Study Protocol and Statistical Analysis Plan

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Assessing the Effectiveness of Low Tidal Volume and Low Driving Pressure in Mechanically Ventilated Severe Hypoxemic Patients: a Multicenter Emulated Target Trial

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1. Background

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening syndrome characterized by severe hypoxemia, opacities on chest imaging, increased permeability, and histological damage due to lung inflammation, (Berlin PMID: 22797452; Matthay PMID: 37487152). Mechanical ventilation is needed to provide oxygen, to maintain adequate ventilation, and to reduce the work of breathing (Thompson PMID: 28792873). Early ventilatory strategies focused on high tidal volumes (V_T) and airway pressures to "normalize" arterial blood gases (Pontoppidan PMID: 14328102; Kumar PMID: 4921310).

Later, experimental (Trambley PMID: 9062352), and clinical (Ranieri PMID: 10404912) studies demonstrated that such ventilatory approaches worsened inflammation, permeability, and histological damage (Ventilator-Induced Lung Injury: VILI) (Slutsky PMID: 24283226). A multicenter randomized clinical trial (RCT) demonstrated that the use of a "lower" V_T (6 mL/kg of predicted body weight) compared to a traditional higher V_T (12 ml/kg of predicted body weight) significantly reduced mortality from 40 %, to 31% (ARDSnet PMID: 10793162). Although, the use of 6 ml/kg was not shown to be superior to anything in between 11 and 6 ml/kg (Tobin PMID: 34186011), and the V_T of the control group (12 ml/kg) has been suggested to be higher than routine treatment and potentially harmful (Eichacker PMID: 12406836**),** the V_T of 6 mL/kg has been proposed as the standard of care (Fan PMID: 28459336).

However, a recent guideline concluded that the use of "lower" V_T (i.e., 4–8 ml/kg) is not supported by statistical significance (Grasselli PMID: 37326646). Moreover, it has been suggested that setting V_T in terms of "milliliters per kilogram of predicted body weight" to normalize V_T to lung size may be misleading (Amato PMID: 25693014; Goligher PMID: 33439781) since it ignores that in patients with ARDS, the proportion of lung available for ventilation is markedly decreased as reflected by lower compliance of the respiratory system [(C_{RS} = V_T / end-inspiratory plateau pressure (P_{PLAT}) - positive end-expiratory pressure (PEEP)] (Gattinoni: PMID: 15812622; Terragni: PMID: 17038660).

In order to scale V_T to C_{RS}, Amato and coworkers calculated driving pressure ($\Delta P = V_T/C_{RS}$) and, analyzing 3562 patients previously enrolled in RCTs, showed that the favorable effects of randomly assigned reductions in V_T depended only on their association with a decrease in ΔP (Amato PMID: 25693014). Goligher and coworkers performed a secondary analysis of 1202 patients included in previously performed RCTs and confirmed Amato's observation suggesting that lung protective ventilation strategies should primarily target ΔP rather than V_T (Goligher PMID: 33439781).

Randomized controlled trials (RCTs) are the gold standard for causal inference (Bhatt PMID: 21829774). However, syndromes such as ARDS pose challenges for RCTs (Legrand PMID: 30303091; Laffey PMID: 30061048; Tonelli PMID: 24667919). Use of observational data to simulate RCT is a recognized method for assessing the effectiveness of a treatment within a real-world, uncontrolled context (Hernan PMID: 34596980; Hernan PMID: 36508210) that may be especially valuable when conducting RCTs is challenging (Dickerman PMID: 31591592; Wang PMID: 37097356).

2. Objectives

The present study set up to answer two questions: (a) “how low V_T must be to provide protective ventilatory settings able to minimize the risk of death due to VILI?”; (b) “if protection from VILI is better achieved by targeting ΔP instead of V_T, what is the optimal target for Δ*P*?”. Solving these questions is pivotal for clinicians to personalized and precise mechanical ventilation practices to reduce the risk of VILI and avoid unnecessary risks associated to protective ventilatory settings (Spece PMID: 29073535; Mikkelsen PMID: 18364057; Pohlman PMID**:** 18824913). Data will be used to obtain the dose-response curve of *lower* V_T and *lower* Δ*P* in mechanically ventilated patients with acute severe hypoxemia.

In a first emulated target trial, we assess ICU mortality in patients undergoing a protective ventilatory approach, targeting various *lower* V_T. In a subsequent emulated target trial, we assessed ICU mortality in patients subjected to a protective ventilatory strategy that targeted varying levels of *lower* Δ*P*. Design and analysis of the emulated target trials were made in order to be as structured, transparent, and reproducible as possible. Comparative outcome analyses were conducted after the final emulated target trials protocol have been fully specified and registered on ClinicalTrials.gov.

3. Study design

Multicentric observational retrospective study.

The study is made of two emulated target trials. Both "*lower VT*" and "*lower ΔP*" target trials were designed following the study design of previously conducted randomized clinical trials in the field of mechanical ventilation (ARDSnet PMID: 10793162; Brower: PMID: 15269312) and ARDS (*DOI: 10.1164/rccm.201012-2090OC; DOI: 10.1056/NEJMoa1901686; DOI: 10.1056/NEJ-Moa1401520*).

We used all consecutive adult patients diagnosed with hypoxemic respiratory failure included in the multicenter database *MargheritaTre* (M3) of the Italian Group for the Evaluation of Interventions in Intensive Care Medicine (GiViTI) (Finazzi PMID: 29972378).

3.1 Ethics

The MargheritaTre projecect was approved by the Ethics Review Board of the coordinating centre (Ospedale Maggiore, Bologna) and of all the participating centres. Informed consent was collected according to national and european regulation.

3.2 Participating centers

GiViTI is a network of about 200 Italian ICUs born in 1991, with tha aim of improving the quality of care and optimize resource utilization through benchmarking activities and research projects. The group is coordinated by the Laboratory of Clinical Data Science of the Istituto di Ricerche Farmacologiche Mario Negri IRCCS (IRFMN) and collaborates with regional, national and international universities and institutions.

In collaboration with intensivists, critical care nurses, computer scientists and data scientists, GiViTI developed the *MargheritaTre* electronic health record. The EHR serves multiple purposes: integrating medical practice, assessing the quality of care, conducting critical research projects and physio-pathological studies. *MargheritaTre* is currently in use in more than Italian 80 ICUs, of which 50 participated in the associated research project, receiving Ethics approval and sending data to the GiViTI coordinating centre.

4. Data collection

4.1 Software architecture

M3 has a client/server architecture, with one server per ICU, installed in the internal network of each hospital. Clients are typically installed on bedside computers and at control desks. They have a modular graphical interface that allows doctors and nurses to input and visualize data for diagnosis, therapies, laboratory tests, etc. Automatic services import data from monitors, devices, and from the hospital information system and save them in the database through the server. To ensure proper data protection, clinical data patients' direct identifiers, such as name, surname, birth date, social security number are stored in separated databases.

From each server, only the database containing clinical data is sent in a pseudonymized form to a dedicated server of IRFMN. The database with personal direct identifiers is not transferred. Thus, this information is not accessible for the study by software design. In the IRFMN database, each patient's record has a sequential identification code that is unique to each admission and not derived from direct identifiers.

In accordance with the European regulation 2016/679 for the protection of data (GDPR), the data controller for the M3 research project is IRFMN, which is responsible for management and analyses.

4.2 Database description

The M3 database at IRFMN contains records of more than 140,000 ICU admissions from 50 ICUs. Data are stored in a relational PostgresSQL database containing more than 150 tables. To ease data analysis, information is organized in about 20 views, each corresponding to a single aspect of patients' clinical management (e.g., vital signs, laboratory tests, drug administration, nutrition, etc...).

The database contains about 10^8 clinical notes, 10^8 values of vital signs, 10^7 laboratory tests, 10^7 drug administrations. A complete description of the size of each view is reported in Table 1 of Finazzi PMID: 29972378).

4.3 Data quality

The M3 software architecture and the development procedures are designed to ensure quality and uniformity of data.

M3 does not allow for ICU-specific customization of the database structure and of the collected variables. Any modification to the software must be evaluated by the M3 study group and by the coordinating center before implementation. Approved changes are then released to all ICUs.

Most information is stored by M3 in structured form (see Table 1 in Finazzi PMID: 29972378): vital signs from ICU monitors, results of blood gas analyses and laboratory tests, pharmacological

therapies, procedures and treatments, nursing activities, infections, organ failures, injuries. To facilitate data analysis, clinical notes, anamnesis, and epicrisis are a partially structured: notes can be composes by selecting tags from a list of about 500 keywords and integrated with free-text.

To prevent input errors, most information is automatically imported from monitors, devices, and laboratory informative systems. All data are validated by either doctors or nurses to minimize the presence of artifacts and ensure that only clinically relevant information is stored in the database.

5. Study population

Target Trial

Inclusion criteria: (a) age ≥18 years; (b) invasive mechanical ventilation for ≤96 hours; (c) presence of all the followings for ≤ 24 hours: (i) severe hypoxemia as identified by arterial oxygen tension (PaO2) to inspiratory oxygen fraction (FiO2) ratio (P/F) ≤ 300 mmHg; (ii) hypoxemia developed within one week of a known clinical insult and not fully explained by cardiac failure or fluid overload (Berlin PMID: 22797452; Matthay PMID: 37487152). *Exclusion criteria*: pregnancy; New York Heart Association Class IV; acute coronary syndrome; severe COPD; chronic respiratory insufficiency with home ventilation or oxygen therapy; chronic liver disease; patients were receiving ECMO therapy; acute brain injury; patients were moribund and/or clinician decided to limit therapeutic interventions; poorly controlled neoplasm; patients transferred from other ICUs; patients transferred to the ICU from the Emergency Department after a duration exceeding 24 hours in the Emergency Department. The latter criteria ensure that the patient has not been ventilated for more that 96 hours at randomization.

Emulated Target Trial

Inclusion and exclusion criteria are the same as in the target trial (see Table 1). Their implementation using specific variable definitions of M3 database are detailed in S2.

6. Interventions

Target Trial

Patients will be ventilated with assist/control modes of mechanical ventilation (constant flow/constant pressure) until weaning criteria are met: P/F ratio > 250 mmHg; PEEP ≤ 8 cmH2O and lower than the previous day; FiO_2 < 0.5 and lower than the previous day; systolic arterial pressure ≥ 85 mmHg (ARDSnet PMID: 10793162; Brower: PMID: 15269312).

In the *lower* V_T target trial, patients would be randomly assigned to one of these two groups:

- **VT1**: 6.0 ml/kg PBW ≤ V_T ≤ 8.0 ml/kg PBW with P_{PLAT} ≤ 30 cmH_2O;
- **VT2:** 8.0 ml/kg PBW < V_T ≤ 10.0 ml/kg PBW with P_{PLAT} ≤ 30 cmH_2O.

The value of V_T inside the range fixed by the intervention arm and positive end-expiratory pressure (PEEP) will be set according to clinical judgement.

In the *lower* Δ*P* target trial patients would be randomly assigned to one of these two Δ*P* groups:

- **ΔP1**: *7*.0 cmH_2O ≤ Δ*P* ≤ 12.0 cmH_2O with V_T ≤ 10.0 ml/kg PBW;
- **ΔP2**: 12.0 cmH_2O < Δ*P* ≤ 18.0 cmH_2O with V_T ≤ 10.0 ml/kg PBW.

The value of Δ*P* inside the range fixed by the intervention arm and positive end-expiratory pressure (PEEP) will be set according to clinical judgement.

The determination of breakpoints for defining the treatment arms was guided by analyzing the distributions of V_T and Δ*P* from the recorded observed data in *MargheritaTre*. For both treatment strategies, the 10th, 50th, and 90th percentiles of these distributions were rounded to the nearest integers. The breakpoints for V_T treatments were defined as follows: the 10th percentile (5.94 ml/kg) was rounded to 6 ml/kg, the 50th percentile (7.54 ml/kg) was rounded to 8 ml/kg, and the 90th percentile (9.99 ml/kg) was rounded to 10 ml/kg. Similarly, for Δ*P* the 10th percentile (7.45 cmH_2O) was rounded to 7 cmH2O, the 50th percentile (12.17 cmH_2O) was rounded to 12 cmH_2O, and the 90th percentile (18.29 cmH_2O) was rounded to 18 cmH2O. The rounded percentiles were hence used to define the ranges for the comparative effectiveness study.

Predicted body weight (PBW) will be calculated according to the following formulae: **PBW (Males)** = 50 + 0.91 [height (cm) -152.4]. Compliance of the respiratory system will be calculated as (C_{RS} = V_T / P_{PLAT} - PEEP) (Gattinoni: PMID: 15812622; Terragni: PMID: **17038660**). Driving pressure will be calculated as ($\Delta P = V_T/C_{RS}$).

Emulated Target Trial

To simulate patients' trajectories in the emulated *lower* V_T target trial, the value of V_T will be set according to the following algorithm:

- **VT1**
  - if the natural value of $V_T <$ 6.0 ml/kg PBW, then the intervention value will be set to 6.0 ml/kg PBW;
  - if 6.0 ml/kg PBW ≤ the natural value of $V_T \leq$ 8.0 ml/kg PBW, then the intervention value will be set equal to the natural value;
  - if the natural value of $V_T >$ 6.0 ml/kg PBW, then the intervention value will be modified set to 8.0 ml/kg PBW.
- **VT2**
  - if the natural value of $V_T \leq$ 8.0 ml/kg PBW, then the simulated value will be set to 8.0 ml/kg PBW;
  - if 8.0 ml/kg PBW < the natural value of $V_T <$ 10.0 ml/kg PBW, then the simulated value will be set equal to the natural value;
  - if the natural value of $V_T \geq$ 10.0 ml/kg PBW, then the simulated value will be set to 10.0 ml/kg PBW.

In each intervention arm of the target trial, the intervention is sustained until weaning criteria are met. For instance, if in the *lower* V_T trial a patient is assigned to Arm VT1 ($6.0 \leq V_T \leq 8.0$ ml/kg PBW, with $P_{PLAT} \leq 30$ cmH_2O), the protocol prescribes that any value of V_T should be set according to clinical judgement inside the corresponding range. When weaning criteria are met, extubation may be attempted, it may either fail or not, or any other mechanical ventilation regime may be chosen, according to clinical practice.

To simulate this complex dynamic scenario, in the simulated trial we implement a dynamic intervention, where the categorical treatment variable V_T is sustained to the level corresponding to $6.0 \leq V_T \leq 8.0$ ml/kg, as above described, until weaning criteria are met. After the latter condition is satisfied, the treatment variable is allowed to follow its natural value, any other type of mechanical ventilation, or no mechanical ventilation. Accordingly, we introduce a binary variable tracing when the patient is intubated or not.

To simulate patients' trajectories in the emulated *lower* ΔP target trial, the value of ΔP will be set according to the following algorithm:

- **ΔP1**
  - if the natural value of $\Delta P <$ 7.0 cmH_2O, then the intervention value will be set to 7.0 cmH_2O;
  - if 7.0 $cmH_2O \leq$ the natural value of $\Delta P \leq$ 12.0 cmH_2O, then the intervention value will be set equal to the natural value;
  - if the natural value of $\Delta P >$ 12.0 cmH_2O, then the intervention value will be modified set to 12.0 cmH_2O.
- **ΔP2**
  - if the natural value of $\Delta P <$ 12.0 cmH_2O, then the intervention value will be set to 12.0 cmH_2O;
  - if 12.0 $cmH_2O \leq$ the natural value of $\Delta P \leq$ 18.0 cmH_2O, then the intervention value will be set equal to the natural value;

- if the natural value of $\Delta P > 18.0$ cmH_2O, then the intervention value will be modified set to 18.0 cmH_2O.

In each intervention arm of the target trial, the intervention is sustained until weaning criteria are met. For instance, if in the *lower* ΔP trial a patient is assigned to Arm $\Delta P1$ ($7.0 \leq \Delta P1 \leq 12.0$ cmH_2O, with $V_T \leq 10$ ml/kg PBW), the protocol prescribes that any value of ΔP should be set according to clinical judgement inside the corresponding range. When weaning criteria are met, extubation may be attempted, it may either fail or not, or any other mechanical ventilation regime may be chosen, according to clinical practice.
To simulate this complex dynamic scenario, in the simulated trial we implement a dynamic intervention, where the categorical treatment variable ΔP is sustained to the level corresponding to $7.0 \leq \Delta P \leq 12.0$ cmH_2O, as above described, until weaning criteria are met. After the latter condition is satisfied, the treatment variable is allowed to follow its natural value, any other type of mechanical ventilation, or no mechanical ventilation. Accordingly, we introduce a binary variable tracing when the patient is intubated or not.

7. Outcomes

Target Trial

Primary endpoint: ICU all-cause mortality. All patients will be classified as either alive if "alive at ICU discharge" or dead if "dead at ICU discharge".

Secondary endpoint: Number of ventilator-free days (VFDs) during the 14 days in ICU immediately after randomization. Number of days of unassisted breathing to ICU discharge day after randomization, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing.

If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to ICU discharge day, VFDs will be counted from the end of the last period of assisted breathing to ICU discharge day unless a period of assisted breathing was less than 24 hours, and the purpose of assisted breathing was a surgical procedure. If a patient dies prior to end of follow-up or is still receiving assisted breathing at the end of follow-up, his/her VFDs will be zero.

Unassisted breathing is defined as any of the following: spontaneously breathing with face mask, nasal prong oxygen, or room air; t-tube breathing; tracheostomy mask breathing; continuous positive airway pressure (CPAP) $\leq$ 5 cmH_2O without pressure support (PS) or invasive mechanical ventilation (IMV) assistance; use of CPAP or bilevel positive airway pressure (BIPAP) solely for sleep apnea management.

Emulated Target Trial

The primary endpoint is defined as in the target trial. To compute the secondary end-point, ventilator free days are computed from the dataset of the simulated trajectories. Follow-up time is 14 days after randomization. The follow-up time is limited to 14 days to guarantee that a non-negligible fraction of patients is not dead or discharged from ICU before the end of follow-up.

8. Statistical methods

8.1 Statistical analyses

Target Trial

Primary analysis. Intention-to-treat analysis would be conducted comparing primary and secondary outcome variables among the different V_T and ΔP groups using the chi-squared and Mann-Whitney test for mortality and VFD, respectively.

In per-protocol analysis patients would be censored when they deviated from their assigned strategy. The per-protocol effect would be estimated after adjustment for baseline variables and for time-varying variables associated with adherence to a ventilation strategy according the treatment arms. Mortality will be adjusted using a multivariate logistic regression model including variables the following variables: age, risk of death according to the SAPS score at admission, arterial pH and P/F ratio at study entry (Amato PMID: 25693014).

Secondary analysis. Two secondary analysis will be conducted to (1) determine a dose-response relationship, relating the magnitude of a dose of the intervention (the V_T and ΔP level) to the clinical response (the primary and secondary endpoints described above), and (2) compare which is the best policy, between fixing V_T versus fixing ΔP. Best policy is defined as the one with best treatment effect among those used in intervention arms.

Analysis of dose–response relationships will be investigated using marginal structural models (MSM) with inverse probability of treatment weighting (IPTW) (Lipkovich: PMID: 18179713; Lipkovich: PMID: 23060290) and with dynamic linear mixed-effects models (DLME) (Xu Steven Xu: PMID: 22407972).

Sensitivity analyses. The robustness of the result will be assessed though sensitivity analyses as listed in Table 1.

Emulated Target Trial

Primary analysis. The effect size of interventions on ICU mortality will be evaluated by *g*-estimation methods (McGrath: PMID: 32656541), which allow to estimate the risk of the outcome as if everybody in the population received the same intervention. Replicating the analysis for each intervention arm and for the natural course, one can obtain the counterfactual outcome corresponding to each intervention, evaluated on the same population.

G-estimation methods require the evaluation of complex multidimensional integrals, that can be computed through Montecarlo techniques. For each intervention arm, starting from the same baseline conditions, we shall simulate patients histories and evaluate the risk of the outcome for each history. Finally, the average risk for each arm is computed by averaging this results over all the histories.

Patients histories are simulated by sampling covariates' values, treatments, and outcomes at every follow-up time from proper joint statistical distributions, conditioned to past values of covariates

and treatments. We shall estimate those conditional distributions through parametric regression analysis (e.g., generalized linear models).

The first step of the simulation is the initializations of baseline conditions for the simulated trajectories. This step is common to all interventions arms, in order to evaluate effect sizes of every intervention on the same population. For each simulated trajectory we randomly extract one patient from the observed dataset and baseline values of covariates are set to the baseline values of this observed patient.

Second, for each intervention arm, trajectories are simulated starting from these initial conditions with an iterative algorithm, starting from the first time after baseline, t_1, and iterating over times up to the last follow-up time. The values of patients' covariates and treatments at each time $t = t_i$ are sampled from joint statistical distributions conditioned to the values assumed by those variables at times $t < t_i$.

At each time step of the simulation it is possible to modify the value the treatment would have naturally assumed under clinical practice, replacing it with the value prescribed by the protocol of the clinical trial for the considered intervention arm. Using the simulated values of the covariates at $t = t_i$ and the possibly modified value of the treatment, one can compute the risk to the outcome at $t = t_{i+1}$ and simulate the outcome, by sampling from a Bernoulli distribution. If the simulated outcome is dead the trajectory is ended, otherwise it will be prolonged, repeating the same procedure for $t = t_{i+1}$.

We shall compute 95% confidence intervals by boostrap analysis with at least 500 samples.

The effect on the secondary endpoint will be computed from the datasets of the simulated trajectories for the four interventions.

Secondary analyses. Dose response curves will be constructed using g-estimation methods for continuous treatments. For a given V_T or ΔP, we define a dynamic intervention by setting either the treatment V_T or ΔP to the intervention value until weaning criteria are satisfied. After that the natural course is followed.

The optimal strategy between fixing V_T or ΔP will be identified by comparing the average effect sizes evaluated for the primary analysis in the two emulated target trials.

Sensitivity analyses. The same sensitivity analyses listed for the target trial will be performed in the emulated trial. In addition, the same study design (inclusion and exclusion criteria) and data analysis applied to the Toronto data set (Urner: PMID: 36971437).

8.2 Sample size

Target Trial

Lower V_T target trial.

A previous randomized clinical trial showed an approximately 10% drop of mortality rate reducing V_T from 12 ml/kg PBW to 6 ml/kg PBW (from 40% to 30%, respectively) (ARDSnet PMID: 10793162). Hager and coworkers showed a linear relationship between P_{PLAT} and outcome (Hager: PMID: 16081547). Assuming the relationship between V_T and P_{PLAT} is linear we estimated a 2%

change in mortality rate for every ml/kg PBW change of V_T. Assuming the mortality of the 6.0-8.0 ml/kg PBW group to be around 30% (ARDSnet PMID: 10793162), we expected an increase in mortality to 34% with a V_T > 8 ml/kg PBW.

Using chi-squared test on the contingency table, a sample size of about 4300 patients would be required to detect at least one difference among the three groups with power of 80% and and type-I error of 5% (Cohen, Statistical Power Analysis for the Behavioral Sciences).

Lower ΔP target trial.

A pilot randomized clinical trial showed an approximately 16% reduction of mortality rate reducing Δ*P* from 15 cmH_2O to 10 cmH_2O (from 53% to 37%, respectively) (Pereira Romano: PMID: 32069068). Since Amato and coworkers showed that a change of slope in the relationship between ΔP and risk of death occurs at a value of Δ*P* of approximately 15 cmH_2O (Amato PMID: 25693014), we estimated a 3% change in mortality rate for every cmH_2O change of Δ*P*. Assuming the mortality of the > 12 cmH_2O group to be around 53%, we expected a reduction in mortality rate to 44%, with a 7 cmH_2O < Δ*P* ≤ 12 cmH_2O.

Using chi-squared test on the contingency table, a sample size of about 1000 patients would be required to detect at least one difference among the three groups with power of 80% and error I type of 5%.

Emulated Target Trial

We expect that to properly estimate effect size in either *lower* V_T or *lower* Δ*P* emulated trials, the sample size should be the same order of magnitude as the corresponding randomized trials. According to these considerations, 4300 patients, i.e., 2150 patients per arm, would be sufficient to detect possible differences in the primary outcome.

While in a real randomized controlled trial each patient undergoes a single intervention, in the emulated trial the counterfactual outcomes corresponding to all interventions are simulated for every patient.

However, this is possible only if the observed dataset contains enough information to explore the full space of treatments considered in the intervention arms, as required by the summation over histories in the *g*-computation, that is if there is enough variability in the treatments in the observed datasets.

For these considerations, it is not possible to precisely estimate the required sample size. Nevertheless we may argue that, if in the observed dataset, the numbers of patients receiving treatment in the range of VT1 and VT2 (ΔP1 and ΔP2, respectively) are comparable the required order of magnitude is about 4300 patients.

8.3 Feasibility analysis of the emulated target trial

Feasibility analyses of the *lower* V_T and of the *lower* ΔP emulated trials were performed (a) drawing CONSORT diagram table for cohort inclusion and exclusion criteria; (b) tabulating follow-up times for each treatment group (c) tabulating patient characteristics by treatment group, including balance metrics; (d) tabulating the number of overall outcome events (with no exposure-specific event counts or rates). The initial power analysis was conducted after preliminary 1:1 high dimensional propensity score matching (Schneeweiss: PMID: 19487948) based on age, risk of death according to the SAPS score at admission, arterial pH and P/F ratio at study entry (Amato PMID: 25693014).

8.4 Statistical tools

All the analyses will be performed with R software. *g*-estimation method will be implemented using the package gfoRmula.

Table 1. Summary of protocols of target trial and emulated target trial.

	TARGET TRIAL	TARGET TRIAL EMULATION
Inclusion Criteria	ALL THE FOLLOWINGS: (a) age ≥ 18 years. (b) all the following conditions present continuously for 24 hours commencing within 36 hours of ICU admission, while the patient is undergoing invasive mechanical ventilation in either flow or pressure-regulated assist/controlled modes: a. arterial oxygen tension (PaO2) to inspiratory oxygen fraction (FiO2) ratio P/F ≤ 300 mmHg b. hypoxemia developed within one week of a known clinical insult c. hypoxemia not fully explained by cardiac failure or fluid overload*	(a) same as TT (b) same as TT*
Exclusion Criteria	ANY OF THE FOLLOWINGS: (a) pregnancy (b) expected duration of mechanical ventilation < 48h (c) severe or moderate COPD (d) chronic liver disease (e) acute brain injury (f) patient admitted for palliative sedation (g) tumor with metastases (h) prior cardiac arrest (i) New York Heart Association Class IV (j) acute coronary syndrome (k) patients transferred from other ICUs (l) patients transferred to the ICU from the Emergency Department after a duration exceeding 24 hours in the Emergency Department (m) patients on Pressure Support Ventilation and/or patients in whom end-inspiratory plateau pressure was not measured	(a) same as TT* (b) same as TT* (c) same as TT* (d) same as TT* (e) same as TT* (f) same as TT* (g) same as TT* (h) same as TT* (i) same as TT*
Treatment strategies	Mode of mechanical ventilation: constant flow/constant pressure, assist/control; RR up to 35 bpm. PEEP will be set according to clinical judgement. Predicted Body Weight (PBW) will be calculated according to the following formulae: **PBW (Males)** = 50+0.91 [height (cm)-152.4]; **PBW (Females)** = 45.5 + 0.91 height (cm)-152.4]. Oxygenation Goal: PaO_2 55-80 mmHg or SpO_2 88-95%; Arterial pH Goal: 7.30-7.45. ***TIDAL VOLUME GUIDED PROTECTIVE VENTILATION*** Tidal volume (V_T) will be set to: **Arm VT 1.** V_T 6.0-8.0 ml/kg PBW with $P_{PLAT} \leq 30$ cmH_2O; **Arm VT 2.** V_T 8.0-10.0 ml/kg PBW with $P_{PLAT} \leq 30$ cmH_2O. ***DRIVING PRESSURE GUIDED PROTECTIVE VENTILATION*** Driving pressure (ΔP) will be set to: **Arm ΔP1.** 7.0-12.0 cmH_2O with $V_T \leq 10.0$ ml/kg PBW; **Arm ΔP2.** 12.0- 18.0 cmH_2O with $V_T \leq 10.0$ ml/kg PBW. The value of V_T and ΔP in the corresponding arm interval is chosen according to clinical judgement. Intervention will be maintained until the patient will be considered eligible for respiratory weaning when all the following criteria will be met: • (P/F) > 250 mmHg • PEEP ≤ 8 cmH_2O and lower than the previous day • FiO_2 < 0.5 and lower than the previous day	**Simulated interventions** For each treatment arm, the value of the continuous variable V_T (ΔP, respectively) is set equal to its natural value if the natural value is inside the range of the corresponding arm. Otherwise, it is set equal to the value at of the edge of the range which is closer to the natural value (e,g. For VT1, if the natural value of V_T is lower than 6 ml/kg PBW, the intervention value is set to 6 ml/kg PBW; if the natural value is greater than 8 ml/kg PBW, the intervention value is set to 8 ml/kg PBW), Treatment corresponding to the TT intervention is maintained until patient is eligible for respiratory weaning, then the natural value of treatment is applied (either no mechanical ventilation or ventilation with natural value of V_T or ΔP.

	• systolic arterial pressure ≥ 85 mmHg	
Treatment assignment	Randomization	Simulation of dynamic interventions on the same population
Primary End-Point	**ICU all-cause mortality:** All patients will be classified as either alive if *alive at ICU discharge* or dead if *dead during ICU stay*	Same as TT
Secondary End-Point	**Number of ventilator free-days during follow-up**	Same as TT
Secondary Analysis	• Dose response curve for V_T and ΔP • Comparison of best policy with fixed V_T versus best policy with fixed ΔP. Best policy is defined as the one with best treatment effect among those used in intervention arms.	• Treatment effect computed simulating a modified treatment policy with constant V_T and ΔP, respectively until conditions for weaning are satisfied, then natural value of treatment • Same as TT
Follow up	14 days after randomization	Same as TT
Causal Contrasts	**Intention-to-treat effect** Effect on study outcomes will be analyzed in those patients that were assigned to the treatment arm. **Per-protocol effect** Effect on study outcomes will be analyzed in those patients that effectively received the treatment (either tidal volume or driving pressure).	**Observation analogue of per-protocol effect** Effect on study outcomes will be analyzed using simulated treatment strategies.
Statistical Analysis	In the per-protocol analysis, patients will be censored when they deviated from their assigned strategy. The per-protocol effect will be estimated after adjustment for baseline variables and for time-varying variables associated with adherence to a ventilation strategy according the treatment arms. Subgroup analysis by previously selected baseline clinical (age, severity of ARDS, SAPS and SOFA scores) and physiological (quartiles of compliance, driving pressure, Plateau Pressure, ventilatory index) variables.	The per-protocol effect under full adherence will be estimated using the g-estimation methods. The value of each density function for all possible covariate histories was estimated under parametric modeling assumptions. **Confounders** **baseline:** demographics, comorbidities (Charlson Index), respiratory and cardiovascular components of SOFA scores at ICU admission. **time varying:** P/F, PEEP, FiO_2, SaO_2, respiratory frequency, and systolic pressure. **Competing events** ICU discharge prior to end of follow-up Subgroup analysis same as the target trial
Sensitivity Analysis	• Same inclusion criteria but no exclusion criteria • patients satisfying radiological criteria for ARDS • patients ventilated in flow regulated assist/controlled modes vs. patients ventilated with pressure-regulated assist/controlled modes • P/F 300-200 vs. P/F 200-100 vs. P/F < 100 • quartiles of static compliance • quartiles of dynamic compliance • quartiles of peak pressure • quartiles of static pressure • quartiles of mechanical power • presence of inclusion criteria (c) starting from within 12 hours from ICU admission	• Same as TT

* see Appendix.

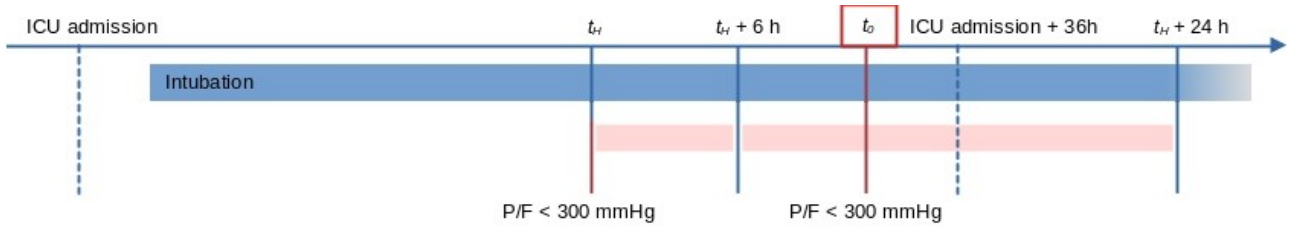
Appendix

Implementation of inclusion and exclusion criteria in the emulated target trial in the database MargheritaTre

Inclusion criteria

Inclusion criterion (c) was modified as follows to ensure that the patient is hypoxemic for 24 h starting within 36 h from ICU admission.
We defined t_H as the first time at which the P/F value $\leq$ 300 mmHg within 36 h from ICU admission while patient is intubated. Inclusion criteria are considered satisfied if there is at least one value of P/F $\leq$ 300 mmHg between t_H + 6h and t_H + 24h. See Fig. S2.1. If there is such a time where hypoxia is confirmed, the patients is eligible for the study and can be enrolled. The time of hypoxia confirmation it defined as t_0.

Figure A.1: Graphical representation of inclusion criterion (c) for hypoxemia



Exclusion criteria

Expected duration of mechanical ventilation < 48h was implemented by excluding patients admitted for monitoring/weaning from ventilation after surgery.

Patients with one of the following comorbidities or diagnoses at ICU admission were excluded

Comorbidities

ALS
Asthma
Bronchodysplasia
Chronic obstructive pulmonary disease (COPD) moderate
Chronic obstructive pulmonary disease (COPD) severe
Congenital heart disease
Heart failure NYHA class 4
Infarction
Moderate or severe liver disease
Moderate chronic pneumopathy
Myocardial infarction
Myocardiopathy
Myocarditis
Neuromuscular/neurodegenerative disease
Non-congenital valvulopathy

Pulmonary hypertension
Restrictive lung disease
Severe chronic pneumopathy
Tumor with metastases
Valvulopathy

Diagnoses at ICU admission

Abnormalities of pulmonary venous return
Abnormalities of thoracic veins and arteries
Abnormalities of systemic veins
Acute cardiac ischemia
Acute congenital valvulopathy
Acute myocardial infarction
Anterior AMI
Anterolateral AMI
Inferior AMI
Inferolateral AMI
Inferoposterior AMI
Lateral AMI
Posterior AMI
Aortic valve failure
ASD ostium primum
Cardiogenic pulmonary edema
Cardiomegaly
Chronic cardiac ischemia
Chronic obstructive asthma with exacerbation
Chronic obstructive bronchitis with exacerbation
Coma from other causes
Congestive heart failure
COPD
Coronaropathy
Dilated cardiomyopathy
Dysfunction of prosthetic valve
Extrinsic asthma
Extrinsic asthma with asthmatic status
Extrinsic asthma with exacerbation
Hypertensive cardiomyopathy
Hypertensive heart disease with congestive failure
Intrinsic asthma
Intrinsic asthma with asthmatic status
Intrinsic asthma with flare-up
Ischemic heart disease
Left heart failure
Left/right heart abnormalities
Malignant tumors, lung
Mitral valve insufficiency
NSTEMI
Patent Foramen Ovale / ASD ostium secundum
Pericardial effusion (nontraumatic)
Pregnancy, other specified complications

Primary dilated cardiomyopathy
Primary pulmonary hypertension
Pulmonary emphysema
Pulmonary fibrosis
Pulmonary hypertension secondary to valvulopathy
Pulmonary metastases
Pulmonary valve disorders
Secondary cardiomyopathy
Septal defects
Single ventricle
Toxic coma
Transposition of the Great Arteries (TGA)
Tricuspid valve disorders
VSD (ventricular septal defect)