Statistical Analysis Plan

Avoidance of endotracheal suction in routine, post-operative cardiac patients.

Version 1.1

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A single centre, non-inferiority, randomised controlled trial assessing the safety and efficacy of avoiding endotracheal suction in patients having planned cardiac surgery who are ventilated for ≤12 hours.

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Abbreviations and Definitions

AE	Adverse Event
ABG	Arterial Blood Gas
BMI	Body Mass Index - a person's weight in kilograms (kg) divided by height in meters^2.
CABG	Coronary Artery Bypass Graft
CPOT	Critical Care Pain Observation Tool
eCRF	Electronic Case Report Form
ETS	Endotracheal Suction
ETT	Endotracheal Tube
FiO_2	Fraction of Inspired Oxygen
HFOT	High Flow Oxygen Therapy
HR	Heart Rate
ICU	Intensive Care Unit
ITT	Intention to Treat
MAP	Mean Arterial Pressure
MV	Mechanical Ventilation
NYHA	New York Heart Association classification. Measure of heart failure symptoms graded I-IV
PaO_2	Partial Pressure Oxygen in Arterial Blood
P/F Ratio	Ratio of partial pressure of oxygen (PaO_2) in arterial blood to the fraction of inspired oxygen (FiO_2) being delivered (PaO_2/FiO_2 Ratio)
PP	Per Protocol
RASS	Richmond Agitation and Sedation Scale
SpO_2	Peripheral Capillary Oxygen Saturation

Introduction

Non-communicable diseases (NCD's) now account for more global deaths in both developed and developing countries (1) with NCDs now the leading cause of death in all developing economies with the exception of sub-Saharan Africa (2). Ischaemic heart disease is the leading cause of NCD deaths (1,2) with cardiac surgery one of the most commonly performed surgeries both worldwide (3) and in New Zealand (NZ) (4). Although common, cardiac surgery is major surgery, not without risk, and requires postoperative admission to an Intensive Care Unit (ICU) with at least an overnight stay. During the ICU admission the patient remains sedated and mechanically ventilated until cardiovascularly stable and assessed as ready for extubation. It is anticipated that patients will be ready to extubate within 3-6 hours of admission to ICU with transfer to the ward the following day.

Mechanical ventilation (MV) mandates the use of an artificial airway (endotracheal tube, ETT), this maintains the patient's airway allowing MV while the patient is sedated. Although MV is a frequent intervention in ICU (5), both the ETT and MV carry risks with potential complications including an increased risk of infection (6), inflammatory injury to the airways (7,8), ventilator lung injury as a result of repeated over distension of the lungs (9,10) and pain and distress for the patient (11–13). Part of airway management includes providing endotracheal suction

(ETS). ETS removes secretions from the lungs that the patient is unable to clear by coughing, prevents build-up of biofilm within the ETT and maintains the integrity of the ETT (14–16). However, ETS can contribute to potential complications including trauma to the lungs and airways, hypoxia, cardiac arrhythmias and atelectasis (6,17,18), it is also known to be a painful procedure for the patient (12). ETS is one of the most frequent nursing procedures performed in ICU (5) and is an important part of airway management for patients who have extended periods of MV, however the evidence that underpins clinical practice is acknowledged to be of low quality (19). There is no published evidence about the avoidance of ETS in patients who have planned short term MV in ICU.

Previous research has identified that the majority of nurses perform ETS at the point of extubation (5,20). The rationale is that this will prevent aspiration of any secretions sitting above the ETT cuff when the balloon is deflated at extubation, however there is laboratory evidence that a positive pressure breath at extubation may prevent aspiration (21,22).

Given the known risks associated with ETS we consider that further investigation into the safety and efficacy of avoidance of ETS in the uncomplicated post-operative cardiac surgical patient is warranted. We plan a randomised controlled trial (RCT) assessing the safety and efficacy of avoidance of ETS in patients having planned cardiac surgery and who are ventilated for ≤ 12 hours.

Study hypothesis

Avoiding ETT suction in patients ventilated for ≤12 hours following cardiac surgery is not inferior to usual care suction, including prior to extubation.

H_0: The P/F ratio in the intervention group will be inferior than the P/F ratio in the usual care group by greater than a 10% non-inferiority margin in favour of the usual care group.

$H_{1:}$ The P/F ratio in the intervention group will be non-inferior to the P/F ratio in the usual care group allowing a 10% non-inferiority margin.

Study Aims and Objectives

The aims of the study are:

- Assess the safety and efficacy of avoidance of endotracheal suction in patients receiving mechanical ventilation for ≤12 hours.
- To investigate and describe the patient experience of both the endotracheal tube and endotracheal suction and to provide education and feedback to the nursing staff.

The objectives are

- Analyse the difference in P/F ratio between groups evaluating any difference in variances assessed for non-inferiority. If the intervention group is non-inferior to the usual care group this will to provide the first data about the efficacy of avoiding ETS in this patient cohort.
- To compare safety outcomes between groups by evaluating cardiovascular complications, ventilation complications and rates of escalation of oxygen therapy. If the intervention group has a no greater incidence of complications this will provide data about the safety of avoiding ETS in this patient cohort.
- To record behavioural pain score of patients before, during and following ETS (for those receiving ETS).
- Describe the patient experience of both the ETT and ETS and report patients pain scores as recall by the patient the following day. This data will inform education and training for nursing staff and will add to the body of knowledge about patients experience of the ETT and ETS while in ICU following cardiac surgery.

Study Design

The ARETS (Avoidance of Endotracheal Suction in Routine post-operative Cardiac Patients) study is a single centre, non-inferiority, randomised controlled trial assessing the safety and efficacy of avoiding endotracheal suction in patients having planned cardiac surgery who are ventilated for ≤12 hours. Non-inferiority design requires that the non-inferiority margin is pre-specified and the International Council for Harmonisation provides guidelines for the conduct of clinical trials, including selecting a non-inferiority margin. The guidelines state that "the determination of the margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment, should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative" (23). Therefore, in consultation with senior medical staff on the ICU and an independent statistician, and using available data and clinical expertise within the group, a non-inferiority margin of 10% was considered clinically acceptable for the primary outcome - PaO_2/FiO_2 (P/F) ratio.

Study population and eligibility criteria

Participants will be patients scheduled for cardiac surgery with cardiopulmonary bypass, who are anticipated to receive mechanical ventilation for 12 hours or less.

Inclusion criteria

- ≥16 years old,
- Patients having cardiac surgery with cardiopulmonary bypass (CPB),
- Extubation expected within 12 hours of admission to CVICU

Exclusion criteria

- Documented difficult intubation
- Expected ventilation >12 hours
- Clinician preference for the patient to receive ETT suction.

Randomisation

Patients will be randomised 1:1 to either usual care including ETT suction or usual care with no ETT suction, including at the time of extubation, that is either immediately before or simultaneously with ETT removal. Research nurses or the clinical nurse coordinator will screen the patients on admission to ICU and if it is anticipated that the patient will be extubated within 12 hours of admission to ICU randomisation will occur. Allocation concealment will be achieved by the use of sequentially numbered, opaque, sealed envelopes containing the allocation on a slip of paper folded once. Non-study personnel will prepare the allocation envelopes and an independent statistician will generate the random sequence generation.

Variables Collected

	Pre-operative	Pre-extubation	Post extubation (through to 6 hours post extubation)	Day 1
Baseline Demographics	x			
Comorbidities	x			
Smoking status	x			
EuroSCORE	x			
Arterial blood gases (ABGs)		x	x	
Physiology – HR, MAP, respiratory rate		x	x	
Complications			x	x
Pain scores		x		
Patient interview				x
Adverse event monitoring		x	x	x

Sample Size

Based upon previous work done in the same unit with a similar patient population (24) in a sample of 130 participants receiving supplemental oxygen four hours post extubation, the mean P/F ratio was 301 (SD 83.9). We hypothesised that there would be less variability in the mean P/F ratio for patients not receiving supplemental oxygen (no data is available for this group), and therefore used a SD of 80 for the sample size calculations. We estimated that if there is truly no difference between the standard treatment and the intervention, then 166

patients would be required to be 80% sure that the lower limit of a one-sided 95% confidence interval will be above the 10% non-inferiority limit (P/F ratio no worse than 270). Recruitment will continue until 166 patients achieve the primary outcome. It is not anticipated that there will be any loss to follow up, as all the data will be collected prior to the patients leaving hospital. The G Power sample size calculator was used for sample size calculation (25).

Study Outcomes

Primary Outcome.

The primary outcome of this study is the PaO_2/FiO_2 (P/F) ratio 6 hours after extubation (+/- one hour). P/F ratio is defined as the ratio of partial pressure of oxygen (PaO_2) in arterial blood to the fraction of inspired oxygen (FiO_2) being delivered. It is used to quantify the degree of respiratory dysfunction and reduction in gaseous exchange. A lower P/F ratio is linked with worse gaseous exchange with P/F ratio calculations influenced by the percentage FiO_2 being delivered, therefore spontaneously breathing extubated patients receiving supplemental oxygen that is mixed with entrained room air will be unable to have an accurate P/F ratio calculated. For this reason, the 6-hour post extubation ABG collected to derive the primary outcome will be taken with the participant breathing room air and not receiving supplemental oxygen. Where this is not clinically appropriate, for example those patients receiving high flow oxygen therapy (HFOT), this ABG will be taken with the patient receiving HFOT. HFOT overcomes entrained room air thus providing an accurate FiO_2 to calculate the P/F ratio. Both the PaO_2 and the FiO_2 will be recorded as part of the ABG data collection, and the P/F ratio will be calculated using these measurements.

Secondary Outcomes

- Frequency of escalation of oxygen therapy defined as oxygen therapy increased from nasal prongs/simple face mask to any non-invasive ventilation within 6 hours of extubation. This does not include participants who are extubated onto HFOT or who require HFOT for the 6 hour post extubation ABG collected to calculate the P/F ratio as described in the protocol.
- Tachycardia (>100bpm) defined as one recorded heart rate >100 bpm anytime from admission to ICU to 6 hours post extubation.
- Increased mean arterial pressure (MAP) (>85mmHg) defined as one recorded MAP > 85mmHg anytime from admission to ICU to 6 hours post extubation.
- Increased respiratory rate (>25bpm) defined as one recorded increased respiratory rate >25 bpm anytime from admission to ICU to 6 hours post extubation.
- Complications of extubation including laryngeal spasm, vomiting, aspiration, and oxygen desaturation as measured by SpO_2 <90% 30 minutes after extubation. These complications are defined as occurring at least once 30 minutes following extubation.

- Oxygen desaturation as measured by SpO_2 <90%, defined as one recorded SpO_2 <90% anytime from admission to ICU to 6 hours post extubation, with or without the requirement for escalation of oxygen therapy.
- Re-intubation rates any time from extubation through to 6 hours post extubation.
- Pain scores before, during and after ETS. These will be recorded 10 minutes prior to ETS, during ETS and 10 minutes after ETS for those patients who have ETS performed.
- Patient experience as reported by the patient at a brief interview the following day. This will be recorded using numerical pain scale to report pain from the ETT and ETS, 0 = no pain and 10 = the worst pain imaginable. These interviews will be conducted by experienced research nurses who are unblinded to the intervention and did not provided nursing care for study patients.

With the exception of the pain scores and patient experience, all of the secondary outcome measures will be recorded if the participant has one event within the study period, i.e. through to 6 hours post extubation. This is to facilitate comprehensive safety data collection as to the best of our knowledge this intervention has not previously been performed. Pain scores will be collected at two time points, once with the patient lightly sedated (RASS -3 to +1), using the Richmond Agitation and Sedation Scale (RASS), this is a validated tool to measure agitation sedation levels in ICU (26) and once with the patient awake (RASS 0) and prior to extubation. The critical care pain observation tool (CPOT) (27) is a validated behavioural pain scoring tool and will be used for this study.

Data Sources

All data will be collected by trained research nurses and entered directly onto a password protected electronic case report form (eCRF). The REDCap platform will be used (28,29) and is hosted by the Medical Research Institute of New Zealand (MRINZ). MRINZ has the required security certificates and firewalls in place to protect patient data.

CONSORT Statement

All study participants will be accounted for using the methods recommended by the Consolidated Standards of Reporting Trials (CONSORT) Statement (30). The screening log will be used to provide data about the number of participants screened, numbers who declined and why, numbers consented and randomised and numbers not randomised on admission to ICU. These data will be presented in a flow chart (Figure 1). Data will be provided that describes the numbers allocated to the intervention and usual care group and numbers who did not receive the allocated intervention.

Statistical Analysis

There is currently debate in the literature about which is the best statistical analysis model to use for non-inferiority studies (31–33), with recommendations that both Per Protocol (PP) and Intention to Treat (ITT) should be the lead analysis. The CONSORT group issued a statement extension in 2010 with guidelines for reporting non-inferiority studies (34), recommending that the primary analysis is performed as a PP population analysis, with analysis repeated for sensitivity reasons using an ITT analysis. Data analysis for non-inferiority studies also requires that a confidence interval (CI) approach be used, and we follow these 2010 CONSORT recommendations in this statistical analysis plan. Data will be extracted into IBM SPSS Statistics (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY:IBM Corp.), which will be used for all analyses. Figure and Table shells for displaying results are displayed at the end of this document.

Baseline characteristics and Co-morbidities

The baseline and demographic data will include gender, age, surgery, EuroSCORE II, smoking status, co-morbidities such as diabetes, chronic obstructive pulmonary disease, left ventricular function. Baseline data for all participants achieving the primary outcome will be presented according to treatment group. All continuous variables will be tested for normality; data will be presented as means and standard deviations where normally distributed and otherwise as medians and inter-quartile ranges. Binary and categorical variables will be presented as N (%) in each treatment group. Potential differences in treatment groups according to categorical variables will be assessed using a Chi-square test, or Fisher's exact test where there are low cell counts ($n<5$).

Primary Outcome analysis

The primary outcome analysis will test for differences in P/F ratio between the two treatment groups, which will be analysed for the PP population including only those participants who received their allocated intervention with no major protocol deviations and who had a 6-hour (+/- 1 hour) post extubation ABG recorded. As described above, a sensitivity analysis of the primary analysis will also be assessed for the ITT population. If the PP analysis supports non-inferiority but the ITT sensitivity analysis does not, reasons for this will be investigated and discussed. Analysis will be conducted using a one-tailed Student's *t*-test, or a Mann-Whitney U test if the outcome does not follow a normal distribution. A confidence interval (CI) approach will be used with a one tailed 5% level of significance to assess and report non-inferiority, whereby non-inferiority will only be claimed if the lower limit of the CI does not exceed the 10% non-inferiority margin.

As this is an individualised randomised control trial, we expect baseline data and comorbidities to be similar in both groups. Baseline data will be checked, and if factors are strongly imbalanced adjustments will be made for these in the primary analysis using analysis of covariance.

Secondary outcomes analysis

A Students t-test (for normally distributed variables) or a Mann-Whitney U test (for non-normal distributions) will be used to assess differences in treatment groups for continuous secondary outcomes as described above. Additional data presented by treatment group will include the number of protocol deviations, ABGs performed out of range, numbers of patients excluded on admission to ICU and numbers of patients ventilated for over 12 hours.

A safety analysis will also be conducted using a modified PP analysis. The modification will be to include all patients who were excluded from the primary analysis because collection of the ABG used to calculate the primary outcome was outside the prescribed time i.e. later then 6 hours (+/- one hour) post-extubation. This analysis will include all the safety related secondary outcomes. This will maximise the power to detect any adverse safety signals.

Excluded patients

Those participants who are ventilated for over 12 hours will not have a 6-hour post extubation ABG collected so the primary outcome cannot be calculated. For this reason they will be excluded from the primary outcome analysis. Data about this group will be presented using descriptive statistics, including their baseline data and reasons for prolonged ventilation. This will help to assess whether this group of participants were different at baseline and the reasons for prolonged ventilation.

Data Safety Monitoring Board (DSMB) & Data Monitoring

There will be 100% monitoring of the primary outcome and consents and the first 10 patients will have 100% monitoring to ensure data quality. There will be monitoring of a further 10 patients meeting the primary outcome. Independent monitoring will be provided by MRINZ. For patient safety a data safety monitoring committee (DSMC) has been assembled, they will review the first 50 and 100 patients. The DSMC will consist of an independent statistician and two experienced researchers who are independent of the study. They will receive unblinded reports of the primary and secondary outcome measures in addition to adverse events.

Ethics

The study has been given both full ethical approval (15/NTB/138) and institutional approval.

Dissemination

Results will be published in appropriate peer reviewed journals and presented at both local and international meetings. The results will also be presented to the staff in ICU and be used for teaching both current and new staff.

Conclusion

The findings will add to the body of knowledge about both ETS and the patient experience and can be used to develop nursing practice and improve patient care.

Tables & Figures

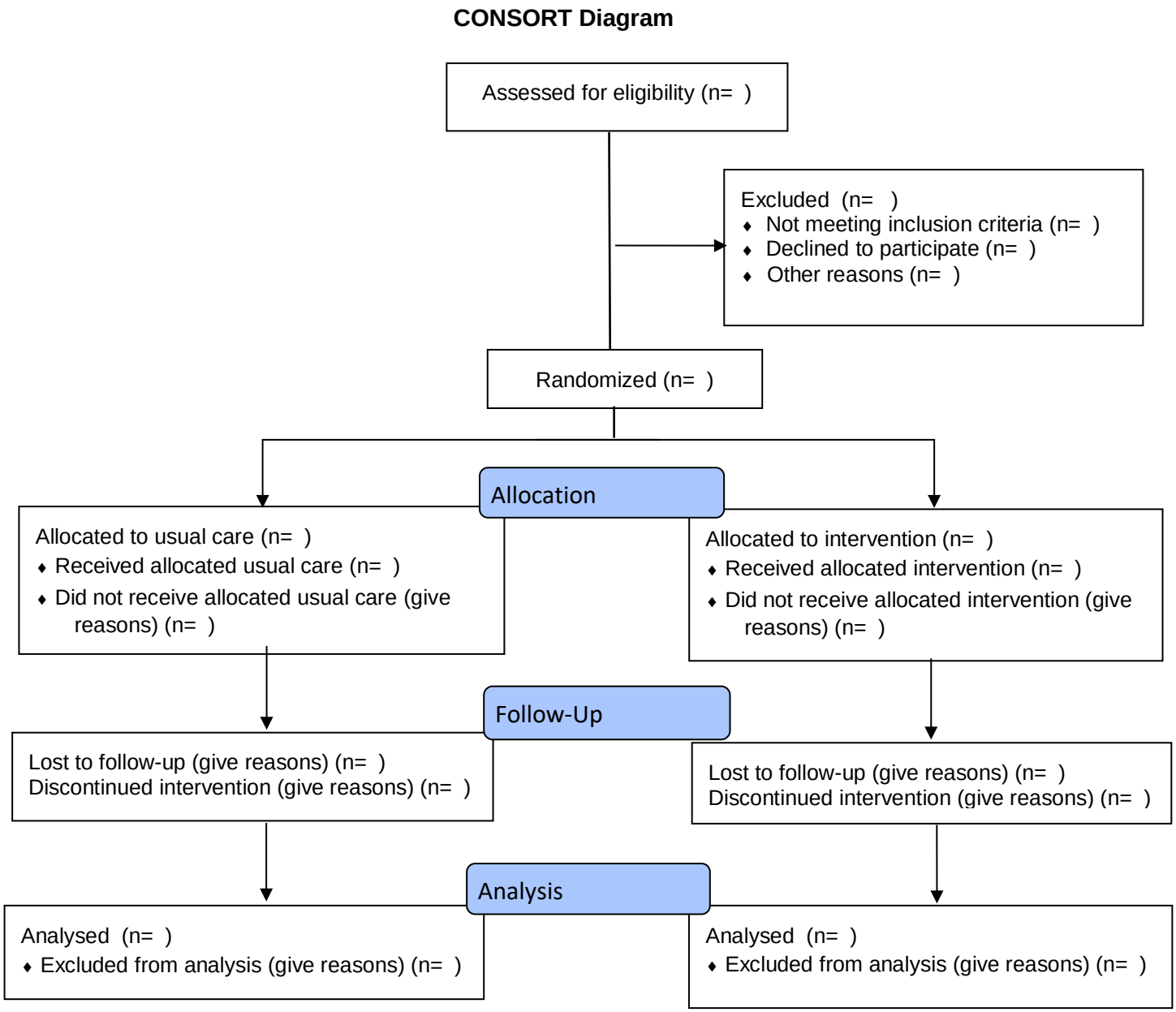

Figure 1: consort diagram

Table 1:-Baseline characteristic and co-morbidities.

	Usual Care *N (%) or mean ± SD*	Intervention *N (%) or mean ± SD*
Age, years		
Gender, Female Male		
Ethnicity NZ European NZ Maori Asian Other		
EuroSCORE		
Smoking status Yes No Ex-smoker		
BMI, kg/m^2		
Diabetes		
Chronic pulmonary disease		
Previous cardiac surgery		
Recent MI		
NYHA New York Heart Association functional classification I II III IV		
Class 4 angina		

Table 2: Surgery and ventilation

	Usual Care *N (%) or mean ± SD*	Intervention *N (%) or mean ± SD*
Type of Surgery - isolated CABG - single non-CABG - 2 procedures - 3 procedures		
Duration of surgery (hours)		
Duration of ventilation (hours)		
Length of ICU stay (hours)		
Patients ventilated >12 hours		

Table 3: Primary and secondary outcomes

	Usual Care	Intervention	Confidence interval	P value
Primary outcome	n (%)	n (%)		
P/F ratio: PP analysis				
P/F ratio: ITT analysis				
P/F ratio: modified PP analysis				
Secondary outcomes	mean ± SD	mean ± SD		
Heart Rate (per minute)				
Respiratory Rate (per minute)				
MAP, (mmHg)				

Table 4: Suction data

	N (%) or mean ± SD
Suction cannister pressure (mmHg)	
Number of suction episodes performed per patient in usual care	
Off protocol suction	

Table 5: Safety and Complication outcomes

	Usual Care n (%)	Intervention n (%)	P value
Laryngeal spasm			
Vomiting			
Aspiration			
Escalation of oxygen therapy			
Desaturation (<90% SpO2)			
Re-intubation			
Respiratory rate >25			
Tachycardia >100bpm			
Increased MAP >85mmHg			
Return to theatre			

Table 6: Pain scores and patient experience

	Usual Care *N (%) or mean ± SD*	Intervention *N (%) or mean ± SD*	P value
Pain scores during ETS while the patient remains intubated			
CPOT Before During 10 minutes after			
Numerical pain score Before During 10 minutes after			
Patient recall			
Memory of the ETT			
Numerical pain score as described by the patient the following day			
Memory of ETS			
Numerical pain score as described by the patient the following day			

Table 7: Group characteristics and co-morbidities for those ventilated >12 hours

	Usual Care *N (%) or mean ± SD*	Intervention *N (%) or mean ± SD*
Patients ventilated >12 hours		
Age (years)		
Gender Female Male		
Ethnicity NZ European NZ Maori Asian Other		
EuroSCORE		
Smoking status Yes No Ex-smoker		
BMI, kg/m^2		
Diabetes		
Chronic pulmonary disease		
Previous cardiac surgery		
Recent MI		
NYHA New York Heart Association functional classification I II III IV		
Class 4 angina		

Table 8: Surgery and ventilation data for those ventilated >12 hours

	Usual Care *N (%) or mean ± SD*	Intervention *N (%) or mean ± SD*
Type of Surgery - isolated CABG - single non-CABG - 2 procedures - 3 procedures		
Duration of surgery (hours)		
Duration of ventilation (hours)		
Length of ICU stay (hours)		

Table 9: Exclusions

	Totals N(%)
Patients excluded on admission to ICU N (%) List reasons when available	
Final ABG outside the protocol timeframe N (%)	

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