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PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in ICUs in Asia

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020841
Article Type:	Protocol
Date Submitted by the Author:	27-Nov-2017
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Keywords:	mechanical ventilation, invasive ventilation, ARDS, outcomes, middle-income countries, resource-limited settings

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Manuscripts

PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in ICUs in Asia

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Word count manuscript: 3974 words (abstract: 300 words)

Number of inserts: 2 tables and 2 figures

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ABSTRACT

Introduction

Current evidence on epidemiology and outcomes of invasively mechanically ventilated intensive care unit (ICU) patients is predominantly gathered in resource-rich settings. Patient case-mixes and patterns of critical illnesses, and probably also ventilation practices are likely to be different in resource-limited settings. We aim to investigate the epidemiological characteristics, ventilation practices and clinical outcomes of patients receiving mechanical ventilation in ICUs in Asia.

Methods and analysis

PRoVENT-iMIC (study of PRactice of VENTilation in Middle Income Countries) is an international multicentre observational study to be undertaken in approximately 60 ICUs in 11 Asian countries. Consecutive patients aged 18 years or older who are receiving invasive ventilation in participating ICUs during a predefined 28-day period are to be enrolled, with a daily follow-up of 7 days. The primary outcome is ventilatory management (including tidal volume [V_T] expressed as mL/kg predicted bodyweight [PBW], and positive end-expiratory pressure [PEEP] expressed as cm H₂O) during the first three days of mechanical ventilation – compared between patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in case the diagnosis of ARDS can be made on admission). Secondary outcomes include occurrence of pulmonary complications and all-cause ICU mortality. The PRoVENT-iMIC study is registered at ClinicalTrials.gov, NCT 03188770.

Ethics and dissemination

PRoVENT-iMIC will be the first international study that prospectively assesses ventilation practices, outcomes and epidemiology of invasively ventilated patients in

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3 ICUs in Asia. The results of this large study, to be disseminated through conference
4 presentations and publications in international peer-reviewed journals, are of ultimate
5 importance when designing trials of invasive ventilation in resource-limited ICUs.
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10 Access to source data will be made available through national or international
11 anonymized datasets upon request and after agreement of the PRoVENT-iMIC steering
12 committee.
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17 **KEYWORDS:** mechanical ventilation; invasive ventilation; ARDS; outcomes; middle-
18 income countries; resource-limited settings.
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21 **TRIAL REGISTRATION:** PRoVENT-iMIC is registered at www.clinicaltrials.gov with trial
22 identification number NCT 03188770.
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26 27 28 **STRENGTHS AND LIMITATIONS OF THIS STUDY:** 29

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31 • PRoVENT-iMIC is an international multicentre observational study with a wide
32 representation of Asian countries, allowing inferences on epidemiology,
33 management and outcomes of mechanical ventilation across the entire
34 subcontinent.
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38 • The attention on ventilation practice will provide robust data on this specific
39 domain while the 7 days follow-up will allow precise recording of pulmonary
40 complications at their origin.
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45 • The study will have a sample size large enough to obtain precise estimates of
46 pulmonary complications and ICU mortality and to examine potential associations
47 between ventilation practice and these outcomes.
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51 • One limitation is the potential constraint of laboratory data, generating a limited
52 dataset not comprising daily severity scores useful for statistical controlling
53 purposes.
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- The conceivable limitation in blood gas analysis and imaging examinations may limit the documentation of insurgence or worsening of ARDS and other pulmonary complications.

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INTRODUCTION

Invasive mechanical ventilation is a frequently applied intervention in patients in intensive care units (ICUs) and a mandatory strategy in patients under general anaesthesia for surgery. There is increased understanding how invasive ventilation can harm the lungs, in ICU patients with the acute respiratory distress syndrome (ARDS) [1], as well as in ICU patients with less injured or uninjured lungs, and in surgery patients who usually have healthy lungs [2]. A central cause is that invasive ventilation with positive pressure may overdistend one lung area while failing to recruit another, compromising gas exchange but also, and more importantly, increasing or inducing pulmonary injury. There is convincing evidence that this harm can be partly prevented by adjusting volume and pressure settings on the ventilator. Indeed, use of low tidal volumes (V_T) [3–5], to prevent overdistension, and sufficient positive end–expiratory pressure (PEEP) [3,5,6], to prevent alveolar collapse or atelectrauma, have both been found to improve outcomes of various types of patients, and their use is increasingly recommended [7–9].

Practice of invasive ventilation has evolved over time, with a more extensive use of ventilator settings that are proven to prevent against so–called ventilator–induced lung injury. The recent LUNG SAFE (‘Large observational study to UNderstand the Global impact of Severe Acute respiratory Failure’) showed that by now up to two in every three patients with ARDS receive so–called lung–protective ventilation[10]. Results of PRoVENT (‘PRactice of VENTilation in critically ill patients without ARDS at onset of ventilation study’) are in line with those from LUNG SAFE, showing that one in every two ICU patients without ARDS receive ventilation with lung–protective settings[11]. Results of LAS VEGAS (‘Local ASsessment of VEntilatory management during General

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3 Anaesthesia for Surgery study') even suggests increased use of lung-protective
4 ventilation in the operating rooms [12]. It should be noticed, though, that LUNG SAFE,
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Anaesthesia for Surgery study') even suggests increased use of lung-protective ventilation in the operating rooms [12]. It should be noticed, though, that LUNG SAFE, PRoVENT, and LAS VEGAS were mainly performed in high-income countries, and exclusively recruiting patients in resource-rich centres, which limits the generalizability of their results to lower-income countries and resource-limited settings. Historical descriptions of cohorts of invasively ventilated patients in resource-poor settings have been published, but these were all small in size, and while suggesting the existence of ventilator-related deaths they largely failed to report key ventilator parameters [13–15]. Continued use of high V_T has been reported in a recent Brazilian study [16], while a study from India suggests a change towards the use of lower V_T [17].

There are several reasons to consider important differences with regard to practice of ventilation between resource-rich and resource-limited settings. The disparity in resources may limit the availability as well as the safety of certain ventilator settings [18]. Awareness of the impact of invasive ventilation on lung tissue, and the benefit of using lung-protective ventilation settings could be severely limited [19]. V_T and PEEP may be poorly titrated due to insufficient staffing, and due to the absence of arterial blood gas monitoring, pulse oximetry or capnography [20]. Other reasons not to implement use of low V_T and sufficient levels of PEEP include alleged side effects associated with their use, like the need for higher respiratory rates, increased sedation requirements, and even the promotion of patient-ventilator asynchrony. As invasive ventilation with higher PEEP may cause hemodynamic instability, limited access to fluids and vasoactive drugs may hamper its use. Finally, as resource-poor ICUs are usually situated in tropical countries their case-mix and indications for invasive ventilation are strikingly different [17].

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3 To gain a better insight into the ventilation practice, outcomes and
4 epidemiological characteristics of ICU patients receiving invasive ventilation in resource-
5 limited settings, we plan to perform the PRoVENT-iMIC ('Practice of VENTilation in
6 Middle-Income Countries study'), a prospective observational cohort study in ICUs in
7 Asia. We also aim to describe the association between certain ventilator settings and
8 patient-centred outcomes. We hypothesize that practice of ventilation is highly variable,
9 in particular with respect to V_T and PEEP settings. This understanding is fundamental to
10 planning any intervention study in these countries in the future.
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METHODS and ANALYSIS

Design and Setting

PRoVENT-iMIC is an international multicentre observational study in consecutive ICU patients receiving invasive mechanical ventilation during a 28-day period, expected to run in approximately 60 centres in the following Asian countries: Thailand, Vietnam, Myanmar, Pakistan, Nepal, Bangladesh, Malaysia, Sri Lanka, Maldives, Iran and India. These countries belong to the low or middle-income economies, as classified by the World Bank[21]. PRoVENT-iMIC is conducted in accordance with the declaration of Helsinki and is registered at www.clinicaltrials.gov (trial identification number NCT 03188770). Figure 1 shows the study flow-chart.

Study population

Consecutive patients intubated for ventilation during a predefined period of 28 days will be enrolled. Inclusion is not restricted to patients who are intubated in the ICU: also patients who started invasive ventilation in the emergency room, normal ward, community, or operating room directly preceding the present ICU admission are eligible for participation. The exclusion criteria include age < 18 years, use of non-invasive ventilation not followed by invasive ventilation, patients whose invasive mechanical ventilation started before the 28-day period of inclusion, and patients transferred from another hospital under invasive ventilation.

Patients will be stratified in three groups for comparison of the primary and secondary endpoints: patients without ARDS, patients without but at risk for development of ARDS, according to the Lung Injury Prediction Score (LIPS) [22], and patients with ARDS, according to the Berlin Definition[23]. Patients with ARDS will also

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3 be stratified according to severity of ARDS, based on the oxygenation (mild, moderate
4 and severe ARDS categories).
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7 *Study conduct*

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10 Local investigators will screen all patients who start invasive ventilation in one of the
11 participating ICUs during a predefined period of 28-day, lasting from 8:00 AM on the
12 Monday of the first week to 7.59 AM on the Monday four weeks later. The exact starting
13 date will be flexible for participating centres and shall be determined by the national
14 study coordinator, but all sites must have started before October 1, 2018.
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21 *Data to be collected*

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23 Baseline and demographic variables will be collected on the day of admission, including
24 gender, age, actual or estimated weight and height, smoking status, comorbidities
25 including chronic obstructive pulmonary disease (COPD), active cancer, heart failure,
26 diabetes mellitus, chronic kidney failure, liver cirrhosis and arterial hypertension, the
27 presence of ARDS according to the Berlin Definition, the LIPS, reason for ICU
28 admission. On the day of start of invasive ventilation we will document the reason for
29 starting mechanical ventilation, and whether the patient received non-invasive ventilation
30 before intubation.
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42 Every day, until day 3 from admission in the ICU, until ICU discharge or death,
43 whichever comes first, the ventilation status and ventilation characteristics will be
44 collected, including ventilation mode, V_T size, respiratory rate (set and measured), peak
45 and plateau (with volume-controlled modes) or maximum airway pressure (with
46 pressure-controlled modes), PEEP, inspired oxygen fraction, peripheral oxygen
47 saturation, blood gas analysis data when available (PaO_2 , PaCO_2 , arterial bicarbonate,
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3 arterial pH), end-tidal CO₂, when available and hemodynamic parameters like heart rate
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5 and systolic blood pressure.
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8 Every day, until day 7, ICU discharge or death, whichever comes first, the
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10 occurrence of pulmonary complications will be scored, including new requirement of
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12 invasive ventilation after initial extubation, pulmonary infections, atelectasis,
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14 pneumothorax, pleural effusions, new pulmonary infiltrates and development or
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16 worsening of ARDS.
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19 On the day of ICU discharge (maximum 60 days after recruitment) outcome will
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21 be recorded as follows: death, discharge to ward, to medium care or high dependency
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23 unit, discharge to home for palliative care, or transfer to another ICU. The date of
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25 extubation, reintubation and tracheostomy (if performed) will also be recorded in this
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27 moment.
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29 30 *Study endpoints*

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32 The primary endpoint is V_T-size in millilitres per kilogram of predicted body weight
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34 (ml/kg PBW) and PEEP in centimetres of water (cm H₂O) used amongst diverse ICU
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36 patient categories during the first three days of mechanical ventilation. Secondary
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38 clinical endpoints include other ventilation parameters (including respiratory system
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40 driving pressure), the proportion of patients at risk of ARDS as stratified by the LIPS, or
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42 ARDS defined by the Berlin Definition, the occurrence of pulmonary complications,
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44 length of stay in ICU, duration of invasive ventilation and all-cause ICU-mortality.
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48 49 *Definitions*

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51 All cause ICU-mortality is defined as any death in the ICU. ICU length of stay is defined
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53 as the time between ICU admission and ICU discharge or death in ICU. The number of
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55 days of ventilation is defined as time between endotracheal intubation and successful
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3 extubation (in case of intermittent mechanical ventilation via a tracheostomy, every day
4 a patient needs ventilation counts as one extra day, irrespective of the duration of
5 ventilation on that specific day). In case of non-invasive ventilation, the duration will be
6 assessed separated from the assessment of invasive ventilation.
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12 Only pulmonary complications that occur after the first 24 hours of invasive
13 ventilation will be considered in analysis, as events preceding this time point may very
14 well be considered the potential reason for intubation. A pulmonary infection requires the
15 presence of new or changed lung opacities on chest radiography and/or new or changed
16 sputum plus at least a temperature > 38.3 °C or a white blood cell count $>12,000$ per
17 microliter of blood. Atelectasis require the presence of increased density (lung opacity)
18 on one or more chest radiographs with displacement of the fissures toward the area of
19 atelectasis, crowding of pulmonary vessels and bronchi in the atelectatic region, upward
20 displacement of hemidiaphragm ipsilateral to the side of atelectasis, that may be
21 accompanied by shift of the mediastinum or hilum towards the affected area and
22 compensatory overinflation in the unaffected lung [24]. Pleural effusion is suggested by
23 lung opacification with shift of the mediastinum, hilum or hemi-diaphragm towards the
24 non-affected area. Pneumothorax requires the presence of air in the pleural space with
25 no vascular bed surrounding the visceral pleura. ARDS is defined according to the Berlin
26 Definition [23] with alternative oxygenation criteria based on SpO_2/FiO_2 applicable only
27 when blood gas analysis data is unavailable (Table 1a and 1b) [25,26]. Worsening of
28 ARDS is defined as any change in the prior classification (i.e., from mild to moderate or
29 severe ARDS, or from moderate to severe ARDS).
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53 *Data management*

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3 Data will be collected from a paper medical chart, or an electronic patient data
4 management system if available. Local investigators transcribe the collected data
5 directly onto an anonymized internet-based electronic CRF (REDCap – Research
6 Electronic Data Capture[27], www.projectredcap.org). In some centres data may be
7 recorded on paper CRF and successively transcribed on the electronic CRF at a later
8 time point. Access to the data-entry system is protected by a personalized username
9 and password. The data will be kept on a central secured server located at the Hospital
10 Israelita Albert Einstein, Sao Paulo, Brazil. The structure of the electronic CRF is
11 detailed in Figure 2. A screening-log with limited patient data will be completed with all
12 the included and excluded patients during the enrolment window. Participating centres
13 are instructed to enter data for the daily follow-up using values obtained as close as
14 possible to 08:00 AM, but only when the patient is stable at that time point. The study
15 day for the recording of pulmonary complications will be defined as the natural 24h
16 period from 00:00 until 23:59, to ensure that data is captured only once. Data for ICU-
17 discharge will be collected until a maximum of 60 days after ICU admission, after which
18 the CRF for that patient will be closed.

39 *Study sites*

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41 PRoVENT-iMIC will be conducted in 11 Asian countries, with a varying number of ICUs
42 per country. Participating ICUs are selected on the basis of willingness to participate.
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44 There are no a priori established requirements for participation, and private as well as
45 public centres are eligible to represent real-life practices. A one-time web-based pre-
46 study survey on structure, organizational aspects and delivery of care in the participating
47 centres will be performed.

54 *Statistical Analysis Plan*

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3 No formal sample size calculation was performed, but we expect each centre to enrol 20
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5 to 40 patients in the allocated time period, yielding a total of 1,200 to 2,400 patients. We
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7 consider this figure sufficient to analyse the study endpoints.
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10 Normally distributed variables will be expressed by their mean and standard
11 deviation; not normally distributed variables will be expressed by their medians and
12 interquartile ranges; categorical variables will be expressed as n (%). In test groups of
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14 continuous normally distributed variables, Student's t-test will be used. Likewise if
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16 continuous data are not normally distributed the Mann Whitney U test will be used.
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18 Categorical variables will be compared with the Chi-square test or Fisher's exact test or
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20 when appropriate as relative risks. Statistical uncertainty will be expressed by 95%
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22 confidence levels.
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28 The primary outcome (V_T size [ml/kg PBW] and PEEP [cm H₂O] levels during the
29 first three days of mechanical ventilation) – will be analysed and compared between
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31 patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in
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33 case the diagnosis of ARDS could be made on admission). If the data is normally
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35 distributed, one way Analysis of Variance (ANOVA) or two-way ANOVA assessing the
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37 time–interaction between groups and days of observation will be used. When not
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39 normally distributed the Kruskal–Wallis test or Friedman test assessing the time–
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41 interaction between groups and days of observation will be used.
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47 Univariate analysis will be performed to identify potential factors associated with
48 outcomes including, but not limited to, ventilator settings (in particular V_T and PEEP). A
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50 multivariate logistic regression model will be used to determine which of those factors
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52 are independent. A stepwise approach will be used to enter new terms into the model,
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3 with a limit of $P < 0.2$ to enter the terms. Time to event variables is analysed using Cox
4 regression and visualized by Kaplan–Meier.
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7 Time–course variables (e.g. repeated measures of ventilator parameters, vital
8 signs, oxygenation parameters and others) are also analysed by linear mixed model.
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10 The linear mixed models procedure expands the generalized linear model (GLM) so that
11 the data are permitted to exhibit correlated and non–constant variability.
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16 Pre–specified subgroups in the analyses studying potential associations between
17 ventilator settings and outcome will be: (1) patients at low risk of ARDS vs. patients at
18 risk of ARDS; (2) patients without ARDS vs. patients with ARDS; (3) reason for ICU
19 admission; and (4) reason for start of invasive ventilation. Statistical analyses will be
20 conducted using R (www.r-project.org). A P –value of less than 0.05 will be considered
21 statistically significant.
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30 *Study organization*

31 The Steering Committee is composed of a selection of PROVE Network investigators
32 plus the national coordinators from each participating country. These investigators were
33 involved in the design of PRoVENT–iMIC. National coordinators are responsible for
34 identifying and recruiting local participating centres. They assist and train the local
35 investigators and oversee the conduct of the study, including administrative
36 management, record keeping and data management. Local investigators in individual
37 participating centres will provide scientific and structural leadership, ensuring local
38 ethical and regulatory approvals are obtained before start of patient inclusion. National
39 Coordinators and Local Investigators are expected to guarantee the quality and security
40 of the data collected.
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3 Prior to start of the study, study teams in each centre will undergo a web-based
4 training session on how to capture data in the electronic CRF. All study team members
5 will be provided with a manual of operations with instructions on how to accurately fill the
6 forms and the screening log. Incomplete or incorrectly entered electronic CRFs will be
7 signalled to the local investigators by the national and international coordinator, for
8 further review of the missing or flagged data.
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ETHICS AND DISSEMINATION

The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford, United Kingdom, exempted the study from ethical review on the 2nd of June 2017. Data management, monitoring and reporting of the study will be performed in accordance with the International Conference on Harmonization – Good Clinical Practice guidelines.

All participating centres will also submit the study protocol to the national or local Institutional Review Board for ethical judgment, as applicable by the current regulations in the country. Due to the strict observational design and anonymous collection of data, informed consent may not be required in most countries. However, where informed consent is required, this must be approved by the local ethical committee before the start of inclusion.

The study will be reported following the Strengthening the reporting of Observational Studies in Epidemiology (STROBE) statement guidelines and checklists[28]. The results of this study will be published in a peer-reviewed medical journal. After publication of the primary results, on request the pooled dataset will be available for all members of the PRoVENT-iMIC collaboration for secondary analysis, after judgment and approval of scientific quality and validity of the proposed analysis by the Steering Committee.

DISCUSSION

PRoVENT–iMIC is designed to characterize the epidemiology, ventilator management, occurrence of pulmonary complications and outcomes in invasively ventilated patients in an estimated 60 ICUs in 11 Asian countries. The results of PRoVENT–iMIC will help to understand current ventilation practice in South and Southeast Asia, particularly with respect to variability in ventilator settings amongst patients without, at risk for or with established ARDS. Results of this study will be used to plan future trials of ventilation in ICU patients in these settings.

PRoVENT–iMIC has several strengths. First, we will have a sample size large enough to obtain precise estimates of pulmonary complications and ICU mortality and to examine potential associations between ventilation practice and patient outcomes. Second, the study sample is not restricted to certain patient diagnostic categories. Third, the attention on ventilation practice will provide robust data on this specific domain while the 7 days follow–up will allow precise recording of pulmonary complications at their origin. And finally, the wide representation of Asian countries will allow inferences on geo–economic differences in epidemiology, management and outcomes of mechanical ventilation across the entire subcontinent.

The focus on South and Southeast Asia follows our scarce knowledge about clinical practices and ventilation strategies used in critically ill patients in this and other resource–limited settings [20]. The burden of critical illness in low– and middle–income countries is higher than generally perceived and it is expected to increase with an aging population [29]. Additionally, ICUs are increasingly being set up in the region, especially in busy urban settings. A recent survey highlighted considerable variation in structure, organization and critical care delivery in Asian ICUs, but did not shed light on ventilation

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3 management and patient-centred ventilation-associated outcomes [30]. This
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5 information, however, is crucial for future trials of ventilation in ICU patients in these
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7 settings, as we need to know whether critically ill patients across Asia equally benefit
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9 from lung-protective ventilation as those in Western countries. Additionally, for proper
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11 power calculations, information with regard to potential primary endpoints, like the
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13 incidence of development of ARDS, duration of ventilation or death, is highly needed.
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15 PRoVENT-iMIC will be the first observational study that can provide this information for
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17 settings in South Asia. Results restricted to individual settings could also be valuable for
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19 local clinicians seeking to improve their local practice, training planning and identify local
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21 priorities for quality improvement within their departments.
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27 There is now strong evidence-based support for various ICU process-based
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29 interventions such as lung protective ventilation[31], conservative fluid management
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31 strategies[32] and weaning protocols[33]. While centre- or country-specific practices or
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33 restrictions of resources are potential challenges that affect implementation of all these
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35 interventions, we focus on the management of ventilation and especially on the
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37 employment of lung-protective ventilation where feasibility may represent an issue
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39 specific to resource-limited settings. Recent literature has underlined the potential role
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41 of the driving pressure (the pressure amplitude during each artificial breath) and its
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43 determinants in the development of ventilator-associated lung injury. Results from
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45 PRoVENT-iMIC will provide further data to enable us to discriminate the effects of V_T
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47 size, PEEP and driving pressure on outcomes in patients with, at risk of, or without
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49 ARDS.
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54 PRoVENT-iMIC will provide important data regarding outcomes following
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56 invasive ventilation, including a wide range of clinically important pulmonary
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3 complications. Historical studies from low–resource settings documented mortality rates
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5 to exceed 70%[13–15]. However more recent data from South America and India have
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7 documented mortality rates of ~40%, similar to that in high–income countries[16,17].
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9 This suggests that mortality in ventilated patients has the potential to improve in low–
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11 resource settings[11,12,34]. Although many factors may influence mortality, several
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13 underappreciated factors related to invasive ventilation may have contributed, including
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15 reduced need for invasive ventilation per se, improvements in safety of invasive
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17 ventilation and in liberation from invasive ventilation.
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21 Our interest in patients at risk of ARDS follows a global recent shift in ARDS
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23 research. It is now clear that ARDS is rarely present at the time of the initial healthcare
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25 encounter, and typically develops during the hospital course, usually between days 2
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27 and 5 in patients with predisposing conditions or risk factors[35]. Hence increasing
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29 efforts are being directed toward early identification of patients at risk with a goal of
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31 prevention and early treatment prior to the development of a fully established syndrome.
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33 This is probably equally important in resource–limited settings where the predisposing
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35 conditions and risk modifiers for ARDS may differ and limited escalation of therapy is
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37 often the case. PRoVENT–iMIC will be the first study to evaluate prospectively the role
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39 of LIPS in these settings. Although the poor predictive accuracy of the LIPS does not
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41 currently support its use in everyday clinical practice [36], it has enabled enrolment in
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43 clinical trials of ARDS prevention [22] and may yield an initial idea on the patients at risk
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45 of and disease progression in the Asian settings under study.
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51 PRoVENT–iMIC has some noticeable shortcomings. The definition of ‘middle–
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53 income’ country is rather artificial as the level of health expenditure, local resources and
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55 other geo–cultural factors might affect the processes of care in a larger extent than
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3 national income classification. Despite the inclusion of ICUs from 11 countries, which
4 improves study generalizability, caution is needed when applying the results to
5 supposedly similar settings, as substantial intra- and trans-national variations in ICU
6 resources, staffing and organization exist. Second, the case report form used in
7 PROVENT-iMIC is not exhaustive and does not include data regarding extra-pulmonary
8 complications, hospital-discharge outcomes or other ICU processes of care that may
9 indirectly affect ventilation. Similarly, due to the time window restricted to the ICU stay,
10 we will apply the LIPS at ICU admission and not in the first 6 hours after hospital
11 admission, as originally designed. Mortality may be underestimated in some settings
12 where due to local practices there is the possibility to be discharged home in case of
13 terminal conditions or family decision. To address this we made sure the data collection
14 form captures this event whenever it represents the reason of discharge. Third, due to
15 the limitation of laboratory data we will have a limited dataset that will not comprise daily
16 severity scores useful for statistical controlling purposes. Also, the conceivable limitation
17 in blood gas analysis and radiology exams may limit the documentation of insurgence or
18 worsening of ARDS and other pulmonary complications. Finally, participation in
19 international studies like PROVENT-iMIC always bears the risk of biased to those
20 centres that do not fully or reliably represent ICU-care in general in the participating
21 countries.
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CONCLUSIONS

PRoVENT-iMIC is designed to understand the epidemiology, practice of ventilation, and outcomes of critically-ill patients receiving invasive ventilation in a large set of South Asian countries. Results of this study could help identify practices that may best explain differences in outcomes, and could be used in designing new trials of ventilation in these settings.

For peer review only

Author affiliations

Contributors

LP, AGA, ASN, AMD and MJS were equally responsible for writing of the manuscript and participated in study design. FP, PP participated in study design and assisted in writing of the manuscript. AA, AB, KC, AF, RaH, ReH, MH, HAI, KI, SI, GK, BK, HM, BN, RP, SS, LT, SG, NNT, NMY, MGdA reviewed the manuscript and agreed with submission.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for profit sectors.

Competing interests

None

Ethics approval

The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford, United Kingdom, exempted the study from ethical review on the 2nd of June 2017. IRB approval was obtained from Sri Lanka, Bangladesh and Malaysia and is underway in Myanmar, Iran, India, Vietnam, Thailand, Nepal, Pakistan and Maldives.

REFERENCES

- 1 Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2014;**370**:980. doi:10.1056/NEJMc1400293
- 2 Serpa N, Schultz M, Slutsky A. Current concepts of protective ventilation during general anaesthesia. *Swiss Med Wkly* 2015;**145**:w14211. doi:10.4414/smw.2015.14211
- 3 Putensen C, Theuerkauf N, Zinserling J, *et al.* Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. *Ann Intern Med* 2009;**151**:566–76.
- 4 Serpa Neto A, Cardoso SO, Manetta JA, *et al.* Association Between Use of Lung-Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress Syndrome. *JAMA* 2012;**308**:1651. doi:10.1001/jama.2012.13730
- 5 Güldner A, Kiss T, Serpa Neto A, *et al.* Intraoperative Protective Mechanical Ventilation for Prevention of Postoperative Pulmonary Complications. *Anesthesiology* 2015;**123**:692–713. doi:10.1097/ALN.0000000000000754
- 6 Briel M, Meade M, Mercat A, *et al.* Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;**303**:865–73. doi:10.1001/jama.2010.218
- 7 Ferguson ND. Low Tidal Volumes for All? *JAMA* 2012;**308**:1689. doi:10.1001/jama.2012.14509
- 8 Serpa Neto A, Nagtzaam L, Schultz MJ. Ventilation with lower tidal volumes for critically ill patients without the acute respiratory distress syndrome: a systematic

- 1
2
3 translational review and meta-analysis. *Curr Opin Crit Care* 2014;**20**:25–32.
4
5 doi:10.1097/MCC.000000000000044
6
7
8 9 Dellinger RP, Levy MM, Rhodes A, *et al*. Surviving sepsis campaign: International
9
10 guidelines for management of severe sepsis and septic shock, 2012. *Intensive*
11
12 *Care Med* 2013;**39**:165–228. doi:10.1007/s00134-012-2769-8
13
14
15 10 Bellani G, Gattinoni L, Haren F Van, *et al*. Epidemiology, Patterns of Care, and
16
17 Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care
18
19 Units in 50 Countries. *JAMA* 2016;**315**:2526–33.
20
21
22 11 Neto AS, Barbas CS V, Simonis FD, *et al*. Epidemiological characteristics, practice
23
24 of ventilation, and clinical outcome in patients at risk of acute respiratory distress
25
26 syndrome in intensive care units from 16 countries (PRoVENT): an international,
27
28 multicentre, prospective study. 2016;**4**:882–93. doi:10.1016/S2213-
29
30 2600(16)30305-8
31
32
33 12 Epidemiology, practice of ventilation and outcome for patients at increased risk of
34
35 postoperative pulmonary complications. *Eur J Anaesthesiol* 2017;**34**:492–507.
36
37 doi:10.1097/EJA.0000000000000646
38
39
40 13 Sinclair JR, Watters DA, Davison M. Outcome of mechanical ventilation in Central
41
42 Africa. *Ann R Coll Surg Engl* 1988;**70**:76–9.
43
44
45 14 Rajapakse VP, Wijesekera S. Outcome of mechanical ventilation in Sri Lanka. *Ann*
46
47 *R Coll Surg Engl* 1989;**71**:344–6.
48
49
50 15 Sudarsanam TD, Jeyaseelan L, Thomas K, *et al*. Predictors of mortality in
51
52 mechanically ventilated patients. *Postgrad Med J* 2005;**81**:780–3.
53
54 doi:10.1136/pgmj.2005.033076
55
56
57 16 Azevedo LC, Park M, Salluh JI, *et al*. Clinical outcomes of patients requiring
58
59
60

- 1
2
3 ventilatory support in Brazilian intensive care units: a multicenter, prospective,
4 cohort study. *Crit Care* 2013;**17**:R63. doi:10.1186/cc12594
5
6
7
8 17 Karthikeyan B, Kadiravan T, Deepanjali S, *et al*. Case-Mix, Care Processes, and
9 Outcomes in Medically-Ill Patients Receiving Mechanical Ventilation in a Low-
10 Resource Setting from Southern India: A Prospective Clinical Case Series. *PLoS*
11 *One* 2015;**10**:e0135336. doi:10.1371/journal.pone.0135336
12
13
14
15
16
17 18 Serpa Neto A, Schultz MJ, Festic E. Ventilatory support of patients with sepsis or
18 septic shock in resource-limited settings. *Intensive Care Med* 2016;**42**:100–3.
19 doi:10.1007/s00134-015-4070-0
20
21
22
23
24 19 Haniffa R, Lubell Y, Cooper BS, *et al*. Impact of a structured ICU training
25 programme in resource-limited settings in Asia. *PLoS One* 2017;**12**:e0173483.
26 doi:10.1371/journal.pone.0173483
27
28
29
30
31 20 Dünser MW, Baelani I, Ganbold L, *et al*. A review and analysis of intensive care
32 medicine in the least developed countries*. *Crit Care Med* 2006;**34**:1234–42.
33 doi:10.1097/01.CCM.0000208360.70835.87
34
35
36
37
38 21 The World Bank. World Bank Country Classification.
39 [https://datahelpdesk.worldbank.org/knowledgebase/topics/19280-country-](https://datahelpdesk.worldbank.org/knowledgebase/topics/19280-country-classification)
40 [classification](https://datahelpdesk.worldbank.org/knowledgebase/topics/19280-country-classification) (accessed 1 May 2017).
41
42
43
44
45 22 Gajic O, Dabbagh O, Park PK, *et al*. Early identification of patients at risk of acute
46 lung injury: evaluation of lung injury prediction score in a multicenter cohort study.
47 *Am J Respir Crit Care Med* 2011;**183**:462–70. doi:10.1164/rccm.201004-0549OC
48
49
50
51
52 23 The ARDS Definition Task Force*, Ranieri VM, Rubenfeld GD, *et al*. Acute
53 respiratory distress syndrome: the Berlin Definition. *JAMA J Am Med Assoc*
54 2012;**307**:1. doi:10.1001/jama.2012.5669
55
56
57
58
59
60

- 1
2
3 24 Ashizawa K, Hayashi K, Aso N, *et al.* Lobar atelectasis: diagnostic pitfalls on chest
4 radiography. *Br J Radiol* 2001;**74**:89–97. doi:10.1259/bjr.74.877.740089
5
6
7 25 Riviello ED, Kiviri W, Twagirumugabe T, *et al.* Hospital Incidence and Outcomes of
8 the Acute Respiratory Distress Syndrome Using the Kigali Modification of the
9 Berlin Definition. *Am J Respir Crit Care Med* 2016;**193**:52–9.
10
11
12
13
14
15
16
17 26 Rice TW, Wheeler AP, Bernard GR, *et al.* Comparison of the SpO₂/FIO₂ ratio
18 and the PaO₂/FIO₂ ratio in patients with acute lung injury or ARDS. *Chest*
19
20
21
22
23
24 27 Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)-
25
26
27
28
29
30
31
32
33 28 von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of
34
35
36
37
38
39
40
41
42 29 Adhikari NKJ, Fowler RA, Bhagwanjee S, *et al.* Critical care and the global burden
43
44
45
46
47
48
49 30 Arabi YM, Phua J, Koh Y, *et al.* Structure, Organization, and Delivery of Critical
50
51
52
53
54
55
56 31 Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, *et al.*
57
58
59
60

- 1
2
3 Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes
4 for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *N Engl J Med*
5 2000;**342**:1301–8. doi:10.1056/NEJM200005043421801
6
7
8
9
10 32 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome
11 (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, *et al.* Comparison
12 of two fluid-management strategies in acute lung injury. *N Engl J Med*
13 of two fluid-management strategies in acute lung injury. *N Engl J Med*
14 2006;**354**:2564–75. doi:10.1056/NEJMoa062200
15
16
17
18
19 33 Girard TD, Kress JP, Fuchs BD, *et al.* Efficacy and safety of a paired sedation and
20 ventilator weaning protocol for mechanically ventilated patients in intensive care
21 (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*
22 (London, England) 2008;**371**:126–34. doi:10.1016/S0140-6736(08)60105-1
23
24
25
26
27
28 34 Esteban A, Frutos-Vivar F, Muriel A, *et al.* Evolution of Mortality over Time in
29 Patients Receiving Mechanical Ventilation. *Am J Respir Crit Care Med*
30 2013;**188**:220–30. doi:10.1164/rccm.201212-2169OC
31
32
33
34
35 35 Gajic O, Dabbagh O, Park PK, *et al.* Early Identification of Patients at Risk of
36 Acute Lung Injury: Evaluation of Lung Injury Prediction Score in a Multicenter
37 Cohort Study. *Am J Respir Crit Care Med* 2010;:1–33. doi:10.1164/rccm.201004-
38 0549OC
39
40
41
42
43
44 36 Festic E, Kor DJ, Gajic O. Prevention of acute respiratory distress syndrome. *Curr*
45 *Opin Crit Care* 2015;**21**:82–90. doi:10.1097/MCC.000000000000174
46
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FIGURE LEGENDS

Figure 1: Flowchart of inclusion of PRoVENT-iMIC

Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.

Figure 2. Sequence of data submission in the electronic case report form

Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit.

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Figure 1

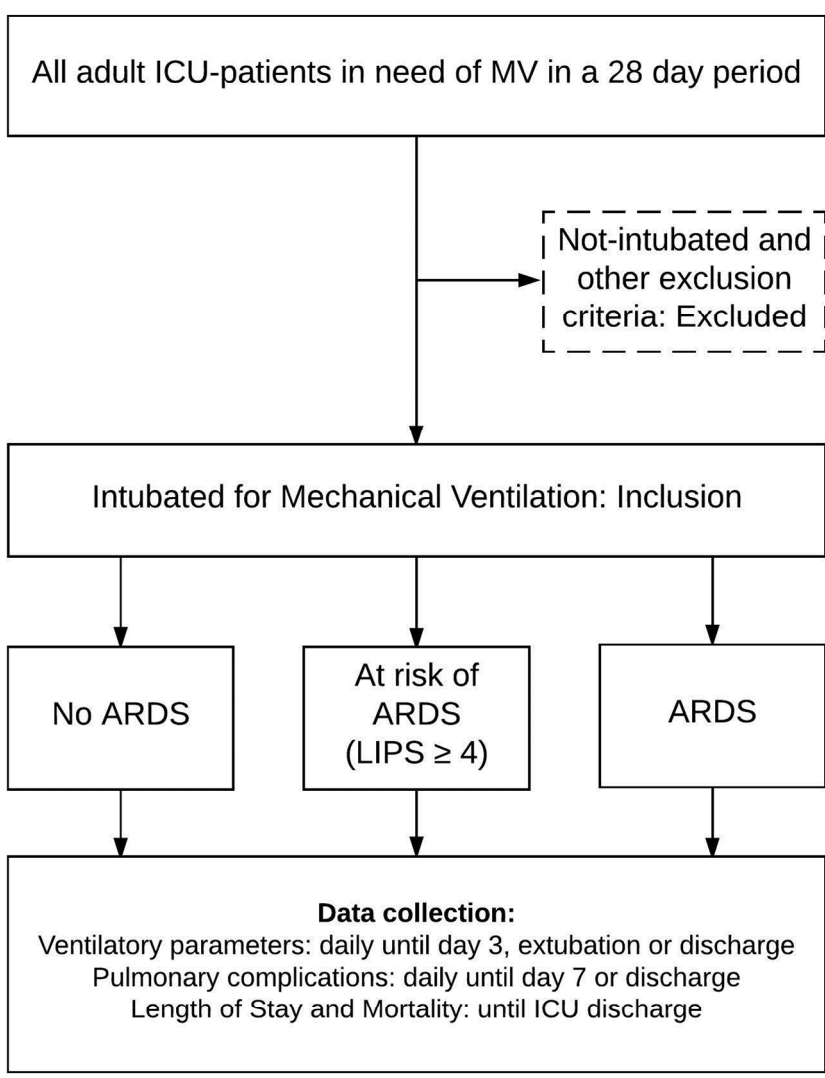
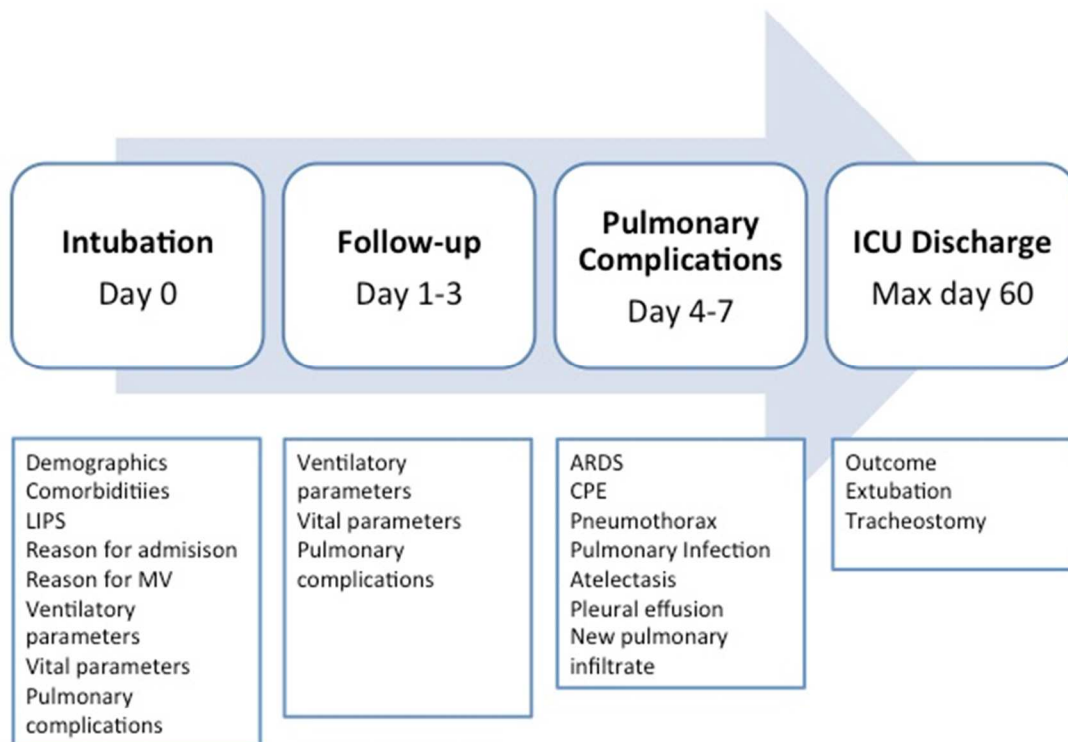


Figure 2



view only

Table 1a. The Berlin definition of ARDS

Criteria	Definition		
Time	Within one week of a known clinical insult, or new/worsening respiratory symptoms		
Chest imaging ¹	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules		
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic oedema if no risk factor present (e.g., echocardiography)		
Oxygenation ²	Mild	Moderate	Severe
	$200 < \text{PaO}_2/\text{FiO}_2 \leq 300$	$100 < \text{PaO}_2/\text{FiO}_2 \leq 200$	$\text{PaO}_2/\text{FiO}_2 \leq 100$
	PEEP or CPAP ³ ≥ 5 cm H ₂ O	PEEP ≥ 5 cm H ₂ O	PEEP ≥ 5 cm H ₂ O

Abbreviations: ARDS, acute respiratory distress syndrome; PaO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

¹chest X-ray or CT scan; ²if altitude higher than 1,000 meters, correction factor should be made as follows: $\text{PaO}_2/\text{FiO}_2 \times (\text{barometric pressure}/760)$; ³this may be delivered noninvasively in the mild acute respiratory distress syndrome

Table 1b. Alternative Oxygenation criteria (if PaO₂ data unavailable)

Criteria	Mild ARDS	Moderate ARDS	Severe ARDS
Oxygenation	$235 < \text{SpO}_2/\text{FiO}_2 \leq 315$	$150 < \text{SpO}_2/\text{FiO}_2 \leq 235$	$\text{SpO}_2/\text{FiO}_2 \leq 150$
	PEEP or CPAP ≥ 5 cmH ₂ O	PEEP ≥ 5 cmH ₂ O	PEEP ≥ 5 cmH ₂ O

Abbreviations: SpO₂, pulse oximetry oxygen saturation; FiO₂, fraction of inspired oxygen

Table 2. Lung Injury Prediction Score (LIPS) calculation worksheet^{17,34}

Predisposing Conditions	Score	Risk Modifiers	Score
Shock	2	Alcohol Abuse	1
Aspiration	2	BMI > 30 kg/m ²	1
Sepsis	1	Hypoalbuminemia	1
Pneumonia	1.5	Chemotherapy	1
High-Risk Surgery		FiO ₂ > 0.35 (> 4 l/min)	2
Orthopedic Spine	1	RR > 30 bpm	1.5
Acute Abdomen	2	SpO ₂ < 95%	1
Cardiac	2.5	Acidosis (pH < 7.35)	1.5
Aortic Vascular	3.5	Diabetes Mellitus*	- 1
Emergency surgery	1.5		
High-Risk Trauma			
Traumatic Brain Injury	2		
Smoke Inhalation	2		
Near-Drowning	2		
Lung Contusion	1.5		
Multiple Fractures	1.5		

Abbreviations: BMI, body mass index; FiO₂, fraction of inspired oxygen; RR, respiratory Rate; SpO₂, pulse oximetry oxygen saturation.

*(to consider only in septic patients)

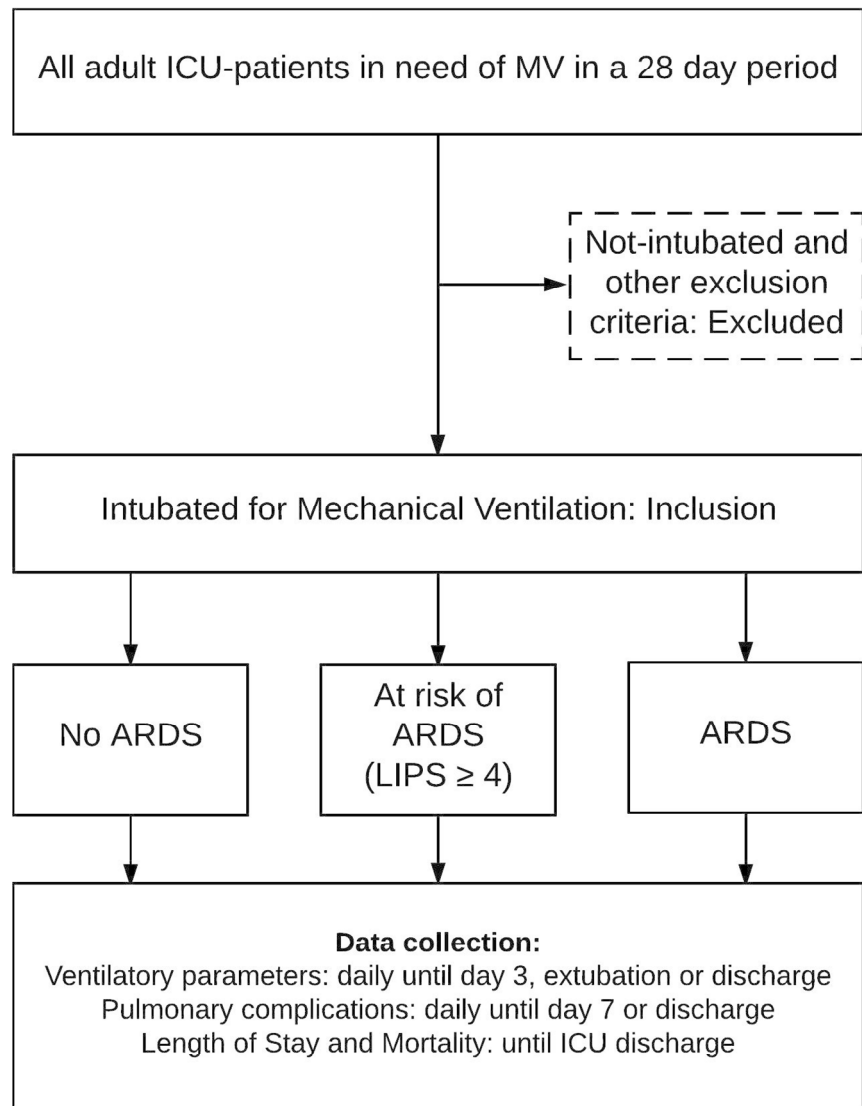


Figure 1: Flowchart of inclusion of PROVENT-iMIC^{!!} + . Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.^{!!} +

120x152mm (300 x 300 DPI)

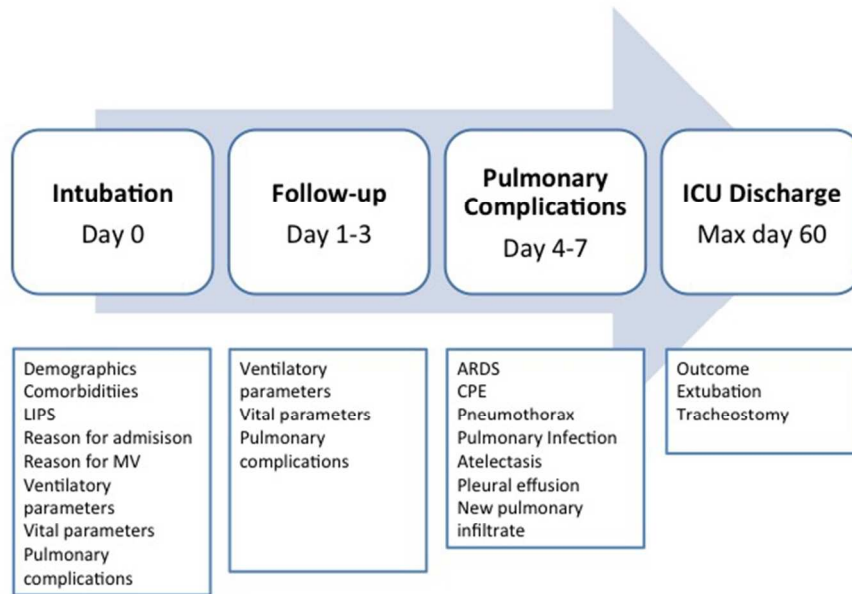


Figure 2: Sequence of data submission in the electronic case report form!! † . Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit. !! †

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BMJ Open

PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in intensive care units in Asia

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020841.R1
Article Type:	Protocol
Date Submitted by the Author:	30-Jan-2018
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Primary Subject Heading :	Intensive care
Secondary Subject Heading:	Epidemiology, Global health, Respiratory medicine
Keywords:	mechanical ventilation, invasive ventilation, ARDS, outcomes, middle-income countries, resource-limited settings

SCHOLARONE™
Manuscripts

Review only

PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in Intensive Care Units in Asia

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33 Word count manuscript: 3974 words (abstract: 300 words)

34 Number of inserts: 2 tables and 2 figures

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3 **77 ABSTRACT**

4
5 **78 *Introduction***

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8 **79** Current evidence on epidemiology and outcomes of invasively mechanically ventilated
9
10 **80** intensive care unit (ICU) patients is predominantly gathered in resource-rich settings.
11
12 **81** Patient case-mixes and patterns of critical illnesses, and probably also ventilation
13
14 **82** practices are likely to be different in resource-limited settings. We aim to investigate the
15
16 **83** epidemiological characteristics, ventilation practices and clinical outcomes of patients
17
18 **84** receiving mechanical ventilation in ICUs in Asia.

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21 **85 *Methods and analysis***

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24 **86** PRoVENT-iMIC (study of PRactice of VENTilation in Middle Income Countries) is an
25
26 **87** international multicentre observational study to be undertaken in approximately 60 ICUs
27
28 **88** in 11 Asian countries. Consecutive patients aged 18 years or older who are receiving
29
30 **89** invasive ventilation in participating ICUs during a predefined 28-day period are to be
31
32 **90** enrolled, with a daily follow-up of 7 days. The primary outcome is ventilatory
33
34 **91** management (including tidal volume [V_T] expressed as mL/kg predicted bodyweight
35
36 **92** [PBW], and positive end-expiratory pressure [PEEP] expressed as cm H₂O) during the
37
38 **93** first three days of mechanical ventilation – compared between patients at no risk for
39
40 **94** ARDS, patients at risk for ARDS and in patients with ARDS (in case the diagnosis of
41
42 **95** ARDS can be made on admission). Secondary outcomes include occurrence of
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44 **96** pulmonary complications and all-cause ICU mortality. The PRoVENT-iMIC study is
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46 **97** registered at ClinicalTrials.gov, NCT 03188770.

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51 **98 *Ethics and dissemination***

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54 **99** PRoVENT-iMIC will be the first international study that prospectively assesses
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56 **100** ventilation practices, outcomes and epidemiology of invasively ventilated patients in

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3 101 ICUs in Asia. The results of this large study, to be disseminated through conference
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5 102 presentations and publications in international peer-reviewed journals, are of ultimate
6
7 103 importance when designing trials of invasive ventilation in resource-limited ICUs.
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10 104 Access to source data will be made available through national or international
11
12 105 anonymized datasets upon request and after agreement of the PRoVENT-iMIC steering
13
14 106 committee.

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16
17 107 **KEYWORDS:** mechanical ventilation; invasive ventilation; ARDS; outcomes; middle-
18
19 108 income countries; resource-limited settings.

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21 109 **TRIAL REGISTRATION:** PRoVENT-iMIC is registered at www.clinicaltrials.gov with trial
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23 110 identification number NCT 03188770.

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27 28 112 **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

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31 113 • PRoVENT-iMIC is an international multicentre observational study with a wide
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33 114 representation of Asian countries, allowing inferences on epidemiology,
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35 115 management and outcomes of mechanical ventilation across the entire
36
37 116 subcontinent.
- 38
39 117 • The attention on ventilation practice will provide robust data on this specific
40
41 118 domain while the 7 days follow-up will allow precise recording of pulmonary
42
43 119 complications at their origin.
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45 120 • The study will have a sample size large enough to obtain precise estimates of
46
47 121 pulmonary complications and ICU mortality and to examine potential associations
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49 122 between ventilation practice and these outcomes.
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51 123 • One limitation is the potential constraint of laboratory data, generating a limited
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53 124 dataset not comprising daily severity scores useful for statistical controlling
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55 125 purposes.
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3 126 • The conceivable limitation in blood gas analysis and imaging examinations may
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5 127 limit the documentation of insurgence or worsening of ARDS and other pulmonary
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7 128 complications.
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130 INTRODUCTION

131 Invasive mechanical ventilation is a frequently applied intervention in patients in
132 intensive care units (ICUs) and a mandatory strategy in patients under general
133 anaesthesia for surgery. There is increased understanding how invasive ventilation can
134 harm the lungs, in ICU patients with the acute respiratory distress syndrome (ARDS) [1],
135 as well as in ICU patients with less injured or uninjured lungs, and in surgery patients
136 who usually have healthy lungs [2]. A central cause is that invasive ventilation with
137 positive pressure may overdistend one lung area while failing to recruit another,
138 compromising gas exchange but also, and more importantly, increasing or inducing
139 pulmonary injury. There is convincing evidence that this harm can be partly prevented by
140 adjusting volume and pressure settings on the ventilator. Indeed, use of low tidal
141 volumes (V_T) [3–5], to prevent overdistension, and sufficient positive end–expiratory
142 pressure (PEEP) [3,5,6], to prevent alveolar collapse or atelectrauma, have both been
143 found to improve outcomes of various types of patients, and their use is increasingly
144 recommended [7–9]. Furthermore, the driving pressure seems to be another key
145 variable in the development of injury caused by mechanical ventilation, as a large
146 individual patient data metaanalysis showed a clear and consistent association between
147 driving pressure and mortality [10].

148 Practice of invasive ventilation has evolved over time, with a more extensive use of
149 ventilator settings that are proven to prevent against so–called ventilator–induced lung
150 injury. The recent LUNG SAFE (‘Large observational study to UNderstand the Global
151 impact of Severe Acute respiratory Failure’) showed that by now up to two in every three
152 patients with ARDS receive so–called lung–protective ventilation[11]. Results of
153 PRoVENT (‘PRactice of VENTilation in critically ill patients without ARDS at onset of

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3 154 ventilation study') are in line with those from LUNG SAFE, showing that one in every two
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5 155 ICU patients without ARDS receive ventilation with lung-protective settings[12]. Results
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7 156 of LAS VEGAS ('Local ASsessment of VEntilatory management during General
8
9 157 Anaesthesia for Surgery study') even suggests increased use of lung-protective
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11 158 ventilation in the operating rooms [13]. It should be noticed, though, that LUNG SAFE,
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13 159 PRoVENT, and LAS VEGAS were mainly performed in high-income countries, and
14
15 160 exclusively recruiting patients in resource-rich centres, which limits the generalizability
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17 161 of their results to lower-income countries and resource-limited settings. Historical
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19 162 descriptions of cohorts of invasively ventilated patients in resource-poor settings have
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21 163 been published, but these were all small in size, and while suggesting the existence of
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23 164 ventilator-related deaths they largely failed to report key ventilator parameters [14–16].
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25 165 Continued use of high V_T has been reported in a recent Brazilian study [17], while a
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27 166 study from India suggests a change towards the use of lower V_T [18].

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33 167 There are several reasons to consider important differences with regard to
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35 168 practice of ventilation between resource-rich and resource-limited settings. The
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37 169 disparity in resources may limit the availability as well as the safety of certain ventilator
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39 170 settings [19]. Awareness of the impact of invasive ventilation on lung tissue, and the
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41 171 benefit of using lung-protective ventilation settings could be severely limited [20]. V_T and
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43 172 PEEP may be poorly titrated due to insufficient staffing, and due to the absence of
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45 173 arterial blood gas monitoring, pulse oximetry or capnography [21]. Other reasons not to
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47 174 implement use of low V_T and sufficient levels of PEEP include alleged side effects
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49 175 associated with their use, like the need for higher respiratory rates, increased sedation
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51 176 requirements, and even the promotion of patient-ventilator asynchrony. As invasive
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53 177 ventilation with higher PEEP may cause hemodynamic instability, limited access to fluids
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3 178 and vasoactive drugs may hamper its use. Finally, as resource-poor ICUs are usually
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5 179 situated in tropical countries their case-mix and indications for invasive ventilation are
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8 180 strikingly different [18].
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10 181 To gain a better insight into the ventilation practice, outcomes and
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12 182 epidemiological characteristics of ICU patients receiving invasive ventilation in resource-
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14 183 limited settings, we plan to perform the PRoVENT-iMIC ('Practice of VENTilation in
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17 184 Middle-Income Countries study'), a prospective observational cohort study in ICUs in
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19 185 Asia. We also aim to describe the association between certain ventilator settings and
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22 186 patient-centred outcomes. We hypothesize that practice of ventilation is highly variable,
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24 187 in particular with respect to V_T and PEEP settings. This understanding is fundamental to
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26 188 planning any intervention study in these countries in the future.
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190 **METHODS and ANALYSIS**

191 *Design and Setting*

192 PRoVENT-iMIC is an international multicentre observational study in consecutive ICU
193 patients receiving invasive mechanical ventilation during a 28-day period, expected to
194 run in approximately 60 centres in the following Asian countries: Thailand, Vietnam,
195 Myanmar, Pakistan, Nepal, Bangladesh, Malaysia, Sri Lanka, Maldives, Iran and India.
196 These countries belong to the low or middle-income economies, as classified by the
197 World Bank [22]. PRoVENT-iMIC is conducted in accordance with the declaration of
198 Helsinki and is registered at www.clinicaltrials.gov (trial identification number NCT
199 03188770). Figure 1 shows the study flow-chart.

200 *Study population*

201 Consecutive patients intubated for ventilation during a predefined period of 28 days are
202 enrolled. Inclusion is not restricted to patients who are intubated in the ICU, as also
203 patients who started invasive ventilation in the emergency room, normal ward,
204 community, or operating room directly preceding the present ICU admission are eligible
205 for participation, without any minimum or maximum hours of ventilation needed for
206 inclusion. The exclusion criteria include age < 18 years, use of non-invasive ventilation
207 not followed by invasive ventilation, patients whose invasive mechanical ventilation
208 started before the 28-day period of inclusion, and patients transferred from another
209 hospital under invasive ventilation.

210 Patients will be stratified in three groups for comparison of the primary and
211 secondary endpoints: patients without ARDS, patients without but at risk for
212 development of ARDS, according to the Lung Injury Prediction Score (LIPS, Table 1)
213 [23], and patients with ARDS, according to the Berlin Definition [24]. Patients with ARDS

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3 214 will also be stratified according to severity of ARDS, based on the oxygenation (mild,
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5 215 moderate and severe ARDS categories).

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8 216 *Study conduct*

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10 217 Local investigators will screen all patients who start invasive ventilation in one of the
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12 218 participating ICUs during a predefined period of 28-day, lasting from 8:00 AM on the
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14 219 Monday of the first week to 7.59 AM on the Monday four weeks later. The exact starting
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16 220 date will be flexible for participating centres and shall be determined by the national
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18 221 study coordinator. Data collection has started in November 2017 in some sites; all sites
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20 222 are expected to initiate the service evaluation within one year after the overall start.

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23 223 *Data to be collected*

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25 224 Baseline and demographic variables will be collected on the day of admission, including
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27 225 gender, age, actual or estimated weight and height, smoking status, comorbidities
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29 226 including chronic obstructive pulmonary disease (COPD), active cancer, heart failure,
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31 227 diabetes mellitus, chronic kidney failure, liver cirrhosis and arterial hypertension, the
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33 228 presence of ARDS according to the Berlin Definition, the LIPS, reason for ICU
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35 229 admission. On the day of start of invasive ventilation we will document the reason for
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37 230 starting mechanical ventilation, and whether the patient received non-invasive ventilation
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39 231 before intubation.

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42 232 Every day, until day 3 from admission in the ICU, until ICU discharge or death,
43
44 233 whichever comes first, the ventilation status and ventilation characteristics will be
45
46 234 collected, including ventilation mode, V_T size, respiratory rate (set and measured), peak
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48 235 and plateau pressure, PEEP, inspired oxygen fraction, peripheral oxygen saturation,
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50 236 blood gas analysis data when available (PaO_2 , $PaCO_2$, arterial bicarbonate, arterial pH),
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3 237 end-tidal CO₂, when available and hemodynamic parameters like heart rate and systolic
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5 238 blood pressure.
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7 239 Every day, until day 7, ICU discharge or death, whichever comes first, the
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9 240 occurrence of pulmonary complications will be scored, including new requirement of
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11 241 invasive ventilation after initial extubation, pulmonary infections, atelectasis,
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13 242 pneumothorax, pleural effusions, new pulmonary infiltrates and development or
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15 243 worsening of ARDS.
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18 244 On the day of ICU discharge (maximum 60 days after recruitment) outcome will
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20 245 be recorded as follows: death, discharge to ward, to medium care or high dependency
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22 246 unit, discharge to home for palliative care, or transfer to another ICU. The date of
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24 247 extubation, reintubation and tracheostomy (if performed) will also be recorded in this
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26 248 moment.
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29 249 *Study endpoints*

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31 250 The primary endpoint is V_T-size in millilitres per kilogram of predicted body weight
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33 251 (ml/kg PBW) and PEEP in centimetres of water (cm H₂O) used amongst diverse ICU
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35 252 patient categories during the first three days of mechanical ventilation. Secondary
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37 253 clinical endpoints include other ventilation parameters (including respiratory system
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39 254 driving pressure, the proportion of patients at risk of ARDS as stratified by the LIPS, or
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41 255 ARDS defined by the Berlin Definition, the occurrence of pulmonary complications,
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43 256 length of stay in ICU, duration of invasive ventilation and all-cause ICU-mortality.
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47 257 *Definitions*

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49 258 All cause ICU-mortality is defined as any death in the ICU. ICU length of stay is defined
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51 259 as the time between ICU admission and ICU discharge or death in ICU. The number of
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53 260 days of ventilation is defined as time between endotracheal intubation and successful
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3 261 extubation (in case of intermittent mechanical ventilation via a tracheostomy, every day
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5 262 a patient needs ventilation counts as one extra day, irrespective of the duration of
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7 263 ventilation on that specific day). In case of non-invasive ventilation, the duration will be
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10 264 assessed separated from the assessment of invasive ventilation. The presence of
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12 265 spontaneous activity will be identified by any recorded difference between the set and
13
14 266 measured respiratory rate.

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17 267 Driving pressure will be calculated by subtracting the level of PEEP from the
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19 268 plateau pressure (Pplat in volume-control ventilation) or maximal airway pressure
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21 269 (Pmax in pressure control ventilation). Pplat and Pmax are considered reliable for this
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23 270 calculation if the patient is receiving complete ventilatory assistance without evidence of
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25 271 spontaneous activity, i.e., only when the set respiratory rate equals the measured
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27 272 respiratory rate. Peak airways pressures will not be used to compute driving pressure as
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29 273 these represent a poor surrogate of the plateau pressure. Only pulmonary complications
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31 274 that occur after the first 24 hours of invasive ventilation will be considered in analysis, as
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33 275 events preceding this time point may very well be considered the potential reason for
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35 276 intubation. A pulmonary infection requires the presence of new or changed lung
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37 277 opacities on chest radiography and/or new or changed sputum plus at least a
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39 278 temperature > 38.3 °C or a white blood cell count $>12,000$ per microliter of blood.
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41 279 Atelectasis require the presence of increased density (lung opacity) on one or more
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43 280 chest radiographs with displacement of the fissures toward the area of atelectasis,
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45 281 crowding of pulmonary vessels and bronchi in the atelectatic region, upward
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47 282 displacement of hemidiaphragm ipsilateral to the side of atelectasis, that may be
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49 283 accompanied by shift of the mediastinum or hilum towards the affected area and
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51 284 compensatory overinflation in the unaffected lung [25]. Pleural effusion is suggested by
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3 285 lung opacification with shift of the mediastinum, hilum or hemi-diaphragm towards the
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5 286 non-affected area. Pneumothorax requires the presence of air in the pleural space with
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7 287 no vascular bed surrounding the visceral pleura. ARDS is defined according to the Berlin
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9 288 Definition [24] with alternative oxygenation criteria based on SpO_2/FiO_2 applicable only
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11 289 when blood gas analysis data is unavailable (Table 2a and 2b) [26,27]. Worsening of
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13 290 ARDS is defined as any change in the prior classification (i.e., from mild to moderate or
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15 291 severe ARDS, or from moderate to severe ARDS).

19 292 *Data management*

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21 293 Data will be collected from a paper medical chart, or an electronic patient data
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23 294 management system if available. Local investigators transcribe the collected data
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25 295 directly onto an anonymized internet-based electronic CRF (REDCap – Research
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27 296 Electronic Data Capture [28], www.projectredcap.org). In some centres data may be
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29 297 recorded on paper CRF and successively transcribed on the electronic CRF at a later
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31 298 time point. Access to the data-entry system is protected by a personalized username
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33 299 and password. The data will be kept on a central secured server located at the Hospital
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35 300 Israelita Albert Einstein, Sao Paulo, Brazil. The structure of the electronic CRF is
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37 301 detailed in Figure 2. A screening-log with limited patient data will be completed with all
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39 302 the included and excluded patients during the enrolment window. Participating centres
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41 303 are instructed to enter data for the daily follow-up using values obtained as close as
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43 304 possible to 08:00 AM, but only when the patient is stable at that time point. The study
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45 305 day for the recording of pulmonary complications will be defined as the natural 24h
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47 306 period from 00:00 until 23:59, to ensure that data is captured only once. Data for ICU-
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49 307 discharge will be collected until a maximum of 60 days after ICU admission, after which
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51 308 the CRF for that patient will be closed.

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3 309 *Study sites*
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5 310 P_{RO}VENT-iMIC will be conducted in 11 Asian countries, with a varying number of ICUs
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7 311 per country. Participating ICUs are selected on the basis of willingness to participate.
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9 312 There are no a priori established requirements for participation, and private as well as
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11 313 public centres are eligible to represent real-life practices. A one-time web-based pre-
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13 314 study survey on structure, organizational aspects and delivery of care in the participating
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15 315 centres will be performed. Each participating centre is surveyed once regarding the
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17 316 following information: hospital characteristics (private vs. public), ICU characteristics
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19 317 (medical vs. surgical vs. mixed, and open vs. closed, number of ICU beds, annual
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21 318 number of patient admitted, number of ventilators available, and other organ support
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23 319 measures), and staffing (nurse to patient ratio, physician to patient ratio, presence of
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25 320 specialized medical staff, and overnight coverage).
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31 321 *Statistical Analysis Plan*
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33 322 No formal sample size calculation was performed, but we expect each centre to enrol 20
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35 323 to 40 patients in the allocated time period, yielding a total of 1,200 to 2,400 patients. We
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37 324 consider this figure sufficient to analyse the study endpoints.
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40 325 Normally distributed variables will be expressed by their mean and standard
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42 326 deviation; not normally distributed variables will be expressed by their medians and
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44 327 interquartile ranges; categorical variables will be expressed as n (%). In test groups of
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46 328 continuous normally distributed variables, Student's t-test will be used. Likewise if
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48 329 continuous data are not normally distributed the Mann Whitney U test will be used.
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50 330 Categorical variables will be compared with the Chi-square test or Fisher's exact test or
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52 331 when appropriate as relative risks. Statistical uncertainty will be expressed by 95%
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54 332 confidence levels.
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3 333 The primary outcome (V_T size [ml/kg PBW] and PEEP [cm H₂O] levels during the
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5 334 first three days of mechanical ventilation) – will be analysed and compared between
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8 335 patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in
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10 336 case the diagnosis of ARDS could be made on admission). If the data is normally
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12 337 distributed, one way Analysis of Variance (ANOVA) or two-way ANOVA assessing the
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14 338 time–interaction between groups and days of observation will be used. When not
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17 339 normally distributed the Kruskal–Wallis test or Friedman test assessing the time–
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19 340 interaction between groups and days of observation will be used.

21 341 Univariate analysis will be performed to identify potential factors associated with
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23 342 outcomes including, but not limited to, ventilator settings (in particular V_T and PEEP). A
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25 343 multivariate logistic regression model will be used to determine which of those factors
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28 344 are independent. A stepwise approach will be used to enter new terms into the model,
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30 345 with a limit of $P < 0.2$ to enter the terms. Time to event variables is analysed using Cox
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33 346 regression and visualized by Kaplan–Meier.

35 347 Time–course variables (e.g. repeated measures of ventilator parameters, vital
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37 348 signs, oxygenation parameters and others) are also analysed by linear mixed model.
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39 349 The linear mixed models procedure expands the generalized linear model (GLM) so that
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42 350 the data are permitted to exhibit correlated and non–constant variability.

44 351 Pre–specified subgroups in the analyses studying potential associations between
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46 352 ventilator settings and outcome will be: (1) patients at low risk of ARDS vs. patients at
47
48 353 risk of ARDS; (2) patients without ARDS vs. patients with ARDS; (3) reason for ICU
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50 354 admission; and (4) reason for start of invasive ventilation. Statistical analyses will be
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53 355 conducted using R (www.r-project.org). A P –value of less than 0.05 will be considered
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56 356 statistically significant.

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3 357 *Study organization*
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5 358 The Steering Committee is composed of a selection of PROVE Network investigators
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7 359 plus the national coordinators from each participating country. These investigators were
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10 360 involved in the design of PRoVENT–iMIC. National coordinators are responsible for
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12 361 identifying and recruiting local participating centres. They assist and train the local
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14 362 investigators and oversee the conduct of the study, including administrative
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16 363 management, record keeping and data management. Local investigators in individual
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18 364 participating centres will provide scientific and structural leadership, ensuring local
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20 365 ethical and regulatory approvals are obtained before start of patient inclusion. National
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22 366 Coordinators and Local Investigators are expected to guarantee the quality and security
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24 367 of the data collected.
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28 368 Prior to start of the study, study teams in each centre will undergo a web–based
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30 369 training session on how to capture data in the electronic CRF. All study team members
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32 370 will be provided with a manual of operations with instructions on how to accurately fill the
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34 371 forms and the screening log. Incomplete or incorrectly entered electronic CRFs will be
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36 372 signalled to the local investigators by the national and international coordinator, for
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38 373 further review of the missing or flagged data.
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3 376 **ETHICS AND DISSEMINATION**
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5 377 The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford,
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7 378 United Kingdom, exempted the study from ethical review on the 9th of June 2017. Data
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10 379 management, monitoring and reporting of the study will be performed in accordance with
11
12 380 the International Conference on Harmonization – Good Clinical Practice guidelines.
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14 381 All participating centres will also submit the study protocol to the national or local
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16 382 Institutional Review Board for ethical judgment, as applicable by the current regulations
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18 383 in the country. Due to the strict observational design and anonymous collection of data,
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20 384 informed consent may not be required in most countries. However, where informed
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22 385 consent is required, this must be approved by the local ethical committee before the
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24 386 start of inclusion.
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28 387 The study will be reported following the Strengthening the reporting of
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30 388 Observational Studies in Epidemiology (STROBE) statement guidelines and checklists
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32 389 [29]. The results of this study will be published in a peer-reviewed medical journal. After
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34 390 publication of the primary results, on request the pooled dataset will be available for all
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36 391 members of the PRoVENT–iMIC collaboration for secondary analysis, after judgment
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38 392 and approval of scientific quality and validity of the proposed analysis by the Steering
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40 393 Committee.
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3 395 **DISCUSSION**
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5 396 PRoVENT–iMIC is designed to characterize the epidemiology, ventilator management,
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7 397 occurrence of pulmonary complications and outcomes in invasively ventilated patients in
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10 398 an estimated 60 ICUs in 11 Asian countries. The results of PRoVENT–iMIC will help to
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12 399 understand current ventilation practice in South and Southeast Asia, particularly with
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14 400 respect to variability in ventilator settings amongst patients without, at risk for or with
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16 401 established ARDS. Results of this study will be used to plan future trials of ventilation in
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18 402 ICU patients in these settings.
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21 403 PRoVENT–iMIC has several strengths. First, its prospective design will allow a
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23 404 higher accuracy of data capturing with regard to exposures, confounders and endpoints
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25 405 compared to studies that used a retrospective design [30]. While a prospective design
26
27 406 may cause sources of bias or establish causal effects, it minimizes the chance of
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29 407 residual confounding by unmeasured variables, a common limitation with a retrospective
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31 408 design, as has frequently been used in mechanical ventilation epidemiological studies
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33 409 [31–33]. We will have a sample size large enough to obtain precise estimates of
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35 410 pulmonary complications and ICU mortality and to examine potential associations
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37 411 between ventilation practice and patient outcomes. Second, the study sample is not
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39 412 restricted to certain patient diagnostic categories. Third, the attention on ventilation
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41 413 practice will provide robust data on this specific domain while the 7 days follow–up will
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43 414 allow precise recording of pulmonary complications at their origin. And finally, the wide
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45 415 representation of Asian countries will allow inferences on geo–economic differences in
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47 416 epidemiology, management and outcomes of mechanical ventilation across the entire
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53 417 subcontinent.
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3 418 The focus on South and Southeast Asia follows our scarce knowledge about
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5 419 clinical practices and ventilation strategies used in critically ill patients in this and other
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7 420 resource-limited settings [21]. The burden of critical illness in low- and middle-income
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9 421 countries is higher than generally perceived and it is expected to increase with an aging
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11 422 population [34]. Additionally, ICUs are increasingly being set up in the region, especially
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13 423 in busy urban settings. A recent survey highlighted considerable variation in structure,
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15 424 organization and critical care delivery in Asian ICUs, but did not shed light on ventilation
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17 425 management and patient-centred ventilation-associated outcomes [35]. This
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19 426 information, however, is crucial for future trials of ventilation in ICU patients in these
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21 427 settings, as we need to know whether critically ill patients across Asia equally benefit
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23 428 from lung-protective ventilation as those in Western countries. Additionally, for proper
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25 429 power calculations, information with regard to potential primary endpoints, like the
26
27 430 incidence of development of ARDS, duration of ventilation or death, is highly needed.
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29 431 PRoVENT-iMIC will be the first observational study that can provide this information for
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31 432 settings in South Asia. Results restricted to individual settings could also be valuable for
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33 433 local clinicians seeking to improve their local practice, training planning and identify local
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35 434 priorities for quality improvement within their departments.
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42 435 There is now strong evidence-based support for various ICU process-based
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44 436 interventions such as lung protective ventilation[36], conservative fluid management
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46 437 strategies[37] and weaning protocols [38]. While centre- or country-specific practices or
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48 438 restrictions of resources are potential challenges that affect implementation of all these
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50 439 interventions, we focus on the management of ventilation and especially on the
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52 440 employment of lung-protective ventilation where feasibility may represent an issue
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54 441 specific to resource-limited settings. Recent literature has underlined the potential role
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3 442 of the driving pressure (the pressure amplitude during each artificial breath) and its
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5 443 determinants in the development of ventilator-associated lung injury. Results from
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7 444 PRoVENT-iMIC will provide further data to enable us to discriminate the effects of V_T
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10 445 size, PEEP and driving pressure on outcomes in patients with, at risk of, or without
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12 446 ARDS.

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14 447 PRoVENT-iMIC will provide important data regarding outcomes following
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16 448 invasive ventilation, including a wide range of clinically important pulmonary
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18 449 complications. Historical studies from low-resource settings documented mortality rates
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20 450 to exceed 70% [14–16]. However more recent data from South America and India have
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22 451 documented mortality rates of ~40%, similar to that in high-income countries[17,18].
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24 452 This suggests that mortality in ventilated patients has the potential to improve in low-
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26 453 resource settings [12,13,39]. Although many factors may influence mortality, several
27
28 454 underappreciated factors related to invasive ventilation may have contributed, including
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30 455 reduced need for invasive ventilation per se, improvements in safety of invasive
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32 456 ventilation and in liberation from invasive ventilation.

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37 457 Our interest in patients at risk of ARDS follows a global recent shift in ARDS
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39 458 research. It is now clear that ARDS is rarely present at the time of the initial healthcare
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41 459 encounter, and typically develops during the hospital course, usually between days 2
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43 460 and 5 in patients with predisposing conditions or risk factors [40]. Hence increasing
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45 461 efforts are being directed toward early identification of patients at risk with a goal of
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47 462 prevention and early treatment prior to the development of a fully established syndrome.
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49 463 This is probably equally important in resource-limited settings where the predisposing
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51 464 conditions and risk modifiers for ARDS may differ and limited escalation of therapy is
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53 465 often the case. PRoVENT-iMIC will be the first study to evaluate prospectively the role
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3 466 of LIPS in these settings. Although the poor predictive accuracy of the LIPS does not
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5 467 currently support its use in everyday clinical practice [41], it has enabled enrolment in
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7 468 clinical trials of ARDS prevention [23] and may yield an initial idea on the patients at risk
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10 469 of and disease progression in the Asian settings under study.

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12 470 PRoVENT-iMIC has some noticeable shortcomings. The definition of 'middle-
13
14 471 income' country is rather artificial as the level of health expenditure, local resources and
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16 472 other geo-cultural factors might affect the processes of care in a larger extent than
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18 473 national income classification. Despite the inclusion of ICUs from 11 countries, which
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20 474 improves study generalizability, caution is needed when applying the results to
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22 475 supposedly similar settings, as substantial intra- and trans-national variations in ICU
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24 476 resources, staffing and organization exist. Second, the case report form used in
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26 477 PRoVENT-iMIC was designed so that it would not induce excessive work-load for the
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28 478 participating centres. Therefore, we decided not to collect data regarding extra-
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30 479 pulmonary complications and hospital-discharge outcomes, neither the amounts of
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32 480 sedation used and sedation levels. Similarly, due to the time window restricted to the
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34 481 ICU stay, we will apply the LIPS at ICU admission and not in the first 6 hours after
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36 482 hospital admission, as originally designed. Mortality may be underestimated in some
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38 483 settings where due to local practices there is the possibility to be discharged home in
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40 484 case of terminal conditions or family decision. To address this we made sure the data
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42 485 collection form captures this event whenever it represents the reason of discharge.
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44 486 Third, due to the limitation of laboratory data we will have a limited dataset that will not
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46 487 comprise daily severity scores useful for statistical controlling purposes. Also, the
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48 488 conceivable limitation in blood gas analysis and radiology exams may limit the
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50 489 documentation of insurgence or worsening of ARDS and other pulmonary complications.
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3 490 Finally, we cannot exclude that ventilator settings applied by treating physicians might
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5 491 be biased by the participation in the study, a problem that also existed in prior
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7 492 multinational studies [11,12]. Also participation in international studies like P_{Ro}VENT–
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9 493 iMIC always bears the risk of biased to those centres that do not fully or reliably
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11
12 494 represent ICU–care in general in the participating countries.
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For peer review only

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3 496 **CONCLUSIONS**
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5 497 P_{RO}VENT–iMIC is designed to understand the epidemiology, practice of ventilation, and
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7 498 outcomes of critically–ill patients receiving invasive ventilation in a large set of South
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10 499 Asian countries. Results of this study could help identify practices that may best explain
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12 500 differences in outcomes, and could be used in designing new trials of ventilation in these
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14 501 settings.
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5 504 **Contributors**
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7 505 LP, AGA, ASN, AMD and MJS were equally responsible for writing of the manuscript
8 and participated in study design. FP, PP participated in study design and assisted in
9 writing of the manuscript. AA, AB, KC, AF, RaH, ReH, MH, HAI, KI, SI, GK, BK, HM, BN,
10 RP, SS, LT, SG, NNT, NMY, MGdA reviewed the manuscript and agreed with
11 submission.
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19 510
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21 511 **Funding**
22
23 512 This research received no specific grant from any funding agency in the public,
24 commercial or not-for profit sectors.
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28 514
29
30 515 **Competing interests**
31

32 516 None
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37 518 **Ethics approval**
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39 519 The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford,
40 United Kingdom, exempted the study from ethical review on the 9th of June 2017. IRB
41 approval was obtained from Sri Lanka, Bangladesh and Malaysia and is underway in
42 Myanmar, Iran, India, Vietnam, Thailand, Nepal, Pakistan and Maldives.
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524 **REFERENCES**

- 525 1 Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*
526 2014;**370**:980. doi:10.1056/NEJMc1400293
- 527 2 Serpa N, Schultz M, Slutsky A. Current concepts of protective ventilation during
528 general anaesthesia. *Swiss Med Wkly* 2015;**145**:w14211.
529 doi:10.4414/smw.2015.14211
- 530 3 Putensen C, Theuerkauf N, Zinserling J, *et al.* Meta-analysis: ventilation strategies
531 and outcomes of the acute respiratory distress syndrome and acute lung injury.
532 *Ann Intern Med* 2009;**151**:566–76.
- 533 4 Serpa Neto A, Cardoso SO, Manetta JA, *et al.* Association Between Use of Lung-
534 Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among
535 Patients Without Acute Respiratory Distress Syndrome. *JAMA* 2012;**308**:1651.
536 doi:10.1001/jama.2012.13730
- 537 5 Güldner A, Kiss T, Serpa Neto A, *et al.* Intraoperative Protective Mechanical
538 Ventilation for Prevention of Postoperative Pulmonary Complications.
539 *Anesthesiology* 2015;**123**:692–713. doi:10.1097/ALN.0000000000000754
- 540 6 Briel M, Meade M, Mercat A, *et al.* Higher vs lower positive end-expiratory
541 pressure in patients with acute lung injury and acute respiratory distress
542 syndrome: systematic review and meta-analysis. *JAMA* 2010;**303**:865–73.
543 doi:10.1001/jama.2010.218
- 544 7 Ferguson ND. Low Tidal Volumes for All? *JAMA* 2012;**308**:1689.
545 doi:10.1001/jama.2012.14509
- 546 8 Serpa Neto A, Nagtzaam L, Schultz MJ. Ventilation with lower tidal volumes for
547 critically ill patients without the acute respiratory distress syndrome: a systematic

- 1
2
3 548 translational review and meta-analysis. *Curr Opin Crit Care* 2014;**20**:25–32.
4
5 549 doi:10.1097/MCC.0000000000000044
6
7
8 550 9 Dellinger RP, Levy MM, Rhodes A, *et al*. Surviving sepsis campaign: International
9
10 551 guidelines for management of severe sepsis and septic shock, 2012. *Intensive*
11
12 552 *Care Med* 2013;**39**:165–228. doi:10.1007/s00134-012-2769-8
13
14 553 10 Amato MBP, Meade MO, Slutsky AS, *et al*. Driving pressure and survival in the
15
16
17 554 acute respiratory distress syndrome. *N Engl J Med* 2015;**372**:747–55.
18
19 555 doi:10.1056/NEJMsa1410639
20
21 556 11 Bellani G, Gattinoni L, Haren F Van, *et al*. Epidemiology, Patterns of Care, and
22
23
24 557 Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care
25
26 558 Units in 50 Countries. *JAMA* 2016;**315**:2526–33.
27
28 559 12 Neto AS, Barbas CS V, Simonis FD, *et al*. Epidemiological characteristics, practice
29
30
31 560 of ventilation, and clinical outcome in patients at risk of acute respiratory distress
32
33 561 syndrome in intensive care units from 16 countries (PRoVENT): an international,
34
35 562 multicentre, prospective study. *Lancet Respir Med* 2016;**4**:882–93.
36
37 563 doi:10.1016/S2213-2600(16)30305-8
38
39
40 564 13 Epidemiology, practice of ventilation and outcome for patients at increased risk of
41
42 565 postoperative pulmonary complications. *Eur J Anaesthesiol* 2017;**34**:492–507.
43
44 566 doi:10.1097/EJA.0000000000000646
45
46
47 567 14 Sinclair JR, Watters DA, Davison M. Outcome of mechanical ventilation in Central
48
49 568 Africa. *Ann R Coll Surg Engl* 1988;**70**:76–9.
50
51 569 15 Rajapakse VP, Wijsekera S. Outcome of mechanical ventilation in Sri Lanka. *Ann*
52
53 570 *R Coll Surg Engl* 1989;**71**:344–6.
54
55
56 571 16 Sudarsanam TD, Jeyaseelan L, Thomas K, *et al*. Predictors of mortality in
57
58
59
60

- 1
2
3 572 mechanically ventilated patients. *Postgrad Med J* 2005;**81**:780–3.
4
5 573 doi:10.1136/pgmj.2005.033076
6
7 574 17 Azevedo LC, Park M, Salluh JI, *et al*. Clinical outcomes of patients requiring
8 ventilatory support in Brazilian intensive care units: a multicenter, prospective,
9 cohort study. *Crit Care* 2013;**17**:R63. doi:10.1186/cc12594
10 575
11
12 576
13
14 577 18 Karthikeyan B, Kadiravan T, Deepanjali S, *et al*. Case-Mix, Care Processes, and
15 Outcomes in Medically-Ill Patients Receiving Mechanical Ventilation in a Low-
16 Resource Setting from Southern India: A Prospective Clinical Case Series. *PLoS*
17 *One* 2015;**10**:e0135336. doi:10.1371/journal.pone.0135336
18
19 579
20
21 580
22
23 581 19 Serpa Neto A, Schultz MJ, Festic E. Ventilatory support of patients with sepsis or
24 septic shock in resource-limited settings. *Intensive Care Med* 2016;**42**:100–3.
25
26 582
27
28 583
29
30 584 20 Haniffa R, Lubell Y, Cooper BS, *et al*. Impact of a structured ICU training
31 programme in resource-limited settings in Asia. *PLoS One* 2017;**12**:e0173483.
32
33 585
34
35 586
36
37 587 21 Dünser MW, Baelani I, Ganbold L, *et al*. A review and analysis of intensive care
38 medicine in the least developed countries*. *Crit Care Med* 2006;**34**:1234–42.
39
40 588
41
42 589
43
44 590 22 The World Bank. World Bank Country Classification.
45
46 591
47 https://datahelpdesk.worldbank.org/knowledgebase/topics/19280-country-
48
49 592
50
51 593 23 Gajic O, Dabbagh O, Park PK, *et al*. Early identification of patients at risk of acute
52 lung injury: evaluation of lung injury prediction score in a multicenter cohort study.
53
54 594
55
56 595
57
58
59
60

- 1
2
3 596 24 The ARDS Definition Task Force*, Ranieri VM, Rubenfeld GD, *et al.* Acute
4
5 597 respiratory distress syndrome: the Berlin Definition. *JAMA J Am Med Assoc*
6
7 598 2012;**307**:1. doi:10.1001/jama.2012.5669
8
9
10 599 25 Ashizawa K, Hayashi K, Aso N, *et al.* Lobar atelectasis: diagnostic pitfalls on chest
11
12 600 radiography. *Br J Radiol* 2001;**74**:89–97. doi:10.1259/bjr.74.877.740089
13
14 601 26 Riviello ED, Kiviri W, Twagirumugabe T, *et al.* Hospital Incidence and Outcomes of
15
16 602 the Acute Respiratory Distress Syndrome Using the Kigali Modification of the
17
18 603 Berlin Definition. *Am J Respir Crit Care Med* 2016;**193**:52–9.
19
20 604 doi:10.1164/rccm.201503-0584OC
21
22
23 605 27 Rice TW, Wheeler AP, Bernard GR, *et al.* Comparison of the SpO₂/FIO₂ ratio
24
25 606 and the PaO₂/FIO₂ ratio in patients with acute lung injury or ARDS. *Chest*
26
27 607 2007;**132**:410–7. doi:10.1378/chest.07-0617
28
29
30 608 28 Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)-
31
32 609 -a metadata-driven methodology and workflow process for providing translational
33
34 610 research informatics support. *J Biomed Inform* 2009;**42**:377–81.
35
36 611 doi:10.1016/j.jbi.2008.08.010
37
38
39 612 29 von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of
40
41 613 Observational Studies in Epidemiology (STROBE) statement: guidelines for
42
43 614 reporting observational studies. *Lancet* 2007;**370**:1453–7. doi:10.1016/S0140-
44
45 615 6736(07)61602-X
46
47
48 616 30 Euser AM, Zoccali C, Jager KJ, *et al.* Cohort Studies: Prospective versus
49
50 617 Retrospective. *Nephron Clin Pract* 2009;**113**:c214–7. doi:10.1159/000235241
51
52
53 618 31 Gajic O, Dara SI, Mendez JL, *et al.* Ventilator-associated lung injury in patients
54
55 619 without acute lung injury at the onset of mechanical ventilation. *Crit Care Med*
56
57
58
59
60

- 1
2
3 620 2004;**32**:1817–24.
4
5 621 32 Rush B, Biagioni BJ, Berger L, *et al.* Mechanical Ventilation Outcomes in Patients
6
7 622 With Pulmonary Hypertension in the United States: A National Retrospective
8
9 623 Cohort Analysis. *J Intensive Care Med* 2017;**32**:588–92.
10
11 624 doi:10.1177/0885066616653926
12
13
14 625 33 Pesaro AEP, Katz M, Katz JN, *et al.* Mechanical Ventilation and Clinical Outcomes
15
16 626 in Patients with Acute Myocardial Infarction: A Retrospective Observational Study.
17
18 627 *PLoS One* 2016;**11**:e0151302. doi:10.1371/journal.pone.0151302
19
20
21 628 34 Adhikari NKJ, Fowler RA, Bhagwanjee S, *et al.* Critical care and the global burden
22
23 629 of critical illness in adults. *Lancet (London, England)* 2010;**376**:1339–46.
24
25 630 doi:10.1016/S0140-6736(10)60446-1
26
27
28 631 35 Arabi YM, Phua J, Koh Y, *et al.* Structure, Organization, and Delivery of Critical
29
30 632 Care in Asian ICUs*. *Crit Care Med* 2016;**44**:e940–8.
31
32 633 doi:10.1097/CCM.0000000000001854
33
34
35 634 36 Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, *et al.*
36
37 635 Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes
38
39 636 for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *N Engl J Med*
40
41 637 2000;**342**:1301–8. doi:10.1056/NEJM200005043421801
42
43
44 638 37 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome
45
46 639 (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, *et al.* Comparison
47
48 640 of two fluid-management strategies in acute lung injury. *N Engl J Med*
49
50 641 2006;**354**:2564–75. doi:10.1056/NEJMoa062200
51
52
53 642 38 Girard TD, Kress JP, Fuchs BD, *et al.* Efficacy and safety of a paired sedation and
54
55 643 ventilator weaning protocol for mechanically ventilated patients in intensive care
56
57
58
59
60

- 1
2
3 644 (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*
4
5 645 (*London, England*) 2008;**371**:126–34. doi:10.1016/S0140-6736(08)60105-1
6
7 646 39 Esteban A, Frutos-Vivar F, Muriel A, *et al.* Evolution of Mortality over Time in
8
9 Patients Receiving Mechanical Ventilation. *Am J Respir Crit Care Med*
10 647
11 2013;**188**:220–30. doi:10.1164/rccm.201212-2169OC
12 648
13
14 649 40 Gajic O, Dabbagh O, Park PK, *et al.* Early Identification of Patients at Risk of
15
16 Acute Lung Injury: Evaluation of Lung Injury Prediction Score in a Multicenter
17 650
18 Cohort Study. *Am J Respir Crit Care Med* 2010;;1–33. doi:10.1164/rccm.201004-
19 651
20 0549OC
21 652
22
23 653 41 Festic E, Kor DJ, Gajic O. Prevention of acute respiratory distress syndrome. *Curr*
24
25 *Opin Crit Care* 2015;**21**:82–90. doi:10.1097/MCC.000000000000174
26 654
27
28 655
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30 656
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3 657 **FIGURE LEGENDS**
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5 658 **Figure 1:** Flowchart of inclusion of PRoVENT-iMIC
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7 659 Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS,
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9 Acute Respiratory Distress Syndrome.
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14 662 **Figure 2.** Sequence of data submission in the electronic case report form
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16 663 Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS,
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18 Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU,
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20 Intensive Care Unit.
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668 **Table 1.** Lung Injury Prediction Score (LIPS) calculation worksheet^{17,34}
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Predisposing Conditions	Score	Risk Modifiers	Score
Shock	2	Alcohol Abuse	1
Aspiration	2	BMI > 30 kg/m ²	1
Sepsis	1	Hypoalbuminemia	1
Pneumonia	1.5	Chemotherapy	1
High-Risk Surgery		FiO ₂ > 0.35 (> 4 l/min)	2
Orthopedic Spine	1	RR > 30 bpm	1.5
Acute Abdomen	2	SpO ₂ < 95%	1
Cardiac	2.5	Acidosis (pH < 7.35)	1.5
Aortic Vascular	3.5	Diabetes Mellitus*	- 1
Emergency surgery	1.5		
High-Risk Trauma			
Traumatic Brain Injury	2		
Smoke Inhalation	2		
Near-Drowning	2		
Lung Contusion	1.5		
Multiple Fractures	1.5		

670 Abbreviations: BMI, body mass index; FiO₂, fraction of inspired oxygen; RR, respiratory
 671 rate; SpO₂, pulse oximetry oxygen saturation.

672 *(To consider only in septic patients)

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674 **Table 2a. The Berlin definition of ARDS**

Criteria	Definition		
Time	Within one week of a known clinical insult, or new/worsening respiratory symptoms		
Chest imaging ¹	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules		
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic oedema if no risk factor present (e.g., echocardiography)		
Oxygenation ²	Mild	Moderate	Severe
	$200 < \text{PaO}_2/\text{FiO}_2 \leq 300$	$100 < \text{PaO}_2/\text{FiO}_2 \leq 200$	$\text{PaO}_2/\text{FiO}_2 \leq 100$
	PEEP or CPAP ³ ≥ 5 cm H ₂ O	PEEP ≥ 5 cm H ₂ O	PEEP ≥ 5 cm H ₂ O

Abbreviations: ARDS, acute respiratory distress syndrome; PaO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

¹chest X-ray or CT scan; ²if altitude higher than 1,000 meters, correction factor should be made as follows: PaO₂/FiO₂ x (barometric pressure/760); ³this may be delivered noninvasively in the mild acute respiratory distress syndrome

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677 **Table 2b. Alternative Oxygenation criteria (if PaO₂ data unavailable)**
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Criteria	Mild ARDS	Moderate ARDS	Severe ARDS
Oxygenation	$235 < \text{SpO}_2/\text{FiO}_2 \leq 315$	$150 < \text{SpO}_2/\text{FiO}_2 \leq 235$	$\text{SpO}_2/\text{FiO}_2 \leq 150$
	PEEP or CPAP ≥ 5 cmH ₂ O	PEEP ≥ 5 cmH ₂ O	PEEP ≥ 5 cmH ₂ O

679 Abbreviations: SpO₂, pulse oximetry oxygen saturation; FiO₂, fraction of inspired oxygen

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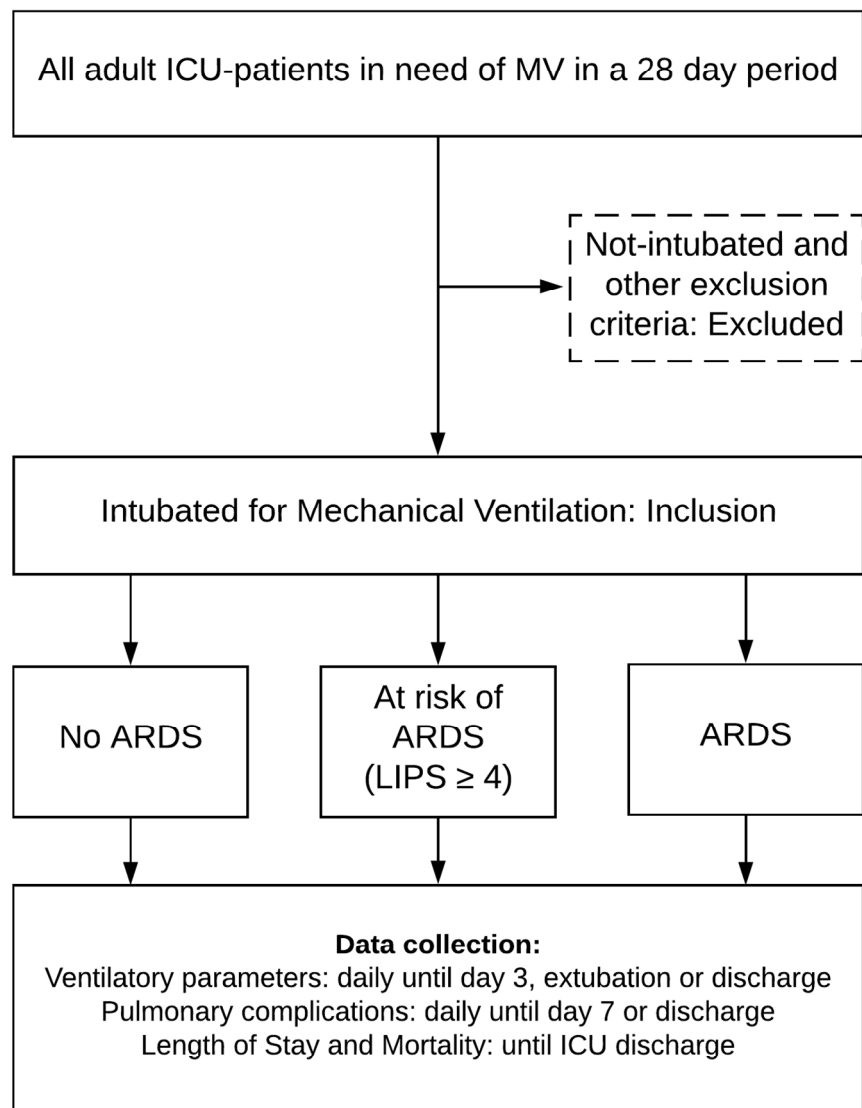


Figure 1. Flowchart of inclusion of PROVENT-iMIC[†]. Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.[†]

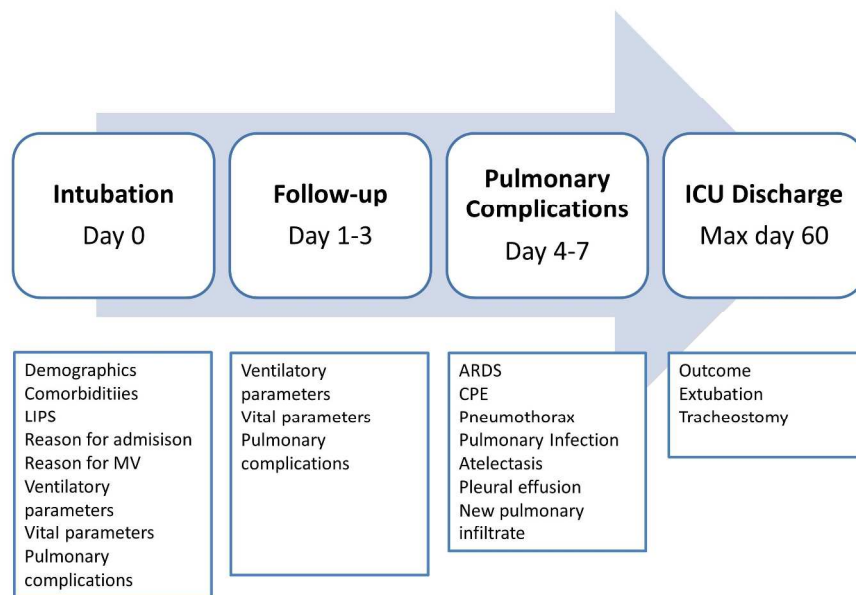


Figure 2. Sequence of data submission in the electronic case report form!! † . Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit. !! †

254x190mm (300 x 300 DPI)

BMJ Open

PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in intensive care units in Asia

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020841.R2
Article Type:	Protocol
Date Submitted by the Author:	19-Mar-2018
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Primary Subject Heading :	Intensive care
Secondary Subject Heading :	Epidemiology, Global health, Respiratory medicine
Keywords :	mechanical ventilation, invasive ventilation, ARDS, outcomes, middle-income countries, resource-limited settings

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PRactice of VENTilation in Middle–Income Countries (PRoVENT–iMIC) – rationale and protocol for a prospective international multicentre observational study in Intensive Care Units in Asia

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31 (www.tropmedres.ac)

32 **PROVE Network, the Protective Ventilation Network (www.provenet.eu)

33 Word count manuscript: 3974 words (abstract: 300 words)

34 Number of inserts: 2 tables and 2 figures

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2
3 **77 ABSTRACT**
4

5 **78 *Introduction***
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7
8 **79** Current evidence on epidemiology and outcomes of invasively mechanically ventilated
9
10 **80** intensive care unit (ICU) patients is predominantly gathered in resource-rich settings.
11
12 **81** Patient case-mixes and patterns of critical illnesses, and probably also ventilation
13
14 **82** practices are likely to be different in resource-limited settings. We aim to investigate the
15
16 **83** epidemiological characteristics, ventilation practices and clinical outcomes of patients
17
18 **84** receiving mechanical ventilation in ICUs in Asia.
19

20
21 **85 *Methods and analysis***
22

23
24 **86** PRoVENT-iMIC (study of PRactice of VENTilation in Middle Income Countries) is an
25
26 **87** international multicentre observational study to be undertaken in approximately 60 ICUs
27
28 **88** in 11 Asian countries. Consecutive patients aged 18 years or older who are receiving
29
30 **89** invasive ventilation in participating ICUs during a predefined 28-day period are to be
31
32 **90** enrolled, with a daily follow-up of 7 days. The primary outcome is ventilatory
33
34 **91** management (including tidal volume [V_T] expressed as mL/kg predicted bodyweight
35
36 **92** [PBW], and positive end-expiratory pressure [PEEP] expressed as cm H₂O) during the
37
38 **93** first three days of mechanical ventilation – compared between patients at no risk for
39
40 **94** ARDS, patients at risk for ARDS and in patients with ARDS (in case the diagnosis of
41
42 **95** ARDS can be made on admission). Secondary outcomes include occurrence of
43
44 **96** pulmonary complications and all-cause ICU mortality. The PRoVENT-iMIC study is
45
46 **97** registered at ClinicalTrials.gov, NCT 03188770.
47
48

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50
51 **98 *Ethics and dissemination***
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53
54 **99** PRoVENT-iMIC will be the first international study that prospectively assesses
55
56 **100** ventilation practices, outcomes and epidemiology of invasively ventilated patients in
57

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2
3 101 ICUs in Asia. The results of this large study, to be disseminated through conference
4
5 102 presentations and publications in international peer-reviewed journals, are of ultimate
6
7 103 importance when designing trials of invasive ventilation in resource-limited ICUs.
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9
10 104 Access to source data will be made available through national or international
11
12 105 anonymized datasets upon request and after agreement of the PRoVENT-iMIC steering
13
14 106 committee.

15
16
17 107 **KEYWORDS:** mechanical ventilation; invasive ventilation; ARDS; outcomes; middle-
18
19 108 income countries; resource-limited settings.

20
21 109 **TRIAL REGISTRATION:** PRoVENT-iMIC is registered at www.clinicaltrials.gov with trial
22
23 110 identification number NCT 03188770.

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27 28 112 **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

- 29
30
31 113 • PRoVENT-iMIC is an international multicentre observational study with a wide
32
33 114 representation of Asian countries, allowing inferences on epidemiology,
34
35 115 management and outcomes of mechanical ventilation across the entire
36
37 116 subcontinent.
- 38
39 117 • The attention on ventilation practice will provide robust data on this specific
40
41 118 domain while the 7 days follow-up will allow precise recording of pulmonary
42
43 119 complications at their origin.
- 44
45 120 • The study will have a sample size large enough to obtain precise estimates of
46
47 121 pulmonary complications and ICU mortality and to examine potential associations
48
49 122 between ventilation practice and these outcomes.
- 50
51 123 • One limitation is the potential constraint of laboratory data, generating a limited
52
53 124 dataset not comprising daily severity scores useful for statistical controlling
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55 125 purposes.
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3 126 • The conceivable limitation in blood gas analysis and imaging examinations may
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5 127 limit the documentation of insurgence or worsening of ARDS and other pulmonary
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7 128 complications.
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130 INTRODUCTION

131 Invasive mechanical ventilation is a frequently applied intervention in patients in
132 intensive care units (ICUs) and a mandatory strategy in patients under general
133 anaesthesia for surgery. There is increased understanding how invasive ventilation can
134 harm the lungs, in ICU patients with the acute respiratory distress syndrome (ARDS) [1],
135 as well as in ICU patients with less injured or uninjured lungs, and in surgery patients
136 who usually have healthy lungs [2]. A central cause is that invasive ventilation with
137 positive pressure may overdistend one lung area while failing to recruit another,
138 compromising gas exchange but also, and more importantly, increasing or inducing
139 pulmonary injury. There is convincing evidence that this harm can be partly prevented by
140 adjusting volume and pressure settings on the ventilator. Indeed, use of low tidal
141 volumes (V_T) [3–5], to prevent overdistension, and sufficient positive end–expiratory
142 pressure (PEEP) [3,5,6], to prevent alveolar collapse or atelectrauma, have both been
143 found to improve outcomes of various types of patients, and their use is increasingly
144 recommended [7–9]. Furthermore, the driving pressure seems to be another key
145 variable in the development of injury caused by mechanical ventilation, as a large
146 individual patient data metaanalysis showed a clear and consistent association between
147 driving pressure and mortality [10].

148 Practice of invasive ventilation has evolved over time, with a more extensive use of
149 ventilator settings that are proven to prevent against so–called ventilator–induced lung
150 injury. The recent LUNG SAFE (‘Large observational study to UNderstand the Global
151 impact of Severe Acute respiratory Failure’) showed that by now up to two in every three
152 patients with ARDS receive so–called lung–protective ventilation[11]. Results of
153 PRoVENT (‘PRactice of VENTilation in critically ill patients without ARDS at onset of

1
2
3 154 ventilation study') are in line with those from LUNG SAFE, showing that one in every two
4
5 155 ICU patients without ARDS receive ventilation with lung-protective settings[12]. Results
6
7 156 of LAS VEGAS ('Local ASsessment of VEntilatory management during General
8
9 Anaesthesia for Surgery study') even suggests increased use of lung-protective
10
11 157 ventilation in the operating rooms [13]. It should be noticed, though, that LUNG SAFE,
12
13 158 PRoVENT, and LAS VEGAS were mainly performed in high-income countries, and
14
15 159 exclusively recruiting patients in resource-rich centres, which limits the generalizability
16
17 160 of their results to lower-income countries and resource-limited settings. Historical
18
19 161 descriptions of cohorts of invasively ventilated patients in resource-poor settings have
20
21 162 been published, but these were all small in size, and while suggesting the existence of
22
23 163 ventilator-related deaths they largely failed to report key ventilator parameters [14-16].
24
25 164 Continued use of high V_T has been reported in a recent Brazilian study [17], while a
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27 165 study from India suggests a change towards the use of lower V_T [18].
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33 167 There are several reasons to consider important differences with regard to
34
35 168 practice of ventilation between resource-rich and resource-limited settings. The
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37 169 disparity in resources may limit the availability as well as the safety of certain ventilator
38
39 170 settings [19]. Awareness of the impact of invasive ventilation on lung tissue, and the
40
41 171 benefit of using lung-protective ventilation settings could be severely limited [20]. V_T and
42
43 172 PEEP may be poorly titrated due to insufficient staffing, and due to the absence of
44
45 173 arterial blood gas monitoring, pulse oximetry or capnography [21]. Other reasons not to
46
47 174 implement use of low V_T and sufficient levels of PEEP include alleged side effects
48
49 175 associated with their use, like the need for higher respiratory rates, increased sedation
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51 176 requirements, and even the promotion of patient-ventilator asynchrony. As invasive
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53 177 ventilation with higher PEEP may cause hemodynamic instability, limited access to fluids
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3 178 and vasoactive drugs may hamper its use. Finally, as resource-poor ICUs are usually
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5 179 situated in tropical countries their case-mix and indications for invasive ventilation are
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7
8 180 strikingly different [18].
9

10 181 To gain a better insight into the ventilation practice, outcomes and
11
12 182 epidemiological characteristics of ICU patients receiving invasive ventilation in resource-
13
14 183 limited settings, we plan to perform the PRoVENT-iMIC ('Practice of VENTilation in
15
16
17 184 Middle-Income Countries study'), a prospective observational cohort study in ICUs in
18
19 185 Asia. We also aim to describe the association between certain ventilator settings and
20
21
22 186 patient-centred outcomes. We hypothesize that practice of ventilation is highly variable,
23
24 187 in particular with respect to V_T and PEEP settings. This understanding is fundamental to
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26 188 planning any intervention study in these countries in the future.
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190 **METHODS and ANALYSIS**

191 *Design and Setting*

192 PRoVENT-iMIC is an international multicentre observational study in consecutive ICU
193 patients receiving invasive mechanical ventilation during a 28-day period, expected to
194 run in approximately 60 centres in the following Asian countries: Thailand, Vietnam,
195 Myanmar, Pakistan, Nepal, Bangladesh, Malaysia, Sri Lanka, Maldives, Iran and India.
196 These countries belong to the low or middle-income economies, as classified by the
197 World Bank [22]. PRoVENT-iMIC is conducted in accordance with the declaration of
198 Helsinki and is registered at www.clinicaltrials.gov (trial identification number NCT
199 03188770). Figure 1 shows the study flow-chart.

200 *Study population*

201 Consecutive patients intubated for ventilation during a predefined period of 28 days are
202 enrolled. Inclusion is not restricted to patients who are intubated in the ICU, as also
203 patients who started invasive ventilation in the emergency room, normal ward,
204 community, or operating room directly preceding the present ICU admission are eligible
205 for participation, without any minimum or maximum hours of ventilation needed for
206 inclusion. The exclusion criteria include age < 18 years, use of non-invasive ventilation
207 not followed by invasive ventilation, patients whose invasive mechanical ventilation
208 started before the 28-day period of inclusion, and patients transferred from another
209 hospital under invasive ventilation.

210 Patients will be stratified in three groups for comparison of the primary and
211 secondary endpoints: patients without ARDS, patients without but at risk for
212 development of ARDS, according to the Lung Injury Prediction Score (LIPS, Table 1)
213 [23], and patients with ARDS, according to the Berlin Definition [24]. Patients with ARDS

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3 214 will also be stratified according to severity of ARDS, based on the oxygenation (mild,
4
5 215 moderate and severe ARDS categories).

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8 216 *Study conduct*

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10 217 Local investigators will screen all patients who start invasive ventilation in one of the
11
12 218 participating ICUs during a predefined period of 28-day, lasting from 8:00 AM on the
13
14 219 Monday of the first week to 7.59 AM on the Monday four weeks later. The exact starting
15
16 220 date will be flexible for participating centres and shall be determined by the national
17
18 221 study coordinator. Data collection has started in November 2017 in some sites; all sites
19
20 222 are expected to initiate the service evaluation within one year after the overall start.

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24 223 *Data to be collected*

25
26 224 Baseline and demographic variables will be collected on the day of admission, including
27
28 225 gender, age, actual or estimated weight and height, smoking status, comorbidities
29
30 226 including chronic obstructive pulmonary disease (COPD), active cancer, heart failure,
31
32 227 diabetes mellitus, chronic kidney failure, liver cirrhosis and arterial hypertension, the
33
34 228 presence of ARDS according to the Berlin Definition, the LIPS, reason for ICU
35
36 229 admission. On the day of start of invasive ventilation we will document the reason for
37
38 230 starting mechanical ventilation, and whether the patient received non-invasive ventilation
39
40 231 before intubation.

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43
44 232 Every day, until day 3 from admission in the ICU, until ICU discharge or death,
45
46 233 whichever comes first, the ventilation status and ventilation characteristics will be
47
48 234 collected, including ventilation mode, V_T size, respiratory rate (set and measured), peak
49
50 235 and plateau pressure, PEEP, inspired oxygen fraction, peripheral oxygen saturation,
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52 236 blood gas analysis data when available (PaO_2 , $PaCO_2$, arterial bicarbonate, arterial pH),
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3 237 end-tidal CO₂, when available and hemodynamic parameters like heart rate and systolic
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5 238 blood pressure.

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7 239 Every day, until day 7, ICU discharge or death, whichever comes first, the
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9 240 occurrence of pulmonary complications will be scored, including new requirement of
10
11 241 invasive ventilation after initial extubation, pulmonary infections, atelectasis,
12
13 242 pneumothorax, pleural effusions, new pulmonary infiltrates and development or
14
15 243 worsening of ARDS.

16
17 244 On the day of ICU discharge (maximum 60 days after recruitment) outcome will
18
19 245 be recorded as follows: death, discharge to ward, to medium care or high dependency
20
21 246 unit, discharge to home for palliative care, or transfer to another ICU. The date of
22
23 247 extubation, reintubation and tracheostomy (if performed) will also be recorded in this
24
25 248 moment.

26 249 *Study endpoints*

27
28 250 The primary endpoint is V_T-size in millilitres per kilogram of predicted body weight
29
30 251 (ml/kg PBW) and PEEP in centimetres of water (cm H₂O) used amongst diverse ICU
31
32 252 patient categories during the first three days of mechanical ventilation. Secondary
33
34 253 clinical endpoints include other ventilation parameters (including respiratory system
35
36 254 driving pressure, the proportion of patients at risk of ARDS as stratified by the LIPS, or
37
38 255 ARDS defined by the Berlin Definition, the occurrence of pulmonary complications,
39
40 256 length of stay in ICU, duration of invasive ventilation and all-cause ICU-mortality.

41 257 *Definitions*

42
43 258 All cause ICU-mortality is defined as any death in the ICU. ICU length of stay is defined
44
45 259 as the time between ICU admission and ICU discharge or death in ICU. The number of
46
47 260 days of ventilation is defined as time between endotracheal intubation and successful
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3 261 extubation (in case of intermittent mechanical ventilation via a tracheostomy, every day
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5 262 a patient needs ventilation counts as one extra day, irrespective of the duration of
6
7 263 ventilation on that specific day). In case of non-invasive ventilation, the duration will be
8
9
10 264 assessed separated from the assessment of invasive ventilation. The presence of
11
12 265 spontaneous activity will be identified by any recorded difference between the set and
13
14 266 measured respiratory rate.

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16
17 267 Driving pressure will be calculated by subtracting the level of PEEP from the
18
19 268 plateau pressure (Pplat in volume-control ventilation) or maximal airway pressure
20
21 269 (Pmax in pressure-control ventilation). Pplat and Pmax are considered reliable for this
22
23
24 270 calculation if the patient is receiving complete ventilatory assistance without evidence of
25
26 271 spontaneous activity, i.e., only when the set respiratory rate equals the measured
27
28 272 respiratory rate. Peak airways pressures will not be used to compute driving pressure as
29
30
31 273 these represent a poor surrogate of the plateau pressure. Only pulmonary complications
32
33 274 that occur after the first 24 hours of invasive ventilation will be considered in analysis, as
34
35 275 events preceding this time point may very well be considered the potential reason for
36
37 276 intubation. A pulmonary infection requires the presence of new or changed lung
38
39
40 277 opacities on chest radiography and/or new or changed sputum plus at least a
41
42 278 temperature > 38.3 °C or a white blood cell count $>12,000$ per microliter of blood.
43
44 279 Atelectasis require the presence of increased density (lung opacity) on one or more
45
46 280 chest radiographs with displacement of the fissures toward the area of atelectasis,
47
48 281 crowding of pulmonary vessels and bronchi in the atelectatic region, upward
49
50 282 displacement of hemidiaphragm ipsilateral to the side of atelectasis, that may be
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52
53 283 accompanied by shift of the mediastinum or hilum towards the affected area and
54
55 284 compensatory overinflation in the unaffected lung [25]. Pleural effusion is suggested by

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2
3 285 lung opacification with shift of the mediastinum, hilum or hemi-diaphragm towards the
4
5 286 non-affected area. Pneumothorax requires the presence of air in the pleural space with
6
7 287 no vascular bed surrounding the visceral pleura. ARDS is defined according to the Berlin
8
9 288 Definition [24] with alternative oxygenation criteria based on SpO_2/FiO_2 applicable only
10
11 289 when blood gas analysis data is unavailable (Table 2a and 2b) [26,27]. Worsening of
12
13 290 ARDS is defined as any change in the prior classification (i.e., from mild to moderate or
14
15 291 severe ARDS, or from moderate to severe ARDS).

19 292 *Data management*

21 293 Data will be collected from a paper medical chart, or an electronic patient data
22
23 294 management system if available. Local investigators transcribe the collected data
24
25 295 directly onto an anonymized internet-based electronic CRF (REDCap – Research
26
27 296 Electronic Data Capture [28], www.projectredcap.org). In some centres data may be
28
29 297 recorded on paper CRF and successively transcribed on the electronic CRF at a later
30
31 298 time point. Access to the data-entry system is protected by a personalized username
32
33 299 and password. The data will be kept on a central secured server located at the Hospital
34
35 300 Israelita Albert Einstein, Sao Paulo, Brazil. The structure of the electronic CRF is
36
37 301 detailed in Figure 2. A screening-log with limited patient data will be completed with all
38
39 302 the included and excluded patients during the enrolment window. Participating centres
40
41 303 are instructed to enter data for the daily follow-up using values obtained as close as
42
43 304 possible to 08:00 AM, but only when the patient is stable at that time point. The study
44
45 305 day for the recording of pulmonary complications will be defined as the natural 24h
46
47 306 period from 00:00 until 23:59, to ensure that data is captured only once. Data for ICU-
48
49 307 discharge will be collected until a maximum of 60 days after ICU admission, after which
50
51 308 the CRF for that patient will be closed.

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2
3 309 *Study sites*
4

5 310 PRoVENT-iMIC will be conducted in 11 Asian countries, with a varying number of ICUs
6
7 311 per country. Participating ICUs are selected on the basis of willingness to participate.
8
9 312 There are no a priori established requirements for participation, and private as well as
10
11 313 public centres are eligible to represent real-life practices. A one-time web-based pre-
12
13 314 study survey on structure, organizational aspects and delivery of care in the participating
14
15 315 centres will be performed. Each participating centre is surveyed once regarding the
16
17 316 following information: hospital characteristics (private vs. public), ICU characteristics
18
19 317 (medical vs. surgical vs. mixed, and open vs. closed, number of ICU beds, annual
20
21 318 number of patient admitted, number of ventilators available, and other organ support
22
23 319 measures), and staffing (nurse to patient ratio, physician to patient ratio, presence of
24
25 320 specialized medical staff, and overnight coverage).
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31 321 *Statistical Analysis Plan*
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33 322 No formal sample size calculation was performed, but we expect each centre to enrol 20
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35 323 to 40 patients in the allocated time period, yielding a total of 1,200 to 2,400 patients. We
36
37 324 consider this figure sufficient to analyse the study endpoints.
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40 325 Normally distributed variables will be expressed by their mean and standard
41
42 326 deviation; not normally distributed variables will be expressed by their medians and
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44 327 interquartile ranges; categorical variables will be expressed as n (%). In test groups of
45
46 328 continuous normally distributed variables, Student's t-test will be used. Likewise if
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48 329 continuous data are not normally distributed the Mann Whitney U test will be used.
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50 330 Categorical variables will be compared with the Chi-square test or Fisher's exact test or
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52 331 when appropriate as relative risks. Statistical uncertainty will be expressed by 95%
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54 332 confidence levels.
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3 333 The primary outcome (V_T size [ml/kg PBW] and PEEP [cm H₂O] levels during the
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5 334 first three days of mechanical ventilation) – will be analysed and compared between
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8 335 patients at no risk for ARDS, patients at risk for ARDS and in patients with ARDS (in
9
10 336 case the diagnosis of ARDS could be made on admission). If the data is normally
11
12 337 distributed, one way Analysis of Variance (ANOVA) or two-way ANOVA assessing the
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14 338 time–interaction between groups and days of observation will be used. When not
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16
17 339 normally distributed the Kruskal–Wallis test or Friedman test assessing the time–
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19 340 interaction between groups and days of observation will be used.

21 341 Univariate analysis will be performed to identify potential factors associated with
22
23 342 outcomes including, but not limited to, ventilator settings (in particular V_T and PEEP). A
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25 343 multivariate logistic regression model will be used to determine which of those factors
26
27 344 are independent. A stepwise approach will be used to enter new terms into the model,
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29 345 with a limit of $P < 0.2$ to enter the terms. Time to event variables is analysed using Cox
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31 346 regression and visualized by Kaplan–Meier.

35 347 Time–course variables (e.g. repeated measures of ventilator parameters, vital
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37 348 signs, oxygenation parameters and others) are also analysed by linear mixed model.
38
39 349 The linear mixed models procedure expands the generalized linear model (GLM) so that
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41 350 the data are permitted to exhibit correlated and non–constant variability.

44 351 Pre–specified subgroups in the analyses studying potential associations between
45
46 352 ventilator settings and outcome will be: (1) patients at low risk of ARDS vs. patients at
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48 353 risk of ARDS; (2) patients without ARDS vs. patients with ARDS; (3) reason for ICU
49
50 354 admission; and (4) reason for start of invasive ventilation. Statistical analyses will be
51
52 355 conducted using R (www.r-project.org). A P –value of less than 0.05 will be considered
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54 356 statistically significant.

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3 357 *Study organization*
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5 358 The Steering Committee is composed of a selection of PROVE Network investigators
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7 359 plus the national coordinators from each participating country. These investigators were
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9
10 360 involved in the design of PRoVENT–iMIC. National coordinators are responsible for
11
12 361 identifying and recruiting local participating centres. They assist and train the local
13
14 362 investigators and oversee the conduct of the study, including administrative
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16 363 management, record keeping and data management. Local investigators in individual
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18 364 participating centres will provide scientific and structural leadership, ensuring local
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20 365 ethical and regulatory approvals are obtained before start of patient inclusion. National
21
22 366 Coordinators and Local Investigators are expected to guarantee the quality and security
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24 367 of the data collected.
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28 368 Prior to start of the study, study teams in each centre will undergo a web–based
29
30 369 training session on how to capture data in the electronic CRF. All study team members
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32 370 will be provided with a manual of operations with instructions on how to accurately fill the
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34 371 forms and the screening log. Incomplete or incorrectly entered electronic CRFs will be
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36 372 signalled to the local investigators by the national and international coordinator, for
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38 373 further review of the missing or flagged data.
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42 374 *Patient and Public Involvement*
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44 375 Patients and public were not directly involved in any phase of this study.
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3 376 **ETHICS AND DISSEMINATION**
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5 377 The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford,
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7 378 United Kingdom, exempted the study from ethical review on the 9th of June 2017. Data
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10 379 management, monitoring and reporting of the study will be performed in accordance with
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12 380 the International Conference on Harmonization – Good Clinical Practice guidelines.
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14 381 All participating centres will also submit the study protocol to the national or local
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16 382 Institutional Review Board for ethical judgment, as applicable by the current regulations
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18 383 in the country. Due to the strict observational design and anonymous collection of data,
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20 384 informed consent may not be required in most countries. However, where informed
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22 385 consent is required, this must be approved by the local ethical committee before the
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24 386 start of inclusion.
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28 387 The study will be reported following the Strengthening the reporting of
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30 388 Observational Studies in Epidemiology (STROBE) statement guidelines and checklists
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32 389 [29]. The results of this study will be published in a peer-reviewed medical journal. After
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34 390 publication of the primary results, on request the pooled dataset will be available for all
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36 391 members of the PRoVENT–iMIC collaboration for secondary analysis, after judgment
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38 392 and approval of scientific quality and validity of the proposed analysis by the Steering
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40 393 Committee.
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3 395 **DISCUSSION**
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5 396 PRoVENT–iMIC is designed to characterize the epidemiology, ventilator management,
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7 397 occurrence of pulmonary complications and outcomes in invasively ventilated patients in
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10 398 an estimated 60 ICUs in 11 Asian countries. The results of PRoVENT–iMIC will help to
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12 399 understand current ventilation practice in South and Southeast Asia, particularly with
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14 400 respect to variability in ventilator settings amongst patients without, at risk for or with
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16 401 established ARDS. Results of this study will be used to plan future trials of ventilation in
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18 402 ICU patients in these settings.
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21 403 PRoVENT–iMIC has several strengths. First, its prospective design will allow a
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23 404 higher accuracy of data capturing with regard to exposures, confounders and endpoints
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25 405 compared to studies that used a retrospective design [30]. While a prospective design
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27 406 may cause sources of bias or establish causal effects, it minimizes the chance of
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29 407 residual confounding by unmeasured variables, a common limitation with a retrospective
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31 408 design, as has frequently been used in mechanical ventilation epidemiological studies
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33 409 [31–33]. We will have a sample size large enough to obtain precise estimates of
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35 410 pulmonary complications and ICU mortality and to examine potential associations
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37 411 between ventilation practice and patient outcomes. Second, the study sample is not
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39 412 restricted to certain patient diagnostic categories. Third, the attention on ventilation
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41 413 practice will provide robust data on this specific domain while the 7 days follow–up will
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43 414 allow precise recording of pulmonary complications at their origin. And finally, the wide
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45 415 representation of Asian countries will allow inferences on geo–economic differences in
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47 416 epidemiology, management and outcomes of mechanical ventilation across the entire
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49 417 subcontinent.
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3 418 The focus on South and Southeast Asia follows our scarce knowledge about
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5 419 clinical practices and ventilation strategies used in critically ill patients in this and other
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7 420 resource-limited settings [21]. The burden of critical illness in low- and middle-income
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9 421 countries is higher than generally perceived and it is expected to increase with an aging
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11 422 population [34]. Additionally, ICUs are increasingly being set up in the region, especially
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13 423 in busy urban settings. A recent survey highlighted considerable variation in structure,
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15 424 organization and critical care delivery in Asian ICUs, but did not shed light on ventilation
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17 425 management and patient-centred ventilation-associated outcomes [35]. This
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19 426 information, however, is crucial for future trials of ventilation in ICU patients in these
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21 427 settings, as we need to know whether critically ill patients across Asia equally benefit
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23 428 from lung-protective ventilation as those in Western countries. Additionally, for proper
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25 429 power calculations, information with regard to potential primary endpoints, like the
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27 430 incidence of development of ARDS, duration of ventilation or death, is highly needed.
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29 431 PRoVENT-iMIC will be the first observational study that can provide this information for
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31 432 settings in South Asia. Results restricted to individual settings could also be valuable for
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33 433 local clinicians seeking to improve their local practice, training planning and identify local
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35 434 priorities for quality improvement within their departments.
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42 435 There is now strong evidence-based support for various ICU process-based
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44 436 interventions such as lung protective ventilation[36], conservative fluid management
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46 437 strategies[37] and weaning protocols [38]. While centre- or country-specific practices or
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48 438 restrictions of resources are potential challenges that affect implementation of all these
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50 439 interventions, we focus on the management of ventilation and especially on the
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52 440 employment of lung-protective ventilation where feasibility may represent an issue
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54 441 specific to resource-limited settings. Recent literature has underlined the potential role
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3 442 of the driving pressure (the pressure amplitude during each artificial breath) and its
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5 443 determinants in the development of ventilator-associated lung injury. Results from
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7 444 PRoVENT-iMIC will provide further data to enable us to discriminate the effects of V_T
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10 445 size, PEEP and driving pressure on outcomes in patients with, at risk of, or without
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12 446 ARDS.

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14 447 PRoVENT-iMIC will provide important data regarding outcomes following
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16 448 invasive ventilation, including a wide range of clinically important pulmonary
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18 449 complications. Historical studies from low-resource settings documented mortality rates
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20 450 to exceed 70% [14–16]. However more recent data from South America and India have
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22 451 documented mortality rates of ~40%, similar to that in high-income countries[17,18].
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24 452 This suggests that mortality in ventilated patients has the potential to improve in low-
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26 453 resource settings [12,13,39]. Although many factors may influence mortality, several
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28 454 underappreciated factors related to invasive ventilation may have contributed, including
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30 455 reduced need for invasive ventilation per se, improvements in safety of invasive
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32 456 ventilation and in liberation from invasive ventilation.

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37 457 Our interest in patients at risk of ARDS follows a global recent shift in ARDS
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39 458 research. It is now clear that ARDS is rarely present at the time of the initial healthcare
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41 459 encounter, and typically develops during the hospital course, usually between days 2
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43 460 and 5 in patients with predisposing conditions or risk factors [40]. Hence increasing
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45 461 efforts are being directed toward early identification of patients at risk with a goal of
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47 462 prevention and early treatment prior to the development of a fully established syndrome.
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49 463 This is probably equally important in resource-limited settings where the predisposing
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51 464 conditions and risk modifiers for ARDS may differ and limited escalation of therapy is
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53 465 often the case. PRoVENT-iMIC will be the first study to evaluate prospectively the role
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3 466 of LIPS in these settings. Although the poor predictive accuracy of the LIPS does not
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5 467 currently support its use in everyday clinical practice [41], it has enabled enrolment in
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7 468 clinical trials of ARDS prevention [23] and may yield an initial idea on the patients at risk
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10 469 of and disease progression in the Asian settings under study.

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12 470 PRoVENT-iMIC has some noticeable shortcomings. The definition of 'middle-
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14 471 income' country is rather artificial as the level of health expenditure, local resources and
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16 472 other geo-cultural factors might affect the processes of care in a larger extent than
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18 473 national income classification. Despite the inclusion of ICUs from 11 countries, which
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20 474 improves study generalizability, caution is needed when applying the results to
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22 475 supposedly similar settings, as substantial intra- and trans-national variations in ICU
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24 476 resources, staffing and organization exist. Second, the case report form used in
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26 477 PRoVENT-iMIC was designed so that it would not induce excessive work-load for the
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28 478 participating centres. Therefore, we decided not to collect data regarding extra-
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30 479 pulmonary complications and hospital-discharge outcomes, neither the amounts of
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32 480 sedation used and sedation levels. Similarly, due to the time window restricted to the
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34 481 ICU stay, we will apply the LIPS at ICU admission and not in the first 6 hours after
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36 482 hospital admission, as originally designed. Mortality may be underestimated in some
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38 483 settings where due to local practices there is the possibility to be discharged home in
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40 484 case of terminal conditions or family decision. To address this we made sure the data
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42 485 collection form captures this event whenever it represents the reason of discharge.
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44 486 Third, due to the limitation of laboratory data we will have a limited dataset that will not
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46 487 comprise daily severity scores useful for statistical controlling purposes. Also, the
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48 488 conceivable limitation in blood gas analysis and radiology exams may limit the
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50 489 documentation of insurgence or worsening of ARDS and other pulmonary complications.
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3 490 Fourth, as in patients on pressure-control modes flow might not reach zero during
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5 491 inspiration, Pmax might overestimate alveolar pressure, hence overestimating driving
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7 492 pressure. An end-inspiratory occlusion could solve this problem, but is almost never
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10 493 performed in many centers. As this study only uses data that is collected as part of
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12 494 standard care, all analysis regarding driving pressure will be done separately for patients
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14 495 on pressure-control modes and volume-control modes. Finally, we cannot exclude that
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16 496 ventilator settings applied by treating physicians might be biased by the participation in
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18 497 the study, a problem that also existed in prior multinational studies [11,12]. Also
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20 498 participation in international studies like PRoVENT-iMIC always bears the risk of biased
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22 499 to those centres that do not fully or reliably represent ICU-care in general in the
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24 500 participating countries.
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3 502 **CONCLUSIONS**
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5 503 P_{RO}VENT-iMIC is designed to understand the epidemiology, practice of ventilation, and
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7 504 outcomes of critically-ill patients receiving invasive ventilation in a large set of South
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10 505 Asian countries. Results of this study could help identify practices that may best explain
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12 506 differences in outcomes, and could be used in designing new trials of ventilation in these
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14 507 settings.
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3 509 **Author affiliations**
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5 510 **Contributors**
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7
8 511 LP, AGA, ASN, AMD and MJS were equally responsible for writing of the manuscript
9
10 512 and participated in study design. FP, PP participated in study design and assisted in
11
12 513 writing of the manuscript. AA, AB, KC, AF, RaH, ReH, MH, HAI, KI, SI, GK, BK, HM, BN,
13
14 514 RP, SS, LT, SG, NNT, NMY, MGdA reviewed the manuscript and agreed with
15
16
17 515 submission.
18

19 516

20
21 517 **Funding**
22

23
24 518 This research received no specific grant from any funding agency in the public,
25
26 519 commercial or not-for profit sectors.
27

28 520

29
30 521 **Competing interests**
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32
33 522 None
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37 524 **Ethics approval**
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40 525 The Oxford Tropical Research Ethical Committee (OxTREC) at the University of Oxford,
41
42 526 United Kingdom, exempted the study from ethical review on the 9th of June 2017. IRB
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44 527 approval was obtained from Sri Lanka, Bangladesh and Malaysia and is underway in
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46 528 Myanmar, Iran, India, Vietnam, Thailand, Nepal, Pakistan and Maldives.
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530 **REFERENCES**

- 531 1 Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*
532 2014;**370**:980. doi:10.1056/NEJMc1400293
- 533 2 Serpa N, Schultz M, Slutsky A. Current concepts of protective ventilation during
534 general anaesthesia. *Swiss Med Wkly* 2015;**145**:w14211.
535 doi:10.4414/smw.2015.14211
- 536 3 Putensen C, Theuerkauf N, Zinserling J, *et al.* Meta-analysis: ventilation strategies
537 and outcomes of the acute respiratory distress syndrome and acute lung injury.
538 *Ann Intern Med* 2009;**151**:566–76.
- 539 4 Serpa Neto A, Cardoso SO, Manetta JA, *et al.* Association Between Use of Lung-
540 Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among
541 Patients Without Acute Respiratory Distress Syndrome. *JAMA* 2012;**308**:1651.
542 doi:10.1001/jama.2012.13730
- 543 5 Güldner A, Kiss T, Serpa Neto A, *et al.* Intraoperative Protective Mechanical
544 Ventilation for Prevention of Postoperative Pulmonary Complications.
545 *Anesthesiology* 2015;**123**:692–713. doi:10.1097/ALN.0000000000000754
- 546 6 Briel M, Meade M, Mercat A, *et al.* Higher vs lower positive end-expiratory
547 pressure in patients with acute lung injury and acute respiratory distress
548 syndrome: systematic review and meta-analysis. *JAMA* 2010;**303**:865–73.
549 doi:10.1001/jama.2010.218
- 550 7 Ferguson ND. Low Tidal Volumes for All? *JAMA* 2012;**308**:1689.
551 doi:10.1001/jama.2012.14509
- 552 8 Serpa Neto A, Nagtzaam L, Schultz MJ. Ventilation with lower tidal volumes for
553 critically ill patients without the acute respiratory distress syndrome: a systematic

- 1
2
3 554 translational review and meta-analysis. *Curr Opin Crit Care* 2014;**20**:25–32.
4
5 555 doi:10.1097/MCC.0000000000000044
6
7 556 9 Dellinger RP, Levy MM, Rhodes A, *et al*. Surviving sepsis campaign: International
8
9 guidelines for management of severe sepsis and septic shock, 2012. *Intensive*
10 557
11 *Care Med* 2013;**39**:165–228. doi:10.1007/s00134-012-2769-8
12 558
13
14 559 10 Amato MBP, Meade MO, Slutsky AS, *et al*. Driving pressure and survival in the
15
16 acute respiratory distress syndrome. *N Engl J Med* 2015;**372**:747–55.
17 560
18 doi:10.1056/NEJMsa1410639
19 561
20
21 562 11 Bellani G, Gattinoni L, Haren F Van, *et al*. Epidemiology, Patterns of Care, and
22
23 Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care
24 563
25 Units in 50 Countries. *JAMA* 2016;**315**:2526–33.
26 564
27
28 565 12 Neto AS, Barbas CS V, Simonis FD, *et al*. Epidemiological characteristics, practice
29
30 of ventilation, and clinical outcome in patients at risk of acute respiratory distress
31 566
32 syndrome in intensive care units from 16 countries (PRoVENT): an international,
33 567
34 multicentre, prospective study. *Lancet Respir Med* 2016;**4**:882–93.
35 568
36 doi:10.1016/S2213-2600(16)30305-8
37 569
38
39 570 13 Epidemiology, practice of ventilation and outcome for patients at increased risk of
40
41 postoperative pulmonary complications. *Eur J Anaesthesiol* 2017;**34**:492–507.
42 571
43 doi:10.1097/EJA.0000000000000646
44 572
45
46 573 14 Sinclair JR, Watters DA, Davison M. Outcome of mechanical ventilation in Central
47
48 Africa. *Ann R Coll Surg Engl* 1988;**70**:76–9.
49 574
50
51 575 15 Rajapakse VP, Wijsekera S. Outcome of mechanical ventilation in Sri Lanka. *Ann*
52
53 *R Coll Surg Engl* 1989;**71**:344–6.
54 576
55
56 577 16 Sudarsanam TD, Jeyaseelan L, Thomas K, *et al*. Predictors of mortality in
57
58
59
60

- 1
2
3 578 mechanically ventilated patients. *Postgrad Med J* 2005;**81**:780–3.
4
5 579 doi:10.1136/pgmj.2005.033076
6
7 580 17 Azevedo LC, Park M, Salluh JI, *et al*. Clinical outcomes of patients requiring
8 ventilatory support in Brazilian intensive care units: a multicenter, prospective,
9
10 581 cohort study. *Crit Care* 2013;**17**:R63. doi:10.1186/cc12594
11
12 582
13
14 583 18 Karthikeyan B, Kadiravan T, Deepanjali S, *et al*. Case-Mix, Care Processes, and
15 Outcomes in Medically-Ill Patients Receiving Mechanical Ventilation in a Low-
16
17 584 Resource Setting from Southern India: A Prospective Clinical Case Series. *PLoS*
18
19 585 *One* 2015;**10**:e0135336. doi:10.1371/journal.pone.0135336
20
21 586
22
23 587 19 Serpa Neto A, Schultz MJ, Festic E. Ventilatory support of patients with sepsis or
24 septic shock in resource-limited settings. *Intensive Care Med* 2016;**42**:100–3.
25
26 588 doi:10.1007/s00134-015-4070-0
27
28 589
29
30 590 20 Haniffa R, Lubell Y, Cooper BS, *et al*. Impact of a structured ICU training
31 programme in resource-limited settings in Asia. *PLoS One* 2017;**12**:e0173483.
32
33 591 doi:10.1371/journal.pone.0173483
34
35 592
36
37 593 21 Dünser MW, Baelani I, Ganbold L, *et al*. A review and analysis of intensive care
38 medicine in the least developed countries*. *Crit Care Med* 2006;**34**:1234–42.
39
40 594 doi:10.1097/01.CCM.0000208360.70835.87
41
42 595
43
44 596 22 The World Bank. World Bank Country Classification.
45
46 597 <https://datahelpdesk.worldbank.org/knowledgebase/topics/19280-country->
47
48 598 classification (accessed 17 Dec 2017).
49
50 599 23 Gajic O, Dabbagh O, Park PK, *et al*. Early identification of patients at risk of acute
51 lung injury: evaluation of lung injury prediction score in a multicenter cohort study.
52
53 600
54
55 601 *Am J Respir Crit Care Med* 2011;**183**:462–70. doi:10.1164/rccm.201004-0549OC
56
57
58
59
60

- 1
2
3 602 24 The ARDS Definition Task Force*, Ranieri VM, Rubenfeld GD, *et al.* Acute
4
5 603 respiratory distress syndrome: the Berlin Definition. *JAMA J Am Med Assoc*
6
7 604 2012;**307**:1. doi:10.1001/jama.2012.5669
8
9
10 605 25 Ashizawa K, Hayashi K, Aso N, *et al.* Lobar atelectasis: diagnostic pitfalls on chest
11
12 606 radiography. *Br J Radiol* 2001;**74**:89–97. doi:10.1259/bjr.74.877.740089
13
14 607 26 Riviello ED, Kiviri W, Twagirumugabe T, *et al.* Hospital Incidence and Outcomes of
15
16 608 the Acute Respiratory Distress Syndrome Using the Kigali Modification of the
17
18 609 Berlin Definition. *Am J Respir Crit Care Med* 2016;**193**:52–9.
19
20 610 doi:10.1164/rccm.201503-0584OC
21
22
23 611 27 Rice TW, Wheeler AP, Bernard GR, *et al.* Comparison of the SpO₂/FIO₂ ratio
24
25 612 and the PaO₂/FIO₂ ratio in patients with acute lung injury or ARDS. *Chest*
26
27 613 2007;**132**:410–7. doi:10.1378/chest.07-0617
28
29
30 614 28 Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)-
31
32 615 -a metadata-driven methodology and workflow process for providing translational
33
34 616 research informatics support. *J Biomed Inform* 2009;**42**:377–81.
35
36 617 doi:10.1016/j.jbi.2008.08.010
37
38
39 618 29 Von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of
40
41 619 Observational Studies in Epidemiology (STROBE) statement: guidelines for
42
43 620 reporting observational studies. *Lancet* 2007;**370**:1453–7. doi:10.1016/S0140-
44
45 621 6736(07)61602-X
46
47
48 622 30 Euser AM, Zoccali C, Jager KJ, *et al.* Cohort Studies: Prospective versus
49
50 623 Retrospective. *Nephron Clin Pract* 2009;**113**:c214–7. doi:10.1159/000235241
51
52
53 624 31 Gajic O, Dara SI, Mendez JL, *et al.* Ventilator-associated lung injury in patients
54
55 625 without acute lung injury at the onset of mechanical ventilation. *Crit Care Med*
56
57
58
59
60

- 1
2
3 626 2004;**32**:1817–24.
4
5 627 32 Rush B, Biagioni BJ, Berger L, *et al.* Mechanical Ventilation Outcomes in Patients
6
7 628 With Pulmonary Hypertension in the United States: A National Retrospective
8
9 629 Cohort Analysis. *J Intensive Care Med* 2017;**32**:588–92.
10
11 630 doi:10.1177/0885066616653926
12
13
14 631 33 Pesaro AEP, Katz M, Katz JN, *et al.* Mechanical Ventilation and Clinical Outcomes
15
16 632 in Patients with Acute Myocardial Infarction: A Retrospective Observational Study.
17
18 633 *PLoS One* 2016;**11**:e0151302. doi:10.1371/journal.pone.0151302
19
20
21 634 34 Adhikari NKJ, Fowler RA, Bhagwanjee S, *et al.* Critical care and the global burden
22
23 635 of critical illness in adults. *Lancet (London, England)* 2010;**376**:1339–46.
24
25 636 doi:10.1016/S0140-6736(10)60446-1
26
27
28 637 35 Arabi YM, Phua J, Koh Y, *et al.* Structure, Organization, and Delivery of Critical
29
30 638 Care in Asian ICUs*. *Crit Care Med* 2016;**44**:e940–8.
31
32 639 doi:10.1097/CCM.0000000000001854
33
34
35 640 36 Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, *et al.*
36
37 641 Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes
38
39 642 for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *N Engl J Med*
40
41 643 2000;**342**:1301–8. doi:10.1056/NEJM200005043421801
42
43
44 644 37 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome
45
46 645 (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, *et al.* Comparison
47
48 646 of two fluid-management strategies in acute lung injury. *N Engl J Med*
49
50 647 2006;**354**:2564–75. doi:10.1056/NEJMoa062200
51
52
53 648 38 Girard TD, Kress JP, Fuchs BD, *et al.* Efficacy and safety of a paired sedation and
54
55 649 ventilator weaning protocol for mechanically ventilated patients in intensive care
56
57
58
59
60

- 1
2
3 650 (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*
4
5 651 (*London, England*) 2008;**371**:126–34. doi:10.1016/S0140-6736(08)60105-1
6
7 652 39 Esteban A, Frutos-Vivar F, Muriel A, *et al.* Evolution of Mortality over Time in
8
9 Patients Receiving Mechanical Ventilation. *Am J Respir Crit Care Med*
10 653
11 2013;**188**:220–30. doi:10.1164/rccm.201212-2169OC
12 654
13
14 655 40 Gajic O, Dabbagh O, Park PK, *et al.* Early Identification of Patients at Risk of
15
16 Acute Lung Injury: Evaluation of Lung Injury Prediction Score in a Multicenter
17 656
18 Cohort Study. *Am J Respir Crit Care Med* 2010;;1–33. doi:10.1164/rccm.201004-
19 657
20 0549OC
21 658
22
23 659 41 Festic E, Kor DJ, Gajic O. Prevention of acute respiratory distress syndrome. *Curr*
24
25 *Opin Crit Care* 2015;**21**:82–90. doi:10.1097/MCC.000000000000174
26 660
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28 661
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30 662
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3 663 **FIGURE LEGENDS**
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5 664 **Figure 1:** Flowchart of inclusion of PRoVENT-iMIC
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7 665 Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS,
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10 666 Acute Respiratory Distress Syndrome.
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14 668 **Figure 2.** Sequence of data submission in the electronic case report form
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16 669 Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS,
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19 670 Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU,
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21 671 Intensive Care Unit.
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674 **Table 1.** Lung Injury Prediction Score (LIPS) calculation worksheet^{17,34}
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Predisposing Conditions	Score	Risk Modifiers	Score
Shock	2	Alcohol Abuse	1
Aspiration	2	BMI > 30 kg/m ²	1
Sepsis	1	Hypoalbuminemia	1
Pneumonia	1.5	Chemotherapy	1
High-Risk Surgery		FiO ₂ > 0.35 (> 4 l/min)	2
Orthopedic Spine	1	RR > 30 bpm	1.5
Acute Abdomen	2	SpO ₂ < 95%	1
Cardiac	2.5	Acidosis (pH < 7.35)	1.5
Aortic Vascular	3.5	Diabetes Mellitus*	- 1
Emergency surgery	1.5		
High-Risk Trauma			
Traumatic Brain Injury	2		
Smoke Inhalation	2		
Near-Drowning	2		
Lung Contusion	1.5		
Multiple Fractures	1.5		

676 Abbreviations: BMI, body mass index; FiO₂, fraction of inspired oxygen; RR, respiratory
 677 rate; SpO₂, pulse oximetry oxygen saturation.

678 *(To consider only in septic patients)
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680 **Table 2a. The Berlin definition of ARDS**

Criteria	Definition		
Time	Within one week of a known clinical insult, or new/worsening respiratory symptoms		
Chest imaging ¹	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules		
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic oedema if no risk factor present (e.g., echocardiography)		
Oxygenation ²	Mild	Moderate	Severe
	200 < PaO ₂ /FiO ₂ ≤ 300	100 < PaO ₂ /FiO ₂ ≤ 200	PaO ₂ /FiO ₂ ≤ 100
	PEEP or CPAP ³ ≥ 5 cm H ₂ O	PEEP ≥ 5 cm H ₂ O	PEEP ≥ 5 cm H ₂ O

Abbreviations: ARDS, acute respiratory distress syndrome; PaO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

¹chest X-ray or CT scan; ²if altitude higher than 1,000 meters, correction factor should be made as follows: PaO₂/FiO₂ x (barometric pressure/760); ³this may be delivered noninvasively in the mild acute respiratory distress syndrome

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683 **Table 2b. Alternative Oxygenation criteria (if PaO₂ data unavailable)**
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Criteria	Mild ARDS	Moderate ARDS	Severe ARDS
Oxygenation	235 < SpO ₂ /FiO ₂ ≤ 315	150 < SpO ₂ /FiO ₂ ≤ 235	SpO ₂ /FiO ₂ ≤ 150
	PEEP or CPAP ≥ 5 cmH ₂ O	PEEP ≥ 5 cmH ₂ O	PEEP ≥ 5 cmH ₂ O

685 Abbreviations: SpO₂, pulse oximetry oxygen saturation; FiO₂, fraction of inspired oxygen

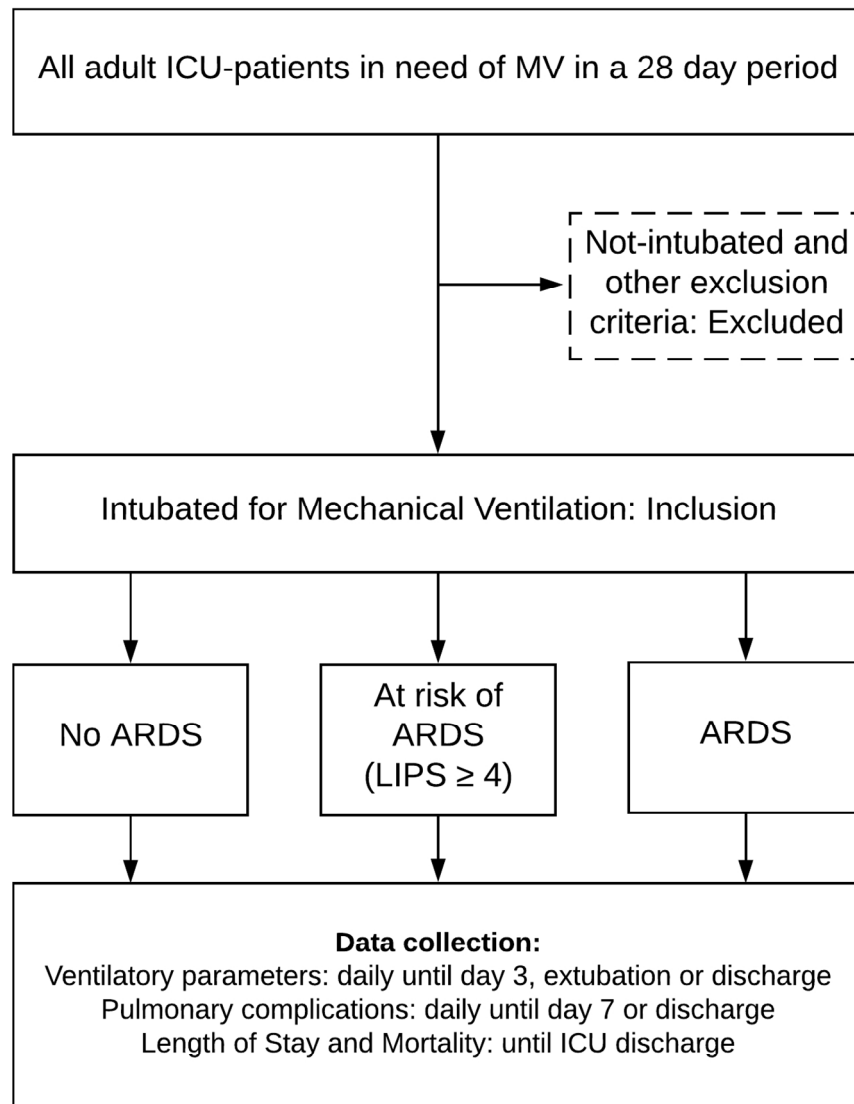


Figure 1. Flowchart of inclusion of PROVENT-iMIC[†]. Abbreviations: MV, Mechanical Ventilation; LIPS, Lung Injury Prediction Score; ARDS, Acute Respiratory Distress Syndrome.[†]

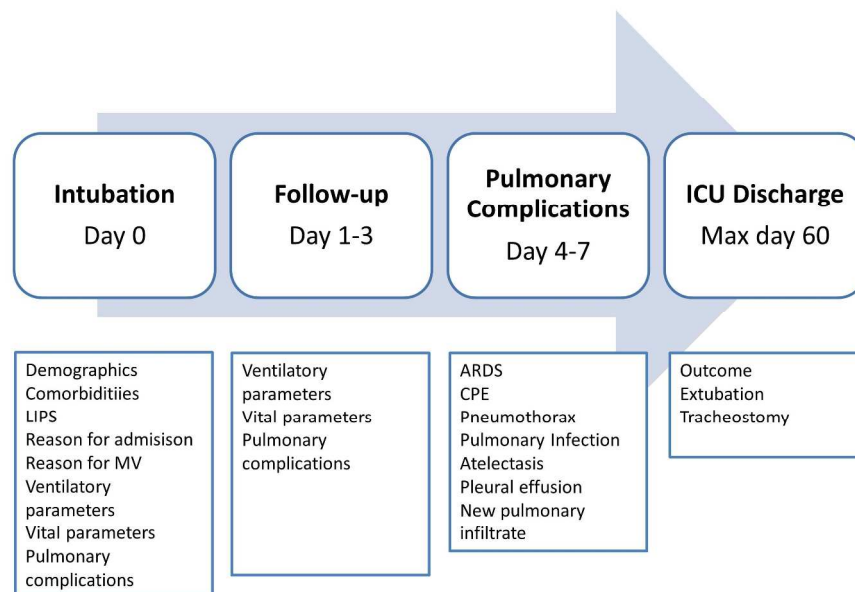


Figure 2. Sequence of data submission in the electronic case report form!! †. Abbreviations: LIPS, Lung Injury Prediction Score; MV, mechanical ventilation, ARDS, Acute Respiratory Distress Syndrome; CPE, cardiogenic pulmonary oedema; ICU, Intensive Care Unit. !! †

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