterm infants will have decreased one month post-discharge; however there will still be a degree of intermittent hypoxia.
Chapter 3

Oximetry Methodology

3.1 The use of oximetry to measure oxygen saturation

3.1.1 Oximetry

As discussed in the previous chapter, the pathological component of any respiratory pause or ‘apnoea’ in preterm infants is likely to be the level of oxygen desaturation, and possibly the bradycardia, rather than the length of the pause (60). Low oxygen saturations can occur without an accompanying pause in breathing, therefore breathing monitors alone would not pick up all events (163). Oxygen saturation monitors (oximeters), are advancing in technology and can now accurately record an extended period of monitoring. Their ease of use and cost effectiveness compared to a full polysomnography (PSG) means that extended oximetry recordings are becoming a more appealing option when assessing paediatric respiratory stability. These oximetry recordings produce a report that includes many different measures of respiratory instability (see attached examples, appendix A). The default report type generated is the ‘summary report’, which is hard to interpret with no visual graphs. The ‘comprehensive report’ is only printed if a separate tick box is checked and is a simple one page report that summarises the oximetry report as well as having a visual graph of time vs SpO₂ which is quick to interpret and gives you an overall picture of the infant’s oxygen saturations over the recording period. The normative values or significance of these more recently accessible measures of respiratory instability are largely unknown. For these reasons, we used 24-hour oximetry as our tool to assess an infant’s respiratory stability, and to generate normative values for measures on these oximetry reports for preterm infants at discharge home from the neonatal unit.

3.1.2 MasimoSET technology

MasimoSET technology has been shown to be more accurate during motion than other oximeters, with one study giving MasimoSET a performance index (percentage of time in which the SpO₂ is within 7% of control value) of 94%, which was the highest of all 20 oximeters tested, with the next best oximeter being the Agilent Virdia at 84% performance index (164). Other studies have confirmed that MasimoSET technology is the most accurate during motion (165-168). The accuracy of the Masimo Rad – 8 (used for this
study) for SpO$_2$ is reported as $\pm$ 3% for neonates for SpO$_2$ values of 70% - 100% and $\pm$4% for SpO$_2$ values of 60% - 80% for neonates (169).

The averaging time used for this study was two seconds, which is the standard averaging time when set to sleep mode. When not in sleep mode the averaging time is eight seconds. It is important to use a short averaging time as longer averaging times may smooth out short desaturations and underestimate the level of intermittent hypoxia (170, 171).

### 3.2 Dealing with artefact

#### 3.2.1 The problem of artefact

Recordings of physiological data will undoubtedly include some artefact. Artefact in oximetry recordings is often caused by movement and is difficult to avoid. Editing infant oximetry recordings compared to adult recordings is complicated as infant oxygen levels can drop quickly (up to 8% per second), partly due to their small pulmonary reserve (49). This means that when analysing oximetry traces for infants, what would be considered artefact in adults (rapid drops in SaO$_2$) could in fact be true desaturations and the process of editing data becomes a lot more time consuming and uncertain. Oximetry SpO$_2$ readings are often verified by observing the concurrent pulse waveform, if this is regular then the SpO$_2$ reading is taken as correct.

In our study, PROFOX Associates, Inc. software was used to download and report the 24-hour oximetry study. This is by far the most common software package used in Australasia for this purpose (69). This software package does not report a concurrent pulse waveform, only pulse and SpO$_2$ traces. When looking at the recordings, there were many sharp desaturations and some areas where the recording completely dropped out, which was suspicious for artefact. MasimoSET technology states that it is accurate during motion, however much of this presumed artefact seen is likely due to movement as it appears to often coincide with an infant’s cares.

A sample comparison of one infant’s oximetry report produced three different ways; unedited data, automatically edited data by PROFOX, and manually edited data, produced some large differences in at least some measures reported. For example percentage time spent less than 90% SpO$_2$ was 4.1% unedited, 2.5% when manually edited and 2.2% when automatically edited. It was clear that a robust method of editing these data was needed in
order to make the data as accurate and consistent between recordings as possible in order
to confidently define normative values.

There are no guidelines to our knowledge on how to remove artefact from these data and
when talking to leading NZ paediatric respiratory clinicians, neonatologists, and
respiratory technicians who look at these oximetry reports frequently, no one could give
clear advice on how to best edit data, admitting it was mainly guess work, with everyone
spoken to indicating that guidelines are required. In fact, when surveyed, only 20% of
neonatal units manually edit their data at all, with only 40% reporting their software
automatically deletes artefact (69). When assessing the literature, there is also no
consensus on how data were edited for studies on oximetry in neonatal populations (Table
3-1).
Table 3-1: Extended oximetry studies on preterm neonatal populations – editing information

<table>
<thead>
<tr>
<th>Authors (year published)</th>
<th>Software</th>
<th>Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhein et al. (2014)</td>
<td>PROFOX</td>
<td>AUTO</td>
<td>All low signal IQ excluded</td>
</tr>
<tr>
<td>Shah et al. (2014)</td>
<td>PROFOX</td>
<td>AUTO and MANUAL</td>
<td>Episodes of desaturations screened and events which were due to poor signal conductance secondary to motion artefact, changing diapers, feeding or excessive motion were deleted</td>
</tr>
<tr>
<td>Pugalenthi et al. (2013)</td>
<td>Labchart software</td>
<td>None</td>
<td>No editing mentioned</td>
</tr>
<tr>
<td>Rhein et al. (2012)</td>
<td>PROFOX</td>
<td>AUTO and MANUAL</td>
<td>Took out all low signal IQ and all desaturation events were visually confirmed to exclude spuriously low values not identified by the software tool</td>
</tr>
<tr>
<td>Lee et al. (2011)</td>
<td>MANUAL</td>
<td></td>
<td>Suspect readings that occurred from unclear causes were retained by introducing a weighting function to down-weight them. This weighted each measurement between 70–100% by 1, while measurements between 0–69% were linearly weighted between 0 and 1</td>
</tr>
<tr>
<td>Harigopal et al. (2011)</td>
<td>PODS software</td>
<td>MANUAL</td>
<td>Deleted obvious artefact (defined as deflection to zero of both SpO2 and heart rate tracings)</td>
</tr>
<tr>
<td>Beresford et al. (2005)</td>
<td>No software mentioned</td>
<td>None</td>
<td>No editing mentioned</td>
</tr>
<tr>
<td>Ng et al. (1998)</td>
<td>No software mentioned</td>
<td>MANUAL</td>
<td>Deleted obvious artefact (defined as deflection to zero of both SpO2 and heart rate tracings)</td>
</tr>
<tr>
<td>Richard et al. (1993)</td>
<td>No software mentioned</td>
<td>None</td>
<td>No editing mentioned</td>
</tr>
<tr>
<td>Spear et al. (1992)</td>
<td>No software mentioned</td>
<td>MANUAL</td>
<td>The pulse signal from the oximeter was recorded to exclude movement artefact</td>
</tr>
<tr>
<td>Poets et al. (1991)</td>
<td>No software mentioned</td>
<td>MANUAL</td>
<td>Traces printed onto graph paper and analysed by two doctors who visually took out low signal artefact often associated with movement</td>
</tr>
</tbody>
</table>
3.2.2 PROFOX Associates, Inc. software: options for editing artefact

PROFOX Associates, Inc. software reports ‘low signal IQ’ which is indicative of when the signal is of low quality and therefore potentially not a true reading. How PROFOX calculates ‘low signal IQ’ is not explicitly defined in PROFOX’s manual or information sheets. It is stated that signal IQ is a signal identification and quality indicator of the pulse rate and oximetry data and measures signal quality using ‘advanced signal processing algorithms’ to create a confidence level, with ‘low signal IQ’ being displayed when there is <30% signal quality (172, 173). They state however, that a reading with a ‘low signal IQ’ is still highly likely to be an accurate recording (173). If the signal is completely disrupted, the recording shows nothing (there is just a gap in the data).

The papers Masimo reference in their Signal IQ technology information document (173) give inconsistent statements. One paper states a 75% specificity and a 100% sensitivity of ‘low signal IQ’ to pick up false desaturations (172), with another stating that ‘low signal IQ’ displays in 80% of false desaturations to less than 85% SpO2, meaning 20% of false desaturations to less than 85% SpO2 would not display ‘low signal IQ’ (174). Another independent paper studied 11 preterm infants in NICU and found that Masimo oximeters have a sensitivity of picking up true desaturations of 72.2 %, and a high false alarm rate at 51% (ratio of false positive alarms and sum of true positive and false positive alarms). These rates were comparable to the other oximeter studied (Nellcor. Tyco Healthcare, Pleasanton California) (175).

The PROFOX software, allows the operator to automatically delete all areas where there is ‘low signal IQ’. There is also a manual editing section, enabling the operator to magnify sections to a minimum of five-minute intervals and manually remove any sections that appear to be artefact. Following editing, there is the option to ‘scan for aberrant data’, and delete these points. ‘Aberrant data’ is defined as any saturation data point where there is a difference in more than 10% SpO2 from the previous and subsequent data point, or a difference in twenty bpm from prior or subsequent data points for pulse (each data point is 2 seconds apart) (169).

The information available about PROFOX’s ‘low signal IQ’, and deleting all ‘low signal IQ’ as an artefact editing tool is not convincing as an accurate way of editing artefact from
data. We believed manually editing the data, using specific rules so consistency between recordings would be maintained, would be a better way of accurately editing artefact from a recording. We hypothesised that the measures reported in an oximetry report generated after manually editing data would be significantly different to reports from unedited or automatically edited data, and therefore be of consequence to the clinician interpreting the report.

3.2.3 Deriving rules for manually editing data

The aim was to develop rules for manual editing of oximetry data that would give reproducible results when applied to the data. We created rules with advice from experts that edit infant reports regularly and focused on practical rules that made logical sense. Three rules were created. The rules were applied with the data expanded so that 30-minute intervals were displayed on the screen. When applying rule number 3, 5-minute intervals were used to give more precise editing of an individual desaturation. The rules used were as follows:

1) Delete any data at the very start or end of the trace until it reaches baseline. (So for the start of the trace, delete all data before a stable baseline is reached for at least 30 seconds)

2) Any areas where the data completely cuts out (either SpO₂ or pulse), delete data before and after this gap until back to baseline on both sides of the data gap.

3) At the end use the 'scan for aberrant data' function, and then choose to edit a larger area rather than just delete that point. Delete the whole desaturation that includes this aberrant data point, or associated desaturation with aberrant pulse data point. If this function identifies a desaturation that is part of a pattern of desaturations, do not delete the desaturation.

Examples of applying these rules are displayed in figures 3-1 to 3-6.

To validate these three rules, five infant discharge oximetry reports were picked at random. These three rules were applied to these five reports, and then a professional who edits infant oximetry reports regularly edited these same five reports manually according to their normal process of editing them (no written rules followed). The results from the comparison of reported measures from these two methods are produced in table 3-1. As you can see, the manual rules created agreed with the expert edit. Most measures had a
median 0% difference, with the seven that did have some difference only ranging from 1% - 3.6% difference in value.

To determine the significance of editing reports, each discharge oximetry report was produced three alternate ways and then compared for differences (see section 4 for results).

1) Unedited: No change to original data
2) Automatically edited: PROFOX software’s options of ‘delete all low signal IQ’ used, and scan for any aberrant points, and deleted the individual point.
3) Manually edited: three manual rules applied (see 3.2.3)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median raw difference</th>
<th>Median percentage difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(range)</td>
<td>(range)</td>
</tr>
<tr>
<td>Total recording time (minutes)</td>
<td>1 (0 - 7)</td>
<td>0% (0 - 0)</td>
</tr>
<tr>
<td>Total valid recording time (minutes)</td>
<td>11 (2 - 64)</td>
<td>1% (0 - 4)</td>
</tr>
<tr>
<td>Highest pulse</td>
<td>0 (0 - 2)</td>
<td>0% (0 - 1)</td>
</tr>
<tr>
<td>Lowest pulse</td>
<td>0 (-6 - 44)</td>
<td>0% (0 - 42)</td>
</tr>
<tr>
<td>Mean pulse</td>
<td>0 (0 - 2)</td>
<td>0% (0 - 1)</td>
</tr>
<tr>
<td>Highest SpO₂</td>
<td>0 (0 - 0)</td>
<td>0% (0 - 0)</td>
</tr>
<tr>
<td>Lowest SpO₂</td>
<td>0 (-9 - 0)</td>
<td>0% (0 - 14)</td>
</tr>
<tr>
<td>Mean SpO₂</td>
<td>0 (0 - 0.2)</td>
<td>0% (0 - 0)</td>
</tr>
<tr>
<td>1SD SpO₂</td>
<td>0.1 (0 - 0.5)</td>
<td>3.6% (0 - 20)</td>
</tr>
<tr>
<td>Time &lt;90% SpO₂</td>
<td>0.1 (0 - 0.9)</td>
<td>2% (0 - 50)</td>
</tr>
<tr>
<td>Time &lt;70% SpO₂</td>
<td>0 (0 - 0)</td>
<td>0% (0 - 0)</td>
</tr>
<tr>
<td>Time &lt;88% SpO₂</td>
<td>0.1 (0 - 0.7)</td>
<td>3% (0 - 54)</td>
</tr>
<tr>
<td>DSI 4%</td>
<td>- 0.2 (-3 - 1.3)</td>
<td>1% (0 - 3)</td>
</tr>
<tr>
<td>DSI 3%</td>
<td>- 0.2 (-3.5 - 1.2)</td>
<td>1% (0 - 3)</td>
</tr>
<tr>
<td>DSI 4% &gt;10secs</td>
<td>0.2 (0.1 - 1.6)</td>
<td>2% (2 - 19)</td>
</tr>
</tbody>
</table>
Figure 3-1: Rule 1, before edit

Figure 3-2: Rule 1, after edit
Figure 3-3: Rule 2, before edit

Figure 3-4: Rule 2, after edit
Figure 3-5: Rule 3, desaturation to be deleted

Figure 3-6: Rule 3, desaturation identified that would NOT be deleted
Values for 24-hour oximetry at discharge

4.1 Methods

4.1.1 Ethics

Ethical approval was gained from the Otago Human Ethics Committee, reference H15/013 (Appendix B).

4.1.2 Participants and consent

Infants were recruited from the Wellington Hospital regional, level three neonatal intensive care unit (NICU).

Eligible infants were born at less than 37 weeks gestational age and to be discharged home from the unit to the Wellington region.

Exclusion criteria were:

- Likelihood of transfer to another hospital prior to discharge home.
- Major congenital anomalies that interfere with cardiorespiratory function, such as lung malformations or structural abnormalities of the airways.

The recruitment period ran from 2nd March 2015 to 11th September 2015. Posters were put up in the unit advertising the study to parents and information was distributed to all staff. Parents of all eligible infants who were to be discharged home from Wellington NICU during the recruitment period were approached and given additional information about the study. Infants were included in the study if their parents gave written consent.

4.1.3 Clinical information collected

Clinical information about each infant enrolled in the study was collected from the infant’s written medical notes in NICU and their discharge summary. Sex and ethnicity of the infant was recorded, as well as information on the infant’s antenatal period, birth/resuscitation, postnatal course in NICU, and current state at the time the discharge
oximetry recording was performed. A detailed list of clinical information collection can be found in Appendix C.

4.1.4 Materials

24-hour oximetry was used to measure infant respiratory stability at discharge. Devices used were one of two SET Rad-8 oximeters (Masimo Corp, Irvine CA). The oximeters were set to ‘sleep mode’, which meant the screen was blank and alarms were turned off so as to not interfere with the infant’s normal care. The averaging time was two seconds. The Masimo Rad-8 oximeters have a 2 second resolution time meaning a data point is recorded every 2 seconds. Before each recording any previous data were cleared from the oximeter.

4.1.5 Data collection process

As we were interested in infant respiratory stability at the time they were deemed clinically ‘stable’ to be discharged home by current NICU protocol, we aimed to perform the 24-hour oximetry as close to discharge as possible. We also ensured the infant had had no immunisations in the 48 hours prior to the study as immunisations have been shown to affect cardiorespiratory stability (176-178). All infants were placed to sleep on their back.

At a time of day that was convenient, often coinciding with infant routine cares, the oximeter probe (MasimoSET LNOP Neo-L adhesive sensor, for <3kg or >40kg) was connected to the infant’s foot (right or left) (Masino instructions for use (169)) on the outer fleshy part, ensuring the LED emitter and sensor lined up. One sensor wrap was placed around the sensor and one on the leg to keep any outside light from affecting the sensor and to also help keep the sensor in place. The signal was checked and then the oximeter left to record data for 24 hours. A form was left with the infant for the parents and/or nurses to document the time of any feeds, cares, baths or disturbances to help with editing data.

Following completion of the 24-h recording period, data were downloaded onto a laptop using PROFOX Associates, Inc. software (Escondido, United states).
Figure 4-1: Infant probe placement

Figure 4-2: Infant probe placement with sensor wrap
4.1.6 Data editing

Comparison of three different ways of editing oximetry reports

Each 24-hour discharge oximetry report was printed in three forms:

**Raw:** The data were not edited in any way

**Auto:** The data were edited automatically using the PROFOX software options
- ‘delete all low signal IQ’
- ‘scan for aberrant points’ (and deleted each point)

**Manual:** The data were edited manually according to the following rules (see Section 3.2)
- Delete any data at the very start or end of the trace until it reaches baseline.
- Any areas where the data completely cuts out (either SpO₂ or pulse), delete data until it reaches baseline on either side of this gap.
- At the end use the 'scan for aberrant data' function, and chose to edit a larger area rather than just delete that point. Delete the whole desaturation that includes this aberrant data point, or associated desaturation with aberrant pulse data point, **unless** the desaturation is part of a section of similar desaturations.

Editing oximetry reports to represent an 'overnight' study

Each 24-hour discharge oximetry report was also edited to resemble a 12-hour 'overnight' study. This was done to determine whether overnight recordings were a comparable alternative to a full 24-hour study. A 12-hour report was generated by selecting just the overnight portion of the oximetry recording from 8:00pm to 8:00am and saving it as a new report.

4.1.7 Data analysis

Data were entered into SPSS and all statistical analysis was done in this software. As the majority of variables were not normally distributed, medians and IQR or full range are presented. Exact Friedmans ANOVA was used to compared three ways of editing oximetry reports and Wilcoxon signed rank test is used to compare 24 with 12 hour oximetry.
4.2 Results

4.2.1 Demographics

i. Recruitment

During the recruitment period (2\textsuperscript{nd} March 2015 - 11\textsuperscript{th} September 2015) there were 169 preterm infants discharged from Wellington NICU, 80 of these were transferred to another unit prior to discharge home. Of the 89 infants that were discharged home from Wellington NICU, 28 were not approached due to either complex social issues or limited time as many of these infants were only admitted to the unit for a few days.

Three infants were not approached as they had serious cardiac abnormalities, therefore excluding them from our study. Three infants died while in the unit. The remaining 55 infants families were approached to participate in the study. Of these, 46 (83.6\%) families consented to being involved in the study. The main reason for refusal was that the family did not want their baby to go back onto monitoring again. Two families withdrew from the study when it came time to do the 24-hour oximetry and three infants were missed due to early discharge. Two infants had the oximeter removed partway through the study, with only 2.5 and 8 hours total recording time, and therefore were excluded from analysis. Another family withdrew from the study part way through the oximetry recording (reason unknown), so were also excluded from analysis.
Figure 4-3: Recruitment process

**ii. Overall subject variables**

General demographics for the group of 38 participants included in the final analysis are presented in table 4-1. There were slightly more females (55.3%) than males (44.7%). Ethnicity distribution was diverse, with a large proportion (11/38, 28.9%) of participants identifying as NZ Maori and/or Pacific Islander. There were five sets of twins that participated in the study, and another two sets of twins where only one of the twins participated. There were also two infants from a group of triplets that participated.
Table 4-1 General demographics of participants included in analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>N = 38</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (55.3)</td>
</tr>
<tr>
<td><em><em>Ethnicity</em>, n (%)</em>*</td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>23 (60.5)</td>
</tr>
<tr>
<td>NZ Maori</td>
<td>8 (21.1)</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>Indian</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Chinese</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>Other European</td>
<td>5 (13.2)</td>
</tr>
<tr>
<td>Multiple birth, n (%)</td>
<td>14 (36.8)</td>
</tr>
<tr>
<td>GA at birth (weeks), median (range)</td>
<td>32.5 (24 - 36)</td>
</tr>
</tbody>
</table>

*participants could identify as more than one ethnicity

**iii. Antenatal variables of participants**

There were 12/38 (31.6%) participants whose mothers did not receive steroids prior to their birth, 44.7% that received a full dose (two doses of steroids prior to birth), 18.4% who only receiving a partial dose (normally one dose too close to birth to administer a second dose) and 5.2% receiving multiple doses of steroids. In the extreme to very preterm infants subgroup (<32 week GA), only 3/12 (25%) of participant mothers did not receive steroids prior to their birth. There were six (15.8%) infants whose mothers smoked, and two cases of chorioamnionitis, both of which were suspected rather than confirmed on histology.

**iv. Birth and resuscitation variables of participants**

The birth and resuscitation variables for all participants are summarised in table 4-2. As well as presenting data for all participants, two subgroups are presented: extremely and very preterm infants (<32 weeks GA), and moderate to late preterm infants (≥32 weeks GA). The majority of births were by caesarean section, with one set of twins being born electively at 36 weeks GA, and the rest being born by emergency caesarean section. Of all the participants, there were four born small for gestational age (SGA) (defined as <10% centile birth weight for GA), all in the moderate to late preterm group. All extreme to very
premature infants needed some form of resuscitation at birth, with 50% of this group requiring endotracheal intubation.

Table 4-2 Birth and resuscitation variables of participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>&lt; 32 weeks GA (n = 12)</th>
<th>≥32 weeks GA (n = 26)</th>
<th>All (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of delivery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caesarean section</td>
<td>8 (66.6)</td>
<td>16 (61.5)</td>
<td>24 (61.2)</td>
</tr>
<tr>
<td>Normal vaginal delivery</td>
<td>4 (33.3)</td>
<td>10 (38.5)</td>
<td>14 (36.8)</td>
</tr>
<tr>
<td>Birth weight (grams), mean (SD)</td>
<td>1243 (373)</td>
<td>2108 (420)</td>
<td>1835 (541)</td>
</tr>
<tr>
<td>Birth weight &lt;10th centile, n (%)</td>
<td>0 (0)</td>
<td>4 (15.4)</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Birth head circumference (cm), mean (SD)</td>
<td>26.8 (2.48)</td>
<td>31.4 (1.59)</td>
<td>29.9 (2.8)</td>
</tr>
<tr>
<td>Birth length (cm), mean (SD)</td>
<td>38.2 (3.74)</td>
<td>43.6 (2.68)</td>
<td>41.9 (3.9)</td>
</tr>
<tr>
<td>APGAR*, median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 minute</td>
<td>6.5 (2-9)</td>
<td>8 (3-9)</td>
<td>8 (2-9)</td>
</tr>
<tr>
<td>5 minutes</td>
<td>8 (7-10)</td>
<td>9 (6-10)</td>
<td>9 (6-10)</td>
</tr>
<tr>
<td>10 minutes</td>
<td>10 (9-10)</td>
<td>10 (8-10)</td>
<td>10 (8-10)</td>
</tr>
<tr>
<td>Resuscitation at birth, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil required</td>
<td>0 (0)</td>
<td>7 (26.9)</td>
<td>7 (18.4)</td>
</tr>
<tr>
<td>Inflation breaths only</td>
<td>0 (0)</td>
<td>1 (3.85)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>IPPV or CPAP (total)</td>
<td>12 (100)</td>
<td>18 (69.2)</td>
<td>30 (78.9)</td>
</tr>
<tr>
<td>With oxygen</td>
<td>11 (91.7)</td>
<td>14 (53.8)</td>
<td>25 (65.8)</td>
</tr>
<tr>
<td>Required intubation</td>
<td>6 (50)</td>
<td>2 (7.7)</td>
<td>8 (21)</td>
</tr>
</tbody>
</table>

* n = 37 (ALL), n = 25 (>32 weeks group), as one infant born at home so no APGAR scores available

v. Course of NICU stay

The group of participants overall had an uneventful NICU stay. The >32 weeks GA subgroup had few complications, with just one requiring surgery for bilateral inguinal
hernia and another infant that had gastro-oesophageal reflux requiring medication. The median (range) highest SBR during an infant’s stay (all infants) was 233 (99-363).

In the < 32 weeks GA subgroup there were 2/12 (16.6%) infants that had an IVH, both grade one, and 4/12 (33.3%) infants that required treatment for a PDA, with two only needing one dose of indomethacin, one needing four doses and one needing six. In this subgroup there were 5/12 (41.7%) infants that had ROP, with four being stage one and one classed at stage three that required laser therapy. Of the 12 infants in this subgroup, five (13.1%) required blood transfusions, with four infants only needing one or two transfusions and one infant needing ten. There was only one recorded case of sepsis (confirmed by blood culture).

**vi. Respiratory variables**

Table 4-3 summarises the respiratory course of all participants and the two subgroups. There was only one infant requiring ventilation by endotracheal tube and this infant was went on to develop CLD. All infants born <32 weeks received caffeine, while only 23.1% of infants in the >32 GA group received caffeine. The median PMA that infant monitoring was stopped was 36 weeks and did not vary between subgroups. Although the minimum time that infants were monitored after stopping caffeine was five days, the median time monitored was longer at nine days. Of the <32 weeks GA subgroup, 6/12 (50%) had at least one Masimo 24-hour pulse oximetry study which was downloaded and reported during their NICU stay, with a total of 9/38 (23.7%) of all infants. Four had this done more than two weeks prior to discharge, 2/9 had this done as a 'fit to fly' test as they were flying home (overseas). Just three of the 38 study infants (7.9%) had the Masimo 24-hour recording done as an assessment for respiratory stability for discharge.

**vii. Participant status at time of discharge oximetry study**

The 24-hour oximetry study was completed as close as possible to the infant’s discharge home. Most infants (52.6%) were discharged home on the same day as completion of their 24-hour oximetry. All but one infant were discharged home within four days of completing the oximetry study (median 0 days, range (0-8)). At the time of the 24-hour oximetry study, infants were generally well as they were about to be discharged home. Variables are described in table 4-4. Postmenstrual age at the time of study varied from 35 to 42 completed weeks. There were two infants who had monitoring from a hospital pulse
oximeter at the same time as the study 24-hour pulse oximetry recording. One of these infants was the infant for whom there was clinical concern about apnoea, and the other was an infant on supplemental oxygen who still had continuous pulse oximetry monitoring and went on to be discharged home with a pulse oximeter.
Table 4-3 Respiratory course of participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>&lt; 32 weeks GA (n = 12)</th>
<th>≥32 weeks GA (n = 26)</th>
<th>All (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required <strong>endotracheal ventilation</strong> during NICU stay*, n (number of days ventilated)</td>
<td>1 (15)</td>
<td>0 (0)</td>
<td>1 (15)</td>
</tr>
<tr>
<td>Required <strong>CPAP</strong> during NICU stay*, n (%)</td>
<td>9 (75.0)</td>
<td>5 (19.2)</td>
<td>14 (36.8)</td>
</tr>
<tr>
<td>Days on CPAP*</td>
<td>21 (2-68)</td>
<td>6 (4-9)</td>
<td>8 (2 - 68)</td>
</tr>
<tr>
<td>Required <strong>additional oxygen</strong> during NICU stay*, n (%)</td>
<td>11 (91.7)</td>
<td>8 (30.8)</td>
<td>19 (50.0)</td>
</tr>
<tr>
<td>Days on oxygen*</td>
<td>38 (2-124)</td>
<td>6.5 (2-18)</td>
<td>10 (2 - 124)</td>
</tr>
<tr>
<td>Received <strong>caffeine</strong>, n (%)</td>
<td>12 (100)</td>
<td>6 (23)</td>
<td>18 (47)</td>
</tr>
<tr>
<td>Days on caffeine</td>
<td>41 (19-86)</td>
<td>20 (6-25)</td>
<td>26 (1-86)</td>
</tr>
<tr>
<td>PMA when caffeine stopped (weeks)</td>
<td>34+5</td>
<td>35+1</td>
<td>34+6</td>
</tr>
<tr>
<td>(33+6 - 38+1)</td>
<td>(34+5 - 36+2)</td>
<td>(33+6 - 38+1)</td>
<td></td>
</tr>
<tr>
<td>Days on monitoring#</td>
<td>51 (25 - 124)</td>
<td>12 (0 - 34)</td>
<td>24.5 (0 - 124)</td>
</tr>
<tr>
<td>PMA when monitoring discontinued (weeks)$</td>
<td>36+3</td>
<td>36+1</td>
<td>36</td>
</tr>
<tr>
<td>(34+5 - 42+1)</td>
<td>(35+4 - 39+2)</td>
<td>(34+5 - 42+1)</td>
<td></td>
</tr>
<tr>
<td>Days monitoring after caffeine stopped</td>
<td>8.5 (5 - 38)</td>
<td>9 (5-28)</td>
<td>9 (5-38)</td>
</tr>
<tr>
<td>Received Massimo study during NICU stay, n (%)</td>
<td>6 (50.0)</td>
<td>3 (11.5)</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>CLD</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are median (range) unless stated.

*Only including infants with > 1 day on respiratory support (excluding resuscitation at birth)

# Either full ECG and oxygen saturation monitoring or pulse oximetry only

$ n = 35 (All), n = 23 (>32 weeks GA) (only including infants that had monitoring)
<table>
<thead>
<tr>
<th>Variables</th>
<th>Number (% - unless stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>(n = 38)</td>
</tr>
<tr>
<td>PMA (weeks), median (range)</td>
<td>37+1 (35+6 – 42+5)</td>
</tr>
<tr>
<td>Weight (grams), median (range)*</td>
<td>2487 (1806 - 3900)</td>
</tr>
<tr>
<td>Method of feeding n (%)</td>
<td></td>
</tr>
<tr>
<td>Breast only</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>Bottle only</td>
<td>7 (18.4)</td>
</tr>
<tr>
<td>Breast (mainly) and bottle top ups</td>
<td>22 (57.9)</td>
</tr>
<tr>
<td>Bottle and NG top ups</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Type of milk</td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>19 (50.0)</td>
</tr>
<tr>
<td>Formula</td>
<td>5 (13.2)</td>
</tr>
<tr>
<td>Formula and breast milk</td>
<td>14 (36.8)</td>
</tr>
<tr>
<td>Most recent Hb (g/L), mean (SD)</td>
<td>134.1 (36.2)</td>
</tr>
<tr>
<td>Number of days since most recent Hb, mean (SD)</td>
<td>4.2 (3.8)</td>
</tr>
<tr>
<td>Clinical concern for apnoea at time of study</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>On oxygen</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Currently monitored#</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Time from study to discharge (days), median (range) $</td>
<td>0 (0-8)</td>
</tr>
</tbody>
</table>

* n = 36

#Masimo

$From end of 24 hour oximetry until discharge home
4.2.2 Results of 24-hour discharge oximetry

i. Comparison of oximetry measures from unedited, automatically edited and manually edited data

Valid recording time

Table 4-5 Total valid recording time

<table>
<thead>
<tr>
<th></th>
<th>Unedited</th>
<th>Auto</th>
<th>Manual</th>
</tr>
</thead>
</table>

The amount of total valid recording time remaining after editing differed significantly between the three ways of editing $X^2 (2, N=38) = 76.00, p = < 0.0001$. Automatically and manually edited reports always had less valid recording time than raw data, and auto always had less valid recording time than manual. Automatically editing the data reduced the median valid recording time by 1 hour 42 minutes, while manually editing the data only reduced the median valid recording time by 13 minutes.

Oximetry measures

Table 4-6 summarises the median value for each oximetry measure, presented for each of the three ways of editing the data: no editing (Raw), edited only by the automatic function in PROFOX (Auto), and manually edited (Manual). Based on the exact Friedmans ANOVA test, there are significant differences between the different ways of editing for all oximetry measures listed. Pairwise Freidmans test (adjusted for multiple comparisons using $p = <0.017$) were performed to see where the differences lay (table 4-7). For the majority of measures, manually editing produced more severe measures of intermittent hypoxia (e.g a higher DSI 4%). The mean $\text{SpO}_2$ and percentage time spent below 90% $\text{SpO}_2$ didn’t change significantly between the two ways of editing.
Table 4-6 Comparison of variables after different editing methods

<table>
<thead>
<tr>
<th>Measures</th>
<th>Raw</th>
<th>Auto</th>
<th>Manual</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SpO$_2$ (%)</td>
<td>97.8 (97.1 – 98.7)</td>
<td>97.9 (97.2 – 98.8)</td>
<td>97.9 (97.3 – 98.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lowest SpO$_2$ (%)</td>
<td>60.0 (45.5 – 66.0)</td>
<td>61.5 (50.8 – 69.8)</td>
<td>65.0 (52.3 – 76.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time spent &lt;90 SpO$_2$ (%)</td>
<td>1.95% (0.80 – 4.68)</td>
<td>1.30% (0.70 – 4.13)</td>
<td>1.25% (0.70 – 4.20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time spent &lt;80 SpO$_2$ (%)</td>
<td>0.2% (0.1 – 0.6)</td>
<td>0.2% (0 – 0.4)</td>
<td>0.1% (0 – 0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DSI 4% (events/h)</td>
<td>53 (34 – 76)</td>
<td>51 (31 – 74)</td>
<td>53 (33 – 75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DSI 3% (events/h)</td>
<td>80 (55 – 105)</td>
<td>77 (53 – 103)</td>
<td>80 (54 – 105)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DSI 4% &gt; 10secs (events/h)</td>
<td>13.6 (8.9 – 17.8)</td>
<td>10.7 (7.0 – 15.1)</td>
<td>13.5 (8.6 – 17.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean pulse (bpm)</td>
<td>157 (148 – 163)</td>
<td>156 (147 – 161)</td>
<td>157 (148 – 163)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Highest pulse (bpm)</td>
<td>214 (208 – 221)</td>
<td>212 (203 – 221)</td>
<td>213 (207 – 221)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lowest pulse (bpm)</td>
<td>39 (27 – 57)</td>
<td>54 (31 – 68)</td>
<td>91 (80 – 102)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Exact friedman’s ANOVA used (df =2)

All median (IQR)
Table 4-7 Difference between manual and automatic editing

<table>
<thead>
<tr>
<th>Difference</th>
<th>Manual improved value from Auto (p &lt; 0.017)</th>
<th>Manual value worse than Auto (p &lt; 0.017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SpO₂</td>
<td>Mean Pulse</td>
<td>DSI 4%</td>
</tr>
<tr>
<td>Lowest SpO₂</td>
<td>Time spent &lt;80% SpO₂</td>
<td>DSI 3%</td>
</tr>
<tr>
<td>Time spent &lt;90% SpO₂</td>
<td>Lowest pulse</td>
<td>DSI 4% &gt;10 secs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Highest Pulse</td>
</tr>
</tbody>
</table>

Percentage difference of editing measures compared to raw

Although all oximetry measures were significantly different when edited the three ways, some of the actual oximetry measures values only differed by a small amount that is unlikely to be clinically significantly different, e.g. median highest pulse: 213.5 (raw), 212 (auto), 213 (manual). To help visualise how significant the difference in the oximetry values were after editing, the percentage difference for the raw compared to each the automatically edited data, and the manually edited data was calculated: (AUTO-RAW)/RAW * 100 and (MANUAL-RAW)/RAW * 100.

The change in value after editing with either automatically, or manually edited data for median SpO₂, lowest SpO₂, DSI 4%, DSI 3%, median pulse, and highest pulse was less than 5%. It is unlikely that a change in value of less than 5% from the original value would have clinical implications, so for these measures, editing oximetry reports (either automatically or manually) is unlikely to make a clinically significant difference.

Time spent below 90% SpO₂, and DSI 4% > 10 seconds had the greatest change in value from the raw data after automatically editing, with more than 10% changes. For manual editing, <90 SpO₂, <80 SpO₂ and lowest pulse had more than 5% changes from the raw data. These differences are illustrated in Table 4-8.
Table 4-8. Comparison of variables after different editing

<table>
<thead>
<tr>
<th>Measures</th>
<th>Auto Median (raw data)</th>
<th>Change from raw *</th>
<th>Percentage change from raw, %**</th>
<th>Manual Change from raw*</th>
<th>Percentage change from raw, %**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SpO₂ (%)</td>
<td>97.8</td>
<td>0.1</td>
<td>-0.1</td>
<td>0.1</td>
<td>-(0 - 0.2)</td>
</tr>
<tr>
<td>Lowest SpO₂ (%)</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time spent &lt;90 SpO₂ (%)</td>
<td>1.95</td>
<td>-0.2</td>
<td>-13.8</td>
<td>-0.2</td>
<td>-(0 - 0.6)</td>
</tr>
<tr>
<td>Time spent &lt;80 SpO₂ (%)</td>
<td>0.2</td>
<td>-0.1</td>
<td>-2.1</td>
<td>-0.1</td>
<td>-(0 - 0.6)</td>
</tr>
<tr>
<td>DSI 4% (events/h)</td>
<td>53.4</td>
<td>-1.6</td>
<td>-3</td>
<td>-0.1</td>
<td>-(0 - 1.9)</td>
</tr>
<tr>
<td>DSI 3% (events/h)</td>
<td>79.8</td>
<td>-1.7</td>
<td>-2.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DSI 4% &gt;10 secs (events/h)</td>
<td>13.6</td>
<td>-2.5</td>
<td>-18.4</td>
<td>-0.1</td>
<td>-(0 - 1.1)</td>
</tr>
<tr>
<td>Mean pulse (bpm)</td>
<td>156.5</td>
<td>-1</td>
<td>-0.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Highest pulse (bpm)</td>
<td>213.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lowest pulse (bpm)</td>
<td>39</td>
<td>0</td>
<td>0</td>
<td>48.5</td>
<td>101.9</td>
</tr>
</tbody>
</table>

* Median change (range)

**Median (IQR)

Summary

Overall, it would appear that for the majority of measures, the editing of oximetry reports, either automatically or manually, would be unlikely to result in any clinically significant differences. Measures that are more likely to change by a larger percentage are lowest pulse/lowest SpO₂, time spent below 90% and DSI4% >10 seconds, with only DSI 4% >10 and lowest pulse having a >10% percentage difference between automatically editing and
manual editing. Automatically editing underestimated the severity of DSI4% >10 s by a median of 17% less than manual editing, and overestimated (101.9%) how low the pulse nadir was compared with manual editing. For DSI 4%, although this is a 17% median difference, the actual median value of 10.7 events/h compared to 13.5 is marginal as to whether this would be considered clinically significant. Therefore, as for the majority of measures there is no clinically significant difference between manual editing and automatically editing, and automatically editing often does help edit artefact from results, from here on, all oximetry results presented will be those that were automatically edited.

**ii. 24-hour oximetry (automatically edited) – measures of intermittent hypoxia**

Figures 4.4 – 4.7 show the spread of values for four measures of intermittent hypoxia. The majority of infants (79%) had on average, between 40 and 119 3% desaturation events per hour, or one or two episodes per minute (figure 4.1). When looking at 4% desaturations longer than 10 seconds, the majority of infants (76%) had six to twenty episodes per hour (figure 4.3). A higher value in any of the four measures was correlated with higher values for the other three measures. (All statistically significant $p = < 0.004$ (spearman’s correlation coefficient)) (See table 4-9)

![Figure 4-4 Number of 3% desaturations per hour (DSI 3%)](imageurl)
Figure 4-5 Number of 4% desaturations per hour (DSI 4%)

Figure 4-6 Number of 4% desaturations that lasted longer than 10 seconds (per hour)
Table 4-9 Inter-correlation between intermittent hypoxia measures

<table>
<thead>
<tr>
<th></th>
<th>DSI 3%</th>
<th>DSI 4%</th>
<th>DSI 4% &gt;10 seconds</th>
<th>Time spent &lt;90% SpO\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI 3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r = 0.976</td>
<td></td>
<td></td>
<td></td>
<td>r = 0.610</td>
</tr>
<tr>
<td>p &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>DSI 4%</td>
<td></td>
<td></td>
<td></td>
<td>r = 0.852</td>
</tr>
<tr>
<td>r = 0.494</td>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>p = 0.003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSI 4% &gt;10 seconds</td>
<td></td>
<td></td>
<td></td>
<td>r = 0.470</td>
</tr>
<tr>
<td>r = 0.470</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.004</td>
</tr>
<tr>
<td>p &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

r = spearman’s rank correlation coefficient (two tailed)

iii. Relationship between infant characteristics and 24-hour oximetry data.

Figure 4.8 shows the negative relationship between DSI 4% >10 seconds and PMA, of the four intermittent hypoxia measures. This was the only significant correlation found. When plotting age in days against intermittent hypoxia measures, again only DSI 4% > 10 seconds was significant.
The number of days on caffeine, birth weight, discharge weight and highest SBR during NICU stay were not significantly correlated with any of the intermittent hypoxia measures. Days spent on $O_2$, GA, and most recent Hb were all correlated with some but not all of the intermittent hypoxia measures, presented in table 4-10 (significance value $p < 0.05$).

Table 4.10 Infant characteristics correlation with intermittent hypoxia at discharge

<table>
<thead>
<tr>
<th></th>
<th>Days on $O_2$</th>
<th>Most recent Hb</th>
<th>GA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI 3%</td>
<td>$r = 0.335$</td>
<td>$r = -0.050$</td>
<td>$r = -0.313$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.040$</td>
<td>$p = 0.766$</td>
<td>$p = 0.056$</td>
</tr>
<tr>
<td>DSI 4%</td>
<td>$r = 0.401$</td>
<td>$r = -0.132$</td>
<td>$r = -0.379$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.013$</td>
<td>$p = 0.430$</td>
<td>$p = 0.022$</td>
</tr>
<tr>
<td>DSI 4% &gt;10seconds</td>
<td>$r = 0.002$</td>
<td>$r = 0.418$</td>
<td>$r = 0.157$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.989$</td>
<td>$p = 0.009$</td>
<td>$p = 0.347$</td>
</tr>
<tr>
<td>Times spent &lt;90%</td>
<td>$r = 0.406$</td>
<td>$r = -0.082$</td>
<td>$r = -0.327$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.011$</td>
<td>$p = 0.623$</td>
<td>$p = 0.045$</td>
</tr>
</tbody>
</table>

$r =$spearman's rank correlation coefficient (two tailed)
Intermittent hypoxia, measured by the four measures listed above did not differ significantly when Pacific Island and Maori ethnicity as a sub group were compared with other ethnicities. Intermittent hypoxia when compared by subgroups of smoking during pregnancy or being male or female also did not differ significantly. The need for oxygen during resuscitation at birth was associated with significantly higher values for DSI 4% (p = 0.025) and time spent below 90% (p = 0.03), but not for DSI 4% >10seconds (p = 0.447) or DSI 3% (p = 0.06). Infants born by NVD had significantly lower values for DSI 3% and DSI 4% at discharge than infants born by caesarean section. (2 – tailed, exact Wilcoxon rank sum test used).

### 4.2.3 Comparing 24-hour with 12-hour oximetry

The results of the comparisons of 24-hour oximetry with the shortened, overnight 12-hour oximetry are presented in table 4-11. There were three cases where the shortened overnight oximetry gave a total valid recording time of < 6 hours; these cases were excluded from analysis (n = 35). The median total valid recording time was 11 hours 17 minutes, range (9 hours 7 minutes - 11 hours 50 minutes).

Variables that changed significantly when the trace was cut to an overnight 12 hour trace were lowest SpO2 and lowest pulse, as well as percentage time spent below 90% and 80% SpO2. None of the three desaturation index measures (measures of intermittent hypoxia) changed significantly. Of the measures that did have statistically significant changes, only lowest pulse has a likely clinically significant change of 32% (table 4-12).
Table 4-11 24-hour vs 12-hour oximetry comparison

<table>
<thead>
<tr>
<th>Measures</th>
<th>24-hour</th>
<th>12-hour</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SpO$_2$(%)</td>
<td>97.8 (97.2 – 98.8)</td>
<td>97.8 (97.2 – 98.8)</td>
<td>0.455</td>
</tr>
<tr>
<td>Lowest SpO$_2$ (%)</td>
<td>62 (53 – 72)</td>
<td>69 (58 – 77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time spent &lt;90 SpO$_2$ (%)</td>
<td>1.2 (0.6 – 4.2)</td>
<td>1.1 (0.5 – 4.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Time spent &lt;80 SpO$_2$ (%)</td>
<td>0.1 (0 – 0.4)</td>
<td>0.1 (0 – 0.5)</td>
<td>0.017</td>
</tr>
<tr>
<td>DSI 4% (events/h)</td>
<td>50.8 (31.1 – 79.5)</td>
<td>54.6 (32.1 – 79.7)</td>
<td>0.499</td>
</tr>
<tr>
<td>DSI 3% (events/h)</td>
<td>78.5 (53.4 – 104.4)</td>
<td>79.2 (50.2 – 104)</td>
<td>0.579</td>
</tr>
<tr>
<td>DSI 4% &gt; 10secs (events/h)</td>
<td>10.9 (7.1 – 15.3)</td>
<td>11.3 (6.5 – 14.7)</td>
<td>0.258</td>
</tr>
<tr>
<td>Mean pulse (bpm)</td>
<td>156 (147 – 161)</td>
<td>155 (148 – 160)</td>
<td>0.407</td>
</tr>
<tr>
<td>Highest pulse (bpm)</td>
<td>210 (203 – 221)</td>
<td>209 (201 – 215)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lowest pulse (bpm)</td>
<td>54 (28 – 69)</td>
<td>78 (54 – 96)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Wilcoxon signed rank test

All median (IQR)

Table 4-12 Percentage differences between 24-hour and 12-hour oximetry

<table>
<thead>
<tr>
<th>Measures</th>
<th>Median (24-hour data)</th>
<th>Change from 24-hour *</th>
<th>Percentage change from 24-hour, %**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SpO$_2$(%)</td>
<td>97.9</td>
<td>0 (-0.5 – 0.9)</td>
<td>0 (-0.5 – 1)</td>
</tr>
<tr>
<td>Lowest SpO$_2$ (%)</td>
<td>61.5</td>
<td>1 (0 – 22)</td>
<td>1.2 (0 – 58.8)</td>
</tr>
<tr>
<td>Time spent &lt;90 SpO$_2$ (%)</td>
<td>1.3</td>
<td>-0.1 (-2.5 – 1.2)</td>
<td>-2.6 (-66.7 – 60)</td>
</tr>
<tr>
<td>Time spent &lt;80 SpO$_2$ (%)</td>
<td>0.2</td>
<td>0 (-1 – 0.3)</td>
<td>0 (-100 – 150)</td>
</tr>
<tr>
<td>DSI 4% (events/h)</td>
<td>51</td>
<td>-0.3 (-14.4 – 7.1)</td>
<td>-0.6 (-29.9 – 12.4)</td>
</tr>
<tr>
<td>DSI 3% (events/h)</td>
<td>77.4</td>
<td>-0.1 (-16.3 – 10)</td>
<td>-0.1 (-24.5 – 15.9)</td>
</tr>
<tr>
<td>DSI 4% &gt; 10secs (events/h)</td>
<td>10.7</td>
<td>-0.3 (-3.4 – 2.3)</td>
<td>-3.3 (-41 – 22.1)</td>
</tr>
<tr>
<td>Mean pulse (bpm)</td>
<td>155.5</td>
<td>0 (-3 – 3)</td>
<td>0 (-2.1 – 2.1)</td>
</tr>
<tr>
<td>Highest pulse (bpm)</td>
<td>212</td>
<td>0 (-18 – 0)</td>
<td>0 (-8.1 – 0)</td>
</tr>
<tr>
<td>Lowest pulse (bpm)</td>
<td>53.5</td>
<td>11 (0 – 90)</td>
<td>32 (0 – 360)</td>
</tr>
</tbody>
</table>

* Median (range)

** All median (IQR)
Chapter 5

Impact of intermittent hypoxia on post-discharge growth and change in 24-hour oximetry one-month post discharge

5.1 Methods

5.1.1 Participants
All infants from the main study who were born less than 32 weeks GA were included in the follow up study (n=12).

5.1.2 Additional clinical information collected
Wellington NICU routinely records weekly weights, head circumference and length for all infants in the unit. These growth measurements were collected. Discharge growth measurements were also recorded.

5.1.3 Data collection process

i. Weekly growth measurements
Infant weight, head circumference and length were recorded at least once a week for four weeks after discharge and final measurements recorded on the date of the home 24-hour oximetry. Most infants were being visited at home by the Wellington NICU home care nursing team at least once a week so wherever possible these visits were attended with the home care team and the measurements taken at this visit used (infant weight, head circumference and length). If the homecare team had discharged the infant from their care, additional visits were made where needed. Measurements from the homecare teams medical notes were obtained for visits we were unable to attend. If needed, the infant’s Plunket book was also checked for any measurements done by the midwife/Plunket. These various methods of data collection were utilised for practical reasons and to ensure we had at least one set of measurements a week.

Growth data were entered into a SPSS spread sheet and Z scores for weight were calculated using the 2013 Fenton growth charts online calculator (179). The rate of change
in Z score (for weight) over the follow up period was calculated. The rate of change in Z score was used to correlate with intermittent hypoxia measures on discharge oximetry using 2-tailed spearman’s rank correlation.

Z-scores have been used to assess growth rates, rather than percentage weight gain or percentiles from growth charts. This is because preterm infants are discharged home at different maturity levels and therefore growth rates would be different. Clinicians track infant growth by plotting weight on growth charts and are only concerned when an infant’s weight starts falling below the percentile curve they were tracking on, rather than simply keeping track of weight gain. Z-scores control for base differences in infant weights and are also the only growth measurements that have been shown to have some statistically significant correlation with neurodevelopmental outcomes in childhood (180).

**ii. Home 24-hour oximetry recording**

As close to four weeks after discharge as possible a repeat 24-hour oximetry recording was done on the infants in their home. The same oximeters (Masimo Rad-8) as the initial discharge oximetry were used. The same settings (‘sleep mode’) and protocol were also followed.

**5.2 Results**

**5.2.1 Demographics**

There were 12 infants recruited for the study that were born <32 weeks GA and eligible for the post-discharge, follow up phase of the study. All consented to be included in this follow up phase. Table 5-1 presents demographic data for this group, 4/12 (33.3%) identified as Maori and/or Pacific Island.
Table 5-1 General demographics of participants <32 weeks GA included in analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td><em><em>Ethnicity</em>, n (%)</em>*</td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>5 (42.7)</td>
</tr>
<tr>
<td>NZ Maori</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Indian</td>
<td>2 (17.7)</td>
</tr>
<tr>
<td>Chinese</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Multiple birth, n (%)</td>
<td>4 (33.0)</td>
</tr>
<tr>
<td>GA at birth (completed weeks), median (range)</td>
<td>29 (24 - 31)</td>
</tr>
</tbody>
</table>

* participants could identify as more than one ethnicity

5.2.2 Impact of intermittent hypoxia on growth rates post discharge

Three variables measured on 24-hour discharge oximetry that identify intermittent hypoxia (3% DSI, 4% DSI for >10 seconds, and percentage time spent <90%) were compared with growth rates after discharge (rate of change in Z scores for weight). None of these correlations were statistically significant; However, time <90% SpO2 did show an apparent trend to negative relationship with postnatal growth.
Figure 5-1 DSI 3% and growth rate comparison

Spearman’s correlation coefficient 0.56 (p = 0.863)

Figure 5-2 DSI 4% > 10 seconds and growth rate comparison

Spearman’s correlation coefficient -0.035 (p = 0.914)
Figure 5-3-Percentage time spent <90%SpO2 and growth rate comparison

5.2.3 Discharge oximetry compared with oximetry performed four weeks post discharge

The follow up 24-hour oximetry was performed as close to four weeks (28 days) after discharge as possible (median 29 days, range 27 – 32). There were 2 infants (from a set of triplets) who did not complete the follow up oximetry due to difficulty with follow up. One infant only had 5 hours 43 minutes of valid recording time for the follow up 24-hour oximetry, so was excluded from analysis (n = 9). Of the nine follow up 24-hour oximetry reports included in this analysis, the median valid recording time was 22 hours 4 mins (range: 21 hours 0 mins - 23 hours 0 mins)

Table 5-2 compares discharge 24 hour oximetry measures with the 4 week post discharge home 24 hour oximetry. All desaturation index measures (DSI 3% (p = 0.02), DSI 4%(p = 0.01) and DSI 4% > 10 seconds (p = 0.04)) were significantly improved (lower values).

Table 5-3 presents the actual value of the change in measures as well as the percentage change. Of the five measures that had statistically significant differences, the change in
values for the three desaturation index measures and percentage time spent <90% SpO₂ would be likely considered clinically significant, as these values improved by 42.7% - 57.4%.

Table 5-2 Home oximetry compared with discharge oximetry (n=9)

<table>
<thead>
<tr>
<th>Measures</th>
<th>Discharge 24-hour oximetry*</th>
<th>Home 24-hour oximetry*</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SpO₂ (%)</td>
<td>98.5 (95.8 – 99.2)</td>
<td>98.7 (98 – 99.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>Lowest SpO₂ (%)</td>
<td>57 (34 – 77)</td>
<td>68 (39 – 78)</td>
<td>0.29</td>
</tr>
<tr>
<td>Time spent &lt;90 SpO₂ (%)</td>
<td>1.4% (0.6-9.8)</td>
<td>0.6% (0.3 – 1.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Time spent &lt;80 SpO₂ (%)</td>
<td>0.2% (0.1-1.3)</td>
<td>0% (0 – 0.15)</td>
<td>0.11</td>
</tr>
<tr>
<td>DSI 4% (events/h)</td>
<td>57.9 (25.1-132.2)</td>
<td>25.5 (7.2 – 49)</td>
<td>0.01</td>
</tr>
<tr>
<td>DSI 3% (events/h)</td>
<td>80.1 (35.3-153.1)</td>
<td>41.5 (13.2 – 64.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>DSI 4% &gt; 10secs (events/h)</td>
<td>7.7 (4 – 15.9)</td>
<td>5.2 (1.9 – 9.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean pulse (bpm)</td>
<td>154 (144 – 160)</td>
<td>150 (136 – 153)</td>
<td>0.03</td>
</tr>
<tr>
<td>Highest pulse (bpm)</td>
<td>205 (186 – 221)</td>
<td>200 (184 – 217)</td>
<td>0.21</td>
</tr>
<tr>
<td>Lowest pulse (bpm)</td>
<td>60 (25 – 92)</td>
<td>53 (25 – 94)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* Median (IQR)

**Wilcoxon signed ranks test
Table 5-3 Percentage differences between discharge and home 24-hour oximetry

<table>
<thead>
<tr>
<th>Measures</th>
<th>Median (discharge)</th>
<th>Change from discharge (home - discharge) *</th>
<th>Percentage change from discharge*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SpO₂ (%)</td>
<td>98.5</td>
<td>0.8</td>
<td>0.8 (-0.9 – 3.50) (-0.9 – 3.7)</td>
</tr>
<tr>
<td>Lowest SpO₂ (%)</td>
<td>57</td>
<td>7</td>
<td>19 (-23 – 32) (-31.9 – 94.1)</td>
</tr>
<tr>
<td>Time spent &lt;90 SpO₂ (%)</td>
<td>1.4</td>
<td>-0.5</td>
<td>-55.5 (-9.2 – 0.2) (-93.9 – 14.3)</td>
</tr>
<tr>
<td>Time spent &lt;80 SpO₂ (%)</td>
<td>0.2</td>
<td>-0.1</td>
<td>-96 (-2.4 – 0.8) (-100.0 – 800.0)</td>
</tr>
<tr>
<td>DSI 4% (events/h)</td>
<td>57.9</td>
<td>-49.2</td>
<td>-50.1 (-106.1 – 6.8) (-87.6 – 27.1)</td>
</tr>
<tr>
<td>DSI 3% (events/h)</td>
<td>80.1</td>
<td>-48.2</td>
<td>-42.7 (-116.2 – 13.1) (-83.5 – 37.1)</td>
</tr>
<tr>
<td>DSI 4% &gt; 10secs (events/h)</td>
<td>7.7</td>
<td>-5.8</td>
<td>-57.4 (-13.5 – 5.5) (-84.9 – 137.5)</td>
</tr>
<tr>
<td>Mean pulse (bpm)</td>
<td>154</td>
<td>-7</td>
<td>-4.5 (-9 – 2) (-5.6 – 1.3)</td>
</tr>
<tr>
<td>Highest pulse (bpm)</td>
<td>205</td>
<td>-2</td>
<td>-1.1 (-13 – 12) (-5.9 – 6.4)</td>
</tr>
<tr>
<td>Lowest pulse (bpm)</td>
<td>60</td>
<td>-8</td>
<td>-13.1 (-63 – 36) (-68.5 – 112.0)</td>
</tr>
</tbody>
</table>

* Median (range)
Chapter 6

Discussion

In this study there were 38 premature infants who, just prior to discharge home from Wellington NICU, had a valid 24-hour oximetry recording performed. Of the 38 participants, 12 were born at less than 32 weeks gestational age and participated in the second part of the study which included recording weekly growth measurements for one month post discharge, as well as performing a repeat 24-hour oximetry in their home one month after discharge.

The proportion of Maori infants in this participant group was 21.1%, which is comparable to NZ Ministry of Health (MOH) data for the year 2014 that shows 25.8% of all infants born were of Maori ethnicity (2). Our study population is slightly over representative of normal local rates for Maori ethnicity of preterm infants, with 17.5% of preterm infants admitted to Wellington NICU in 2014 identifying as Maori (181). There were a high proportion of Pacific Island infants in our study group (23.7%), higher than the MOH data of 10%. This could be in part due to the fact we had a set of triplets that were of Pacific Island decent that increased this group number. The majority of infants were born by caesarean section (61.2%), which is slightly higher than the MOH figures for rates of caesarean section for preterm infants of 46%. Most infant participants needed some resuscitation at birth (57.9% had some resuscitation but without intubation). Half of infants (47.4%) received caffeine treatment during their NICU stay. Being of Maori, Pacific Island, or NZ European ethnicity made no significant difference to intermittent hypoxia values.

The 38 pre-discharge oximetry recordings were analysed in PROFOX software three alternative ways (unedited, automatically edited and manually edited) and compared for differences. There were only a few measures on oximetry reports that were clinically different between type of editing, and therefore we consider automatic editing as the most practical way to edit data.

The pre-discharge 24-hour automatically edited recordings were further reported and analysed. We found that this group of formally premature infants had a high mean SpO₂, however a large amount of intermittent hypoxia was seen. The recordings were also edited
to resemble a 12-hour ‘overnight’ oximetry study and the results compared with the full 24-hour recording. The edited ‘overnight’ recordings were found to be clinically similar to the 24-hour recordings, the pulse nadir being the only clinically significant difference between the two.

For the twelve infants born <32 weeks GA, post-discharge growth (in the form of change in z-score) were compared with degree of intermittent hypoxia on discharge oximetry report, no significant correlation was found. When comparing discharge oximetry with home oximetry 1-month post discharge, mean SpO₂ did not change significantly, however all four measures of intermittent hypoxia had a statistically and clinically significant improvement. These results highlight the significant amount of intermittent hypoxia still experienced by convalescent preterm infants at the time of their discharge home from the neonatal unit. The decrease in levels after one month at home agrees with our hypothesis that the levels of intermittent hypoxia in very preterm infants will have decreased one month post-discharge; however, there will still be a degree of intermittent hypoxia. We hypothesised that there would be a correlation between the amount of intermittent hypoxia experienced at time of discharge and infant growth rates post discharge, however, this study did not show any correlation.

6.1 Discussion of results

6.1.1 24-hour discharge oximetry results

For these results discussed, values produced by automatic editing are used. The baseline oxygen values in these infant studies were always normal with a median ‘mean SpO₂’ for all studies of 97.9%. This is consistent with other similar studies as reported in section 2.3.4. These studies reported medians of 95 - 99.4% but these studies were undertaken using a variety of oximeter devices (70, 80, 83, 84, 86, 87, 89).

The median percentage time spent <90% SpO₂ was 1.3%, which is less than other reported studies (2.2 - 5.6%) (6, 80, 83, 84). Of these four studies, there were two which used Nellcor oximeters and performed the oximetry recording earlier than ‘at discharge’ meaning the infants would have been less mature, possibly a reason for the two higher values of 4% and 5.7% (6, 84).
The most similar study reported previously used Masimo Rad 7 oximeters, assessed the infant at discharge, and used PROFOX software to perform automatic editing on recordings. Although the study only included infants born <32 weeks GA, it still gave the closest value for percentage time spent <90% \(\text{SpO}_2\) to our study of 2.2% (83). When analysing just infants <32 weeks GA in our study group, the percentage time spent less than 90% \(\text{SpO}_2\) was 2%, which is in fact very similar to this study. This study was also the only study in our literature review to report a desaturation index. They report a value for median DSI 4% >10 seconds of 10.2 events/h, which is very similar to the median of 10.7 events/h found in the current study. This value of 10.7 events/h is the full study group <37 weeks GA. The sub group of <32 week GA infants had a lower DSI 4% >10 seconds of 7.7 events/h.

Rath et al. published the most recent study reviewed (December 2015), and did assess infants ‘at discharge’; however, only infants less than 28 weeks GA were included, the sample size was small (15 infants), and again they did not report any desaturation index values (80). The percentage of time spent less than 90% \(\text{SpO}_2\) for this group was 3%, also in keeping with our result of 2.2%.

Our study results add significantly to this literature as we report ‘normal’ values, for preterm infants thought to be clinically well, for oximetry measures produced from new generation oximeters, using the most used oximetry software PROFOX in Australian and New Zealand neonatal units (69). We also report values for the intermittent hypoxia measures DSI 3% and DSI 4 %, which no study has yet reported, and DSI 4% >10 seconds (events/h), which only one previous study has previously reported although only for <32week GA infants. Our study is also the first study to report automatically, manually and unedited results, meaning our results are able to be applied to a greater number of reports as some centres may choose to edit data, while others may just use the raw data, and both could use our reported values (either using the edited or unedited forms) as a guide when interpreting their results.

We have presented oximetry values for convalescent preterm infants who are ready for discharge home from the neonatal unit (table 4.6). Comparison to values in healthy term infants is needed to be able to evaluate whether these values in preterm infants should be considered abnormal and therefore worrying. These results may be ‘normal’ or perhaps
‘expected’ for preterm infants at this stage in their development but still have implications for their long-term outcomes. There are five studies to our knowledge that report oximetry values for healthy term infants within the first week of birth (comparable PMA to our infants) (6, 76, 80, 83, 182, 183). The median ‘mean SpO₂’ for these studies were 97 - 99%, which is very similar to our study (97.9%). Four of the six term infant studies used Masimo technology, so are comparable to our study.

Rhein et al. compared term infants in the first week of life with preterm infants off oxygen and ready for discharge home. They are the only other study to report desaturation index values and they also used 2-second averaging times and new generation Masimo oximeters (83). They report that while mean SpO₂ and time spent below 90% SpO₂ was comparable between the two groups, median DSI 4% > 10 seconds differed significantly (preterm 10.2 events/h vs term 8.2 events/h (p = 0.0001)) (83). As our preterm infant median for DSI 4% > 10 seconds was 10.7 events/h, their term infant value of 8.2 events/h is also significantly better than our preterm infants population.

The only other comparable measure to our study that was reported in these studies was percentage time spent <90% SpO₂. Ng et al. report a median of 2.3% (0.1 – 4.7), Rhein et al. report a median of 2.6% (1.5 - 4.6), while Rath et al. report 0% (0 - 0.8) (80, 83, 182). All studies used Masimo Rad-7 technology and used the delete low signal IQ function, with similar exclusion criteria. Rath et al. only had 15 infants in each group (term and preterm), while the other two studies had 60 term and 100 term infants each. It is unclear why Rath et al. report such different values to the previous two studies, however as their sample size was a lot smaller, the first two studies may be a more accurate representation. In this case, the time spent <90% SpO₂ for term infants from reported studies (2.3-2.6 %) is comparable to the 2.2% value seen in our preterm infant population.

Shah et al. used Nellcor oximeters and so the results from their study are not as comparable as this technology differs from the MasimoSET technology used in this study. They reported that the median percentage time <90% SpO₂ was 3.4 – 3.6% for term infants, a significant difference from their late preterm group (5.6%) (p = 0.002) (6).

As can be seen, there are no studies that report DSI 3% or DSI 4% for term infants and therefore we have no comparison data for our population of premature infants. The one
reported desaturation index of DSI 4% >10 seconds was significantly lower in term infants than preterm infants. Results from studies that report mean SpO₂ and time spent below 90% SpO₂ suggest that these two measures are not significantly different between term infants and preterm infants when they reach term equivalent age. These few studies suggest that while mean SpO₂ does not differ between term infants and convalescent premature infants at term equivalent age, there are higher rates of intermittent hypoxia in the preterm group.

The degree of intermittent hypoxia that these convalescent preterm infants are experiencing would be considered pathological if put in an adult context. Sleep apnoea is often defined by AHI (apnoea hypopnoea index). In adults the AHI is the number of pauses in breathing lasting 10 seconds or more that are associated with a desaturation per hour. An AHI > 5 events/h is considered diagnostic of sleep apnoea, with severe sleep apnoea defined as an AHI > 30. Chung et al. looked at the correlation between desaturation index from pulse oximetry and AHI from PSG (184). Nonin oximeters were used and had an averaging time of 3 seconds, and reports were generated through PROFOX software using the automatic editing function. Good correlation was found between DSI 4% >10 (referred to as the ODI – oxygen desaturation index) and AHI, with ODI >5 events/ h correlating with AHI >5 events/h (184). Romem et al. reported this correlation also (185). Niijima et al. reported that a DSI 4% of >10 events per hour was associated with a diagnosis of sleep apnoea (186). In children, the AHI is derived differently with apnoea defined as two missed breaths or longer. An AHI of less than one event per hour is considered to be normal, an AHI of 1-5 is mildly increased, 5-10 moderately increased, and greater than 10 is moderately severe with treatment generally indicated for AHI >5 (187). Roberts et al. studied a preterm infant population and reported a positive correlation between AHI and both DSI 3% (p = 0.003) and DSI 4% (p = 0.0008) (188).

Our median DSI 4% > 10 seconds in our population was 10.7 events/ h, so if correlating this to AHI, the majority of our participants would be diagnosed with sleep apnoea based on both adult and paediatric criteria.

6.1.2 Artefact editing

During the progression of this thesis, data from the infant 24-hour oximetry reports were noticed to have a lot of apparent artefact, and many fleeting oxygen desaturations that were
hard to assess as to whether they were artefact or in fact true desaturations. The editing of infant oximetry reports is certainly a lot more complex than when editing adult reports. This is because infants desaturate more quickly than adults due in part to their small pulmonary reserve, meaning that sharp steep desaturations that would be defined as clear artefact when seen in adult oximetry reports, cannot be as easily accepted as artefact when they occur in infant oximetry reports (49).

Previous studies were reviewed to establish how to best edit oximetry data in this population. Table 3-1 in Chapter three presents this information. There was a lack of reproducible editing methods described, with 3/11 studies reviewed not reporting any editing and of the remaining studies that did report some editing, it was often vaguely described using phrases such as ‘areas of artefact were excluded’. Of the three studies that used PROFOX software, all three used the automatic editing function to delete low signal IQ. Two of the three studies also reported that they manually screen desaturations to exclude any that were artefactual; however, how they identified an artefactual event compared to a real desaturation from within the oximetry data was not described, therefore making it impossible to determine what were considered artefactual events. We therefore created our own set of manual editing rules, based on data available on what is physiologically possible as discussed in section 3.2.

The manual editing of data as per the rules we created, we believed produced the most accurate oximetry reports for these infants and there were statistically significant differences between most measures reported from the manually edited oximetry reports compared with unedited reports, as well as many measures from the automatically edited report.

The median length of recording time that was excluded from oximetry reports after editing was a lot less when manually edited compared to automatic editing (13 minutes vs 1 hour 42 minutes). This suggests that automatically editing oximetry reports does exclude a lot of data that is in fact considered real when taking the time to manually edit, suggesting that manual editing of oximetry reports is a far more refined method than simply using the automatic ‘delete low signal IQ’ function.
Manual editing however is time consuming, and requires some expertise so to be able to justify spending time manually editing reports, there would have to be clinically significant differences in the oximetry reports produced. Although there were statistically significant differences seen between edited and unedited reports as well as between manual editing and automatic editing, the only measures with clinically significant differences (we used a change of >10% as a measure of clinical significance) between unedited and edited (manual and/or automatic) reports were: pulse nadir, time spent below 90% SpO\textsubscript{2} and DSI 4% >10 seconds.

For percentage time spent <90% SpO\textsubscript{2} there was a clinically significant improvement (i.e the percentage time spent below 90% SpO\textsubscript{2} decreased) after both automatically and manually editing reports. Manual editing produced a slightly larger improvement compared with automatic editing, but the difference between the two ways of editing (manual and auto) was not of clinical significance.

For DSI 4% >10 seconds, there was only a clinically significant improvement after automatically editing data, with no significant change after manual editing. This indicates that automatically editing reports can underestimate the severity of DSI 4% > 10 seconds, as it improves the value compared with manual editing where DSI 4% >10 seconds remains unchanged from unedited reports.

For pulse nadir, manual editing produces a great improvement (median of >100% change), and automatic editing doesn’t produce any median change; therefore, automatically editing data can overestimate how severe the lowest pulse is (compared with manual editing).

The median SpO\textsubscript{2} nadir did not change by more than 10% between types of editing. When looking at individual reports, the SpO\textsubscript{2} nadir either doesn’t change at all (60.5% of cases), or changes by a large amount. Of the cases where the SpO\textsubscript{2} nadir does change, the median change from raw to automatically edited reports was 21.9% (4.5% – 231%), and to manually edited was 29.5% (4.1% – 427.2%). This shows that either way of editing often does improve the SpO\textsubscript{2} nadir by a clinically significant amount, and manual editing often improves the nadir by a greater value. The change in SpO\textsubscript{2} nadir after editing is always an improvement (increase), as artefact can often cause a single very low SpO\textsubscript{2} value.
Therefore, in a significant percentage of cases, the SpO\textsubscript{2} nadir does improve by a clinically significant amount after editing.

Overall, manual editing improves the percentage time spent below 90\% SpO\textsubscript{2}, the SpO\textsubscript{2} nadir, and pulse nadir. Automatically editing of the recordings can produce clinically similar improvements to manual editing in time spent below 90\% SpO\textsubscript{2} and SpO\textsubscript{2} nadir; however, automatic editing also clinically improves (reduces) DSI 4\% >10 seconds (which manual editing does not), and does not improve the pulse nadir like manual editing does.

We can be reassured that the clinically significant changes to reports after manual editing are of a clinical improvement in measures (compared to unedited reports). This means that if unedited reports are used, clinicians may overestimate how bad the infant’s respiratory status is. This could result in infants being kept on additional oxygen for longer or delaying discharge home, rather than undertreating these infants.

As can be seen, the value of manual editing is limited. The majority (7/10) of measures reported on the oximetry reports were clinically similar to the unedited oximetry reports. Automatically editing oximetry reports gives clinically similar results to manual editing in the majority of measures (8/10 of reported measures). Manual editing is time consuming, taking between 5 to 20 minutes per report, while automatic editing takes less than 30 seconds to perform. In view of the time taken to perform manual editing, automatic editing is a reasonable alternative to manual editing as it does improve percentage time spent <90\% SpO\textsubscript{2} similarly to manual editing, while pulse nadir and DSI 4\% >10 seconds are measures to be wary of if automatic editing is performed, as results for these two measures were clinically different from manual editing.

### 6.1.3 24-hour vs 12-hour ‘overnight’ recordings

When comparing the full 24-hour recordings with the edited ‘overnight’ recordings, statistically significant changes were seen. However, apart from pulse nadir, all of the differences were less than 5\%, which is very unlikely to make any clinical difference when interpreting the reports. Therefore, apart from again being wary of the reported nadirs, a full 24-hour oximetry recording does not seem to offer any added value over a 12-hour overnight recording.
We considered the effect of only using overnight recordings on the accuracy of reporting an infant’s overall respiratory status. Adults generally sleep during the night, and are awake during the day, and as sleep has a significant effect on their respiratory status and oxygen levels, an overnight recording in this population would give significantly different reports to a daytime recording. Infants of this age however, generally wake to feed and then sleep, approximately every four hours, with no apparent day/night rhythm. During the day infants may be more disturbed with noise and procedures particularly in the NICU environment. We have only compared full 24-hour recordings with overnight recordings, and not 12-hour daytime recordings with 12-hour night time recordings, however we do not believe a daytime recording would give different results to a ‘overnight’ recording in this population, as both time periods would capture sleep and wake periods equally for preterm infants. This is however a hypothesis, and is therefore a possibility for future research.

6.1.4 Follow-up study

i. One month post discharge oximetry recordings

When comparing discharge oximetry recordings with recordings one month post discharge, there were significant improvements noted in all intermittent hypoxia measures, but no change in mean $\text{SpO}_2$. The changes were substantial, with desaturation indices falling by around 42.7% - 57.4%. For example, the median number of desaturations per hour of 4% or more per hour was 57.9 at discharge and 25.5 one month later. This suggests that measures of intermittent hypoxia are better indicators of respiratory stability over time than mean $\text{SpO}_2$, as while the desaturation indices improved over time the mean $\text{SpO}_2$ remained the same.

Only one other reported study in the literature has studied change in oximetry results over a similar time period. Poets et al. published a paper in 1992 that compared discharge oximetry from convalescent preterm infants to oximetry performed 6 weeks post discharge. This study used Nellcor N100 oximeters and the recordings were printed on graph paper and had to be analysed and scored manually. Median $\text{SpO}_2$ was 99.5% (range 88.7 – 100) at discharge and 100% (95.3 – 100) 6 weeks later, while intermittent hypoxia (measured by number of desaturations per recording to $\leq 80\%$ $\text{SpO}_2$ for $\geq 4$ seconds) improved from a median of 3 (0 – 255) per recording to a median of 0 (0 – 17) per
recording (90). Although these data were collected on now out-dated oximeters and used a very different definition of IH, the trend in results is consistent with our results, with mean SpO2 not changing and IH measures improving significantly.

These results show that respiratory stability in premature infants improves rapidly with advancing maturity. This indicates that a premature infant’s degree of respiratory stability at discharge home from the neonatal unit is still immature, as the amount of intermittent hypoxia experienced still declines significantly after discharge without any specific treatment or intervention.

**ii. Post discharge growth rates**

No correlation was found between growth rates (measured by change in weight Z-score) with degree of intermittent hypoxia at discharge. Our hypothesis was that there would be a correlation between the two with those infants with the more marked IH exhibiting a degree of growth failure in the first month after discharge. Physiologically, as discussed in section 2.1, there is reason to believe that growth would be affected by intermittent hypoxia. One reason this was not seen here could be simply the low numbers of participants in this section of the study. Repeating this study with a larger participant number of participants that generated enough power would be necessary to be able to confidently conclude there is no correlation. Another reason could be that infants that experience more intermittent hypoxia, and therefore more energy expenditure, could compensate for this by increasing their energy intake by consuming more milk, therefore weight gain would be maintained. There are many other factors that contribute to weight gain after discharge, such as how often an infant is fed, what type of milk it is given and any other concurrent illnesses. Although these factors were recorded at each weekly follow up visit for growth, the sample size is too small to be able to account for these potential cofounders, and therefore this could be a reason no correlation was seen.

**6.2 Strengths and limitations**

There were some limitations to this study. As mentioned, when trying to appreciate the significance of such apparent severe intermittent hypoxia values, comparison with normal term infants is required. This study did not include a comparison group, which would ideally be of healthy term infants > 48 hours old. This would have enabled these results to be appreciated in context of ‘normal’ expected values of term infants. We were able to
compare some of our measures with previously reported values in the literature for term infants, but normal values for term infants for DSI 3% and DSI 4% have never been reported in the literature. The difficulty with the comparison group is that healthy term infants do not stay in hospital very long at all, so to be able to get consent and perform a 24-hour study before discharge home would be very difficult. A solution to this is to gain consent as soon as the infant is born and visit the infant at their home within their first week of life to perform a 24-hour oximetry. This was not practical with the current study in the timeframe available.

The follow up period of one-month is short when wanting to consider any future morbidity of intermittent hypoxia in infancy. Ideally a follow up period of a number of years is needed to be able to see any meaningful impact on growth and neurodevelopment. This study was limited to one year, and therefore a one-month follow up period was all that was practical. Investigating growth as a potential impact of IH in premature infants has never been reported before, and therefore this follow up section of the study was considered a pilot study. As mentioned, the small numbers in this follow up group was also a limitation.

Although artefact was thoroughly considered and an attempt was made to best exclude any, there is still the potential for recordings to contain artefact even after manual editing. This is in part due to having only one parameter recorded (pulse oximetry), and there are no other channels such as a pulse waveform, ECG, or nasal airflow to be able to relate each desaturation too. This should be taken into account if ever comparing these desaturations values from this study with full PSG recordings. The values from this study however are designed to be used when interpreting pulse oximetry rather than PSG.

This study has many strengths, including the use of new generation oximeters with 2 second averaging time and PROFOX software. These are the most commonly used oximeters and software in NZ and Australia therefore the results from this study are highly relevant for current clinical practice compared to older studies using older, less accurate oximeters (69). As mentioned, presenting ‘normal’ ranges three alternate ways (unedited, automatically edited and manually edited) makes these results more widely applicable. The appreciation of the degree of artefact in these oximetry recordings is also a strength, as many previous studies appear to have not considered the potential impact of artefact on results.
6.3 Clinical recommendations and implications

6.3.1 Artefact and editing oximetry reports

In general the findings in this study support a recommendation that editing should be performed on oximetry reports to be able to exclude artefact. Automatic editing is a good option for busy clinicians as although manual editing does produce the most accurate reports, there are limited advantages for the large time commitment. If interpreting automatically edited reports, clinicians need to be aware that the pulse nadir may be artefactual and in fact be a lot higher, and that DSI 4% > 10 seconds may be lower than if manual editing has been used. The DSI 3% and DSI 4% values do not differ between types of editing, so are perhaps a more robust measure to consider when quantifying intermittent hypoxia.

If using unedited oximetry reports, the majority of measures are reliable; however, when looking at the percentage time spent <90% SpO₂, clinicians need to be aware that this value could be overestimated due to artefact in the recording. If using this measure to aid clinical decision-making, editing may be warranted to produce a more accurate value, especially if the value is borderline for clinical thresholds (e.g. if using the British Thoracic Society Guidelines of 5% as being acceptable (74), and the percentage time for the infant is say 6%, editing is warranted to be certain that the percentage time spent below 90% SpO₂ is in fact > 5%).

When analysing oximetry reports, clinicians need to be aware that the nadir (both pulse and SpO₂) have a high chance of being artefactual. If using these measures in clinical interpretation and they are worryingly low, editing is useful to be certain that the value is not a product of artefact. Automatic editing is a good first line option to see if the nadir improves. If not, manual editing would be useful to visually view the nadir and decide if it is part of artefact, or it is in fact the true lowest drop in the recording.

6.3.2 12 hour vs 24 hour oximetry

We have demonstrated that 12-hour overnight oximetry reports are clinically very similar to reports produced from full 24-hour oximetry recordings and therefore are an adequate alternative. Setting up an infant with an oximeter just for the overnight period rather than
for a full 24-hours would be more acceptable to both parents and medical staff, as less procedures are performed and an infant is generally moved less at night. Therefore, we recommended performing overnight oximetry rather than 24-hour oximetry, as it is less of a disturbance and produces similar reports.

6.3.3. General recommendations

Desaturation index (DSI 3% / DSI 4%) is rarely reported in the literature, and it appears clinicians are focusing on mean SpO\textsubscript{2} and time spent below 90% when interpreting oximetry reports for infants. We suggest there is value in desaturation indices, and they should be reported and considered more often. We have shown that the desaturation index decreases with advancing PMA, while mean SpO\textsubscript{2} does not, indicating that desaturation indexes are a more sensitive measure of respiratory stability.

There is the question of whether neonatal units should be routinely screening premature infants with pulse oximetry at discharge home from the neonatal unit. Although we have shown these infants are still experiencing a large, and possibly concerning degree of intermittent hypoxia, there is currently not enough evidence in regard to the consequences of high desaturation indices reported from pulse oximetry to decide whether something should be done to decrease this amount of intermittent hypoxia or not. In view of this, before good evidence exists, we would suggest that routine oximetry screening at discharge cannot yet be universally recommended, as it is hard to interpret the significance of any results obtained.

6.4 Directions for future research

As indicated previously, long-term studies looking at the effect of intermittent hypoxia (measured by pulse oximetry) on preterm infant growth and neurodevelopmental are needed. This will enable much needed, precise guidelines to be developed to aid clinician interpretation of pulse oximetry and decision making for treatment of respiratory instability. Infants from this study have the potential to be used for a follow up study, as discharge oximetry recordings have already been performed. The apparent trend of time <90\% SpO\textsubscript{2} having a negative relationship to postnatal growth could indicate that this particular oximetry measure (times spend <90\% SpO\textsubscript{2}) could be a focus for future research.
All studies investigating premature infants and neurodevelopmental outcome are complicated by many potential cofounders. Premature infants often experience many adverse events such as IVH, jaundice, and NEC, and are also at higher risk of impaired neurodevelopment. Infants with more frequent intermittent hypoxia may have experienced more serious medical events, and therefore it is difficult to establish whether it is purely the intermittent hypoxia causing decreased neurodevelopment, or if the other factors had already predisposed them to worse neurodevelopment. Randomised control trials of treatment options for intermittent hypoxia, such as extended caffeine treatment, are needed to be able to determine the true significance of intermittent hypoxia, as if neurodevelopment improves with treatment of IH, that would provide a clear indication that ongoing IH does have some influence on neurodevelopment. An example is a study that would randomise preterm infants to either receive caffeine treatment for one month post – discharge, or discontinue caffeine at the currently accepted time, and then compare long term neurodevelopmental outcome between the two groups. This type of study would provide evidence as to whether we should be concerned about treating the seemingly severe intermittent hypoxia this study has exposed.

Studies reporting normal desaturation indices for term infants are also needed, as no study to our knowledge reports DSI 3% and DSI 4% for healthy term infants in the first week of life. This literature is needed in order to be able to better understand the described premature infant desaturation indexes.

6.5 Conclusion

This study has shown that intermittent hypoxia is frequent in preterm infants and given reference ranges for expected values at discharge in preterm infants. It has shown that rates of IH decline significantly in the one-month post discharge. This study has also established that automatic editing is a good alternative to manual editing, although both pulse nadir and SpO₂ nadir values are to taken with caution as they are often caused by artefact. The study has shown that 12-hour overnight oximetry recordings are comparable to full 24-hour recordings and therefore would be a favourable alternative as overnight recordings are more practical. The long-term natural history of the clinical phenomenon of IH is still to be established. Future research is needed to determine what this means for preterm
infants, whether treatment should be provided for this ‘condition’, and if so how it should be treated.
References


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Appendices

Appendix A Sample PROFOX reports

**Oximetry: Comprehensive Report**

Recording time: 21:20:16  Highest pulse: 225  Highest SpO2: 100%
Excluded sampling: 00:25:18  Lowest pulse: 54  Lowest SpO2: 73%
Total valid sampling: 20:54:58  Mean pulse: 164  Mean SpO2: 97.9%

Time with SpO2<90: 0:07:22, 0.6%
Time with SpO2<80: 0:10:34, 0.4%
Time with SpO2<70: 0:10:00, 0.3%
Time with SpO2<60: 0:10:00, 0.3%
Time with SpO2<88: 0:04:18, 0.3%

The longest continuous time with saturation <=88 was 00:00:36, which started at 04/23/15 01:57:36.

When a desaturation was defined as a decrease of: 4% 3% 2%
Total number of events less than 3 minutes: 506 949 1921
Number of events excluded due to artifact: 0 0 0
Number of events over 3 minutes duration: 12 9 2
Mean high event saturation: 99.1 99.0 98.8
Mean low event saturation: 92.9 94.2 95.5
The mean length of events >=10 sec & <= 3 mins, in secs: 42.5 39.3 26.1
Desaturation event index (number of events per hour): 24.2 45.4 91.8

© 2011 PROFOX Associates, Inc. Oximetry version Masimo RD2011.00-1070
Oximeter: Masimo Rad-8 memory, 2 second resolution.
Oximetry: Summary Report

Recording time: 21:20:16  
Highest pulse: 225  
Highest SpO2: 100%  
Excluded sampling: 00:25:18  
Lowest pulse: 54  
Lowest SpO2: 73%  
Total valid sampling: 20:54:58  
Mean pulse: 164  
Mean SpO2: 97.9%  
1 S.D.: 18.5  
1 S.D.: 1.9

Time with SpO2<90: 0:07:22,  0.6%  
Time with SpO2 =>90: 20:47:36,  99.4%  
Time with SpO2<80: 0:00:34,  0.0%  
Time with SpO2=>80 & <90: 00:06:48,  0.5%  
Time with SpO2<60: 0:00:00,  0.0%  
Time with SpO2=>60 & <70: 00:00:00,  0.0%  
Time with SpO2<88: 0:04:18,  0.3%

The longest continuous time with saturation <=88 was 00:00:36, which started at 04/23/15 01:57:38.

When a desaturation was defined as a decrease of:  
4%  3%  2%

Total number of events less than 3 minutes: 506 949 1921
Number of events excluded due to artifact: 0 0 0
Number of events over 3 minutes duration: 12 9 2
Mean high event saturation: 99.1 99.0 98.8
Mean low event saturation: 92.9 94.2 95.5

The number of events that were > 0 & < 10 seconds: 278 500 1116
=>10 & < 20 seconds: 89 161 415
=>20 & < 30 seconds: 35 84 178
=>30 & < 40 seconds: 25 55 80
=>40 & < 50 seconds: 12 35 36
=>50 & < 60 seconds: 14 29 32
=>60 seconds: 53 85 64

The mean length of events =>10 sec & <= 3 mins, in secs: 42.5 39.3 26.1
Desaturation event index (events =>10 seconds per hour): 10.9 21.5 38.5
Desaturation event index (events >= 0 seconds per hour): 24.2 45.4 91.8

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Oximeter: Masimo Rad-8 memory, 2 second resolution.
Appendix B Ethics

23 February 2015

Professor D Elder
Department of Paediatrics and Child Health (Wgnt)
Children’s Hospital, Wellington Hospital
University of Otago, Wellington

Dear Professor Elder,

I am again writing to you concerning your proposal entitled “24-hour oxygen saturation recordings at discharge in preterm infants”, Ethics Committee reference number H15/013.

Thank you for your letter of 21st February 2015 addressing the issues raised by the Committee.

The Committee thanks you for providing the Peer Review undertaken by Professor Nicola Austin and the locality agreement from the Child Health Governance Group at Capital and Coast District Health Board.

In respect of the issue regarding not passing on relevant information; the Committee notes the letter of support provided by Dr Vaughan Richardson, Clinical Leader, Neonatal Intensive Care Unit at Wellington Regional Hospital and also accepts the further justification provided for not passing on information stating that ‘... there is not yet a solid evidence base for making changes to patient management based on the determination that there is intermittent oxygen desaturation over a 24 hour period when the infant is otherwise regarded as healthy and fit for discharge.’

The Committee notes that you have made a number of changes to the Information Sheet to ensure that participants understand that the research team will not be influencing decisions about a participant’s readiness to be discharged.

On the basis of this response, I am pleased to confirm that the proposal now has full ethical approval to proceed.

The standard conditions of approval for all human research projects reviewed and approved by the Committee are the following:

Conduct the research project strictly in accordance with the research proposal submitted and granted ethics approval, including any amendments required to be made to the proposal by the Human Research Ethics Committee.
Inform the Human Research Ethics Committee immediately of anything which may warrant review of ethics approval of the research project, including: serious or unexpected adverse effects on participants; unforeseen events that might affect continued ethical acceptability of the project; and a written report about these matters must be submitted to the Academic Committees Office by no later than the next working day after recognition of an adverse occurrence/event. Please note that in cases of adverse events an incident report should also be made to the Health and Safety Office:

http://www.otago.ac.nz/healthandsafety/index.html

Advise the Committee in writing as soon as practicable if the research project is discontinued.

Make no change to the project as approved in its entirety by the Committee, including any wording in any document approved as part of the project, without prior written approval of the Committee for any change. If you are applying for an amendment to your approved research, please email your request to the Academic Committees Office:

gary.witte@otago.ac.nz

Jo.farrondediaz@otago.ac.nz

Approval is for up to three years from the date of this letter. If this project has not been completed within three years from the date of this letter, re-approval or an extension of approval must be requested. If the nature, consent, location, procedures or personnel of your approved application change, please advise me in writing.

Yours sincerely,

[Signature]

Mr Gary Witte  
Manager, Academic Committees  
Tel: 479 8256  
Email: gary.witte@otago.ac.nz

C.c. Professor D Elder  Department of Paediatrics and Child Health (Wgnt)
Appendix C Infant characteristics

Antenatal information collected:
- Maternal smoking
- Use of antenatal steroids (including whether a full (double) dose, partial dose or multiple doses had been given)
- Length of rupture of membranes
- Presence of chorioamnionitis (including if it had been confirmed on histology or was just suspected from swabs)
- Presence of multiple gestations including any twin-to-twin transfusion syndrome (TTTS) and birth order

Birth and resuscitation information collected:
- Gestation at birth
- Method of delivery
- Condition of the infant at birth (including APGARS and resuscitation notes)
- Infant birth weight, head circumference and length.
- The CRIB score was calculated (birth weight, gestational age, the presence of congenital malformations, worst base excess, maximum and minimum appropriate fraction of inspired oxygen (F\textsubscript{I}O\textsubscript{2}) during the first 12 h of life)

Postnatal information collected:
- The number of days the infant was on respiratory support (including number of days intubated, on CPAP, on oxygen, and on caffeine)
- The number of days the infant was on cardiorespiratory monitoring and reports of any 24-hour oximetry studies done on the infant during their stay/as a pre-discharge check as part of normal NICU assessment were photocopied.
- Use of any steroids
- Number of blood transfusions the infant had during their stay in NICU
- Highest serum bilirubin (SBR) during their stay in NICU
- Relevant medical conditions: PDA and treatment (medical or surgical), CLD, persistent pulmonary hypertension of the newborn (PPHN), sepsis at any point, reflux
(had to be medicated), IVH and severity, PVL and severity, ROP and severity, and if the infant had any surgery during their stay.

**Information on the infant at time of discharge oximetry:**
- Infant PMA at time of study
- Method of feeding
- Type of milk (Formula/EBM)
- Current use of supplemental oxygen and amount
- Most recent haemoglobin and SBR levels and date of these
- Any current medical issues
- Documentation of clinical concern about apnoea
- Number of days until discharge (from the completion of the 24-hour recording)