**An audit of the incidence and severity of hypoxia in PACU using Hudson mask and heated humidified high flow nasal cannula oxygen therapy**

What is the incidence and severity of hypoxia in the Post Anaesthetic Care Unit (PACU) at Starship Hospital? What risk factors are associated with that hypoxia? Will heated humidified high flow nasal cannula therapy, administered through the Optiflow™, result in a significant decrease in the incidence of hypoxia seen in the PACU?

Protocol Number: 1

A collaborative project conducted by The Department of Anaesthesiology, University of Auckland, Auckland Starship Children’s Hospital

**Study title:** This pilot study is an audit of the incidence and severity of hypoxia in Starship Post Anaesthetic Care Unit (PACU) using standard low flow Hudson mask and heated humidified high flow nasal cannula (HHHFNC) therapy.

**Protocol Number:** 1.0

**Sponsor: Auckland District Health Board (ADHB)**

**AGREEMENT**

This document is confidential. The Investigators declare that they have read the final study protocol and any amendments. The Investigators will conduct the study according to the procedures specified in the study protocol, and in accordance with ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA comments and NH&MRC National Statement on Ethical Conduct in Research Involving Humans.

Paul Baker.................................... 04 10 2015............................

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# ABBREVIATIONS

ACH Auckland City Hospital

ADHB RRC Auckland District Health Board Research Review Committee

ANZCTR Australian New Zealand clinical trials registry

AUC Area under the curve

ASA American Society of Anesthesiologists physical status score

CICO ‘can’t intubate can’t oxygenate’

CPAP Continuous positive airway pressure

FEO2 Fraction expired oxygen

FiO2 Fraction inspired oxygen

FPH Fisher and Paykel Healthcare

HDEC Health and Disability Ethics Committee

HHHFNC Heated humidified high flow nasal cannula therapy

ICU Intensive care unit

IV Intravenous

OR Operating room

NICU Neonatal intensive care unit

PACU Postoperative care unit

RCT randomised controlled trial

SpO2  Peripheral capillary oxygen saturation

#  SUMMARY/SYNOPSIS

**Technique under study:**

Heated humidified high flow nasal cannula therapy (HHHFNC) using the Fisher and Paykel’s Optiflow™ device

**Objectives of the study:**

1. To audit paediatric patients in the post anaesthetic care unit (PACU) at Starship Children’s Hospital to establish the incidence and severity of hypoxia
2. To evaluate the benefit of HHHFNC as a technique to reduce the incidence of hypoxia in the PACU

**Study design:**

An audit will be conducted in Starship PACU to establish the incidence and severity of postoperative hypoxia using current standard oxygen therapy with a Hudson mask. This will be followed by a second audit to establish the impact of HHHFNC on postoperative hypoxia. This is a pilot study. There are no comparable published studies. A previous pilot study has not been conducted. The expected effect is not known.

**Type and number of subjects/patients:**

We will study paediatric patients in the PACU over fourteen weeks (approximately 2000 patients).

**Principal clinical endpoint(s):**

A. Objective data.

1. The total area under the curve (AUC) of SpO2 ≤ 90 (hypoxemia) for the duration of each patients stay in PACU
2. The area under the curve (AUC) of SpO2 ≤ 85 (severe hypoxemia) for the duration of each patients stay in PACU

B. Subjective data

Adverse respiratory events requiring active intervention

**1. INTRODUCTION**

**1.1 Title**

What is the incidence and severity of hypoxia in the PACU? Does heated humidified high flow nasal cannula therapy (HHHFNC) reduce the incidence of hypoxemia during recovery after paediatric anaesthesia?

**1.2 Study Background**

Respiratory complications resulting in hypoxia are the most common adverse events for children in the perioperative period. Although hypoxia is well studied during anaesthesia, little is known about children who become hypoxic whilst recovering from anaesthesia. This study aims to improve our understanding of hypoxia in the PACU by defining its incidence and severity. We will also document risk factors for hypoxia and whether the use of HHHFNC is effective in reducing the incidence of hypoxia while recovering from anaesthesia.

Fisher and Paykel’s Optiflow™ uses modified nasal catheters to deliver heated humidified high flow nasal oxygen comfortably to patients’ at high flow (e.g. 2 litres per kilo per minute). HHHFNC is well established in intensive care settings (where its value in supporting oxygenation in the context of certain types of respiratory failure has been demonstrated) but has only been used in small numbers of patients undergoing anaesthesia. A recent case series has shown that the use of transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) with the Optiflow™ device in adult patients with difficult airways, in combination with adequate maintenance of an open airway, allows these patients to remain oxygenated without breathing for extended periods of time (even up to an hour in some cases) [1](#_ENREF_1). There are no reports using HHHFNC in PACU. Potential advantages for this therapy include reducing the work of breathing and improving the efficiency of ventilation. This may be achieved by washing out nasopharyngeal deadspace, reducing respiratory resistance, improving pulmonary compliance, reducing metabolic work and providing positive distending pressure which may assist lung recruitment. HHHFNC is well tolerated by patients and is easily set up [2](#_ENREF_2" \o "Hutchings, 2015 #95).

Current methods of clinical assessment designed to anticipate patients who are likely to develop hypoxia have low predictive value. It is therefore prudent to treat all patients with oxygen who are unconscious and recovering from anaesthesia. Numerous studies have established the benefit of oxygen therapy during the anaesthetic recovery phase [3](#_ENREF_3" \o "Sear, 2013 #98). Our primary interest is in increasing the margin of safety for patients who develop unanticipated airway difficulties after anaesthesia. It is possible that reducing the incidence of hypoxemia may be worthwhile in its own right. The link between transient hypoxemia and patient outcome is not yet known, and most clinicians agree that a short, transient dip in oxygen saturation is probably of little clinical consequence. However, avoidance of hypoxemia is generally considered best practice. A recent retrospective study found that 6.8% of adult patients (aged ≥ 16 y) undergoing surgery in two large, academic teaching hospitals had a hypoxemic event. Of these, 3.5 % were classed as severe (SpO2 < 85%) with a duration of two minutes or longer [4](#_ENREF_4). Smaller functional residual capacity and increased metabolic requirements make paediatric groups particularly susceptible to inadequate ventilation during surgery. In non-cardiac, paediatric operations, around 35% of patients are thought to experience an episode of intraoperative hypoxemia of at least 1 minute in duration (SpO2 < 90%) [5](#_ENREF_5). Risk of severe hypoxemia was greater in younger age groups, with the highest risk in neonates (92 episodes of hypoxemia for every 100 cases) [5](#_ENREF_5" \o "de Graaff, 2013 #76). There are very few studies concerning hypoxia in the paediatric PACU. Results vary depending on study methodology and the use of oxygen during transport from the OR [6](#_ENREF_6),[7](#_ENREF_7).

**HHHFNC and the Optiflow™ device**

This will be a prospective, audit of paediatric patients recovering from anaesthesia and surgery. In the control group, postoperative oxygenation will be according to standard practice of the attending anaesthetists. In children, this is usually oxygen at 6 L/min through a Hudson mask. Oxygen therapy continues until the patient regains consciousness and oxygen saturations are stable above 94% for several minutes. A trial on air is then commenced at the discretion of the recovery room nurse. If the patient suffers hypoxia at any stage (oxygen saturation < 90%), the nurse calls for help, manoeuvres are applied to ensure a patent airway, oxygen FiO2 is increased to 100%, a T-piece circuit is deployed and the patient is ventilated with continuous positive airway pressure (CPAP) until normal oxygen levels (>94%) are restored.

 In the second stage of the audit, HHHFNC will be provided routinely for postoperative oxygenation. Nasal cannulae will be applied in the operating room before transport to PACU. The patient will receive 6L/min via nasal cannula from an oxygen cylinder for transport to PACU. Upon arrival in PACU, the oxygen tubing will be transferred to the Optiflow using a gas flow of 2 L/Kg/min up to 40 L/min and a starting FiO2 of 35%. Oxygen therapy continues until the patient regains consciousness and oxygen saturations are stable above 94% for several minutes. A trial on air is then commenced at the discretion of the recovery room nurse. If the patient suffers hypoxia at any stage (SpO2 ≤ 90%), the nurse calls for help, manoeuvres are applied to ensure a patent airway, oxygen FiO2 on the Optiflow is increased to 100% and the patient continues on HFNC until normal oxygen levels (>94%) are restored. Change to a T-piece will be available if intermittent positive pressure ventilation is deemed to be necessary.

Individual practices vary, and may include supraglottic airway during recovery and inadequate or no oxygenation in some patients [6](#_ENREF_6),[7](#_ENREF_7). In the control group we will ask anaesthetists to conform with the majority treatment of 6L/min by Hudson mask if possible.

HHHFNC for oxygenation uses high flow, warm, humidified oxygen via Optiflow™ nasal prongs. Humidity makes the treatment more tolerable, while the high flow pushes oxygen down the concentration gradient into the tissues and the alveolar dead space. This device has been used in several clinical settings already, including ICU [8](#_ENREF_8) and paediatric patients, and at several hospitals internationally [9](#_ENREF_9" \o "Manley, 2013 #85). It is currently used in neonatal and paediatric intensive care units, and on the wards at Starship Hospital. It is comfortable to use and has very few additional risks over standard/conventional oxygenation methods [2](#_ENREF_2" \o "Hutchings, 2015 #95). In addition, once fitted it requires no further action on behalf of the anaesthetist or recovery nurse.



**Figure 1.** Optiflow™ therapy. Warm, humid oxygen is delivered via nasal prongs at high flow. Delivery is comfortable and non-invasive. Figure taken from <https://www.fphcare.co.nz/respiratory/adult-and-pediatric-care/optiflow/>

**Rationale of study**

Although many clinicians oxygenate all of their patients following anaesthesia in the recovery phase, the effectiveness of this when conventional methods are used may be dependent on several patient risk factors (for example, those with a difficultairway, patients with co-morbidity such as chronic lung disease, congenital airway anomalies, obstructive sleep apnoea, apnoea associated with immaturity) or poor patient compliance for a face mask. Oxygen therapy in the PACU using HHHFNC may be simpler, more comfortable and therefore more reliably accomplished than conventional methods. This may thereby increase the safety margin for all patients during the vulnerable period between unconsciousness and consciousness following anaesthesia. It may also provide some protection from hypoxemic episodes that occur moderately frequently during the postoperative period (> 6.8% of cases), particularly in neonates and infants [4](#_ENREF_4),[5](#_ENREF_5).

We wish to measure the impact of high flow oxygenation using HHHFNC for paediatric patients following surgery and anaesthesia to see whether this technique reduces the incidence and severity of postoperative episodes of hypoxemia over current techniques.

**Rationale of comparator medication/treatment**

Use of HHHFNC will be compared to patients receiving low flow oxygen through a Hudson face mask. This study will essentially examine oxygen therapy via two different routes, using current Hudson mask oxygen treatment and humidified oxygen at a higher flow.

###

### Studies of relevance

|  |  |
| --- | --- |
|  | **Findings** |
| **de Graaff et al** [**5**](#_ENREF_5) | Prospectively monitored patients aged ≤ 12y undergoing elective non-cardiac surgery (N=575). Incidence of hypoxemia, defined as SpO2 ≤ 90% for a duration of 1 min or more, was recorded. At least 1 episode of hypoxemia occurred in 12% of cases. Lower age was associated with higher rates of hypoxemia, with neonates at the greatest risk. |
| **Ehrenfeld et al** [**4**](#_ENREF_4) | Retrospective review of anaesthetic records for adult, non-cardiac patients (N= 95,407) conducted by our team at Auckland City Hospital and a team in Boston. Hypoxemia (SpO2 ≤ 90% for 2 min or more) occurred during induction in 7.4% of cases. This was severe (SpO2 ≤ 85%) in 4.1 % of cases. |
| **Patel et al** [**1**](#_ENREF_1) | N=25, extended safe apnoea times using Optiflow™ (given for 10 min at 70L/min), without episodes of desaturation to 14 (9‑19) min |
| **Laycock et al** [**7**](#_ENREF_7) | N=105 children aged 2 weeks to 14 years. All breathed air from the OR to PACU. 81 continued on air in PACU. 56/105 (53%) experienced hypoxia (SpO2 < 90%). |

## Conclusion

Postoperative oxygen therapy using HHHFNC therapy may have the potential to reduce postoperative episodes of hypoxemia. This could be achieved by improved patient tolerance of nasal prongs, reduced work of breathing, improved efficacy of ventilation, CPAP, and continuous therapy without interruption. We will measure the impact of HHHFNC for routine postoperative oxygenation using a prospective, audit in paediatric patients.

Our primary study outcomes will be the difference in the total AUC of SpO2 ≤ 90 % (hypoxemia), and SpO2 ≤ 85 % (severe hypoxemia), plus a record of adverse respiratory events requiring active intervention between groups during their stay in PACU.

# 2. OBJECTIVES

We propose to answer the following clinically important question:

Does the provision of routine HHHFNC, for postoperative oxygen therapy in the PACU, reduce the incidence, duration and severity of hypoxemia episodes in paediatric patients? This morbidity will be defined by objective measurement of SpO2 ≤ 90 %, and subjective recordings of a reduction in adverse respiratory events requiring an active intervention.

## 2.1 Primary Objective and Endpoint

1. The difference in AUC of SpO2 ≤ 90 % between HHHFNC and control groups treated in the PACU.
2. Adverse respiratory events requiring an active intervention.
	1. **Secondary Endpoints**
3. The difference in AUC of SpO2 ≤ 85 % between HHHFNC and control groups treated in the PACU.
4. We will conduct subgroup analyses for paediatric patients. Of particular interest will be patients at risk of hypoxia, as found in the control study.

# 3. STUDY DESIGN

##  3.1 Experimental Design

This will be a pilot study in two parts.

1. The first stage in the study will be a prospective audit of hypoxia in the PACU. Using computers loaded with e-Data Grabber software, we will draw SpO2 measurements at 0.1 second intervals from the PACU Drager monitors and store that information on a secure Excel spreadsheet for analysis. Data will be linked to patients by NHI number to enable a study of patient demographics, anaesthetic and surgical history and co-morbidity. Objective assessment of any adverse respiratory events requiring active intervention will also be recorded. These events will include the following:-
	1. Vigorous tactile stimulation
	2. Airway repositioning including chin lift, head tilt, jaw thrust, midline repositioning
	3. Suctioning
	4. Supplemental or increased oxygen delivery or change of airway device including a T-piece
	5. Oral or nasal airway placement
	6. Application of positive pressure or ventilation with bag mask
	7. Pharmacological treatment of respiratory compromise including neostigmine/atropine/glycopyrrolate, naloxone, sugammadex, flumazenil, suxamethonium, propofol.
	8. Tracheal intubation

We plan to record this data from 1000 patients visiting the PACU during the period of the audit. Patients will receive standard oxygen therapy of 6L/min via a Hudson mask whenever possible.

1. The second stage of the study will be another prospective audit using HHHFNC and the Optiflow. Patients will be fitted with an appropriate size for age Optiflow nasal cannula prior to leaving the operating room. They will receive 6L/min oxygen via the nasal prongs during transit from the operating room to the PACU. Upon arrival in the PACU, their nasal prongs will be connected to the Optiflow and they will receive HHHFNC at 2L/Kg/min and FiO2 0.35.

Using computers loaded with e-Data Grabber software, we will draw SpO2 measurements at 0.1 second intervals from the PACU Drager monitors and store that information on a secure Excel spreadsheet for analysis. Data will be linked to patients by NHI number to enable a study of patient demographics, anaesthetic and surgical history and co-morbidity. Objective assessment of any adverse respiratory events requiring active intervention will also be recorded. These events will include the following:-

* 1. Vigorous tactile stimulation
	2. Airway repositioning including chin lift, head tilt, jaw thrust, midline repositioning
	3. Suctioning
	4. Supplemental or increased oxygen delivery or change of airway device including a T-piece
	5. Oral or nasal airway placement
	6. Application of positive pressure or ventilation with bag mask
	7. Pharmacological treatment of respiratory compromise including neostigmine/atropine/glycopyrrolate, naloxone, sugammadex, flumazenil, suxamethonium, propofol.
	8. Tracheal intubation

We plan to record this data from 1000 patients visiting the PACU during the period of the audit.

1. At the end of the study we will analyse the results including a comparision of objective and subjective data from each stage of the study.

 3.2 Subject Selection.

This will be a prospective audit of all patients entering the Starship PACU during the duration of the study. Some patients will be excluded from the HHHFNC group according to exclusion criteria (3.2.3).

3.2.1 **Definition of Disease to be studied** [**10**](#_ENREF_10)(adapted from Bhatt M, et al Annals of Emergency Medicine 2009; 53: 426-435.e4)

1. Oxygen desaturation definition (hypoxia). Oxygen desaturation will be measured objectively using pulse oximetry. Oxygen desaturation is SpO2 ≤90% for at least 1 minute. Severe oxygen desaturation is SpO2 ≤85% for at least 1 minute [5](#_ENREF_5" \o "de Graaff, 2013 #76), *and* subjective measurement of oxygen desaturation determined by one or more of the following interventions intended to improve oxygen saturation [10](#_ENREF_10).
	1. Vigorous tactile stimulation
	2. Airway repositioning including chin lift, head tilt, jaw thrust, midline repositioning
	3. Suctioning
	4. Supplemental or increased oxygen delivery or change of airway device including a T-piece
	5. Oral or nasal airway placement
	6. Application of positive pressure or ventilation with bag mask
	7. Pharmacological treatment of respiratory compromise including neostigmine/atropine/glycopyrrolate, naloxone, sugammadex, flumazenil, dexamethasone, adrenaline, suxamethonium, propofol, Helium.
	8. Tracheal intubation
2. Apnoea definition (central). Cessation or pause of respiratory effort *and* subjective record of one or more of the following interventions:
	1. Vigorous tactile stimulation
	2. Bag mask ventilation
	3. Increase FiO2
	4. Tracheal intubation
	5. Pharmacological treatment of respiratory compromise including neostigmine/atropine/glycopyrrolate, naloxone, sugammadex, flumazenil, dexamethasone, adrenaline, suxamethonium, propofol, Helium.
3. Apnoea definition (obstruction). Partial upper airway obstruction. Includes the presence of one or more of the following:
	1. Stridor
	2. Stertor (snoring)
	3. Chest wall and suprasternal retractions and rapid resolution with one or more of the following interventions
	4. Airway repositioning
	5. Increase FiO2
	6. Suctioning
	7. Oral or nasal airway insertion
	8. Application of positive pressure (without assisted ventilation)
	9. Pharmacological treatment of respiratory compromise including neostigmine/atropine/glycopyrrolate, naloxone, sugammadex, flumazenil, dexamethasone, adrenaline, suxamethonium, propofol, Helium.
4. Laryngospasm. Partial or complete upper airway obstruction with oxygen desaturation caused by involuntary and sustained closure of the vocal cords, not relieved by routine airway manoeuvres or suctioning.

Interventions include:

1. Pull mandible forward (Larson’s manoeuvre)
2. Increase FiO2
3. Continuous positive airway pressure (CPAP)
4. Propofol, suxamethonium or other neuromuscular blockers
5. Tracheal intubation

###  3.2.2 Source and Number

We will conduct this study at Starship Children’s Hospital PACU. All non-cardiac children who enter the PACU postoperatively (who match our eligibility/ineligibility criteria) will be studied.

###  3.2.3 Entrance Criteria[[1]](#footnote-1)

**Inclusion criteria will include the following:**

Males and females, age 16 years and under admitted to PACU following anaesthesia or sedation

**Exclusion Criteria**

1. Current participant on any other clinical study
2. Serious abdominal, cardiac or respiratory malformations including tracheo-oesophageal fistul (TOF), intestinal atresia, omphalocele, gastroschisis, or diaphragmatic hernia.
3. Patients with chronic hypoxia (cardiac, renal, haematological or respiratory etiology)
4. Admitted to PACU with a supraglottic airway (SGA) in situ
5. Admitted to PACU with a tracheal tube in situ
6. Admitted to PACU with a tracheostomy tube in situ

The contraindications for Optiflow are based on that for CPAP because nasal high flow therapy has been shown to produce positive airway pressure, similar to that of CPAP. CPAP therapy is well-established with correspondingly well-established contraindications:

1. **Bubble CPAP Contraindications (Infant)**

|  |  |
| --- | --- |
| **Contraindication** | **Reason for contraindication** |
| Non-spontaneous breathing | Infant must be breathing spontaneously to receive HHFNC |
| Congenital abnormalities or malformations where bi-nasal prongs or nasal mask are contraindicated |  |
| Congenital abnormalities or malformations where positive pressure therapies are contraindicated | HHHFNC therapy requires a suitable open airway to provide positivepressure |
| Nasal trauma/ severe deformity that might be exacerbated by use of nasal prongs or nasal mask | HHHFNC therapy is provided through bi-nasal prongs |

## 3.3 Study intervention

For patients undergoing surgery or sedation during the first stage of the study, anaesthetists will be asked to deliver oxygen by Hudson mask at 6L/min to all patients leaving the operating room and during their stay in PACU (common practice). For the second stage of the study, following surgery and the establishment of spontaneous ventilation, anaesthetists will be asked to fit Optiflow nasal prongs in the OR and deliver oxygen 6L/min until arrival in PACU, then connect them to the Optiflow with 2L/Kg/min up to 40 L/min and FiO2 0.35. Monitoring during transport and in PACU will follow normal practice. At all times the anaesthetist and the recovery room nurse will observe safe patient care and respond to any adverse event with appropriate care (see section 3.2).

## 3.4 Study Procedure

Demographic, anaesthetic and surgical data will be collected from the intraoperative and patient records. Low flow oxygen by Hudson mask is current standard therapy in our hospital. HHHFNC by Optiflow is a non-invasive, comfortable method of delivering oxygen and is now established therapy in several paediatric departments within our hospital and internationally. We therefore do not anticipate that patients will need to be approached individually to provide consent.

### 3.4.1 Sequence of Procedures

Study Flow Chart

|  |  |  |
| --- | --- | --- |
|  | Stage 1 (Control audit) | Stage 2 (Optiflow audit) |
| Informed Consent | NA | NA |
| Roll out of PACU hypoxia audit* Presentations, discussion and demonstration/training for PACU staff by clinical researchers and FPH engineers
 | Yes | Yes |
| DemographicsInformation collection from anaesthetic and clinical records* Entry criteria
* Demographics
* Medical and surgical history
* Anaesthetic & surgical details recorded
* PACU SpO2 recordings
* Daily back up of electronic recordings
* Recording of adverse events requiring active intervention
 | YesYes | YesYes |

### 3.4.2 Steps to be taken if there is clinical evidence of a complication

Postoperative period.

The Optiflow device has an international clinical record of use for over 10 years, in patients ranging from premature neonates to adults. The Optiflow is currently being used at Auckland City Hospital in intensive care, emergency departments and on the wards. This device has an excellent safety record. The nasal prongs will be fitted onto the patient under the supervision of the anaesthetist. The Optiflow will be used in the PACU by PACU nurses who will undergo preliminary training by FPH engineers. Starship Anaesthetic technicians will also receive training from FPH. This study will be monitored by two research students who will oversee the smooth running of the project. If any technical problems arise with the Optiflow, Starship technicians will be available and FPH engineers will be on-call.

The Optiflow set-up is simple and it can be rapidly deployed. We believe that the potential for harm from the Optiflow is minimal.

### 3.4.3 Clinical Observations

Standard patient monitoring according to ANZCA guidelines will apply at all times.

# 4. EXPERIMENTAL CONTROL

##  4.1 Randomisation

This is a pilot audit study which will involve two stages. Stage 1 is a control study, and stage 2 will involve HHHFNC with the Optiflow. Randomisation will not apply.

##  4.2 Blinding Procedure

This is a pilot study which will involve two stages. Stage 1 is a control study, and stage 2 will involve HHHFNC with the Optiflow. Blinding of medical and nursing staff would not be possible and therefore will not apply.

##  4.3 Case Report Forms

Data will be extracted directly from the PACU monitor into a study database. Individuals will be identifiable only by each participant’s unique study identifier. No data that identifies individuals will be recorded.

##  4.4 Compliance Checks

NA

##  4.5 Patient Completion/Withdrawal

In some cases we anticipate that anaesthetists may choose not to use the Optiflow. We will ask the anaesthetist to document this in the anaesthetic record if they choose not to use the device, or if exclusion criteria apply.

##  4.6 Continuation of Therapy

PACU nurses will be advised to keep the Optiflow cannulae attached until the patient is discharged from PACU. This will allow immediate resumption of Optiflow HFNC therapy if or when required.

##  4.7 Adverse Experiences

Any adverse events will be documented.

# 5. DATA MANAGEMENT PROCEDURES

##  5.1 Review and Confirmation of Case Report Forms

An individual computer will be attached to each PACU monitor. The computers will be backed up to an external hard-drive every 24 hours. Research assistants will ensure continuous data entry.

##  5.2 Data Base Production and Verification

1. Direct observation by research assistants will be required to minimize data artifacts [5](#_ENREF_5" \o "de Graaff, 2013 #76).
2. The e-Data Grabber software will not record data which is less than 60 seconds duration.
3. Data will be scrutinized for duplicate entries. This occurrence can be identified by matching three or more identifying patient variables (NHI, patient admission and discharge time on PIMMs and date of birth).
4. Following scrutiny, patients will be assigned a study number and all identifying patient data will be removed. The de-identified database will be kept on a secure research drive at the Department of Anaesthesiology, University of Auckland.
5. Subjective data and demographics will be recorded onto Qualtrics survey software.

# 6. STATISTICAL CONSIDERATIONS

##  6.1 Patient Categories

##  6.2 Sample Size and Power

We found no comparable published studies which would lead to a sample size and power analysis. For this reason a preliminary audit will be conducted to establish the incidence and severity of hypoxia in this PACU. Following stage one of this pilot study, a sample size calculation will be completed by the statistician.

Significance will be set at 0.05

Power set at 0.9

Sample size will depend on the pilot result

The expected effect will not be known until the result of the pilot data is available.

Previous reported studies have not been consistent with current oxygen therapy in the PACU. In these studies, oxygen has been omitted during transport to PACU, or omitted in PACU. Reported incidence of hypoxia in PACU range from 4% (Gift, n=293) [6](#_ENREF_6) to 56% (Laycock, n=105) [7](#_ENREF_7" \o "Laycock, 1988 #79).

##  6.3 Statistical Methods

The AUC of SpO2 ≤ 90 and ≤ 85 will be analysed using general linear models to assess the relationship between hypoxia and HFNC.

##  6.4 Interim Analysis

No interim

## 6.5 Planned Sub-Group Analysis

## 6.6 Missing Data

Missing data will be treated as missing at random and no imputation will be undertaken

## 6.7 Projected rate of recruitment/timeline

We hope to complete stage one of this study by October, and conclude stage two in December.

# 7. PERSONNEL RESPONSIBILITIES

##  7.1 Investigators

An appropriate qualified co-investigator will be responsible for study running, administration, data collection, ethics and publication of results. Two research students will work full-time on this project from September until December. Analysis of study results will be collated by the researchers and analysis of study results will be conducted by the study statistician.

##  7.2 Pharmacist

NA

 **7.3 Monitor**

NA

##  7.4 Sponsor

The JAFA trust has overseen funding of this project. Auckland City Hospital will be responsible for the study and will be the “sponsor” of the study as that term is defined in the guideline entitled “E6 Good Clinical Practice Consolidated Guideline”, published by the US Food and Drug Administration.

Computers used to retrieve data from the Drager PACU monitors have been purchased from a grant provided by the JAFA Trust. In turn, a non-specific research grant from FPH was donated to the JAFA Trust.

The HHHFNC are being provided free of charge by FPH. The Optiflows are on loan from FPH for the duration of the study. FPH have agreed to supply Humidification systems (Airvo™ or MR810) x 9 and Humidification consumables (AA400 or equivalent) x 1 per person.

The Optiflow device is owned by FPH. While FPH will have an interest in the outcome of this study, they will not be involved in the development or the conduct of the study. FPH is not a sponsor of the study and FPH has not initiated the study.

**The following correspondence was received from FPH**

***Results and Publication***

*You agree to provide FPH with the final results of the Study.*

*You also agree to provide FPH with any proposed publications or presentations related to the Study for FPH to comment on prior to publication or presentation.*

*FPH may edit references to FPH products in such publications or presentations. However, both parties acknowledge and agree that FPH may not influence the content of the publications or presentations in any other way whatsoever.*

***No Liability***

*FPH’s contribution and involvement in the Study is in the nature of providing the specified equipment only. FPH has not been and will not be involved in the development of the Study or the conduct of the Study. You and the Hospital confirm that:*

1. *FPH will not be liable for any aspect of the Study;*
2. *FPH has not initiated the Study;*
3. *FPH is not a “sponsor” of the Study for the purposes of ethics committee approval or any other aspect of the Study;*
4. *the Hospital will be responsible for the Study and will be the “sponsor” of the Study, as that term is defined in the guideline entitled “E6 Good Clinical Practice Consolidated Guideline” published by the US Food and Drug Administration;*
5. *the Hospital will ensure that it has the appropriate consents and approvals to carry out the Study at the Hospital; and*
6. *the Hospital will carry out the Study in accordance with Good Clinical Practice, all applicable approvals, laws, regulations and protocols.*

None of the investigators or their relatives has any commercial interest in FPH.

##  7.5 Steering Committee and Adjunct Committees

Steering Committee

**Endpoint Adjudication Committee (EAC)**

An EAC has not yet been appointed

# Data Safety & Monitoring Committee (DSMC)

A DSMC has not yet been appointed

# 8. ADMINISTRATIVE PROCEDURES

##  8.1 Amendments to the Protocol

Amendment and refinement to the statistical plan is likely, based on results from the stage one audit.

##  8.2 Early Termination or Extension of the Study

The appropriate ethics committee and regulatory boards will be notified of study termination or extension, as appropriate.

##  8.6 Confidentiality/Publication of Study Results

Data will be kept in a lockable cabinet at the Department of Anaesthesiology, University of Auckland. This data will be de-identified upon collection of all information pertaining to patient and medical identities. Electronic data will be kept on a secure server within the Department, and any data kept on hard disk storage and will be locked in a secure cabinet at the Department. Again, this data will all be de-identified. Long term storage may be entirely electronic.

Our aim is for the results of this study to be published in a peer-reviewed journal. We expect Dr Paul Baker will be first author and Prof. Alan Merry will be the last author, although ultimately the list of authors on any resulting papers will reflect the contributions to the body of the work published. It is likely that results will also be presented at relevant conferences if the opportunity should arise. No data that can identify individuals will be included in any of the published material.

##  8.7 Retention of Records

Data will be retained at the Department of Anaesthesiology, University of Auckland, for a minimum of 7 years in compliance with study ethics approval.

##  8.8 Audits

NA

# 9. ETHICS PROCEDURES

##  9.1 Guidelines for Good Clinical Practice

This study will be conducted in accordance with the ICH GCP notes for Guidance on Good Clinical Practice (CPMP.ICH.135.95 and annotated with TGA comments).

##  9.2 Precautionary Advice

##  9.3 Participant Information Sheet and Consent Form

We do not anticipate that participant consent will be required for this study. This has been confirmed by the HDEC 15/STH/123 “A prospective observational study of humidified high flow nasal oxygen (Optiflow) in the paediatric recovery room”. This decision was made through the HDEC-Full Review pathway.

##  9.4 Ethics Committee

1. Ethics approval has been confirmed by the HDEC 15/STH/123 “A prospective observational study of humidified high flow nasal oxygen (Optiflow) in the paediatric recovery room”. This decision was made through the HDEC-Full Review pathway.
2. The ADHB RRC (Project a+6846) has approved stage one of this study (31/08/2015). Stage two will be considered at an ADHB RRC meeting on October 18th 2015.

## 9.4 Trial Registration

This study will be registered with the Australian and New Zealand Clinical Trials registry (http://www.anzctr.org.au/).

**Appendix 1, Paediatric Optiflow™guideline**



**Appendix 2,** Starship PACU Hypoxia Study: Budget

|  |  |  |  |
| --- | --- | --- | --- |
| **Item** | **Detail** | **Source** | **Cost (incl. GST)** |
|  |  |  |  |
| Equipment | Computers x 9 | JAFA trust | $4422.90 |
| Equipment | Terabite hard drive | JAFA trust | $186.30 |
| Equipment | Security cables x 9 | JAFA trust | $43.47 |
| Equipment | Data cables x 9 | JAFA trust | $112.70 |
|  |  |  |  |
| Research assistants | Two Swedish elective medical students.  | Linkopings University, Sweden. | Nil |
|  |  |  |  |
| Equipment | Optiflows | Fisher & Paykel Healthcare (FPH) | Nil (on loan) |
| Equipment | Humidification consumables | Fisher & Paykel Healthcare (FPH) | Nil (supplied free of charge by FPH). |
|  |  |  |  |
| Gross cost |  | Donation | $4765.37 |
| Net cost |  |  | Nil |

Please note that this is a nil account. There are no net expenses associated with this study. There are no financial implications associated with this study for ADHB.

This account has been seen by Mr Shailendra Deo who is the Starship Research accountant. A signed “zero” budget is included in the ADHB RCC application.

**References**

1. Patel A, Nouraei SA: Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. Anaesthesia 2015; 70: 323-9

2. Hutchings FA, Hilliard TN, Davis PJ: Heated humidified high-flow nasal cannula therapy in children. Archives of Disease in Childhood 2015; 100: 571-5

3. Sear JW: Oxygen: needed for life. But do we need supplemental oxygen during transfer from the OR to the PACU? Journal of Clinical Anesthesia 2013; 25: 609-11

4. Ehrenfeld JM, Funk LM, Van Schalkwyk J, Merry AF, Sandberg WS, Gawande A: The incidence of hypoxemia during surgery: evidence from two institutions. Canadian Journal of Anaesthesia 2010; 57: 888-97

5. de Graaff JC, Bijker JB, Kappen TH, van Wolfswinkel L, Zuithoff NP, Kalkman CJ: Incidence of intraoperative hypoxemia in children in relation to age. Anesthesia & Analgesia 2013; 117: 169-75

6. Gift AG, Stanik J, Karpenick J, Whitmore K, Bolgiano CS: Oxygen saturation in postoperative patients at low risk for hypoxemia: is oxygen therapy needed? Anesthesia & Analgesia 1995; 80: 368-72

7. Laycock GJ, McNicol LR: Hypoxaemia during recovery from anaesthesia--an audit of children after general anaesthesia for routine elective surgery. Anaesthesia 1988; 43: 985-7

8. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, Devaquet J, Nseir S, Razazi K, Mira JP, Argaud L, Chakarian JC, Ricard JD, Wittebole X, Chevalier S, Herbland A, Fartoukh M, Constantin JM, Tonnelier JM, Pierrot M, Mathonnet A, Beduneau G, Deletage-Metreau C, Richard JC, Brochard L, Robert R, Group FS, Network R: High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. New England Journal of Medicine 2015; 372: 2185-96

9. Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, Donath SM, Davis PG: High-flow nasal cannulae in very preterm infants after extubation. New England Journal of Medicine 2013; 369: 1425-33

10. Bhatt M, Kennedy RM, Osmond MH, Krauss B, McAllister JD, Ansermino JM, Evered LM, Roback MG, Consensus Panel on Sedation Research of Pediatric Emergency Research C, the Pediatric Emergency Care Applied Research N: Consensus-based recommendations for standardizing terminology and reporting adverse events for emergency department procedural sedation and analgesia in children. Annals of Emergency Medicine 2009; 53: 426-435.e4

1. [↑](#footnote-ref-1)