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Study title

Non-Invasive Positive airway Pressure thErapy to Reduce Postoperative Lung complications following Upper abdominal Surgery (NIPPER PLUS): Protocol for a single centre pilot randomised control trial

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ABSTRACT

Introduction: Postoperative pulmonary complications (PPC) are a common serious complication following upper abdominal surgery leading to significant consequences including increased mortality, hospital costs and prolonged hospitalisation. The primary objective of this study is to detect whether there is a possible signal towards PPC reduction with the use of additional intermittent non-invasive ventilation (NIV) compared to continuous high-flow nasal oxygen therapy alone following high-risk elective upper abdominal surgery. Secondary objectives are to measure feasibility of; (1) trial conduct and design, and (2) physiotherapy-led NIV and a high-flow nasal oxygen therapy protocol, safety of NIV and to provide preliminary costs of care information of NIV and high-flow nasal oxygen therapy. **Methods and analysis:** This is a single centre, parallel group, assessor blinded, pilot randomised trial, with 130 high-risk upper abdominal surgery patients randomly assigned via concealed allocation to either (1) usual care of continuous high-flow nasal oxygen therapy for 48 hours following extubation or, (2) usual care plus five additional 30-minute physiotherapy-led NIV sessions within the first two postoperative days. Both groups receive standardised preoperative physiotherapy and postoperative early ambulation. No additional respiratory physiotherapy is provided to either group. Outcome measures will assess incidence of PPC within the first 14 postoperative days, recruitment ability, physiotherapy-led NIV and high-flow nasal oxygen therapy protocol adherence, adverse events relating to NIV delivery and costs of providing a physiotherapy-led NIV and a high-flow nasal oxygen therapy service following upper abdominal surgery. **Ethics and dissemination:** Ethics approval has been obtained from the relevant institution and results will be published to inform future multicentre trials.

Trial registration number: ACTRN12617000269336.

Key words: general surgery, non-invasive ventilation, postoperative care, postoperative complications

Article Summary

Strengths and limitations of this study

- This pilot study is a 130-patient parallel group randomised clinical trial of additional early intermittent postoperative NIV versus continuous high-flow nasal oxygen therapy alone.
- This trial is measuring recruitment ability and feasibility of providing physiotherapy-led NIV and a high-flow nasal oxygen therapy protocol.
- This trial standardises physiotherapy and postoperative ambulation.
- This is a pilot, single centre study unlikely to be powered to determine treatment effectiveness.
- Results of this pilot study will assist the design and conduct of future definitive multicentre trials.

INTRODUCTION

Postoperative pulmonary complications (PPC) are a common serious complication following upper abdominal surgery with a reported incidence of 13-42%[1-6]. Development of a PPC is strongly associated with increased postoperative mortality, morbidity and prolonged hospitalisation[2 3 7].

There are well-reported pathophysiological effects of anaesthesia and upper abdominal surgery on the respiratory system including prolonged lung volume reductions, diaphragm dysfunction, alveolar collapse and reduced mucociliary clearance[8 9]. The combination of which establishes a pathological environment for bacterial growth and impaired pulmonary gas exchange, which can lead to postoperative respiratory failure and/or pneumonia[10 11].

Following surgery, respiratory optimisation and support is warranted to avoid respiratory failure and subsequent reintubation[12]. Conventional low-flow oxygen therapy is commonly administrated via nasal cannula or a face mask to supplement oxygenation yet may not be effective to compensate for loss of lung volume[13]. Whilst oxygen support alone may be sufficient for low-risk patients in the postoperative period, increased attention to patients at high-risk of PPC development to provide additional therapies that aim to increase postoperative lung volumes may be warranted.

Non-Invasive ventilation (NIV) has been shown to reverse reduced lung volumes induced by anaesthesia and abdominal surgery[11]. During NIV the positive airway pressure throughout the breath cycle may re-open atelectatic alveoli, increase lung volume and improve gas exchange[11]. Postoperative NIV has been reported to reduce PPC by half, with a further significant sub-group effect specifically for preventing pneumonia[14-16] following upper abdominal surgery. Whilst the optimal preventative NIV intervention dosage parameters are currently undetermined, the timing of postoperative NIV initiation is argued to have an important influence on its effectiveness with earlier application of NIV thought to lead to more successful alveolar recruitment [17-19]. Despite relatively good evidence supporting the use of NIV in the early postoperative period to reduce PPC, the implementation of broad-scale routine prophylactic NIV use is currently unclear but appears to be limited[4 20]. The reasons for which are unknown yet likely multifactorial, including perceived risks, resources required and associated service costs. It is possible that newer modalities such as high-flow nasal oxygen therapy could be a viable and more feasible alternative than preventative NIV to reduce PPC.

High-flow nasal oxygen therapy delivers heated and humidified oxygen and/or air via nasal prongs at a prescribed accurate fraction of inspired oxygen ($Fi0_2$) and with a maximum flow rate of 60 litres per minute. This constant high gas flow at the nares creates a flow-dependent, low level of positive airway pressure between 5 to 8cm H_20[21 22]. It is hypothesised that this low level of positive pressure increases lung volumes and improves oxygenation[23 24] and may potentially decrease the incidence of respiratory complications post extubation and surgery[25]. Compared with standard oxygen therapy, high-flow nasal oxygen therapy reduces reintubation rates and desaturation episodes in critically ill intensive care unit (ICU) patients with acute respiratory failure[26] and reduces the requirement for escalation of respiratory support following cardiac surgery[27]. When compared to NIV, high-flow nasal oxygen therapy provided to prevent intubation was superior in reducing 90-day morality in patients with acute respiratory failure in ICU[28]. Following cardiothoracic surgery, high-flow nasal oxygen therapy demonstrated equivalence with NIV in reducing post-surgery reintubation in patients who developed respiratory failure or were deemed at risk of respiratory failure following post-surgical extubation[29].

Following major abdominal surgery, it is possible that high-flow nasal oxygen therapy may assist in preventing PPCs. It could be just as effective as NIV and potentially more feasible in terms of resources required and service costs. This has yet to be established as all previous NIV clinical trials[14] investigating the prevention of PPC following abdominal surgery have compared NIV to standard oxygen therapy alone, never to high-flow nasal oxygen therapy. A recent large multicentre randomised control trial (RCT) (OPERA trial)[30] demonstrated no benefit in preventing hypoxemia following major abdominal surgery with the use of preventative high-flow nasal oxygen therapy compared to standard oxygen therapy. Participants were provided with high-flow nasal oxygen therapy postoperatively for a median duration of 15 [IQR 12-18] hours following extubation[30]. As postoperative respiratory failure commonly occurs within 72 hours after surgery[31] and functional residual capacity is shown to reach its lowest value one to two days following upper abdominal surgery[32 33] it may be that high-flow nasal oxygen therapy needs to be prescribed for a longer duration to be clinically effective in preventing PPCs in the postoperative period. It has been recommended that the utility of postoperative high-flow nasal oxygen therapy in high-risk patients when used for longer durations be explored[34].

Due to the growing exploratory evidence supporting the theoretical and proposed clinical benefits of high-flow nasal oxygen therapy[35 36], clinical uptake has increased[37] and the application of high-flow nasal oxygen therapy is becoming widespread in intensive care units (ICU)[38] including at our own

institution[39] and also in other clinical settings including the ward[40]. Given this increasing use of high-flow nasal oxygen therapy yet uncertainty regarding the preventative properties, increased reported patient comfort/tolerance compared to NIV[41] and unknown comparative costs of providing a NIV and/or high-flow nasal oxygen therapy service to high-risk upper abdominal surgery patients, this study is designed to detect whether there is a possible signal towards reduction in PPC with the use of intermittent NIV in addition to continuous high-flow oxygen therapy in the first 48 hours after surgery and measure the feasibility of providing these interventions. This study is also designed to understand the associated costs of service delivery for both these therapies. These findings will assist in designing and conducting future multicentre trials.

Pilot work

Prior to commencing this pilot RCT, we undertook an observational study to test the feasibility and safety of intermittent physiotherapy-led NIV following high-risk elective upper abdominal surgery[39]. Whilst physiotherapy-led NIV was able to be delivered within 24 hours following surgery and was shown to be safe in both ICU and ward patients[39], the main barrier identified to early postoperative NIV was physiotherapy-service related limitations[39]. Due to lengthy surgeries, a large proportion of patients did not return to the ward or ICU until after our hospital's standard physiotherapy working hours. These patients missed receiving the planned initial NIV dose within the target four hours. On average, our patients received their first NIV session at 18 hours post-surgery. To mitigate this problem, we implemented a flexible-hour physiotherapy NIV service in the immediate post-anaesthesia care unit (PACU), also known as the recovery room. Providing NIV in the PACU has been reported to be feasible and safe[42].

Objectives

This project is a pilot RCT with the aim of planning a future definitive multicentre RCT to compare the use of additional intermittent physiotherapy-led NIV to continuous high-flow nasal oxygen therapy alone following elective high-risk upper abdominal surgery to reduce PPC incidence. The primary objective of this pilot study is to detect whether there is a possible signal towards PPC reduction with additional NIV compared to high-flow nasal oxygen therapy. Secondary objectives are to measure the feasibility of; (1) trial conduct and design and (2) physiotherapy-led NIV and a high-flow nasal oxygen therapy protocol, safety of NIV therapy and to provide preliminary costs of care information on NIV and high-flow nasal oxygen therapy following upper abdominal surgery. In addition, this trial will also explore possible effects on post-surgical ICU and hospital length of stay (LOS), unplanned ICU admission at any time-point during the acute post-surgical stay, incidence of

reintubation, in-hospital, 30-day and 12-month all-cause mortality and health related quality of life (HRQoL). As this study is a pilot there is no formal hypothesis.

METHODS

Design

The Non-Invasive Positive airway Pressure therapy to Reduce Postoperative Lung complications following Upper abdominal Surgery (NIPPER PLUS) trial is a prospective, single centre, assessor blinded, parallel group, pilot randomised control trial, with patients randomly assigned via concealed allocation to either usual care (continuous high-flow nasal oxygen therapy for the first 48 hours after surgery and early standardised mobilisation) or intervention (usual care plus five 30-minute NIV sessions). Figure 1 outlines the schedule of enrolment, interventions and assessments. Randomisation is stratified to planned post-surgical destination (ward or high dependency unit (HDU)/ICU). See Figure 2 for a CONSORT diagram of the NIPPER PLUS trial and Table 1 for an overview of the trial methods and design. The methods are reported in accordance with the Standard Protocol Items; Recommendations for Interventional Trials[43] (SPIRIT) guidelines for clinical trials and the Template for Intervention Description and Replication[44] (TIDIeR) reporting of interventions.

Patient and Public Involvement

There was no involvement from patients or the public in the development or the design of this trial.

Setting

The NIPPER PLUS trial is being undertaken at a large regional primary referral publically funded hospital in Australia. The Tasmanian Health Human Research Ethics Committee approved this study (protocol reference H0016207). This study was prospectively registered on 22nd February 2017 prior to start of study commencement with the Australian New Zealand Clinical Trials Registry (ACTRN12617000269336).

Participants and enrolment

All patients having major surgery at our hospital are required to attend a pre-admission assessment clinic within six weeks of surgery. At this clinic, any patient listed for elective major abdominal surgery receives respiratory physiotherapy education on the prevention of PPC and breathing exercise training [45]. For the NIPPER PLUS trial, all patients are screened by the preoperative physiotherapist using the Melbourne Risk Prediction Tool (MRPT)[6] to determine if they are at high-risk of developing a PPC. These patients, and any patient with a planned postoperative admission to

ICU or HDU, are invited by the preoperative physiotherapist to participate in the trial. Eligible patients are provided with a verbal explanation of the trial and provision of written and pictorial information. Consenting patients are required to sign a written consent form. Where the preoperative physiotherapist or the eligible patient is unable to attend the preadmission clinic, the patient is contacted by telephone and invited to enter the trial. The consent form is then signed during their hospital admission. Participant recruitment began in March 2017 and aims to be completed by August 2018, with final follow up to be August 2019.

Eligibility Criteria

Inclusions

Eligible participants are patients meeting the following criteria:

1. Adults (≥ 18 years) undergoing elective upper abdominal surgery, able to understand verbal instructions in English and provide informed consent;
2. Open and/or hand-assisted laparoscopic upper abdominal surgery with an abdominal incision longer than 5 cm that is above, or extending above the umbilicus;
3. At high-risk of PPC defined in hierarchal order; 1. A planned postsurgical admission to ICU/HDU, 2. Identified at high-risk using the Melbourne Risk Prediction Tool (MRPT)[6].

Exclusions

The following exclusion criteria apply:

1. Pre-existing obstructive sleep apnoea where overnight continuous positive airway pressure is required
2. Extreme claustrophobia and inability to tolerate use of a NIV facemask
3. Current hospital patient for a separate episode of care
4. Patients requiring oesophageal surgery or organ transplant
5. Any absolute contraindications for NIV in the period following surgery prior to first NIV session (Table 2)

Randomisation and Allocation

A research assistant independent to the trial prepared 130 sequentially numbered (1-130) opaque envelopes each containing an allocation card wrapped in aluminium foil. Allocation sequence is generated by a web-based computer program (http://www.randomizer.org/). Random allocation is

stratified to planned postsurgical destination (ICU and Ward). One of the aims of this study is the feasibility of high-flow nasal oxygen therapy and NIV application. The ease of application could be biased towards it being more or less feasible in one location over another. Stratification ensures that there will be equal representation of participants at both locations. At our centre, historical data finds that approximately 70% of high-risk upper abdominal surgery patients have a planned postoperative ICU admission. To manage this difference in location distribution, the total sample size of 130 is divided into two blocks with 90 in the ICU block and 40 in the Ward block. The allocation sequence in each block is then determined in a 1:1 ratio, control and intervention. Following construction of the randomisation envelopes the allocation sequence is locked securely in the hospital's research institute and unavailable to site investigators, those who enrol participants and/or assign interventions.

If it arises that the ratio of eligible ward or ICU patients is different than previously ascertained this will mean that one of the blocks (two blocks stratified to location: ICU or ward) of envelopes will become exhausted prior to completion of the trial. If this occurs the next available envelope for the other intended postoperative location (ICU or ward), regardless of the actual postoperative location, will be opened in sequence and so on until the minimum target sample of 130 is met. If the situation occurs where the minimum sample is achieved prior to the completion of the funded time period (see sample size section), a block of non-stratified allocation opaque sealed envelopes will be constructed by an independent administration assistant using the same web-based computer randomisation program at a 1:1 ratio (control:intervention) in a single block of 15, and then repeated as necessary until trial completion.

Entry into the trial is finalised at the end of the surgical procedure where the post-surgical destination is confirmed and exclusion criteria assessed. Eligible consenting patients are then randomised into the trial by a site investigator by opening the next sequentially numbered sealed opaque envelope according to the patient's planned postsurgical destination (ward or ICU/HDU). Once opened, participant's details are written on the envelope to ensure that patients were randomised in presenting order and these are filed securely along with the signed consent form. If a patient is identified as ineligible following surgery completion, they will not be randomised nor entered into the trial. Participants are randomly assigned to receive either i) continuous high-flow nasal oxygen therapy for 48 hours following extubation (control group) or ii) continuous high-flow nasal oxygen therapy for 48 hours following extubation plus five 30 minute sessions of NIV implemented by a physiotherapist over the first two postoperative days (intervention group).

Interventions

Control Group (Usual Care)

All participants receive preoperative respiratory physiotherapy education and training[45]. Postoperatively, an early ambulation program is provided as per a standardised protocol[46] of once daily physiotherapy-directed assisted ambulation (Table 3). Participants are provided with early ambulation until a threshold score is met using a criteria-lead scoring tool[47], or until discharged from hospital, whichever occurs first. If a participant is referred for a mobility review, progression of gait aid or a stairs assessment following discharge from physiotherapy, the participant will be treated at the discretion of the ward physiotherapist and this occasion of service recorded. Following surgery, no respiratory physiotherapy is provided to either group unless the participant develops the primary endpoint - a PPC, physiotherapy will then be provided at the discretion of the attending physiotherapist. The type of treatment/s provided will be documented.

On the day of surgery, a site investigator documents high-flow nasal oxygen therapy orders on each consenting patient's post-anaesthetic observation chart to instruct theatre nursing staff to initiate high-flow nasal oxygen therapy as soon as possible following extubation. These orders specify that the FiO_2 is to be titrated to achieve a saturation of peripheral oxygen (SpO_2) between 92 -96%[48] unless otherwise specified by the attending anaesthetist/ICU consultant. Gas flow rate is set at 50 litres per minute. If a participant is unable to tolerate this flow rate, it can be reduced to a minimum of 30 litres per minute. High-flow nasal oxygen therapy is to be provided continuously for 48 hours from the time of extubation. Changes to flow rate and any removal of high-flow nasal oxygen therapy for more than 15 minutes during the 48-hour period are recorded.

All other aspects of perioperative patient care, including the type of anaesthesia, postoperative analgesia, surgical techniques, and postoperative clinical care are provided at the discretion of the anaesthesia and surgical teams and according to routine clinical practice at our centre. Pragmatically, there will be no attempt to standardise perioperative management or intraoperative ventilation strategies for this study. Our hospital is currently not recognised as an enhanced recovery after surgery (ERAS) site however some individual anaesthesia and surgical teams within our hospital adhere to ERAS principles.

Intervention Group

Care is provided as per the control group above, with the exception of five, 30-minute[11] NIV sessions delivered by a physiotherapist over the first two postoperative days in addition to high-flow nasal

oxygen therapy. The initial NIV dose is delivered within four hours of extubation, followed by twice daily sessions on postoperative day one and two. This service is provided in the PACU, ICU/HDU, or the surgical ward depending on the participant's location at the time of NIV delivery.

Prior to commencing each NIV session all participants are assessed for absolute contraindications for NIV therapy by the treating physiotherapist (Table 2). The NIV sessions are delivered using a ResMed VPAP^{TM} machine (ResMed Ltd, Oxfordshire, UK) with a humidified circuit and standard facemask. This is delivered with participants either sitting up in bed with the bed head raised between 45 – 90 degrees or with the participant sitting out of bed in a high back chair. Expiratory positive airway pressure (EPAP) is set at 10cmH_20[11]. Inspiratory positive airway pressure (IPAP) is initially set at 15cmH_20 and adjusted as required to achieve tidal volumes of at least 6-8mls/kg. Participants with BMI > 30 have a starting EPAP set at 12cmH_20 and a starting IPAP set at 16cmH_20. Deviations from these planned settings are reported and documented. The difference between IPAP and EPAP (known as pressure support ventilation; PSV) is maintained at a minimum of 4cmH_20 and the maximum total pressure (PSV + EPAP) will be no greater than 25cmH_20[11].

If a participant is unable to tolerate the set pressures, reassurance is firstly given to the participant and the following modifications taken in sequential order, until patient tolerance is achieved:

1. Reduce EPAP to 8cmH_20 (set minimum)
2. Reduce IPAP to 12cmH_20 (set minimum) in decrements of 1cmH_20

If the participant remains unable to tolerate the therapy despite pressure titration and reassurance, cessation of NIV therapy will occur and be reported. Pressure rise time is set at the slowest speed (900ms) and the inspiratory trigger is set to the minimum value. Air-leaks are managed by fitting the correct sized mask carefully using the mask measure guide provided by ResMed with focus on minimising leaks around the nasogastric tube if present. The ResMed VPAP^{TM} compensates for air leaks up to 40 litres per minute. Above this a 'high-leak' alarm sounds and the machine is unable to deliver the set pressure. Any high-leak alarm is monitored, recorded and the mask readjusted accordingly. Ideally the duration of NIV is to be 30 minutes of continuous therapy, however if NIV therapy needs to be temporarily stopped, therapy time will cease and reason documented. Once therapy is re-started, timing will recommence. If a participant is unable to continue with NIV therapy within 5 minutes of temporarily ceasing, the session is terminated and the reason documented. Supplemental oxygen is titrated through the ResMed VPAP^{TM} as required to achieve $Sp0_2$ 92-96% unless otherwise specified by the medical team. During each NIV session participants have their high-flow nasal oxygen therapy removed for the duration of NIV therapy and replaced once therapy

is finished. The treating physiotherapist continuously monitors all participants for the duration of the NIV therapy and re-assesses 30-minutes post intervention. Data including; blood pressure, heart rate, respiratory rate and $Sp0_2$ is recorded pre, immediately post and 30-minutes after each NIV session. Any reason resulting in early cessation of NIV intervention or being unable to provide NIV therapy is reported.

All physiotherapists providing the intervention attend NIV training with the ICU Senior Physiotherapist who has 11 years' experience in NIV application. The training session includes familiarisation with the ResMed VPAP^{TM} machine, set-up of equipment, detailed explanation of the intervention protocol and trouble-shooting. The physiotherapists are provided with a training manual and a copy of this manual is also kept with the ResMed VPAP^{TM} to allow reference at any point during the intervention. The training manual consists of all the information provided in the training session. The years of hospital experience of each participating physiotherapist is reported.

Withdrawal from trial

Participants are withdrawn for i) requiring longer than 48 hours of mechanical ventilation following surgery, or ii) withdrawal of consent. All withdrawals are reported.

Outcomes

To detect a possible signal towards PPC reduction with the use of NIV in addition to continuous high-flow oxygen therapy in the first 48 hours after surgery, the primary outcome measure is the development of a PPC within the first 14 postoperative days or hospital discharge whichever occurs. Using the Melbourne Group Scale (MGS) diagnostic Tool Version 2[45] (Table 4) a PPC is diagnosed when four or more of eight screening criteria are present in a 24-hour day. The MGS tool is valid and reliable[49], is sensitive to therapeutic interventions designed to ameliorate postoperative atelectasis and alveolar de-recruitment[46], and widely utilised in upper abdominal surgery trials[4-6]. A blinded assessor assesses participants prospectively and daily for a PPC until the seventh postoperative day. Thereafter, additional PPC assessments are only performed if clinically indicated when there are signs of respiratory deterioration reported in the medical record until postoperative day 14 or hospital discharge, whichever occurs first. To reduce the potential for missing data, retrospective collection of PPC data from the daily medical record will occur when a participant or assessor is unavailable for PPC assessment. Participants scoring three out of the possible eight factors are assessed twice daily to monitor for any further clinical deterioration. A blinded senior physiotherapist confirms a positive diagnosis of a PPC.

Feasibility measures of trial conduct, design and protocol

1) Consent and recruitment ability. Consent rate is anticipated to be ≥90% with recruitment of one to two patients per week.

2) Protocol adherence of physiotherapy-led NIV therapy. Successful physiotherapy-led NIV implementation is set at ≤20% protocol deviations. This is measured and reported by;

    a. Proportion of intervention participants who receive the first NIV session within four hours of surgical- extubation.

    b. Proportion of intervention participants who receive five, 30-minute NIV sessions in the first two postoperative days.

    c. Reasons why NIV therapy could not be delivered or were ceased early.

3) Protocol adherence of high-flow nasal oxygen therapy. Successful high-flow nasal oxygen therapy implementation is set at <20% protocol deviations. This is measured and reported by;

    a. Proportion of participants who receive high-flow nasal oxygen therapy for 48 continuous hours following surgical-extubation.

    b. Time in minutes from extubation following surgery to commencement of high-flow nasal oxygen therapy.

    c. Reasons why high-flow nasal oxygen therapy cannot be delivered or sustained.

4) Safety of NIV therapy measured by; (i) major adverse events relating to NIV therapy defined as; anastomotic leak suspected and confirmed; severe hypotension requiring an increase in medical management; cardiac and/or respiratory arrest; deterioration in medical condition requiring an increase in medical management and (ii) any transient physiological events during or immediately following NIV intervention (Table 2).

5) Costs of a high-flow nasal oxygen therapy and physiotherapy-led NIV therapy service measured by; costs of equipment (NIV masks, high-flow and NIV circuits, cleaning and machine service costs); physiotherapy time (in hours) attributed to delivering the NIV therapy and costs of an ICU and hospital stay measured by average cost of a bed day.

Secondary exploratory outcomes

1) Incidence of Pneumonia[50] defined as new CXR infiltrates with at least two of: temp >38 °C, SOB, cough and purulent sputum, altered respiratory auscultation and WCC >12,000/ml or leukopenia <3000/ml), within the first 14 postoperative hospital days or hospital discharge whichever occurs first.

2) Incidence of systemic inflammatory response syndrome (SIRS) as defined by 2 or more of the following: temp >38 or <36; HR>90; RR>20, or PCO2<32, or ventilation for acute process; WCC>12 or <4, within the first 14 postoperative hospital days or hospital discharge whichever occurs first.

3) Incidence of sepsis, defined as a Sequential Organ Failure Assessment (SOFA) score ≥ 2, within the first 14 postoperative hospital days or hospital discharge whichever occurs first.

4) Post-surgical ICU and hospital length of stay (LOS) in days.

5) Unplanned ICU admission at any time-point during the acute post-surgical stay.

6) Incidence of reintubation at any time-point during the acute post-surgical stay.

7) In-hospital mortality, 30-day and 12-month mortality.

8) Health Related Quality of Life (HRQoL) using the EQ-5D-5L[51] preoperatively, postoperative day seven and day 14 and at 12-months postoperatively.

Blinding

Random allocation occurs following completion of surgery. This ensures pre-admission and operating theatre medical, nursing, and physiotherapy staff are masked to postoperative group assignment. Postoperatively, PPC assessors are independent of routine postoperative clinical care and masked to group allocation. All physiotherapy documentation relating to the NIV intervention is documented and filed separately to ensure PPC assessors remain blinded for the first seven postoperative days and then added to the patient's medical file. If a treatment group participant informs the PPC assessor of their group allocation this is noted and reported. Due to the nature of intervention, postoperative ward staff including nurses, doctors and treating physiotherapists are unable to be blinded.

Data collection

Preoperative variables

To measure baseline characteristics the following variables are collected directly from the participant or the medical record: age (years), gender, height (cm), weight (kg), body mass index (kg/cm^2), planned surgical procedure, surgical category and reason for the procedure, physical health status according to the American Society of Anaesthesiologists (ASA) and rated by the attending anaesthetist at the PAC (score 1 to 5), smoking history (non-smoker, current smoker or ex-smoker having ceased more than 8 weeks preoperatively), smoking pack years (1 pack year = 20 cigarettes per day for 1 year), years since smoking cessation, respiratory status including auscultation signs and $Sp0_2$ (%) on room air, cough strength and presence of sputum, participant-reported history of a chest infection in the previous two weeks, functional co-morbidity index[52], participant-reported estimated maximum metabolic equivalent physical activity using a self-rated physical Specific Activity Questionnaire[53] and any limiting factor to ambulation.

Intraoperative variables

The following variables are collected from the anaesthetic record, operation report and medical record: duration of anaesthesia (in minutes) during surgery; mechanical ventilation parameters including mode of ventilation, level of pressure/volume control, positive end expiratory pressure used and any recruitment manoeuvres performed; average $Fi0_2$ during surgery; type and amount of intraoperative fluid delivered (ml/kg/h); number and type of blood transfusion units; incision type.

Postoperative variables

Postoperative data is collected daily for the first 14 days or until hospital discharge, whichever occurs first for the following variables: time in days from the preoperative physiotherapy session to the operation; location (ICU or surgical ward) and duration in days at each location; duration of analgesia and type (epidural, constant opioid infusion, patient controlled analgesia, patient controlled epidural analgesia, oral, local pain infusion, or other); unplanned ICU admission and ICU LOS; hospital LOS; hours of mechanical ventilation; days of vasopressor use; days and types of oxygen therapy use; total days of nasogastric tube; day and diagnosis of a prolonged postoperative ileus using a standardised criteria[54] of 2 or more of the following factors in a 24-hour period including nausea/vomiting, inability to tolerate normal diet, absence of flatus, abdominal distension, radiologic confirmation, and physician diagnosis of ileus. Postoperative NIV parameters are collected including, time in hours from extubation following surgery to the first NIV session; time each NIV

session is delivered and the grade/seniority of the treating physiotherapist providing the NIV; position of the patient during NIV; duration in minutes of each NIV session; IPAP and EPAP used; pressure titration – reasons if pressure titration occurs and the pressures used; number of times NIV has to temporarily ceased prior to the planned 30-minute session; reasons NIV was unable to be delivered to the participant; any major adverse or transient physiological event which occurs as a direct result of NIV therapy. Postoperative high-flow nasal oxygen therapy parameters are collected including; time in minutes from extubation following surgery onto high-flow nasal oxygen therapy; time and date high-flow nasal oxygen therapy is removed; duration in hours of high-flow nasal oxygen therapy within the first 48 postoperative hours; number of times high-flow nasal oxygen therapy is removed for greater than 15 minutes within the first two postoperative days; average flow rate during the first two postoperative days; average FiO_2 during the first two postoperative days; reasons a participant is unable to have postoperative high-flow nasal oxygen therapy for the first two postoperative days. Early ambulation parameters are collected including: time in hours from end of surgery until time to ambulation >1 min; postoperative day walked longer than 10 min; maximum rating of perceived exertion during ambulation at each session; maximum ambulation stage attained at each session and reasons for a participant being unable to participate in an ambulation session.

Sample Size

This RCT is a pilot trial that has been funded to be conducted for a defined time period (18 months). Current surgical throughput of eligible patients at our hospital predicts that we will recruit a sample of 130 eligible participants (65 per group) in the trial period. If this sample is not reached within the funded time period, recruitment will continue until a minimum sample of 130 is met. If this sample is reached prior to the designated funding period (18 months), recruitment will continue past 130, until this time period is completed. A baseline PPC rate of 18% for the control group (high-flow nasal oxygen therapy alone) is anticipated based on historical LIPPSMAck POP[46] data (n=101) of matched high-risk elective upper abdominal surgery participants who were given the same standardised pre- and postoperative physiotherapy as planned in NIPPER PLUS.

Previous systematic reviews in NIV to prevent pneumonia following surgery report a relative risk reduction of approximately 60%[14 55]. Using inference for proportion calculations for two independent samples; a total sample of 130 (2 groups of 65) would detect a 50% relative risk reduction in PPC between groups (favouring the NIV group, one-sided alpha at 0.05) with only 44% power. This sample will only be adequately powered (80%) if there is a large 75% relative risk reduction in PPC with the application of NIV (18% down to 4%).

Assuming that NIV is superior to high-flow nasal oxygen therapy, an adequately powered study would need a sample of at least 450 (relative risk reduction 50% from a baseline of 18%, alpha two-sided 0.05, beta 80%) which would require a multicentre approach. However, there is also the possibility that high-flow nasal oxygen therapy is just as effective as NIV to prevent PPC. This would require a non-inferiority trial and would require a much larger sample.

This pilot study aims to measure the feasibility of the intervention protocol and provide a baseline estimate of effect to assist in determining the design (superiority or non-inferiority) and conduct of a future multicentre RCT.

Methods: Data collection, management and analysis

Data is collected from participants using a standardised electronic case report form and stored on a password protected electronic hard drive. Research assistants and site investigators responsible for data collection are trained directly by the principal investigator to ensure correct data handling. Any data or participant lost to follow-up will be reported. Once each participant's data set is completed, it is de-identified, entered into a main database, locked, and maintained securely by the principal investigator. All data, consent forms and relevant correspondence are stored according to Australian privacy laws and archived for a minimum of 12 years. On completion of the trial, the database will be made available for independent analysis or as an appendix in the publishing journal if requested.

Statistical methods

The prognostic strength and size of imbalances due to potential confounding baseline variables between groups will be assessed. Adjustment covariates will be selected by backward stepwise regression from covariates that may have the potential for clinically significant alterations in effect sizes. These include: history of a respiratory comorbidity, smoking history, age, length in time of operation, operation category (upper gastrointestinal, colorectal, urological, other), incision type and location[56], intraoperative ventilation strategies[3 57], fluid delivery[58], blood transfusions[59], and mode of post-operative analgesia[60].

The primary outcomes of absolute and relative rates of PPC in the trial groups will be estimated using multivariate robust random effects Poisson generalised linear modelling to allow assessment of binary outcomes with or without adjustment for potential confounding variables (incidence rates and rate ratios, 95 % confidence intervals, P-values). In addition, the effect of time from the end of surgery/anaesthesia to diagnosis of PPC will be compared using Cox proportional hazards regression with and without covariate adjustment (hazards ratio, 95 % confidence intervals, P-values). Graphic representation of this analysis will be performed using the Kaplan-Meier method.

Although this study is not adequately powered, a number of secondary outcomes will be treated as time-to-event analyses, with hazard ratios estimated using Cox proportional hazards regression: 1) The day of first diagnosis of other events will be recorded (pneumonia, SIRS, sepsis, reintubation, death); 2) Treatment group comparison for time from surgery to readiness for discharge, and to actual discharge (LOS), will be made using Cox proportional hazards regression, with successful discharge treated as censoring "failure" and death or no discharge within 30 days treated as censoring "non-failure". Binomial secondary outcomes including unplanned ICU admission, unplanned reintubation will be analysed using mixed effects Poisson regression. Secondary outcomes with irregular distributions, including length of time periods (ICU and total post-operative LOS) and HRQoL, will be evaluated for group differences using mixed effects ordered logistic regression, with mean time (95 % CI) estimated for descriptive purposes using mixed effects linear regression. An intention-to-protocol sensitivity analysis will be performed by excluding from the analysis any participant who did not undergo the planned postoperative NIV intervention treatment. The sensitivity of the outcome estimates to missing data will be evaluated using multiple imputation. All analyses will be performed using Stata version 14 or later (StataCorp, College Station, TX, USA) and analysed on an intention-to-treat basis.

Methods: Monitoring

Data monitoring

The steering committee consists of the principal investigator, local investigator and two academic supervisors who contribute to the design and revision of this study protocol. The principal and local investigators are responsible for the study administrative management and daily co-ordination of the trial ensuring appropriate trial conduct, record keeping and data management.

An independent Data and Safety Monitoring Board (DSMB) monitors the ethics of the study in accordance with the Declaration of Helsinki overseeing safety and conduct of the study.

For the trial, there is a stopping rule for the potential of NIV or high-flow nasal oxygen therapy to be harmful. An unacceptable rate of anastomotic leakage of over 2.5% will trigger consideration for trial termination by the independent DSMB established for the oversight of this clinical trial. To detect a 2.5% anastomotic leakage rate in either group requires a minimum of 57 patients (one-sample test of proportion compared to hypothetical 0.1% rate; power 80%; alpha 0.05). Analysis of anastomotic leakage rates only in both groups will therefore be performed at participant recruitment number 60 using cumulative summation analysis[61].

Any other major adverse events directly relating to the interventions will be reported with oversight from the independent DSMB.

Ethics and Dissemination

The Tasmanian Health Human Research Ethics Committee has granted ethical approval for this trial. Trial results will be disseminated widely through conference presentations and peer-review journal publications.

DISCUSSION

Consequences of PPCs following upper abdominal surgery are well defined, leading to great interest in their prevention. High-risk patients have been shown to be over eight times more likely to develop a PPC compared to individuals identified as low-risk[6] suggesting increased attention is required to improve postoperative outcomes in this high-risk cohort.

Whilst previous clinical studies support the use of preventative NIV therapy following major abdominal surgery[14], implementation of NIV therapy does not appear to be standard postoperative care[4 20] and a number of important methodological limitations exists in previous literature including high-bias risk and minimal reporting of adverse events[14]. Recommendations for future research from the most recent Cochrane review in 2014 include; evaluating the use of NIV in preventing mortality, a targeted approach investigating patients at higher risk for PPCs and must report on all adverse effects of preventative postoperative NIV[14]. The NIPPER PLUS study is designed to begin targeting these recommendations by collecting and reporting on in-hospital, 30-day and 12-month all-cause mortality for all participants and is recruiting participants identified as high-risk of developing a PPC only. High-risk for this study has been defined as either; eligible patients with a planned postoperative admission to ICU/HDU due to this factor being independently associated with the development of a PPC[6] or eligible patients Identified at high risk using the MRPT[6]. The MRPT has been shown to be specific and sensitive in the identification of individuals who are at highest risk of PPC development in the surgical settings including upper abdominal surgery[5 6].

Preventative NIV was associated with no major complications in our observational study[39] and the NIPPER PLUS trial aims to further support this finding by reporting on any adverse event as well as transient physiological events directly relating to NIV therapy during, immediately following and 30-minutes after therapy, therefore contributing to necessary and strongly recommended NIV safety data for both ICU and ward patients.

All previous preventative NIV clinical trials in abdominal surgery compare NIV to standard oxygen therapy only[14], however the application of high-flow nasal oxygen therapy is becoming widespread in ICUs[38] and in other clinical settings[25]. The NIPPER PLUS study is designed with high-flow nasal oxygen therapy as standard care to match current clinical practice within our ICU unit and aims to detect whether there is a possible signal towards PPC reduction with the use of additional intermittent NIV compared to continuous high-flow oxygen therapy alone. The NIPPER PLUS trial is a single-centre study. The effect of high-flow nasal oxygen therapy in high-risk upper abdominal surgery patients is currently unclear. Prior to undertaking expensive fully powered multicentre trials there is a need to build evidence and data from pilot trials for realistic effect size variability estimation and to measure the design, feasibility, safety and potential challenges of treatment protocols. This pilot study aims to inform future definitive trial design and conduct. Indeed, it may be demonstrated that this protocol is unfeasible in its current form and would be futile to progress to multicentre trials without study and protocol re-design.

In conclusion, the NIPPER PLUS trial is a single-centre, assessor-blinded, parallel group, pilot RCT, which aims to detect whether there is a possible signal towards PPC reduction with the use of additional intermittent NIV compared to continuous high-flow oxygen therapy alone following high-risk elective upper abdominal surgery. This trial is measuring recruitment ability, feasibility of implementing a physiotherapy-led NIV and high-flow nasal oxygen therapy protocol, safety of NIV therapy and preliminary costs of care information on a NIV and high-flow nasal oxygen therapy service. This will assist in the design and conduct of future multicentre trials. In addition, this trial will also explore possible effects on post-surgical ICU and hospital LOS, unplanned ICU admission, reintubation rates, in-hospital, 30-day and 12-month mortality. This trial standardises preoperative and postoperative physiotherapy care and is currently recruiting.

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Author Contributions

IB and JL conceived and designed the study and coordinated the trial. LD and SMP assisted in final study design and protocol. JL prepared the first draft of the protocol manuscript, and was responsible for the final manuscript. All authors (JL, IB, IKR, LD, DS and SMP) revised all manuscript drafts, approved the final manuscript and contributed intellectually important content. JL is the guarantor of the paper and takes responsibility for the integrity of the work as a whole, from inception to published article

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Ethics approval

The trial is being conducted in accordance with the Declaration of Helsinki and has undergone ethics review by the Tasmanian Health Human Research Ethics Committee and received approval 08/02/2017 (protocol reference H0016207). All participants will provide written informed consent.

Conflict of interest declaration

The authors have no conflicts of interests

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Table 1 Trial Registration Data Set for NIPPER PLUS trial

Data Category	Information
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry number: ACTRN12617000269336
Date of registration in primary registry	22/02/2017
Secondary identifying numbers	n/a
Trial protocol version	This is Version 2 of the protocol and was enacted on February 2017
Source of monetary or material support	Clifford Craig Foundation ($80,000 AUD)
Contact for public queries	JL, jane.lockstone@ths.tas.gov.au
Contact for scientific queries	JL, jane.lockstone@ths.tas.gov.au
Public title	Does early postoperative non-invasive ventilation (NIV) prevent chest infections following high-risk elective abdominal surgery
Scientific title	NIPPER-PLUS trial – Non-Invasive Positive airway Pressure therapy to Reduce Postoperative Lung Complications following Upper abdominal Surgery: a single centre pilot randomised control trial
Countries of recruitment	Australia
Health condition(s) or problem(s) studied Intervention(s)	Pulmonary complications following high-risk elective upper abdominal surgery Active comparator: Physiotherapy-led postoperative NIV therapy Placebo comparator: high-flow nasal prong oxygen therapy
Key inclusion and exclusion criteria	Ages edible for study: ≥ 18 years Sexes eligible for study: both Accepts health volunteers: No Inclusion criteria: All adults undergoing high-risk elective open and/or advanced hand-assisted laparoscopic abdominal surgery. Exclusion criteria: 1. Any absolute contraindications for NIV in the period following surgery prior to the first NIV session; 2. Oesophageal surgery; 3. Obstructive sleep apnoea requiring CPAP overnight; 4 extreme claustrophobia; 5. not able to understand verbal instructions in English; 6. do not have capacity to give consent themselves; 7. a current hospital patient for a separate episode of care; 8. requiring organ transplant.
Study type	Type: Investigator initiated, interventional, non-pharmacological, pilot study Allocation: Concealed randomisation Intervention model: parallel assignment Masking: assessor blinding Primary purpose: Prevention Phase: Phase 2
Date of first enrolment	23/02/2017
Target sample size	Minimum 130
Recruitment status	Recruiting
Primary Outcome	Postoperative pulmonary complication during the first 14postoperative days
Key secondary outcomes	Recruitment ability, physiotherapy-led NIV and high-flow nasal oxygen therapy protocol adherence, safety of NIV therapy, associated costs of high-flow nasal oxygen therapy and a physiotherapy-led NIV service following upper abdominal surgery. In addition, this study will explore effects on incidence of pneumonia, intensive care unit (ICU) and hospital length of hospital, ICU readmission rates, incidence of reintubation, in-hospital, 30-day and 12-month all-cause mortality and health related quality of life.

Table 2 Contraindications and Adverse events relating to NIV therapy

Absolute Contraindications	Relative Contraindications	Major Adverse Event	Transient physiological event
Cardiac or respiratory arrest	Mildly decreased level of consciousness	Anastomotic leak	hypotension, defined as a decrease in blood pressure >20mmHg determined by pre/post blood pressure observations
Severe agitation or encephalopathy	Progressive severe respiratory failure as reported by the treating physician	Severe hypotension requiring increase in medical management	decrease in $Sp0_2$oxygen saturations >10% from baseline or <85% for >60 seconds
Undrained pneumothorax or intraoperative pneumothorax with ICC in-situ	Uncooperative patient who can be calmed or comforted	cardiac or respiratory arrest	gastric distention as clinically reported by the treating surgeon
Uncontrolled vomiting	$Sp0_2$ falls below >10% below resting level of <85% for >60 seconds	Deterioration in medical condition requiring an increase in medical management	Vomiting during the NIV therapy
Inability to protect airway	MAP < target pressure despite vasopressor		Nasal bridge or facial erythema or ulceration
Severe upper GI bleeding or haemoptysis	Resting HR <50 or >140 or new untreated arrhythmia develops		
Need for immediate intubation	RR <5 or >40 b/min		
Facial trauma			

Abbreviations: HR, heart rate; ICC, intercostal catheter; MAP, Mean arterial pressure; NIV, non-invasive ventilation; RR, respiratory rate; $Sp0_2$, saturation of peripheral oxygen; Upper GI, Upper gastrointestinal; >, greater than; <, less than

Table 3 Early postoperative ambulation protocol[46]

Stage 1 (Safety)	Sit over edge of bed/sit in chair minimum of 2 minutes
Stage 2 (Safety)	March on spot 0-1 minute
Stage 3 (Ambulation)	March on spot/walk away from bedside 1-3 minutes
Stage 4 (Ambulation)	March on spot/walk away from bedside 3 – 6 minutes
Stage 5 (Ambulation)	Walk away from bedside 6 – 10 minutes
Stage 6 (Ambulation)	Walk away from bedside 10 – 15 minutes
Stage 7 (Ambulation)	Walk away from bedside > 15 minutes

PROTOCOL

Provide assisted early ambulation as soon as possible on the first postoperative day.

At each session progress through each stage in sequence. Time achieved in the session is accumulative.

Aim to achieve rating of perceived exertion of greater than 3/10.

Aim to assist patient to ambulate more than 10 minutes (Stage 6 or greater).

Once patient able to ambulate past Stage 3, patient can be assisted to ambulate with a Physiotherapy Assistant, as long as safe to do as determined by the ward physiotherapist.

Interval training is permissible to obtain target walking time. Each interval of rest time must not exceed the preceding work time. Total session time is the accumulative work time.

Provide assisted early ambulation once a day until discharged according to the discharge scoring tool[47]

Table 4 Postoperative pulmonary complications diagnostic tool: Melbourne Group Score Version 2[45]

Diagnosis confirmed when 4 or more of the following criteria are present anytime in the 24-hour period 00:01 to 24:00 on a single postoperative day:

1. New abnormal breath sounds on auscultation different to preoperative assessment
2. Productive of yellow or green sputum different to preoperative assessment
3. Pulse oximetry oxygen saturation (SpO_2) < 90% on room air on more than one consecutive postoperative day
4. Raised maximum oral temperature > 38°C on more than one consecutive day
5. An unexplained white cell count greater than 11 $x10^9$/L
6. Presence of infection on sputum culture report
7. Chest radiograph (CXR) report of collapse/consolidation. Chest radiograph (CXR) report of collapse/consolidation. When a CXR has been taken but no report available, a ward medical officer, or a senior respiratory physiotherapist with more than 10 years' experience will be asked to report.
8. Physician's diagnosis of pneumonia, lower or upper respiratory tract infection, an undefined chest infection or prescription of an antibiotic for a respiratory infection

Figure 1 NIPPER PLUS participant timeline and schedule of events

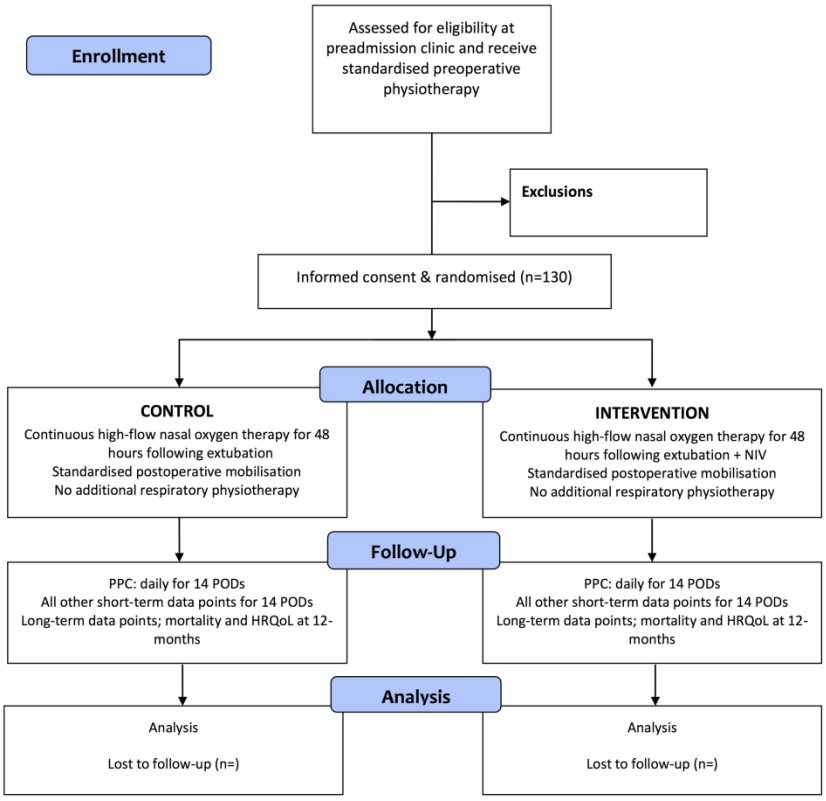
		Enrolment	Allocation		Post Allocation			Close out	
	TIMEPOINT	***Listed for elective surgery***	***Pre-admission clinic***	***Day of surgery***	***POD 1-7***	***POD 8-14***	***Hospital D/C***	***POD 30***	***12 month***
ENROLMENT:	*Enrolment*		X						
	Eligibility screen	X							
	Informed consent		X						
	Random Allocation			X					
INTERVENTIONS:	***Control;** High-flow nasal oxygen therapy*			X	X				
	***Intervention:** High-flow nasal oxygen therapy plus intermittent postoperative NIV*			X	X				
VARIABLES:	*Demographics, medical history, HRQoL*		X						
	Intraoperative variables				X				
	Postoperative variables				X	X	X		
OUTCOMES:	*PPC*				X	X			
	Recruitment ability, physiotherapy-led NIV and high-flow nasal oxygen therapy protocol adherence				X				
	Major adverse events and/or transient physiological events of NIV				X				
	Associated costs of physiotherapy-led NIV & a high-flow nasal oxygen therapy service				X	X	X		
	Pneumonia, Hospital and ICU LOS, ICU readmission and reintubation rates, in-hospital mortality				X	X	X		
	HRQoL (EQ-5D-5L)				X	X			X
	30-day and 12-month all-cause mortality							X	X

Abbreviations: D/C; discharge, ICU; intensive care unit, LOS; length of stay, NIV; Non-invasive ventilation, POD; postoperative day, PPC; postoperative pulmonary complication, HRQoL; health-related quality of life

Figure 1 NIPPER PLUS participant timeline and schedule of events

279x361mm (300 x 300 DPI)

Figure 2 CONSORT flow diagram for the NIPPER PLUS study



Abbreviations: NIV, non-invasive ventilation, PPC; postoperative pulmonary complication, POD; postoperative day, HRQoL; health-related quality of life

Figure 2 CONSORT flow diagram for the NIPPER PLUS study

279x361mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	25 (Table1)
Protocol version	#3	Date and version identifier	25 (Table1)
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and	#5b	Name and contact information for the trial sponsor	N/A

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	9-11

		administered	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15-16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	7-8

concealment mechanism		central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14,15,16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12, 16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical	16-17

missing data		methods to handle missing data (eg, multiple imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17-18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17-18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of	#28	Financial and other competing interests for principal	20

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16, 18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	Page 3-4	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Page 3-5	_____
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Page 10-11	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Page 9-11	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Page 11	_____
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Page 9-10	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Page 9-10	_____

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Page 9 -11	
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	Page 9-11	
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	N/A	
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

TIDieR checklist

BMJ Open

Non-Invasive Positive airway Pressure thErapy to Reduce Postoperative Lung complications following Upper abdominal Surgery (NIPPER PLUS): Protocol for a single centre pilot randomised control trial

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Primary Subject Heading:	Surgery
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Keywords:	Adult surgery < SURGERY, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Adult anaesthesia < ANAESTHETICS

Study title

Non-Invasive Positive airway Pressure thErapy to Reduce Postoperative Lung complications following Upper abdominal Surgery (NIPPER PLUS): Protocol for a single centre pilot randomised control trial

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Word count: 6534

ABSTRACT

Introduction: Postoperative pulmonary complications (PPC) are a common serious complication following upper abdominal surgery leading to significant consequences including increased mortality, hospital costs and prolonged hospitalisation. The primary objective of this study is to detect whether there is a possible signal towards PPC reduction with the use of additional intermittent non-invasive ventilation (NIV) compared to continuous high-flow nasal oxygen therapy alone following high-risk elective upper abdominal surgery. Secondary objectives are to measure feasibility of; (1) trial conduct and design, and (2) physiotherapy-led NIV and a high-flow nasal oxygen therapy protocol, safety of NIV and to provide preliminary costs of care information of NIV and high-flow nasal oxygen therapy. **Methods and analysis:** This is a single centre, parallel group, assessor blinded, pilot randomised trial, with 130 high-risk upper abdominal surgery patients randomly assigned via concealed allocation to either (1) usual care of continuous high-flow nasal oxygen therapy for 48 hours following extubation or, (2) usual care plus five additional 30-minute physiotherapy-led NIV sessions within the first two postoperative days. Both groups receive standardised preoperative physiotherapy and postoperative early ambulation. No additional respiratory physiotherapy is provided to either group. Outcome measures will assess incidence of PPC within the first 14 postoperative days, recruitment ability, physiotherapy-led NIV and high-flow nasal oxygen therapy protocol adherence, adverse events relating to NIV delivery and costs of providing a physiotherapy-led NIV and a high-flow nasal oxygen therapy service following upper abdominal surgery. **Ethics and dissemination:** Ethics approval has been obtained from the relevant institution and results will be published to inform future multicentre trials.

Trial registration number: ACTRN12617000269336.

Key words: general surgery, non-invasive ventilation, postoperative care, postoperative complications

Article Summary

Strengths and limitations of this study

- This pilot study is a 130-patient parallel group randomised clinical trial of additional early intermittent postoperative NIV versus continuous high-flow nasal oxygen therapy alone.
- This trial is measuring recruitment ability and feasibility of providing physiotherapy-led NIV and a high-flow nasal oxygen therapy protocol.
- This trial standardises physiotherapy and postoperative ambulation.
- This is a pilot, single centre study unlikely to be powered to determine treatment effectiveness.
- Results of this pilot study will assist the design and conduct of future definitive multicentre trials.

INTRODUCTION

Postoperative pulmonary complications (PPC) are a common serious complication following upper abdominal surgery with a reported incidence of 13-42%[1-6]. Development of a PPC is strongly associated with increased postoperative mortality, morbidity and prolonged hospitalisation[2 3 7].

There are well-reported pathophysiological effects of anaesthesia and upper abdominal surgery on the respiratory system including prolonged lung volume reductions, diaphragm dysfunction, alveolar collapse and reduced mucociliary clearance[8 9]. The combination of which establishes a pathological environment for bacterial growth and impaired pulmonary gas exchange, which can lead to postoperative respiratory failure and/or pneumonia[10 11].

Following surgery, respiratory optimisation and support is warranted to avoid respiratory failure and subsequent reintubation[12]. Conventional low-flow oxygen therapy is commonly administrated via nasal cannula or a face mask to supplement oxygenation yet may not be effective to compensate for loss of lung volume[13]. Whilst oxygen support alone may be sufficient for low-risk patients in the postoperative period, increased attention to patients at high-risk of PPC development to provide additional therapies that aim to increase postoperative lung volumes may be warranted.

Non-Invasive ventilation (NIV) has been shown to reverse reduced lung volumes induced by anaesthesia and abdominal surgery[11]. During NIV the positive airway pressure throughout the breath cycle may re-open atelectatic alveoli, increase lung volume and improve gas exchange[11]. Postoperative NIV has been reported to reduce PPC by half, with a further significant sub-group effect specifically for preventing pneumonia[14-17] following upper abdominal surgery. Whilst the optimal preventative NIV intervention dosage parameters are currently undetermined, the timing of postoperative NIV initiation is argued to have an important influence on its effectiveness with earlier application of NIV thought to lead to more successful alveolar recruitment [18-20]. Despite relatively good evidence supporting the use of NIV in the early postoperative period to reduce PPC, the implementation of broad-scale routine prophylactic NIV use is currently unclear but appears to be limited[4 21]. The reasons for which are unknown yet likely multifactorial, including perceived risks, resources required and associated service costs. It is possible that newer modalities such as high-flow nasal oxygen therapy could be a viable and more feasible alternative than preventative NIV to reduce PPC.

High-flow nasal oxygen therapy delivers heated and humidified oxygen and/or air via nasal prongs at a prescribed accurate fraction of inspired oxygen ($Fi0_2$) and with a maximum flow rate of 60 litres per

minute. This constant high gas flow at the nares creates a flow-dependent, low level of positive airway pressure between 5 to 8cm H_20[22 23]. It is hypothesised that this low level of positive pressure increases lung volumes and improves oxygenation[24 25] and may potentially decrease the incidence of respiratory complications post extubation and surgery[26]. Compared with standard oxygen therapy, high-flow nasal oxygen therapy reduces reintubation rates and desaturation episodes in critically ill intensive care unit (ICU) patients with acute respiratory failure[27] and reduces the requirement for escalation of respiratory support following cardiac surgery[28]. When compared to NIV, high-flow nasal oxygen therapy provided to prevent intubation was superior in reducing 90-day morality in patients with acute respiratory failure in ICU[29]. Following cardiothoracic surgery, high-flow nasal oxygen therapy demonstrated equivalence with NIV in reducing post-surgery reintubation in patients who developed respiratory failure or were deemed at risk of respiratory failure following post-surgical extubation[30].

Following major abdominal surgery, it is possible that high-flow nasal oxygen therapy may assist in preventing PPCs. It could be just as effective as NIV and potentially more feasible in terms of resources required and service costs. This has yet to be established as all previous NIV clinical trials[14 17] investigating the prevention of PPC following abdominal surgery have compared NIV to standard oxygen therapy alone, never to high-flow nasal oxygen therapy. A recent large multicentre randomised control trial (RCT) (OPERA trial)[31] demonstrated no benefit in preventing hypoxemia following major abdominal surgery with the use of preventative high-flow nasal oxygen therapy compared to standard oxygen therapy. Participants were provided with high-flow nasal oxygen therapy postoperatively for a median duration of 15 [IQR 12-18] hours following extubation[31]. As postoperative respiratory failure commonly occurs within 72 hours after surgery[32] and functional residual capacity is shown to reach its lowest value one to two days following upper abdominal surgery[33-35] it may be that high-flow nasal oxygen therapy needs to be prescribed for a longer duration to be clinically effective in preventing PPCs in the postoperative period. It has been recommended that the utility of postoperative high-flow nasal oxygen therapy in high-risk patients when used for longer durations be explored[36].

Due to the growing exploratory evidence supporting the theoretical and proposed clinical benefits of high-flow nasal oxygen therapy[37 38], clinical uptake has increased[39] and the application of high-flow nasal oxygen therapy is becoming widespread in intensive care units (ICU)[40] including at our own institution[41] and also in other clinical settings including the ward[42]. Given this increasing use of high-flow nasal oxygen therapy yet uncertainty regarding the preventative properties, increased

reported patient comfort/tolerance compared to NIV[43] and unknown comparative costs of providing a NIV and/or high-flow nasal oxygen therapy service to high-risk upper abdominal surgery patients, this study is designed to detect whether there is a possible signal towards reduction in PPC with the use of intermittent NIV in addition to continuous high-flow oxygen therapy in the first 48 hours after surgery and measure the feasibility of providing these interventions. This study is also designed to understand the associated costs of service delivery for both these therapies. These findings will assist in designing and conducting future multicentre trials.

Pilot work

Prior to commencing this pilot RCT, we undertook an observational study to test the feasibility and safety of intermittent physiotherapy-led NIV following high-risk elective upper abdominal surgery[41]. Whilst physiotherapy-led NIV was able to be delivered within 24 hours following surgery and was shown to be safe in both ICU and ward patients[41], the main barrier identified to early postoperative NIV was physiotherapy-service related limitations[41]. Due to lengthy surgeries, a large proportion of patients did not return to the ward or ICU until after our hospital's standard physiotherapy working hours. These patients missed receiving the planned initial NIV dose within the target four hours. On average, our patients received their first NIV session at 18 hours post-surgery. To mitigate this problem, we implemented a flexible-hour physiotherapy NIV service in the immediate post-anaesthesia care unit (PACU), also known as the recovery room. Providing NIV in the PACU has been reported to be feasible and safe[44].

Objectives

This project is a pilot RCT with the aim of planning a future definitive multicentre RCT to compare the use of additional intermittent physiotherapy-led NIV to continuous high-flow nasal oxygen therapy alone following elective high-risk upper abdominal surgery to reduce PPC incidence. The primary objective of this pilot study is to detect whether there is a possible signal towards PPC reduction with additional NIV compared to high-flow nasal oxygen therapy. Secondary objectives are to measure the feasibility of; (1) trial conduct and design and (2) physiotherapy-led NIV and a high-flow nasal oxygen therapy protocol, safety of NIV therapy and to provide preliminary costs of care information on NIV and high-flow nasal oxygen therapy following upper abdominal surgery. In addition, this trial will also explore possible effects on post-surgical ICU and hospital length of stay (LOS), unplanned ICU admission at any time-point during the acute post-surgical stay, incidence of reintubation, in-hospital, 30-day and 12-month all-cause mortality and health related quality of life (HRQoL). As this study is a pilot there is no formal hypothesis.

METHODS

Design

The Non-Invasive Positive airway Pressure therapy to Reduce Postoperative Lung complications following Upper abdominal Surgery (NIPPER PLUS) trial is a prospective, single centre, assessor blinded, parallel group, pilot randomised control trial, with patients randomly assigned via concealed allocation to either usual care (continuous high-flow nasal oxygen therapy for the first 48 hours after surgery and early standardised mobilisation) or intervention (usual care plus five 30-minute NIV sessions). Figure 1 outlines the schedule of enrolment, interventions and assessments. Randomisation is stratified to planned post-surgical destination (ward or high dependency unit (HDU)/ICU). See Figure 2 for a CONSORT diagram of the NIPPER PLUS trial and Table 1 for an overview of the trial methods and design. The methods are reported in accordance with the Standard Protocol Items; Recommendations for Interventional Trials[45] (SPIRIT) guidelines for clinical trials and the Template for Intervention Description and Replication[46] (TIDIeR) reporting of interventions.

Patient and Public Involvement

There was no involvement from patients or the public in the development or the design of this trial.

Setting

The NIPPER PLUS trial is being undertaken at a large regional primary referral publically funded hospital in Australia. The Tasmanian Health Human Research Ethics Committee approved this study (protocol reference H0016207). This study was prospectively registered on 22nd February 2017 prior to start of study commencement with the Australian New Zealand Clinical Trials Registry (ACTRN12617000269336).

Participants and enrolment

All patients having major surgery at our hospital are required to attend a pre-admission assessment clinic within six weeks of surgery. At this clinic, any patient listed for elective major abdominal surgery receives respiratory physiotherapy education on the prevention of PPC and breathing exercise training [47]. For the NIPPER PLUS trial, all patients are screened by the preoperative physiotherapist using the Melbourne Risk Prediction Tool (MRPT)[6] to determine if they are at high-risk of developing a PPC. These patients, and any patient with a planned postoperative admission to ICU or HDU, are invited by the preoperative physiotherapist to participate in the trial. Eligible patients are provided with a verbal explanation of the trial and provision of written and pictorial

information. Consenting patients are required to sign a written consent form. Where the preoperative physiotherapist or the eligible patient is unable to attend the preadmission clinic, the patient is contacted by telephone and invited to enter the trial. The consent form is then signed during their hospital admission. Participant recruitment began in March 2017 and aims to be completed by August 2018, with final follow up to be August 2019.

Eligibility Criteria

Inclusions

Eligible participants are patients meeting the following criteria:

1. Adults (≥ 18 years) undergoing elective upper abdominal surgery, able to understand verbal instructions in English and provide informed consent;
2. Open and/or hand-assisted laparoscopic upper abdominal surgery with an abdominal incision longer than 5 cm that is above, or extending above the umbilicus;
3. At high-risk of PPC defined in hierarchal order; 1. A planned postsurgical admission to ICU/HDU, 2. Identified at high-risk using the Melbourne Risk Prediction Tool (MRPT)[6].

Exclusions

The following exclusion criteria apply:

1. Pre-existing obstructive sleep apnoea where overnight continuous positive airway pressure is required
2. Extreme claustrophobia and inability to tolerate use of a NIV facemask
3. Current hospital patient for a separate episode of care
4. Patients requiring oesophageal surgery or organ transplant
5. Any absolute contraindications for NIV in the period following surgery prior to first NIV session (Table 2)

Randomisation and Allocation

A research assistant independent to the trial pre-prepared 130 sequentially numbered (1-130) opaque envelopes each containing an allocation card wrapped in aluminium foil. Allocation sequence is generated by a web-based computer program (http://www.randomizer.org/). Random allocation is stratified to planned postsurgical destination (ICU and Ward). One of the aims of this study is the feasibility of high-flow nasal oxygen therapy and NIV application. The ease of application

could be biased towards it being more or less feasible in one location over another. Stratification ensures that there will be equal representation of participants at both locations. At our centre, historical data finds that approximately 70% of high-risk upper abdominal surgery patients have a planned postoperative ICU admission. To manage this difference in location distribution, the total sample size of 130 is divided into two blocks with 90 in the ICU block and 40 in the Ward block. The allocation sequence in each block is then determined in a 1:1 ratio, control and intervention. Following construction of the randomisation envelopes the allocation sequence is locked securely in the hospital's research institute and unavailable to site investigators, those who enrol participants and/or assign interventions.

If it arises that the ratio of eligible ward or ICU patients is different than previously ascertained this will mean that one of the blocks (two blocks stratified to location: ICU or ward) of envelopes will become exhausted prior to completion of the trial. If this occurs the next available envelope for the other intended postoperative location (ICU or ward), regardless of the actual postoperative location, will be opened in sequence and so on until the minimum target sample of 130 is met. If the situation occurs where the minimum sample is achieved prior to the completion of the funded time period (see sample size section), a block of non-stratified allocation opaque sealed envelopes will be constructed by an independent administration assistant using the same web-based computer randomisation program at a 1:1 ratio (control:intervention) in a single block of 15, and then repeated as necessary until trial completion.

Entry into the trial is finalised at the end of the surgical procedure where the post-surgical destination is confirmed and exclusion criteria assessed. Eligible consenting patients are then randomised into the trial by the lead or a site investigator only by opening the next sequentially numbered sealed opaque envelope according to the patient's planned postsurgical destination (ward or ICU/HDU). Once opened, participant's details are written on the envelope to ensure that patients were randomised in presenting order and these are filed securely along with the signed consent form. If a patient is identified as ineligible following surgery completion, they will not be randomised nor entered into the trial. Participants are randomly assigned to receive either i) continuous high-flow nasal oxygen therapy for 48 hours following extubation (control group) or ii) continuous high-flow nasal oxygen therapy for 48 hours following extubation plus five 30 minute sessions of NIV implemented by a physiotherapist over the first two postoperative days (intervention group).

Interventions

Control Group (Usual Care)

All participants receive preoperative respiratory physiotherapy education and training[47]. Postoperatively, an early ambulation program is provided as per a standardised protocol[48] of once daily physiotherapy-directed assisted ambulation (Table 3). Participants are provided with early ambulation until a threshold score is met using a criteria-lead scoring tool[49], or until discharged from hospital, whichever occurs first. If a participant is referred for a mobility review, progression of gait aid or a stairs assessment following discharge from physiotherapy, the participant will be treated at the discretion of the ward physiotherapist and this occasion of service recorded. Following surgery, no respiratory physiotherapy is provided to either group unless the participant develops the primary endpoint - a PPC, physiotherapy will then be provided at the discretion of the attending physiotherapist. The type of treatment/s provided will be documented.

On the day of surgery, a site investigator documents high-flow nasal oxygen therapy orders on each consenting patient's post-anaesthetic observation chart to instruct theatre nursing staff to initiate high-flow nasal oxygen therapy as soon as possible following extubation. These orders specify that the FiO_2 is to be titrated to achieve a saturation of peripheral oxygen (SpO_2) between 92 -96%[50] unless otherwise specified by the attending anaesthetist/ICU consultant. Gas flow rate is set at 50 litres per minute. If a participant is unable to tolerate this flow rate, it can be reduced to a minimum of 30 litres per minute. High-flow nasal oxygen therapy is to be provided continuously for 48 hours from the time of extubation. Changes to flow rate and any removal of high-flow nasal oxygen therapy for more than 15 minutes during the 48-hour period are recorded.

All other aspects of perioperative patient care, including the type of anaesthesia, postoperative analgesia, surgical techniques, and postoperative clinical care are provided at the discretion of the anaesthesia and surgical teams and according to routine clinical practice at our centre. Pragmatically, there will be no attempt to standardise perioperative management or intraoperative ventilation strategies for this study. Our hospital is currently not recognised as an enhanced recovery after surgery (ERAS) site however some individual anaesthesia and surgical teams within our hospital adhere to ERAS principles.

Intervention Group

Care is provided as per the control group above, with the exception of five, 30-minute[11] NIV sessions delivered by a physiotherapist over the first two postoperative days in addition to high-flow nasal oxygen therapy. The initial NIV dose is delivered within four hours of extubation, followed by twice

daily sessions on postoperative day one and two. This service is provided in the PACU, ICU/HDU, or the surgical ward depending on the participant's location at the time of NIV delivery.

Prior to commencing each NIV session all participants are assessed for absolute contraindications for NIV therapy by the treating physiotherapist (Table 2). The NIV sessions are delivered using a ResMed VPAP™ machine (ResMed Ltd, Oxfordshire, UK) with a humidified circuit and standard facemask. This is delivered with participants either sitting up in bed with the bed head raised between 45 – 90 degrees or with the participant sitting out of bed in a high back chair. Expiratory positive airway pressure (EPAP) is set at $10cmH_20$[11]. Inspiratory positive airway pressure (IPAP) is initially set at $15cmH_20$ and adjusted as required to achieve tidal volumes of at least 6-8mls/kg. Participants with BMI > 30 have a starting EPAP set at $12cmH_20$ and a starting IPAP set at $16cmH_20$. Deviations from these planned settings are reported and documented. The difference between IPAP and EPAP (known as pressure support ventilation; PSV) is maintained at a minimum of $4cmH_20$ and the maximum total pressure (PSV + EPAP) will be no greater than $25cmH_20$[11].

If a participant is unable to tolerate the set pressures, reassurance is firstly given to the participant and the following modifications taken in sequential order, until patient tolerance is achieved:

1. Reduce EPAP to $8cmH_20$ (set minimum)
2. Reduce IPAP to $12cmH_20$ (set minimum) in decrements of $1cmH_20$

If the participant remains unable to tolerate the therapy despite pressure titration and reassurance, cessation of NIV therapy will occur and be reported. Pressure rise time is set at the slowest speed (900ms) and the inspiratory trigger is set to the minimum value. Air-leaks are managed by fitting the correct sized mask carefully using the mask measure guide provided by ResMed with focus on minimising leaks around the nasogastric tube if present. The ResMed VPAP™ compensates for air leaks up to 40 litres per minute. Above this a 'high-leak' alarm sounds and the machine is unable to deliver the set pressure. Any high-leak alarm is monitored, recorded and the mask readjusted accordingly. Ideally the duration of NIV is to be 30 minutes of continuous therapy, however if NIV therapy needs to be temporarily stopped, therapy time will cease and reason documented. Once therapy is re-started, timing will recommence. If a participant is unable to continue with NIV therapy within 5 minutes of temporarily ceasing, the session is terminated and the reason documented. Supplemental oxygen is titrated through the ResMed VPAP™ as required to achieve $Sp0_2$ 92-96% unless otherwise specified by the medical team. During each NIV session participants have their high-flow nasal oxygen therapy removed for the duration of NIV therapy and replaced once therapy is finished. The treating physiotherapist continuously monitors all participants for the duration of the

NIV therapy and re-assesses 30-minutes post intervention. Data including; blood pressure, heart rate, respiratory rate and $Sp0_2$ is recorded pre, immediately post and 30-minutes after each NIV session. Any reason resulting in early cessation of NIV intervention or being unable to provide NIV therapy is reported.

All physiotherapists providing the intervention attend NIV training with the ICU Senior Physiotherapist who has 11 years' experience in NIV application. The training session includes familiarisation with the ResMed VPAP™ machine, set-up of equipment, detailed explanation of the intervention protocol and trouble-shooting. The physiotherapists are provided with a training manual and a copy of this manual is also kept with the ResMed VPAP™ to allow reference at any point during the intervention. The training manual consists of all the information provided in the training session. The years of hospital experience of each participating physiotherapist is reported.

Withdrawal from trial

Participants are withdrawn for i) requiring longer than 48 hours of mechanical ventilation following surgery, or ii) withdrawal of consent. All withdrawals are reported.

Outcomes

To detect a possible signal towards PPC reduction with the use of NIV in addition to continuous high-flow oxygen therapy in the first 48 hours after surgery, the primary outcome measure is the development of a PPC within the first 14 postoperative days or hospital discharge whichever occurs first. Using the Melbourne Group Scale (MGS) diagnostic Tool Version 2[48] (Table 4) a PPC is diagnosed when four or more of eight screening criteria are present in a 24-hour day. The MGS tool is valid and reliable[51], is sensitive to therapeutic interventions designed to ameliorate postoperative atelectasis and alveolar de-recruitment[48], and widely utilised in upper abdominal surgery trials[4-6 48]. An assessor blinded to group allocation, who has no clinical involvement with the study assesses participants prospectively and daily for a PPC until the seventh postoperative day. Thereafter, additional PPC assessments are only performed if clinically indicated when there are signs of respiratory deterioration reported in the medical record until postoperative day 14 or hospital discharge, whichever occurs first. To reduce the potential for missing data, retrospective collection of PPC data from the daily medical record will occur when a participant or assessor is unavailable for PPC assessment. Participants scoring three out of the possible eight factors are assessed twice daily to monitor for any further clinical deterioration. A blinded senior physiotherapist confirms a positive diagnosis of a PPC.

Feasibility measures of trial conduct, design and protocol

1) Consent and recruitment ability. Consent rate is anticipated to be ≥90% with recruitment of one to two patients per week.

2) Protocol adherence of physiotherapy-led NIV therapy. Successful physiotherapy-led NIV implementation is set at ≤20% protocol deviations. This is measured and reported by;

    a. Proportion of intervention participants who receive the first NIV session within four hours of surgical- extubation.

    b. Proportion of intervention participants who receive five, 30-minute NIV sessions in the first two postoperative days.

    c. Reasons why NIV therapy could not be delivered or were ceased early.

3) Protocol adherence of high-flow nasal oxygen therapy. Successful high-flow nasal oxygen therapy implementation is set at <20% protocol deviations. This is measured and reported by;

    a. Proportion of participants who receive high-flow nasal oxygen therapy for 48 continuous hours following surgical-extubation.

    b. Time in minutes from extubation following surgery to commencement of high-flow nasal oxygen therapy.

    c. Reasons why high-flow nasal oxygen therapy cannot be delivered or sustained.

4) Safety of NIV therapy measured by; (i) major adverse events relating to NIV therapy defined as; anastomotic leak suspected and confirmed; severe hypotension requiring an increase in medical management; cardiac and/or respiratory arrest; deterioration in medical condition requiring an increase in medical management and (ii) any transient physiological events during or immediately following NIV intervention (Table 2).

5) Costs of a high-flow nasal oxygen therapy and physiotherapy-led NIV therapy service measured by; costs of equipment (NIV masks, high-flow and NIV circuits, cleaning and machine service costs); physiotherapy time (in hours) attributed to delivering the NIV therapy and costs of an ICU and hospital stay measured by average cost of a bed day.

Secondary exploratory outcomes

1) Incidence of Pneumonia[52] defined as new CXR infiltrates with at least two of: temp >38 °C, SOB, cough and purulent sputum, altered respiratory auscultation and WCC >12,000/ml or leukopenia <3000/ml), within the first 14 postoperative hospital days or hospital discharge whichever occurs first.

2) Incidence of systemic inflammatory response syndrome (SIRS) as defined by 2 or more of the following: temp >38 or <36; HR>90; RR>20, or PCO2<32, or ventilation for acute process; WCC>12 or <4, within the first 14 postoperative hospital days or hospital discharge whichever occurs first.

3) Incidence of sepsis, defined as a Sequential Organ Failure Assessment (SOFA) score ≥ 2, within the first 14 postoperative hospital days or hospital discharge whichever occurs first.

4) Post-surgical ICU and hospital length of stay (LOS) in days.

5) Unplanned ICU admission at any time-point during the acute post-surgical stay.

6) Incidence of reintubation at any time-point during the acute post-surgical stay.

7) In-hospital mortality, 30-day and 12-month mortality.

8) Health Related Quality of Life (HRQoL) using the EQ-5D-5L[53] preoperatively, postoperative day seven and day 14 and at 12-months postoperatively.

Blinding

Random allocation occurs following completion of surgery. This ensures pre-admission and operating theatre medical, nursing, and physiotherapy staff are masked to postoperative group assignment. Postoperatively, PPC assessors are independent of routine postoperative clinical care and masked to group allocation. All physiotherapy documentation relating to the NIV intervention is documented and filed separately to ensure PPC assessors remain blinded for the first seven postoperative days and then added to the patient's medical file. If a treatment group participant informs the PPC assessor of their group allocation this is noted and reported. Due to the nature of intervention, postoperative ward staff including nurses, doctors and treating physiotherapists are unable to be blinded.

Data collection

Preoperative variables

To measure baseline characteristics the following variables are collected directly from the participant or the medical record: age (years), gender, height (cm), weight (kg), body mass index (kg/cm^2), planned surgical procedure, surgical category and reason for the procedure, physical health status according to the American Society of Anaesthesiologists (ASA) and rated by the attending anaesthetist at the PAC (score 1 to 5), smoking history (non-smoker, current smoker or ex-smoker having ceased more than 8 weeks preoperatively), smoking pack years (1 pack year = 20 cigarettes per day for 1 year), years since smoking cessation, respiratory status including auscultation signs and $Sp0_2$ (%) on room air, cough strength and presence of sputum, participant-reported history of a chest infection in the previous two weeks, functional co-morbidity index[54], participant-reported estimated maximum metabolic equivalent physical activity using a self-rated physical Specific Activity Questionnaire[55] and any limiting factor to ambulation.

Intraoperative variables

The following variables are collected from the anaesthetic record, operation report and medical record: duration of anaesthesia (in minutes) during surgery; mechanical ventilation parameters including mode of ventilation, level of pressure/volume control, positive end expiratory pressure used and any recruitment manoeuvres performed; average $Fi0_2$ during surgery; type and amount of intraoperative fluid delivered (ml/kg/h); number and type of blood transfusion units; incision type.

Postoperative variables

Postoperative data is collected daily for the first 14 days or until hospital discharge, whichever occurs first for the following variables: time in days from the preoperative physiotherapy session to the operation; location (ICU or surgical ward) and duration in days at each location; duration of analgesia and type (epidural, constant opioid infusion, patient controlled analgesia, patient controlled epidural analgesia, oral, local pain infusion, or other); unplanned ICU admission and ICU LOS; hospital LOS; hours of mechanical ventilation; days of vasopressor use; days and types of oxygen therapy use; total days of nasogastric tube; day and diagnosis of a prolonged postoperative ileus using a standardised criteria[56] of 2 or more of the following factors in a 24-hour period including nausea/vomiting, inability to tolerate normal diet, absence of flatus, abdominal distension, radiologic confirmation, and physician diagnosis of ileus. Postoperative NIV parameters are collected including, time in hours from extubation following surgery to the first NIV session; time each NIV

session is delivered and the grade/seniority of the treating physiotherapist providing the NIV; position of the patient during NIV; duration in minutes of each NIV session; IPAP and EPAP used; pressure titration – reasons if pressure titration occurs and the pressures used; number of times NIV has to temporarily ceased prior to the planned 30-minute session; reasons NIV was unable to be delivered to the participant; any major adverse or transient physiological event which occurs as a direct result of NIV therapy. Postoperative high-flow nasal oxygen therapy parameters are collected including; time in minutes from extubation following surgery onto high-flow nasal oxygen therapy; time and date high-flow nasal oxygen therapy is removed; duration in hours of high-flow nasal oxygen therapy within the first 48 postoperative hours; number of times high-flow nasal oxygen therapy is removed for greater than 15 minutes within the first two postoperative days; average flow rate during the first two postoperative days; average FiO_2 during the first two postoperative days; reasons a participant is unable to have postoperative high-flow nasal oxygen therapy for the first two postoperative days. Early ambulation parameters are collected including: time in hours from end of surgery until time to ambulation >1 min; postoperative day walked longer than 10 min; maximum rating of perceived exertion during ambulation at each session; maximum ambulation stage attained at each session and reasons for a participant being unable to participate in an ambulation session.

Sample Size

This RCT is a pilot trial that has been funded to be conducted for a defined time period (18 months). Current surgical throughput of eligible patients at our hospital predicts that we will recruit a sample of 130 eligible participants (65 per group) in the trial period. If this sample is not reached within the funded time period, recruitment will continue until a minimum sample of 130 is met. If this sample is reached prior to the designated funding period (18 months), recruitment will continue past 130, until this time period is completed. A baseline PPC rate of 18% for the control group (high-flow nasal oxygen therapy alone) is anticipated based on historical LIPPSMAck POP[48] data (n=101) of matched high-risk elective upper abdominal surgery participants who were given the same standardised pre- and postoperative physiotherapy as planned in NIPPER PLUS.

Previous systematic reviews in NIV to prevent pneumonia following surgery report a relative risk reduction of approximately 60%[14 57]. Using inference for proportion calculations for two independent samples; a total sample of 130 (2 groups of 65) would detect a 50% relative risk reduction in PPC between groups (favouring the NIV group, one-sided alpha at 0.05) with only 44% power. This sample will only be adequately powered (80%) if there is a large 75% relative risk reduction in PPC with the application of NIV (18% down to 4%).

Assuming that NIV is superior to high-flow nasal oxygen therapy, an adequately powered study would need a sample of at least 450 (relative risk reduction 50% from a baseline of 18%, alpha two-sided 0.05, beta 80%) which would require a multicentre approach. However, there is also the possibility that high-flow nasal oxygen therapy is just as effective as NIV to prevent PPC. This would require a non-inferiority trial and would require a much larger sample.

This pilot study aims to measure the feasibility of the intervention protocol and provide a baseline estimate of effect to assist in determining the design (superiority or non-inferiority) and conduct of a future multicentre RCT.

Methods: Data collection, management and analysis

Data is collected from participants using a standardised electronic case report form and stored on a password protected electronic hard drive. Research assistants and site investigators responsible for data collection are trained directly by the principal investigator to ensure correct data handling. Any data or participant lost to follow-up will be reported. Once each participant's data set is completed, it is de-identified, entered into a main database, locked, and maintained securely by the principal investigator. All data, consent forms and relevant correspondence are stored according to Australian privacy laws and archived for a minimum of 12 years. On completion of the trial, the database will be made available for independent analysis or as an appendix in the publishing journal if requested.

Statistical methods

As our study is stratified to postoperative location (ICU/WARD) only, there is a possibility of significant baseline differences between groups. This will be managed according to the prognostic strength and size of imbalances due to potential confounding baseline variables between groups being assessed[58]. Adjustment covariates will be selected by backward stepwise regression from covariates that may have the potential for clinically significant alterations in effect sizes. These include: smoking history, age, length in time of operation, operation category (upper gastrointestinal, colorectal, urological, other), incision type and location[59], intraoperative ventilation strategies[3 60], fluid delivery[61], blood transfusions[62], and mode of post-operative analgesia[63].

The primary outcomes of absolute and relative rates of PPC in the trial groups will be estimated using multivariate robust random effects Poisson generalised linear modelling to allow assessment of binary outcomes with or without adjustment for potential confounding variables (incidence rates and rate ratios, 95 % confidence intervals, P-values). In addition, the effect of time from the end of surgery/anaesthesia to diagnosis of PPC will be compared using Cox proportional hazards regression

with and without covariate adjustment (hazards ratio, 95 % confidence intervals, P-values). Graphic representation of this analysis will be performed using the Kaplan-Meier method.

Although this study is not adequately powered, a number of secondary outcomes will be treated as time-to-event analyses, with hazard ratios estimated using Cox proportional hazards regression: 1) The day of first diagnosis of other events will be recorded (pneumonia, SIRS, sepsis, reintubation, death); 2) Treatment group comparison for time from surgery to readiness for discharge, and to actual discharge (LOS), will be made using Cox proportional hazards regression, with successful discharge treated as censoring "failure" and death or no discharge within 30 days treated as censoring "non-failure". Binomial secondary outcomes including unplanned ICU admission, unplanned reintubation will be analysed using mixed effects Poisson regression. Secondary outcomes with irregular distributions, including length of time periods (ICU and total post-operative LOS) and HRQoL, will be evaluated for group differences using mixed effects ordered logistic regression, with mean time (95 % CI) estimated for descriptive purposes using mixed effects linear regression. An intention-to-protocol sensitivity analysis will be performed by excluding from the analysis any participant who did not undergo the planned postoperative NIV intervention treatment. The sensitivity of the outcome estimates to missing data will be evaluated using multiple imputation. All analyses will be performed using Stata version 14 or later (StataCorp, College Station, TX, USA) and analysed on an intention-to-treat basis.

Methods: Monitoring

Data monitoring

The steering committee consists of the principal investigator, local investigator and two academic supervisors who contribute to the design and revision of this study protocol. The principal and local investigators are responsible for the study administrative management and daily co-ordination of the trial ensuring appropriate trial conduct, record keeping and data management.

An independent Data and Safety Monitoring Board (DSMB) monitors the ethics of the study in accordance with the Declaration of Helsinki overseeing safety and conduct of the study.

For the trial, there is a stopping rule for the potential of NIV or high-flow nasal oxygen therapy to be harmful. An unacceptable rate of anastomotic leakage of over 2.5% will trigger consideration for trial termination by the independent DSMB established for the oversight of this clinical trial. To detect a 2.5% anastomotic leakage rate in either group requires a minimum of 57 patients (one-sample test of proportion compared to hypothetical 0.1% rate; power 80%; alpha 0.05). Analysis of anastomotic

leakage rates only in both groups will therefore be performed at participant recruitment number 60 using cumulative summation analysis[64].

Any other major adverse events directly relating to the interventions will be reported with oversight from the independent DSMB.

Ethics and Dissemination

The Tasmanian Health Human Research Ethics Committee has granted ethical approval for this trial. Trial results will be disseminated widely through conference presentations and peer-review journal publications.

DISCUSSION

Consequences of PPCs following upper abdominal surgery are well defined, leading to great interest in their prevention. High-risk patients have been shown to be over eight times more likely to develop a PPC compared to individuals identified as low-risk[6] suggesting increased attention is required to improve postoperative outcomes in this high-risk cohort.

Whilst previous clinical studies support the use of preventative NIV therapy following major abdominal surgery[11 14 17], implementation of NIV therapy does not appear to be standard postoperative care[4 21] and a number of important methodological limitations exists in previous literature including high-bias risk and minimal reporting of adverse events[14]. Recommendations for future research include; evaluating the use of NIV in preventing mortality, a targeted approach investigating patients at higher risk for PPCs and must report on all adverse effects and possible complications of preventative postoperative NIV[14 17]. The NIPPER PLUS study is designed to begin targeting these recommendations by collecting and reporting on in-hospital, 30-day and 12-month all-cause mortality for all participants and is recruiting participants identified as high-risk of developing a PPC only. High-risk for this study has been defined as either; eligible patients with a planned postoperative admission to ICU/HDU due to this factor being independently associated with the development of a PPC[6] or eligible patients Identified at high risk using the MRPT[6]. The MRPT has been shown to be specific and sensitive in the identification of individuals who are at highest risk of PPC development in the surgical settings including upper abdominal surgery[5 6].

Preventative NIV was associated with no major complications in our observational study[41] and the NIPPER PLUS trial aims to further support this finding by reporting on any adverse event as well as transient physiological events directly relating to NIV therapy during, immediately following and 30-

minutes after therapy, therefore contributing to necessary and strongly recommended NIV safety data for both ICU and ward patients.

All previous preventative NIV clinical trials in abdominal surgery compare NIV to standard oxygen therapy only[14 17], however the application of high-flow nasal oxygen therapy is becoming widespread in ICUs[40] and in other clinical settings[26]. The NIPPER PLUS study is designed with high-flow nasal oxygen therapy as standard care to match current clinical practice within our ICU unit and aims to detect whether there is a possible signal towards PPC reduction with the use of additional intermittent NIV compared to continuous high-flow oxygen therapy alone. The NIPPER PLUS trial is a single-centre study. The effect of high-flow nasal oxygen therapy in high-risk upper abdominal surgery patients is currently unclear. Prior to undertaking expensive fully powered multicentre trials there is a need to build evidence and data from pilot trials for realistic effect size variability estimation and to measure the design, feasibility, safety and potential challenges of treatment protocols. This pilot study aims to inform future definitive trial design and conduct. Interpretation of results will be evaluated in context of the studies limitations and indeed, it may be demonstrated that this protocol is unfeasible in its current form and would be futile to progress to multicentre trials without study and protocol re-design.

In conclusion, the NIPPER PLUS trial is a single-centre, assessor-blinded, parallel group, pilot RCT, which aims to detect whether there is a possible signal towards PPC reduction with the use of additional intermittent NIV compared to continuous high-flow oxygen therapy alone following high-risk elective upper abdominal surgery. This trial is measuring recruitment ability, feasibility of implementing a physiotherapy-led NIV and high-flow nasal oxygen therapy protocol, safety of NIV therapy and preliminary costs of care information on a NIV and high-flow nasal oxygen therapy service. This will assist in the design and conduct of future multicentre trials. In addition, this trial will also explore possible effects on post-surgical ICU and hospital LOS, unplanned ICU admission, reintubation rates, in-hospital, 30-day and 12-month mortality. This trial standardises preoperative and postoperative physiotherapy care and is currently recruiting.

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Author Contributions

IB and JL conceived and designed the study and coordinated the trial. LD and SMP assisted in final study design and protocol. JL prepared the first draft of the protocol manuscript, and was responsible for the final manuscript. All authors (JL, IB, IKR, LD, DS and SMP) revised all manuscript drafts, approved the final manuscript and contributed intellectually important content. JL is the guarantor of the paper and takes responsibility for the integrity of the work as a whole, from inception to published article

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Ethics approval

The trial is being conducted in accordance with the Declaration of Helsinki and has undergone ethics review by the Tasmanian Health Human Research Ethics Committee and received approval 08/02/2017 (protocol reference H0016207). All participants will provide written informed consent.

Conflict of interest declaration

The authors have no conflicts of interests

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Table 1 Trial Registration Data Set for NIPPER PLUS trial

Data Category	Information
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry number: ACTRN12617000269336
Date of registration in primary registry	22/02/2017
Secondary identifying numbers	n/a
Trial protocol version	This is Version 2 of the protocol and was enacted on February 2017
Source of monetary or material support	Clifford Craig Foundation ($80,000 AUD)
Contact for public queries	JL, jane.lockstone@ths.tas.gov.au
Contact for scientific queries	JL, jane.lockstone@ths.tas.gov.au
Public title	Does early postoperative non-invasive ventilation (NIV) prevent chest infections following high-risk elective abdominal surgery
Scientific title	NIPPER-PLUS trial – Non-Invasive Positive airway Pressure therapy to Reduce Postoperative Lung Complications following Upper abdominal Surgery: a single centre pilot randomised control trial
Countries of recruitment	Australia
Health condition(s) or problem(s) studied Intervention(s)	Pulmonary complications following high-risk elective upper abdominal surgery Active comparator: Physiotherapy-led postoperative NIV therapy Placebo comparator: high-flow nasal prong oxygen therapy
Key inclusion and exclusion criteria	Ages edible for study: ≥ 18 years Sexes eligible for study: both Accepts health volunteers: No Inclusion criteria: All adults undergoing high-risk elective open and/or advanced hand-assisted laparoscopic abdominal surgery. Exclusion criteria: 1. Any absolute contraindications for NIV in the period following surgery prior to the first NIV session; 2. Oesophageal surgery; 3. Obstructive sleep apnoea requiring CPAP overnight; 4 extreme claustrophobia; 5. not able to understand verbal instructions in English; 6. do not have capacity to give consent themselves; 7. a current hospital patient for a separate episode of care; 8. requiring organ transplant.
Study type	Type: Investigator initiated, interventional, non-pharmacological, pilot study Allocation: Concealed randomisation Intervention model: parallel assignment Masking: assessor blinding Primary purpose: Prevention Phase: Phase 2
Date of first enrolment	23/02/2017
Target sample size	Minimum 130
Recruitment status	Recruiting
Primary Outcome	Postoperative pulmonary complication during the first 14 postoperative days
Key secondary outcomes	Recruitment ability, physiotherapy-led NIV and high-flow nasal oxygen therapy protocol adherence, safety of NIV therapy, associated costs of high-flow nasal oxygen therapy and a physiotherapy-led NIV service following upper abdominal surgery. In addition, this study will explore effects on incidence of pneumonia, intensive care unit (ICU) and hospital length of hospital, ICU readmission rates, incidence of reintubation, in-hospital, 30-day and 12-month all-cause mortality and health related quality of life.

Table 2 Contraindications and Adverse events relating to NIV therapy

Absolute Contraindications	Relative Contraindications	Major Adverse Event	Transient physiological event
Cardiac or respiratory arrest	Mildly decreased level of consciousness	Anastomotic leak	hypotension, defined as a decrease in blood pressure >20mmHg determined by pre/post blood pressure observations
Severe agitation or encephalopathy	Progressive severe respiratory failure as reported by the treating physician	Severe hypotension requiring increase in medical management	decrease in $Sp0_2$oxygen saturations >10% from baseline or <85% for >60 seconds
Undrained pneumothorax or intraoperative pneumothorax with ICC in-situ	Uncooperative patient who can be calmed or comforted	cardiac or respiratory arrest	gastric distention as clinically reported by the treating surgeon
Uncontrolled vomiting	$Sp0_2$ falls below >10% below resting level of <85% for >60 seconds	Deterioration in medical condition requiring an increase in medical management	Vomiting during the NIV therapy
Inability to protect airway	MAP < target pressure despite vasopressor		Nasal bridge or facial erythema or ulceration
Severe upper GI bleeding or haemoptysis	Resting HR <50 or >140 or new untreated arrhythmia develops		
Need for immediate intubation	RR <5 or >40 b/min		
Facial trauma			

Abbreviations: HR, heart rate; ICC, intercostal catheter; MAP, Mean arterial pressure; NIV, non-invasive ventilation; RR, respiratory rate; $Sp0_2$, saturation of peripheral oxygen; Upper GI, Upper gastrointestinal; >, greater than; <, less than

Table 3 Early postoperative ambulation protocol[48]

Stage 1 (Safety)	Sit over edge of bed/sit in chair minimum of 2 minutes
Stage 2 (Safety)	March on spot 0-1 minute
Stage 3 (Ambulation)	March on spot/walk away from bedside 1-3 minutes
Stage 4 (Ambulation)	March on spot/walk away from bedside 3 – 6 minutes
Stage 5 (Ambulation)	Walk away from bedside 6 – 10 minutes
Stage 6 (Ambulation)	Walk away from bedside 10 – 15 minutes
Stage 7 (Ambulation)	Walk away from bedside > 15 minutes

PROTOCOL

Provide assisted early ambulation as soon as possible on the first postoperative day.

At each session progress through each stage in sequence. Time achieved in the session is accumulative.

Aim to achieve rating of perceived exertion of greater than 3/10.

Aim to assist patient to ambulate more than 10 minutes (Stage 6 or greater).

Once patient able to ambulate past Stage 3, patient can be assisted to ambulate with a Physiotherapy Assistant, as long as safe to do as determined by the ward physiotherapist.

Interval training is permissible to obtain target walking time. Each interval of rest time must not exceed the preceding work time. Total session time is the accumulative work time.

Provide assisted early ambulation once a day until discharged according to the discharge scoring tool[49]

Table 4 Postoperative pulmonary complications diagnostic tool: Melbourne Group Score Version 2[48]

Diagnosis confirmed when 4 or more of the following criteria are present anytime in the 24-hour period 00:01 to 24:00 on a single postoperative day:

1. New abnormal breath sounds on auscultation different to preoperative assessment
2. Productive of yellow or green sputum different to preoperative assessment
3. Pulse oximetry oxygen saturation (SpO_2) < 90% on room air on more than one consecutive postoperative day
4. Raised maximum oral temperature > 38°C on more than one consecutive day
5. An unexplained white cell count greater than 11 $x10^9$/L
6. Presence of infection on sputum culture report
7. Chest radiograph (CXR) report of collapse/consolidation. Chest radiograph (CXR) report of collapse/consolidation. When a CXR has been taken but no report available, a ward medical officer, or a senior respiratory physiotherapist with more than 10 years' experience will be asked to report.
8. Physician's diagnosis of pneumonia, lower or upper respiratory tract infection, an undefined chest infection or prescription of an antibiotic for a respiratory infection

Figure Legends

Figure 1 NIPPER PLUS participant timeline and schedule of events; *Abbreviations: D/C; discharge, ICU; intensive care unit, LOS; length of stay, NIV; Non-invasive ventilation, POD; postoperative day, PPC; postoperative pulmonary complication, HRQoL; health-related quality of life*

Figure 2 CONSORT flow diagram for the NIPPER PLUS study; *Abbreviations: NIV, non-invasive ventilation, PPC; postoperative pulmonary complication, POD; postoperative day, HRQoL; health-related quality of life*

Figure 1 NIPPER PLUS participant timeline and schedule of events

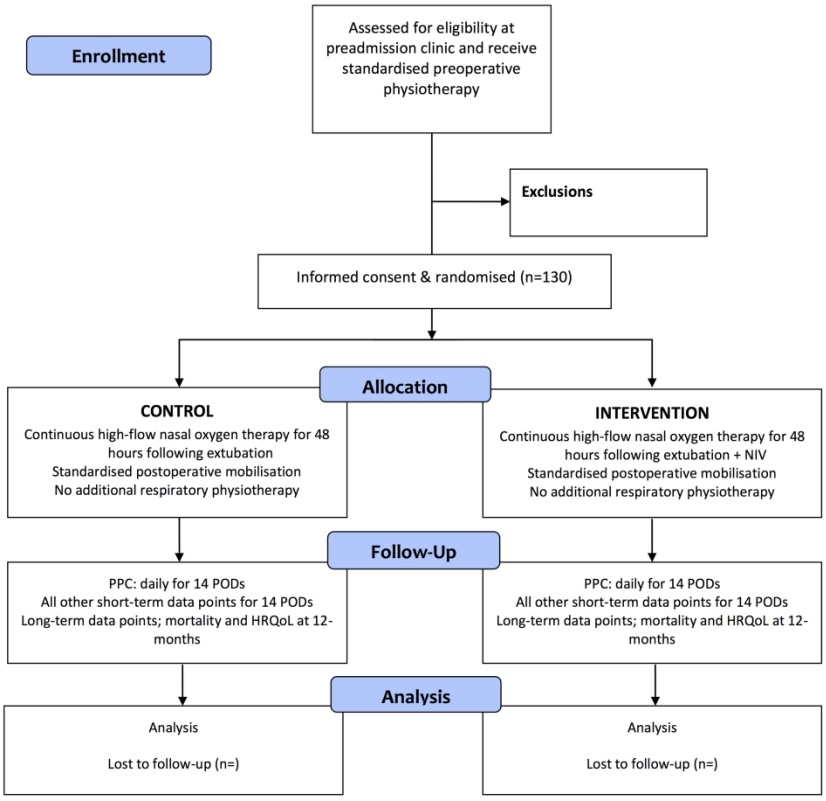
		Enrolment	Allocation		Post Allocation			Close out	
	TIMEPOINT	***Listed for elective surgery***	***Pre-admission clinic***	***Day of surgery***	***POD 1-7***	***POD 8-14***	***Hospital D/C***	***POD 30***	***12 month***
ENROLMENT:	*Enrolment*		X						
	Eligibility screen	X							
	Informed consent		X						
	Random Allocation			X					
INTERVENTIONS:	***Control;** High-flow nasal oxygen therapy*			X	X				
	***Intervention:** High-flow nasal oxygen therapy plus intermittent postoperative NIV*			X	X				
VARIABLES:	*Demographics, medical history, HRQoL*		X						
	Intraoperative variables				X				
	Postoperative variables				X	X	X		
OUTCOMES:	*PPC*				X	X			
	Recruitment ability, physiotherapy-led NIV and high-flow nasal oxygen therapy protocol adherence				X				
	Major adverse events and/or transient physiological events of NIV				X				
	Associated costs of physiotherapy-led NIV & a high-flow nasal oxygen therapy service				X	X	X		
	Pneumonia, Hospital and ICU LOS, ICU readmission and reintubation rates, in-hospital mortality				X	X	X		
	HRQoL (EQ-5D-5L)				X	X			X
	30-day and 12-month all-cause mortality							X	X

Abbreviations: D/C; discharge, ICU; intensive care unit, LOS; length of stay, NIV; Non-invasive ventilation, POD; postoperative day, PPC; postoperative pulmonary complication, HRQoL; health-related quality of life

Figure 1 NIPPER PLUS participant timeline and schedule of events

279x361mm (300 x 300 DPI)

Figure 2 CONSORT flow diagram for the NIPPER PLUS study



Abbreviations: NIV, non-invasive ventilation, PPC; postoperative pulmonary complication, POD; postoperative day, HRQoL; health-related quality of life

Figure 2 CONSORT flow diagram for the NIPPER PLUS study

279x361mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	26 (Table1)
Protocol version	#3	Date and version identifier	26 (Table1)
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and	#5b	Name and contact information for the trial sponsor	N/A

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17-18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	9-11

		administered	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15-16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	7-8

concealment mechanism		central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14,15,16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12, 16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
Statistics: analysis population and	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical	16-17

missing data		methods to handle missing data (eg, multiple imputation)	
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17-18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17-18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of	#28	Financial and other competing interests for principal	20

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16, 18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	Page 3-4	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Page 3-5	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Page 10-11	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Page 9-11	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Page 11	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Page 9-10	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Page 9-10	

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Page 9 -11	
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	Page 9-11	
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	N/A	
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

TIDieR checklist