



WorldwidE AssessmeNt of Separation of pAtients From ventilatory assistancE (WEAN SAFE STUDY)  
**Study protocol**

**Proponent:** The study is proposed by the Acute Respiratory Failure Section of the European Society of Intensive Care Medicine (ESICM), is endorsed by ESICM and supported by ESICM Trials Group.

**Study design:** Prospective, observational, multi-center, international cohort study

**Steering Committee:**

Giacomo Bellani (Co-Principal Investigator)

John Laffey (Co-Principal Investigator)

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Laurent Brochard

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+ Prospectively: top 2 recruiting countries (normalized by population) and top 2 recruiting countries (absolute value) will be invited to join the steering committee for data analysis, manuscript drafting, etc.

**Executive Committee:** Giacomo Bellani, John Laffey, Tàì Pham, Leo Heunks, Laurent Brochard

**National Coordinators:** National Coordinators are will be that of recruiting centers in your country, facilitating communication of centers with the steering committee (and vice-versa), supporting centers with site activation, eCRF access and patient recruitment.

A complete list of National Coordinators can be found in the Annex.

**Key Achievements to Date:**

- October 2016: Presentation of the study at LIVES 2016 in Milan during the ARF section meeting
- November 2016: application to ESICM for endorsement and use of eCRF
- March 2017: Inaugural Investigator meeting at ISICEM 2017
- May 2017: Confirmation of ESICM Trials Group support for WEAN SAFE
- May 2017: Confirmation of National Coordinators; Start of center recruitment
- Spring - Summer 2017: Finalization of study protocol/paper CRF and development of eCRF
- September - October 2017: Second investigator meeting at LIVES 2017; Formal study launch

**Next steps - Projected Timeline:**

- October 2017 – March 2018: Patient recruitment window
- Summer 2018: Initial data analysis
- October 2018: Presentation of initial analyses at LIVES 2018

## Background:

Successful weaning of patients from invasive mechanical ventilation represents a crucial step in the recovery process following severe respiratory failure [1-3], and is a key clinical challenge for ICU clinicians. Many of the serious complications of IMV are directly related to the duration of ventilation [4, 5]. Failure to successfully separate patients from IMV contributes directly to poorer patient outcomes: including longer duration of ventilation, longer length of stay in the ICU and in the hospital, and higher patient mortality [6, 7]. Patients spend a considerable amount of time in being liberated from invasive mechanical ventilation. The systematic utilization of approaches to reduce the duration of ventilation are therefore of fundamental importance [8-10].

Despite the importance of the weaning period, this process is not rigorously defined, with wide variations in definitions and practices. In addition, the specific impact of weaning difficulties on patient outcomes is still poorly understood. While guidelines do exist on the classification of weaning, a key recent study has shown that these are not applicable to all patients [11]. Moreover different practices exist in regard to weaning procedures and some confusion exists even in what should be considered the beginning of weaning process. This is an important problem, because general recommendations regarding the entire weaning process may encompass completely different causes and consequences of its prolongation and therefore may be totally inappropriate for individual patients.

The WEAN SAFE study will aim to address key issues relating to weaning from invasive MV. WEAN SAFE will have a structure similar to LUNG SAFE [12], in that a large set of patients receiving invasive MV will be enrolled, without setting “weaning” as an inclusion criterion, but rather attempting to identify the weaning process “retrospectively”.

## Study Objectives:

Although there are published guidelines about when and how to start the weaning process, we do not know whether these recommendations are used or are feasible, what are the barriers for their implementation and what is the real life impact of an early or late weaning process for the patient.

There is also significant uncertainty about when the process of weaning from IMV is really starting, in our understanding of the impact of sedation management, and knowledge regarding current weaning practices and how this is associated with outcomes.

WEAN SAFE aims to describe, in a large population of ICU patients, the current procedures for weaning, the applicability of existing classification systems to ‘real world’ weaning from IMV, and centers/management/patients’ characteristics associated to duration of weaning. WEAN SAFE will answer the following questions:

- What is the frequency of delayed weaning from invasive mechanical ventilation?
- What are the current approaches taken to wean patients from invasive mechanical ventilation?
- What are the factors that are used to determine when patients are in the weaning phase?
- What are the barriers to effective weaning from invasive mechanical ventilation?
- What factors (patient, institutional, medical practice) contribute to failed attempts to wean from invasive mechanical ventilation?
- What is the impact of sedation management on weaning from invasive mechanical ventilation?
- What is the impact of premorbid conditions and of frailty on weaning from invasive mechanical ventilation?
- What is the utility of existing classifications for weaning from invasive mechanical ventilation?
- What is the impact of early versus delayed and/or failed weaning from invasive mechanical ventilation?
- What regional or geo-economic differences exist regarding weaning from invasive mechanical ventilation?
- What is the therapeutic resource use in patients with delayed weaning from invasive mechanical ventilation?

### Screening:

- All patients aged >16 admitted in the ICU after commencement of the enrollment period, and that are in receipt of invasive ventilator support, will be screened daily until ICU discharge or death.

### Inclusion Criteria:

- A patient will be included if he/she is undergoing Invasive mechanical ventilation on the second morning (between 6am and 10 am) after initiation of mechanical ventilation or after ICU admission (if ventilation was already in place at time of ICU admission).

### Exclusion Criteria:

- Lack of informed consent (where this is a requirement of the local ethics committee)
- Patients already present in the ICU at the beginning of the study, independently of the form of ventilatory support

**Note that previous enrollment in the same study is NOT an exclusion criteria. Data on previous enrollment will be captured by the eCRF.**

### Intervention Required:

Due to the observational design of the study, no intervention is required.

### Enrollment in Concomitant Studies:

Due to the observational nature of the present study, patients enrolled in other observational/ interventional studies CAN be enrolled in the present study. Details of co-enrollment will be recorded in the electronic CRF (eCRF).

### Sample Size:

We aim to collect a large “convenience sample”, with > 5,000 patients. Based on the LUNG SAFE data, we can estimate to enroll about 11 patients invasively ventilated on Day 2 following intubation per participating ICU in a 4 week period. We are therefore targeting the enrollment of 500 registered ICUs (considering a 10% dropout).

### Data Collection Period:

Each one of the participating ICUs will collect the data over a period of four consecutive weeks, to be selected by the site investigators within a six-month “window” from October 2017 to March 2018.

### Patients Screening and Study Days:

Patients > 16 years old in the ICU will be screened daily for fulfillment of the study criteria.

- Screening Days
  - Patient screening begins at the first data collection time-point (see next section) at which the patient is receiving invasive ventilator support in the participating ICU.
  - The patient is screened again the next day. For patients not receiving invasive ventilator support on the second screening day the screening process is complete. Survival status on ICU discharge will be recorded on these patients.
- Study Days
  - All patients who have undergone invasive mechanical ventilation on 2 consecutive screening days, and who do not fulfill any exclusion criteria, are enrolled in the Study. This is study day 1.
  - Daily progress forms are completed until ICU discharge, day 90 in ICU, or patient death.
- Patients in ICU who are not undergoing invasive mechanical ventilator support, including those previously enrolled in the study, will be re-evaluated daily for the presence of inclusion criteria.

### Data Collection:

Data collection will be web based, using conditional Data Collection screens, i.e. data collectors will be automatically guided as to which sections to complete based on data entered indicating whether Inclusion Criteria are met. Data collection must be done **at a fixed time for that particular ICU, which can be between 6 and 10am** each day.

**ICU Participation Form (Form 0):** This is completed once only by each participating ICU just prior to study commencement. It will provide a set of data concerning its own size, staff, and case-mix.

**Screening Form:** Completed for all patients, over 16 years of age, admitted in participating ICUs

**Study Form 1:** Completed on all patients that have undergone invasive mechanical ventilation on 2 consecutive screening days, and who do not fulfill any exclusion criteria

**Daily Form 2:** Completed daily on all patients enrolled in the study if they received invasive MV over the last 24 hours.

**Daily Form 3:** Completed daily on all patients enrolled in the study if they have not received invasive MV over the last 24 hours.

**Outcomes Form 4:** Completed on patients at ICU discharge and finalized at either hospital discharge or day 90 [whichever comes first] respectively.

### Ethical Approval and Patient Consent:

As this study is purely observational, the data collected are part of routine clinical care, and the data will be anonymized, then informed patient consent may well not be necessary. However, there are considerable variations by country in regard to this. Each PI will notify their relevant ethics committee, in compliance with the local legislation and rules, and complete any required ethics committee processes. In most countries, a National Coordinator will liaise with participating centers, helping to obtain IRB approval.

### Data Anonymization and De-Identification:

The study will not electronically store any data which allow direct patient's identification (such as name and/or date of birth), as the eCRF does not allow entry of any data that can be used to identify a patient. The patient is assigned a unique identifier number, termed the study ID, which is generated by the eCRF and used to identify the data. Once the database is closed, this cannot be linked back to the individual patient.

To facilitate data collection, site coordinators may choose to locally retain a record connecting the patient's initials and Study ID. At the end of the study, verification of all data in the database will be carried out, and the local site coordinator will be asked to verify specific data as needed. Once this is done, the database will be locked before beginning any statistical analysis. Individual site coordinators will then be asked to destroy all identifying information, including any local record linking the patient's initials to their Study ID. Thereafter, data can only be identified with the unique Study ID.

After study completion, the database will be stored securely to avoid accidental or unauthorized disclosure or access and all procedures related to data management will comply with the EU directive on data protection 95/46/EC. Further details can be found in the document signed by CLINFILE, provider of the electronic CRF. Access to the database will only be granted to the WEAN SAFE investigators to perform the statistical analysis described in the plan attached. WEAN SAFE investigators have the right to propose additional analysis of the data collected, subject to approval from the Principal investigators.

### Publication and Authorship:

The data collected belongs to the WEAN SAFE Investigators, and substantial authorship opportunities are available to participants. A more detailed policy will follow, but the very successful principles as for LUNG SAFE will be followed. Study results will be published by the WEAN SAFE-nominated Executive Committee.

Each participating center and its two lead investigators will be named as collaborators on the published manuscript. Of importance, this collaborator credit will also appear on PubMed when one searches for your name.

In addition, the national coordinators from the top 2 recruiting countries (normalized by population), and the top 2 recruiting countries (absolute value) will be invited to participate in manuscript drafting and offered authorship. There will also be opportunities for each 'WEAN SAFE Investigator' to propose sub-studies, and where these proposals are accepted, to receive authorship credit on these.

## References:

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