This protocol has been written in line with the NHMRC *National Statement on Ethical Conduct in Human Research 2007* and the *Australian Code for the Responsible Conduct of Research 2007*

Background:

Post-operative pulmonary complications (PPC) are the most common complication following major abdominal surgery[1]. PPC are costly to both the hospital and patient. Unpublished data (n=699) from recently completed multi-centre trials[2] found a longer length of stay (LOS) (MD 5 days, 95% CI 4 to 7 days), and greater hospital costs (MD $AUD16K, 95% CI $12K to $25K) in those with PPC compared to those without following upper abdominal, prolonged lower abdominal, laparoscopic, and hernia surgery[3]. Most concerning is significantly worse 30-day mortality rate (9% v 1%, p=0.01) in patients who developed a PPC in the first seven postsurgical days. This mortality association agrees with meta-analysis findings in abdominal and thoracic surgery[4]. PPC was determined using an eight-factor diagnostic screening tool utilised by physiotherapists to detect PPC potentially preventable with therapeutic interventions [5-9].

Despite the known seriousness of PPC, definitive knowledge of incidence rates is lacking. Published incidences range greatly (from 10 to 80%). This variation can be due to surgery types being investigated (e.g. hernia repair compared to oesophagectomy) or sensitivity of diagnostic criteria used to detect a PPC[8]. Previous research has predominantly utilised definitions of PPC limited to severe typologies such as acute respiratory failure, lung injury, or pulmonary oedema[10,11]. There is a risk that less severe, yet clinically significant PPC (such as pneumonia, severe atelectasis, and upper respiratory tract infections) is under-reported. Additionally, previous trials are limited to public metropolitan hospitals, older age groups, and major open upper abdominal and thoracic surgery groups[12,13]. Little is known on complication rates following emergency surgery, organ transplants, neurosurgery, open cardiac, major ENT surgery, and minimally invasive abdominal surgery.

The combination of insensitive measurement of PPC and lack of contemporary incidence rates in a wide range of surgery and hospital types means it is not possible to estimate with confidence which surgical groups are currently at highest risk of clinically significant PPC. The most cited paper on allocating risk of respiratory failure across a range of surgical groups is now 16 years old[11]. Resource allocation of prophylactic interventions like physiotherapy may not be based upon current evidence. Hospitals could be over-treating some surgical groups and, most concerning, under-treating others. The current physiotherapy service delivery to non-orthopaedic surgical patients has not been measured robustly and is unknown.

Considering the high mortality and hospital costs of PPC there is an urgent need to measure PPC prevalence over a range of hospital types and surgical groups using consistent diagnostic criteria, and to investigate the current use of physiotherapy interventions to reduce PPC incidence and improve recovery following major non-orthopaedic surgery.

Primary Aim: Determine the incidence of PPC using standardised diagnostic criteria in the first 7 postoperative days following major non-orthopaedic surgery.

Secondary Aims: Following major non-orthopaedic surgery; 1. Determine the incidence of pneumonia, systemic inflammatory response syndrome (SIRS), sepsis, ICU LOS, unplanned ICU readmission rates, reintubation rates, hospital LOS, and in-hospital mortality. 2. Audit physiotherapy service delivery. 3. Investigate associative relationships between causative factors and preventative therapies for PPC. 4. Ascertain concordance between generic assessment of PPC, pneumonia, SIRS, and sepsis. 5. To develop risk predication models in different surgical groups for those at risk of developing PPC.

Hypothesis: Determination of PPC incidence and other outcomes within a large multi-centre observational trial utilising standardised diagnostic criteria will allow benchmarking in comparison to other centres. Results will inform targeted delivery of physiotherapy and other medical services to reduce preventable PPC in risk populations. Data will inform RCT sample size calculations to test interventions to reduce PPC.

Design and setting: Prospective observational cohort study conducted within ICU/HDU and acute surgical wards at participating centres over a minimum one week or up to a maximum of 12 months over the trial period of April 2017 to December 2018 inclusive. Thirty major metropolitan and inner regional hospitals in Australia, New Zealand, Sweden, USA, Malaysia, and Singapore will be purposively sampled via direct approach from the Chief Investigator to participate in this study. All remaining Australian hospitals will be stratified to state, rurality, and private/public status and 30 additional hospitals will be randomly sampled from each group and invited to participate.

Inclusions: All adults having emergency and elective surgery involving a surgical incision/s anywhere in the abdomen, thorax, spine, or head, with a minimum of a two (2) night hospital stay fitting the following hierarchical criteria;

1. All surgical patients admitted to ICU/HDU postoperatively.
   Including, but not limited to, transplants, abdominal, thoracic, cardiac, neurosurgery, ENT, spinal, trauma.
2. Surgical patients admitted to an acute surgical ward with the following operations:
   Open* upper abdominal surgery, open vascular abdominal surgery, laparoscopic assisted or hand-assisted abdominal surgery, advanced laparoscopic surgery (colorectal, UGI, bariatric surgery), open cardiac surgery, open thoracic surgery
3. Only when anaesthetic time is >180mins and admitted to a surgical ward.
   Open lower abdominal surgery, abdominal/thoracic laparoscopic** surgery, neuro surgery, spinal surgery.

*Open procedure – where any incision ≥5cm, or where the combined length of laparoscopic incisions ≥5cm
**Laparoscopic procedure – where each incision is <5cm and the combined length of incisions are <5cm

Exclusions: Where the procedure is solely a gynaecological procedure, inguinal hernia repair, peripheral orthopaedic surgery, burns grafting, currently recruited CHESTY patients who have had repeat surgical procedure/s within the primary episode of care for which they were originally included in CHESTY, and patients whose surgery did not occur on-site or those admitted to day-surgery unit or short-stay surgical unit.

Optional inclusions: Sites can volunteer to collect data on the following patient groups:
Admission for blunt chest wall trauma (non-surgical)
ENT surgery where patients are admitted directly to the ward and where surgery is >180min
Orthopaedic surgery where patients are admitted to ICU/HDU, or, when admitted to the ward and where the surgery is > 180mins, including, but not limited to, total knee replacement, total hip replacement, hip hemiarthoplasty, open reduction and external/internal fixation of long bones in the lower limb (for this group the exclusion criteria for orthopaedic surgery becomes null)

Screening for eligibility and recruitment of patients:
All new surgical patients admitted to ICU, HDU, or surgical wards will be screened by a site investigator for eligibility according to the specified criteria. Eligible patients will have their specified health information collected for the next 7 postoperative days, or until discharge whichever occurs first. Any eligible patient that each participating site is unable to collect data on for those 7 consecutive days will be allocated as missed for recruitment and the reason detailed, e.g. transferred to another centre; resource limitations; Patient consent to participate is not required as there is no divergence from each site's usual care. No extra-ordinary assessments or treatments are being performed for this trial outside of the usual care. There is negligible risk to the patient to participate.

For feasibility in this unfunded trial, it is allowable for sites to pre-specify a particular surgical cohort (eg neurosurgery) or location (ICU or ward) to focus data collection on over a pre-specified time frame (eg 4 weeks) or to a predetermined sample size (eg 50) and then to switch to a different surgical cohort (eg. Only collect data on 50 consecutive neurosurgery patients and then 50 consecutive thoracic surgery patients and then 50 cardiac surgery patients and so on).

Privacy/confidentiality/data security:
Patients - All data will be identifiable during the onsite data collection process and will be kept securely by the site investigators acting within their specific Health Organisation's legislative requirements for ensuring confidentiality of health information and storage. Identifiable data during the onsite data collection process is necessary to enable accurate and valid data collection of eligible patients by the site investigators and ward physiotherapists during the inpatient stay. Once the patient's data set is complete, the datasheet will have the patient's name and DOB removed and the data can only be re-identified if needed with the individual's medical record identifying number only. Once data is entered into the on-line secure database, the data is immediately de-identified and locked. Principal and co-

ordinating investigators outside of each participating site will not be able to re-identify the data once the data has been lodged and locked. The main CHESTY database will be permanently unable to re-identify data to a particular patient.

Sites - Each participating site will be provided with an individual identifying code name which is known only to them and the Co-ordinating Chief Investigator. Participating sites will be able to analyse their own outcomes in comparison to other participating sites using this individual identifying code. Each site will remain de-identified from each other during benchmarking analysis.

Data security - Each site is required to store the identifiable collected information securely according to the *Australian Code for the Responsible Conduct of Research 2007*. The original research data (paper data sheets and/or electronic data sheets) will be retained securely by each site for 15 years from date of publication of the first CHESTY paper. Sites must provide safe and secure storage of the research data that is covered by institutional policies on research data ownership and security. Paper based data collection is to be secured in a locked facility approved by the participating institution. Electronic based data collection is to be secured in password protected local area network computer drives supported by institution's Information Technology services. All research data, including electronic data, is to be stored in a durable, indexed and retrievable form. Once the defined minimum 15 years has transpired the data will be destroyed following advice from each institution's IT services for destruction of electronic data. Each participating site's identifiable data remains the property of the participating site. The de-identified main CHESTY database remains the property of the CHESTY Collaboration and usage for publication will be guided by signed agreement amongst the collaboration.

Outcome measures:

Primary: Consecutive eligible patients are assessed **daily** from the first to the seventh post-operative day, or day of discharge whichever occurs first, for a PPC using the Melbourne Group Score V3 [2,5,6].

Figure 1: PPC diagnostic criteria

When four (4) or more of the following criteria* are present anytime in the 24hour period 00:01 to 24:00 on a single POD:

1. New abnormal breath sounds on auscultation different to preoperative assessment
2. Production of yellow, green, or brown sputum different to pre-morbid status
3. Pulse oximetry oxygen saturation ($Sp0_2$) <90% on room air or FiO_2 0.21 on more than one consecutive post-operative day**
4. Raised maximum body temperature >38°C on more than one consecutive post-operative day
5. Chest radiograph report of collapse/consolidation***
6. An otherwise unexplained white cell count greater than 11, or less than 3.
7. Presence of infection on sputum culture report***
8. Physician's diagnosis of postoperative pulmonary complication (e.g. atelectasis, pneumonia, AECOPD, respiratory failure, upper respiratory tract infection) **OR** prescription of an antibiotic specific for respiratory infection

**If a therapist, nurse or physician documents in the medical record the occurrence of a criterion at any time in the 24hr time period, this is taken as a default positive finding. If no documentation present, blinded assessor is required to assess this directly.*

***For ventilated patients, if $FiO_2 \geq 0.5$ or PEEP ≥ 8, assume criterion 3 is present (do not alter PEEP or FiO_2), for all other patients set FiO_2 to 0.21 and PEEP to 5 and observe SpO_2 for two minutes. If SpO_2 drops below 90% immediately reinstate previous PEEP and FiO_2. If not permissible to adjust ventilator settings assume +ve.*
For spontaneously ventilating patients, assume +ve if O_2 therapy delivery has an estimated $FiO_2 \geq 0.4$

****If daily measures are not made for CXR or sputum samples carry over a positive diagnosis for either of these criteria to the next consecutive postoperative day.*

Secondary measures are:

1. Pneumonia[14] defined as new CXR infiltrates with at least two of: temp >38°C, SOB, cough and purulent sputum, altered respiratory auscultation and WCC >12 x 10^9/l or leukopenia < 3 x 10^9/l

2. Systemic inflammatory response syndrome (SIRS) as defined by 2 or more of the following criteria: temp >38 or <36; HR>90; RR>20, or ventilation for acute process; WCC>12 or <4.

3. Sepsis;

- ICU/HDU patients using the Sequential Organ Failure Assessment (SOFA) score defined as ≥ 2 point change[15]. Variables in SOFA: PaO_2/FiO_2 ratio, GCS, MAP, Vasopressor use, type, and dose rate, Serum Creatinine or Urine output, Bilirubin, and Platelet count.

- Ward patients using the quick SOFA (qSOFA) score defined as any 2 of 3 criteria; Respiratory rate ≥ 22, altered mentation, systolic blood pressure ≤ 100

4. ICU LOS and unplanned ICU readmission rates, reintubation rates, bronchoscopy rates, hospital LOS, in-hospital mortality during the initial episode of care.

Data collection: Data will be collected using a validated standardised piloted electronic/paper-based case report form[2] previously trialled in two multi-centre international clinical trials of 700 surgical patients. Data will be entered by site investigators onto a secure on-line purposive built case report form utilising the REDCap Consortium database platform which is approved by Health Departments and Universities in the USA and Australia for secure patient data entry for research purposes. Data occurring on weekends and public holidays can be collected in retrospect on the next available working day. Missing data fields can be filled through retrospective audit of the medical record from the available information.

Data fields: Data will be collected from the anaesthetic record, operation report, and existing medical record;

- Patient age, gender, weight, and height.
- Smoking status (current, ex-smoker, non-smoker, pack years if available)
- Presence of any of the following documented co-morbidities;
  - Respiratory (e.g. Asthma, COPD, ARDS, chronic respiratory diagnosis
  - Ischemic Heart Disease (e.g. Angina, Heart Attack)
  - Congestive cardiac failure/disease
  - Neurological disease including stroke/TIA/Parkinsons/any type of neuromuscular disease
  - Diabetes (type 1 or 2)
  - Upper GI disease (e.g. reflux, cystitis, ulcers)
  - Cancer diagnosis within past 2 years
- Calendar day of surgery
- Type of surgery
- Reason for surgery
- Emergency or elective procedure
- Incision type and location
- Duration of anaesthesia in minutes
- Intraoperative mechanical ventilation parameters and PEEP
- Average intraoperative FiO_2 delivery
- Total amount of intraoperative fluid delivered (mls)
- Numbers of intra-operative blood transfusion units
- Postoperative location (ICU, surgical ward, other)
- Duration in days at each location
- Hours of postoperative invasive mechanical ventilation
- Hours and type of NIV use
- Days and types of oxygen therapy use
- Days of nasogastric tube insertion.
- Epidural use in the first 3 postoperative days
- Unplanned ICU readmission
- Mechanical ventilation re-intubation rates
- Total hospital LOS including sub-acute rehabilitation if required.
- In-hospital mortality during the initial episode of care.

The following data will be taken from each patient's standard observations chart, medical record, pathology reports, or radiology reports daily for the first 7 postoperative days (Post-op day 1 = midnight on the day of surgery to 24:00hr that day). If parameter wasn't measured as part of standard routine care, it is recorded as missing.
For all patients:

- Maximum oral or tympanic temperature

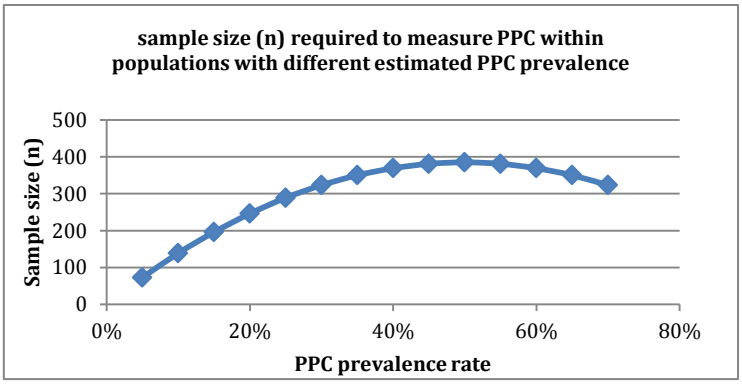
- Minimum systolic blood pressure
- Maximum heart rate
- Maximum respiratory rate
- Any report of breathlessness at rest
- Any report of altered mentation (e.g. confusion, delirium, drowsiness)
- Auscultation assessment which reports the least favourable of respiratory signs or symptoms
- Cough/sputum status indicating a presence of sputum and the darkest colour mentioned
- Chest X-ray report of collapse/consolidation/infiltrates

Only for patients in ICU/HDU:

- Minimum PaO_2 as measured from an arterial blood gas assessment
- Maximum FiO_2 of inspired gas
- Minimum mean arterial blood pressure
- Vasopressor usage and dosage
- Minimum Platelet level ($x10^3/\mu L$)
- Maximum Bilirubin level (mg/dL or µmol/L)
- Maximum Creatinine level (mg/dL or µmol/L)
- Minimum urine output (mL/d)
- Maximum white cell count (WCC), or the minimum when the WCC is <4
- Minimum Glasgow Coma Scale

The audit of physiotherapy practice service activity will note the delivery of any of the following therapies that may have been provided to the patient as part of routine care provision for each patient at each site; pre-operative physiotherapy interventions, post-operative respiratory physiotherapy interventions, respiratory exercises, positive expiratory pressure device and incentive spirometer use, use of non-invasive positive pressure breathing, manual hyperinflation, ventilator hyperinflation, use of a cough assist machine, and other . Occasions of physiotherapy service (number, calendar day of week). Professional group providing early ambulation sessions (nurse, physiotherapist, and assistant) and number of sessions provided.

Sample Size: To determine the incidence of PPC across all surgical groups with a range of estimated PPC prevalence 10-70% will require a minimum sample of 70 - 400 (95%CI, 5% precision) per sub-type dependent on the baseline PPC prevalence rate. To accurately determine PPC incidence across many surgical sub-types will require a total sample size >3000.



Statistical methods: Biostatistician, Dr Iain Robertson, is conducting the statistical methods for CHESTY.

Authorship rights: Hospitals who collect data on more than 100 consecutive patients will be part of the CHESTY Collaborative writing group. Sites can add another author for every 100 patients recruited.
The primary paper will be written according to STROBE guidelines[16].

Funding: This is an un-funded investigator-initiated trial. Nominal start-up funding of $500 for Australian hospitals for the first 100 patients recruited with pro-rata funding for every participant after the initial 100 has been secured from existing research grant monies. Further research grants will be sought during 2017-2018 to contribute further to the conduct of the trial.

Benefits of being involved: Being part of a large multicentre international trial will allow benchmarking of each hospital's services. A large sample size will allow statistical analysis of potential associative factors that both prevent and cause PPC. Results of this trial will inform appropriate prophylactic evidence based resource allocation and provide associative data to inform the development of future interventional RCT to test promising preventative therapeutic interventions.

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Sites that have committed to participate and recruit >100 patients:

1. Launceston General Hospital – Launceston	19. Concord Hospital – Sydney
2. Royal Hobart Hospital – Hobart	20. Liverpool Hospital – Sydney
3. Royal Melbourne Hospital – Parkville	21. Hornsby Hospital – Sydney
4. Peter MacCallum Cancer Centre - Parkville	22. Gosford Hospital - Gosford
5. Melbourne Private Hospital – Parkville	23. Flinders Medical Centre – Adelaide
6. The Austin – Melbourne	24. Fiona Stanley Hospital – Perth
7. St Vincent's – Melbourne	25. Sir Charles Gairdner Hospital - Perth
8. Monash Health – Melbourne	26. North Shore Hospital – NZ
9. Northeast Health Wangaratta – Wangaratta	27. Middlemore Hospital – NZ
10. Albury Base Hospital – Albury	28. Christchurch Hospital – NZ
11. Canberra Hospital – Canberra	29. Wellington Hospital - NZ
12. Gold Coast Hospital – Gold Coast	30. Hospital Canselor Tuanku Muhriz – Malaysia
13. Logan Hospital - Brisbane	31. Kentucky University Hospital - USA
14. Princess Alexandra Hospital – Brisbane	32. Sahlgrenska University Hospital – Sweden
15. Coffs Harbour Hospital – Coffs Harbour	33. Södersjukhuset Hopsital - Sweden
16. Wollongong Hospital –Wollongong	
17. St George Hospital – Sydney	
18. Macquarie University Hospital - Sydney	

CHESTY Steering Committee

Principal Investigator	Ianthe Boden
Administering institution	Launceston General Hospital, Tasmania, Australia

Members

Dr Julie Reeve, Auckland University of Technology
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Dr Doa El-Ansary, Swinburne University
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