

Sedation, Analgesia and Delirium **MANagement: an international audit of adult medical, surgical, trauma, and neuro-intensive care patients**

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- Health Services and Research in Outcomes
- Post-Operative Intensive Care

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SUMMARY

Title	Sedation, <u>AN</u>algesia and <u>De</u>lirium <u>MAN</u>agement: an international audit of medical, surgical, trauma, and neuro-intensive care patients.
Abbreviation	SAnDMAN (Sub-study: SAnDMAN COVID-19)
Study design	International multicenter retrospective observational cohort study
Sponsor	Sinai Health, Toronto – ON (Canada)
Background and Rationale	Rigorous and well-conducted research over the last 2 decades shows that sedation, analgesia, and delirium monitoring and management can impact important patient-centered outcomes in the intensive care unit (ICU). Sedation protocols have been developed worldwide with the objective to reduce cumulative sedation, favour analgesia-first strategies, and avoidance of benzodiazepines as potential contributors to ICU delirium and cognitive dysfunction. Despite the wealth of literature and strong recommendations available there is a large variance in practice of sedation, analgesia and delirium management in ICU worldwide as demonstrated by several national self-reported clinician surveys. There are no large-scale international data regarding sedative and analgesic administration practices, and adherence to evidence-based strategies and guidelines. The data generated from this study will inform global research and educational and quality improvement initiatives.
Objectives	The over-arching objective of this international retrospective observational study is to capture an overview of sedation, analgesia and delirium management strategies used in ICUs around the world. We aim to describe patterns of sedative and analgesic use, as well as the local availability and use of sedation, analgesia and delirium protocols for management of critically ill, mechanically ventilated patients. We will collect data for patients admitted to ICU before and during the COVID-19 pandemic to explore how practice has changed during this exceptional timeframe (SAnDMAN COVID-19 Sub-study).
Methods	<p>Sample Size: We aim to collect data from >2000 patients internationally from a minimum of 100 ICUs.</p> <p>Inclusion criteria:</p> <p><u>Main study:</u></p> <ol style="list-style-type: none"> 1. “Standard ICU arm”: Adults (≥18 years) admitted to a participating ICU from the 1st October 2019 until the 1st March 2019, or prior to the COVID-19 surge in the country, who are invasively mechanically ventilated for more than 12 hours will be included. We will include medical, surgical, trauma and neurological/neurosurgical patients who are COVID-19 negative. <p><u>COVID-19 sub-study:</u></p> <ol style="list-style-type: none"> 1. “COVID-19 ICU arm”: Adults (≥18 years) admitted to a participating ICU from the 1st January 2020 until the 31st August 2020 who are invasively mechanically ventilated for more than 12 hours will be included. We will include patients admitted with a confirmed diagnosis of acute respiratory failure due to COVID-19 infection (suspected or confirmed). 2. “Non-COVID-19 ICU arm”: Adults (≥18 years) admitted to a participating ICU from the 1st January 2020 until the 31st August 2020 who are invasively mechanically ventilated for more than 12 hours will be included. We will include medical, surgical, trauma and neurological/neurosurgical patients who are not admitted for COVID-19. <p>Exclusion criteria: none.</p>

	Data Collection: Baseline demographic data will be collected as well as data on sedation, analgesia, delirium, and restraint management for the first 7 consecutive days of invasive mechanical ventilation. Data entry will be facilitated by an electronic Case Report Form with established range and value checks.
Endpoints	Our primary endpoint is the use of analgesics, sedatives, anti-psychotics, paralytics, and use of assessment tools for pain, sedation and delirium. Our secondary endpoint is use of sedation/analgesia/delirium/restraint protocols or policies; and adherence to existing guidelines on the management of sedation, analgesia and delirium.
Duration of study	Participating ICUs will screen and collect data for up to 20 mechanically ventilated patients per arm admitted to their ICU from the 1 st October 2019. We recognize that all ICUs may not be able to start on the same day, so given the large number of ICUs, we will collect data until the 1 st August 2021. Extensions to the data collection period will be considered on a case-by-case basis. Patients in the different arms will be recruited according to the date of the COVID-19 surge in the specific country (for example: Main study patients: from 1 st October to 31 st December 2019; COVID-19 sub-study patients: from 1 st January to 31 st August 2020). The date of the COVID-19 surge is exploratory and is defined as the date of the 50 th COVID-19 patient admitted to ICU in the specific country.
Study Registration	The study will be registered on Clinicaltrials.gov

ABSTRACT

Sedation management in critically ill patients has a significant impact on their short-term and long-term outcomes. Despite strong evidence and prescriptive international guidelines, there appears to be tremendous variability in sedation management internationally. However, there are no large-scale multinational data describing sedation, analgesia and delirium practices in the intensive care unit (ICU). We propose a retrospective multicentre, multinational study to describe patterns of sedative, analgesic, and antipsychotic drug use and the level of adherence to evidence based strategies and guidelines in critically ill patients. Within this international audit, we will collect data in academic and non-academic ICUs, on heterogeneous populations of critically ill patients, including medical, surgical, trauma, and neuro-intensive care patients. We will collect data for patients admitted to ICU before and during the COVID-19 pandemic to additionally explore how practice has changed during this exceptional timeframe. It is vital to understand current practices around the world. The data generated from this study will inform research, educational and quality improvement initiatives for a diverse patient population.

INTRODUCTION

Background

Present State of Knowledge

Rigorous and well-conducted research over the last 2 decades shows that sedation, analgesia, and delirium monitoring and management can impact important patient-centered outcomes in the intensive care unit (ICU). Randomized trials consistently demonstrate short-term and long-term benefits of minimal sedation in mechanically ventilated patients, such as reduced duration of mechanical ventilation, ICU length of stay, mortality, and improved psychological outcomes. In addition, deep sedation within the first 48 hours of mechanical ventilation (MV) has been associated with longer duration of MV, more tracheostomy procedures and higher mortality (1-4).

Recommended sedation minimization strategies to reduce the likelihood of sedative bioaccumulation and prolonged sedation include a sedation protocol, daily sedation interruption, intermittent rather than continuous sedation, and an analgesia-first regimen. Regarding specific sedative agents, guidelines and clinical studies suggest avoidance of benzodiazepines in critically ill patients, unless there are specific indications (5).

The occurrence of ICU delirium has significant consequences, including higher mortality, cognitive dysfunction, and reduced discharge to home. Routine monitoring for delirium using validated tools leads to early detection, evaluation for reversible causes, and the implementation of non-pharmacologic interventions. Clearly, the use of evidence-based practice regarding drugs, monitoring, and administration strategies has the potential to affect patient outcome.

Many seminal trials in this area have enabled the development of thoughtful and well-crafted guidelines, which provide evidence-based recommendations regarding sedation and analgesia management for clinicians who care for critically ill patients. These guidelines include the Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium (PAD) from the Society of Critical Care Medicine (SCCM) (6), German guidelines (7), and French guidelines (8).

Evidence based strategies are still not being used

Despite the wide availability of clinical practice guidelines, compliance with evidence-based strategies and recommendations remains poor, as evidenced by many practice surveys and audits around the world (9-14). A recent international clinician survey from all regions of the world, representing 1521 respondents from 47 countries, reported progress in the use of ABCDEF strategies, but very significant room for improvement (10). The strengths of this survey include the broad scope, with sampling across all regions of the world, including low and middle-income countries, and detailed exploration of the ABCDEF bundle. The major limitation of this survey is that clinicians' perceived practice may not reflect actual practice (15). Overall, in the last two decades the perceived variation of sedation, analgesia and delirium management practice has been assessed by several authors and more than 30 surveys have been published since 1999.

Possible barriers to adherence with accepted practices include a lack of knowledge, lack of acceptance, lack of a local change champion, lack of personnel for implementation, or availability and cost of

recommended medications. Language may be a barrier as well, as a recent survey of 165 Polish ICUs attributed the poor adherence with routine delirium assessment (9) to the lack of availability of a delirium tool in Polish or another eastern European language.

Rationale for an international practice audit

Individual clinician surveys suffer from response bias and may not reflect actual practice. Therefore, an audit of actual practices across centers and countries is essential to describe current PAD management. While previous surveys are informative, most are small, are limited to academic hospitals, are not international, report perceived practice (and not actual practice), and do not represent heterogeneous patient populations, such as medical, surgical, cardiac, and neurological patients. A recent literature search identified 8 point of prevalence studies and practice audits (Table 1).

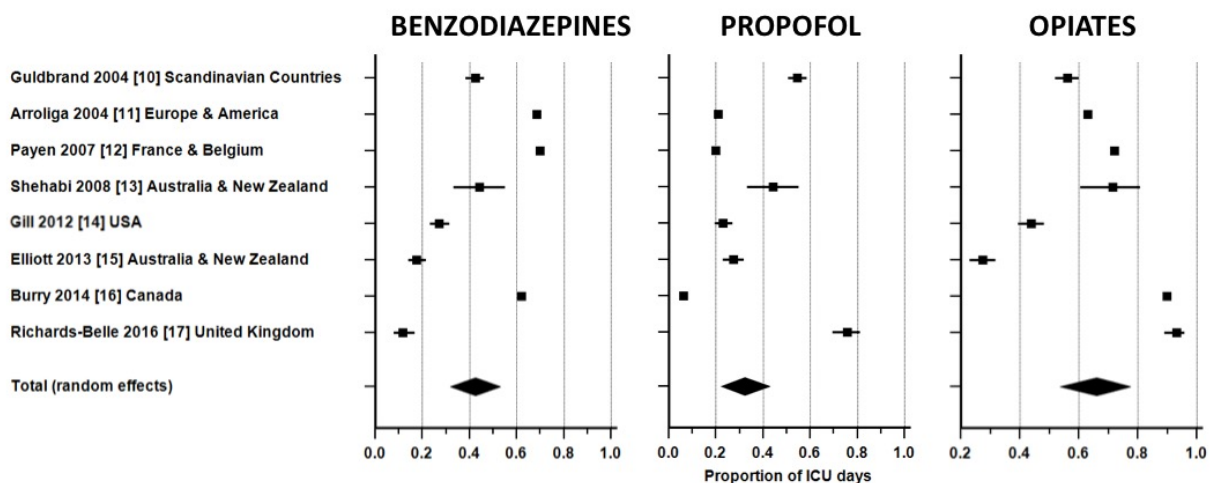
Table 1: Point of prevalence studies published between 1999-2018 evaluating the use of sedation and analgesia.

Author/year	Country/ Region	Sampling period	n, Population	Response Rate (%)	Methodology
Guldbrand 2004 [10]	Nordic	2002	Part I: 88 ICUs Part II: 202 patients	36	Part I: Self-administered survey, Part II: 5 days of patient data. Internet-based.
Arroliga 2005 [11]	International	NR	5183 adult patients >12 hours MV	N/A	Prospective practice audit
Payen 2007 [12]	France	2004	1382 patients	N/A	Prospective audit on days 2, 4, and 6 of ICU stay
Shehabi 2008 [13]	Australia and New Zealand	2005 - 2006	Part I: 23 ICUs Part II: 234 patients	N/A	Part I: web-based questionnaire Part II: point of prevalence study
Gill 2012 [14]	USA	NR	Part I: 85 ICUs Part II: 496 patients	Part I: 36% Part II: N/A	Part I: web-based questionnaire Part II: Prospective Audit
Elliott 2013 [15]	Australia and New Zealand	2009 and 2010	569 patients (41 ICUs)	N/A	Point of prevalence study

Burry 2014 [16]	Canada	2008-2009	51 ICUs, 712 patients	N/A	Point of prevalence study
Richards-Belle 2016 [17]	UK	2014	214 ICU directors 516 patients	Part I: 91%	Part I: Web-based questionnaire followed by email and telephone follow-up interview Part II: point of prevalence study

Most of these studies explored single countries or regions (10, 12-17). Only one study included more continents, and its data were collected in the context of a large observational cohort study on outcomes of mechanical ventilation (11,18). In a preliminary meta-analysis (unpublished data, see Figure 1) that we conducted of 8 point of prevalence studies, we identified important heterogeneity in sedation and analgesia practices.

Figure 1. Meta-analysis of 8 Point of Prevalence Studies published between 1999 and 2016.



STATISTICS	BENZODIAZEPINES	PROPOFOL	OPIATES
Random effects			
I ² (Inconsistency)*	99.48%	99.49%	99.63%
Significance level	P<0.0001	P<0.0001	P<0.0001
Total Sample Size	25876	25876	25876
Proportion	42.30%	32.07%	66.15%
95% CI for Proportion	31.85% - 53.11%	22.33% - 42.68%	53.58% - 77.70%

Heterogeneity test: I^2 is calculated as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and 'df' the degrees of freedom.

There are currently no large-scale international data describing actual sedative and analgesic administration practices, and adherence to evidence-based strategies and guidelines. The proposed practice audit will complement the recent global clinician survey (19) and will allow us to contrast clinicians' self-reported perceived practice and actual practice.

Given the limitations of previous surveys and point of prevalence studies, we propose a multicenter international observational study of PAD management practices in diverse populations of critically ill, mechanically ventilated adults, including medical, surgical, trauma, and neuro-intensive care patients.

COVID-19 Outbreak

In December 2019, a new respiratory pathogen SARS-CoV2 has been identified in Wuhan, China as the cause of pneumonia and severe acute respiratory failure in more than 80,000 subjects and led to the death of more than 3,000 Chinese inhabitants. The virus has spread rapidly across the world from January 2020, leading the World Health Organisation to declare a Public Health Emergency of International Concern on the 20th January 2020, and to announce a name for the new coronavirus disease: COVID-19.

Patients with COVID-19 present with a wide range of symptoms, but the most severe cases require ICU admission and invasive respiratory support as well as sedation, analgesia and muscular paralysis. On the 11th April 2020, it is estimated that more than 1,700,000 cases have been identified with a worldwide death toll of 103,233 patients worldwide. On the 10th April 2020, the number of patients admitted to ICU in the United Kingdom only has been estimated to be almost 4000 (ICNARC report on COVID-19 in critical care 10/4/2020) and 49,892 active cases remain in serious or critical conditions worldwide. Reports from other countries such as China, Italy and Spain, suggest the frequent use of high doses of sedatives and neuromuscular paralysis in this cohort to facilitate ventilation strategies. This could lead in several countries to shortages of vital drugs to perform surgery and sedate patients admitted to ICU. However, there is a lack of structured evidence about sedation, pain and delirium management in this cohort during their ICU stay.

Therefore, we propose the SAnDMAN-COVID sub-study to explore the variability and practice of sedation in this unique cohort of patients and to assess the differences between the management with patients admitted to ICU prior to the ICU pandemic. Additionally, we would like to investigate the differences in sedation, analgesia and delirium management in patients admitted to ICU without COVID-19 before and during the pandemic to assess if/how the pandemic has affected sedation protocols and management in other ICU cohorts.

Objectives

The over-arching objective of this international retrospective observational study is to capture an overview of sedation, analgesia and delirium management strategies used in ICUs.

Our specific primary objectives are:

- 1) To describe international practice in ICU, and practice variation in the use of drugs, and monitoring for PAD (main study);
- 2) To describe the variation of sedation, analgesia and delirium management during the SARS-CoV2 pandemic in the COVID-19 cohort in patients with confirmed or suspected SARS-CoV2 infection (COVID-19 Sub-study).

The secondary objectives are:

- 3) To quantify the adherence to the PAD clinical guidelines (5);
- 4) To describe and compare management between specific ICU patient groups:
 - Medical patients (specifically sepsis and acute respiratory distress syndrome (ARDS))
 - Surgical patients
 - Trauma and Burns patients
 - Neurocritical care patients
 - Cardiogenic shock patients
 - Patients receiving palliative care
- 5) To describe and compare management between COVID-19 negative ICU patient groups before and during the pandemic (COVID-19 Sub-study).

Hypotheses

We hypothesize the following:

- 1) Benzodiazepines are still commonly used;
- 2) Opioid and sedative infusions are preferentially used over intermittent dosing;
- 3) There is poor adherence (<50% of patient-days) with pain, sedation and delirium assessment;
- 4) There is poor adherence (<50% of patient-days) with sedation protocols and daily sedative interruption;
- 5) There is significant international variability in practices;
- 6) There is significant variability conditional to patients' principal diagnosis (e.g. surgical versus neuro-intensive care patients);
- 7) Suspected or confirmed COVID-19 mechanically ventilated patients require higher level of sedation and more frequent pharmacological muscle paralysis compared to general ICU patients (COVID-19 sub-study);
- 8) General ICU patients (non-COVID-19) sedation practices varied before and during the pandemic (COVID-19 sub-study).

To address these hypotheses, the investigators will evaluate practice in ICUs, and identify barriers to the implementation of evidence-based practices and how these have changed during the COVID-19 pandemic. The data acquired will represent ICUs from 6 regions: Europe, North America, South America, Africa, Asia and Oceania, and will thus be generalizable. These data will inform educational, research and quality initiatives in ICUs around the world.

METHODS

Study Design

We will conduct a retrospective observational international study to gain a comprehensive picture of ICU practices regarding sedation, agitation, and delirium management, and evaluate if practice patterns adhere to the PAD guidelines (5) and a sub-study of both patients with suspected and diagnosed COVID-19. This research will be led by the co-principal investigators and the executive committee. Each site investigator will collect data for the first 7 days of mechanical ventilation for up to 20 consecutive patients admitted into their respective ICU(s) from the 1st October 2019. We will recruit patients from both academic and community hospitals internationally. Data collection will remain open until the 1st August 2021 to allow centres to participate on flexible start dates. Extensions to the data collection period will be considered on a case-by-case basis. Patients in the different arms will be recruited according to the date of the COVID-19 surge in the specific country (for example: Main study patients: from 1st October to 31st December 2019; COVID-19 sub-study patients: from 1st January to 31st August 2020).

Methods Centre

The Methods Centre will be located at Oxford University Hospitals and University of Oxford (Nuffield Department of Clinical Neurosciences). Part-time research staff will communicate with sites and serve as a resource for site recruitment, ethics applications, data entry, queries, and any questions that arise about the study.

Participating Centres

To obtain broad cross-sectional representation we will recruit participating sites ICUs internationally in all 6 geographic regions: Africa, Asia, Europe, North America, South America, and Oceania. We anticipate participation of at least 40 sites from each region (10). We will identify a National Coordinator in each country to assist with identification of eligible sites and to serve as a national resource for ethics applications and logistical support. The National Coordinators will also ensure equal representation of hospital type (university affiliated, community teaching hospital, and community non-teaching hospital) from each region. Different ICUs from the same hospital will be considered as separate centres.

Identification of participating sites will be achieved through personal contacts of the National Coordinator and the Steering committee, through screening of sites which have participated in similar international audits (e.g. LUNGSAFE), and through the ESICM membership. We will personally invite physicians to participate as site leads. If we receive funding through ESICM we will also advertise the opportunity to contribute through the ESICM website and email distribution list.

From the experience of previous ESICM Trials Group audits (e.g., LUNGSAFE, APRONET, DeCubicUs), we anticipate participation of a minimum of 200 International ICUs.

Each site will obtain local institutional Research Ethics Board approval if this is required for observational studies with no long-term follow-up. Explicit patient informed consent ideally will not be required for this study due to the retrospective observational, non-interventional study design. No personal patient

identifiers will be collected. Each participating site will complete a data sharing agreement with the sponsoring site.

Patients

Inclusion Criteria:

Main study:

The participants may be recruited if ALL of the following apply:

1. Standard ICU arm:

- All male or female aged ≥ 18 years admitted to a participating Intensive Care Units who are invasively mechanically ventilated for more than 12 hours will be included.
- Patients admitted with medical, surgical, trauma, burns, neurological and neurosurgical clinical problems.
- Admitted to ICU prior to the COVID-19 surge in the specific country.

COVID-19 sub-study

Participants may be recruited in the COVID-19 sub-study if ALL the following apply:

1. COVID-19 ICU arm:

- All male or female aged ≥ 18 years admitted to a participating Intensive Care Units who are invasively mechanically ventilated for more than 12 hours will be included.
- Patients admitted with pneumonia and/or acute respiratory failure due to SARS-CoV2 or suspected COVID-19.

2. Non-COVID-19 ICU arm:

- All male or female aged ≥ 18 years admitted to a participating Intensive Care Units who are invasively mechanically ventilated for more than 12 hours will be included.
- Patients admitted with medical, surgical, trauma, burns, neurological and neurosurgical clinical problems.
- No confirmed or suspected COVID-19 disease.

Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Patients admitted to non-acute care units

Data will be collected for a 7-day period (labelled study days 1-7) selected by the site investigator. We will include up to 20 patients per arm per centre who are admitted to ICU and mechanically ventilated from the 1st October 2019 until the 31st August 2020. For these patients, data collection will start on the day of initiation of mechanical ventilation.

Patients in the different arms will be recruited according to the date of the COVID-19 surge in the specific country (for example: Main study patients: from 1st October to 31st December 2019; COVID-19 sub-study patients: from 1st January to 31st August 2020). The date of the COVID-19 surge is exploratory and is defined as the date of the 50th COVID-19 patient admitted to ICU in the specific country. If a specific country had admitted less than 50 COVID-19 patients by the 31st August 2020, the Executive committee will review the possibility for that country to participate in the Main study only.

ICU data will be collected until one of the following endpoints: 1) liberation from mechanical ventilation for 24 hours or more; 2) ICU discharge if they are transferred out of the ICU mechanically ventilated; 3) death in ICU; or 4) a maximum of 7 days. For ICU survivors, we will record the length of ICU stay, hospital stay and status on discharge (including death) if available.

Variables

Within this retrospective multicentre observational study, the following completely anonymised data will be recorded:

A. Site Demographics (Appendix A)

Core data includes University-affiliation, presence of trainees, total hospital and ICU bed numbers, ICU physician and nurse staffing ratio and characteristics, presence of a pharmacist on ICU rounds, use of validated tools for pain, sedation and delirium, and the local availability of sedation/analgesia/delirium/restraint/mobilization protocols or policies.

B. Patient Demographics and Outcomes (Appendix B)

Core data includes age, sex, admission diagnosis and categories (e.g. surgical, medical, trauma, palliative, burns, or others), and clinical outcomes (ICU and hospital length of stay, days of mechanical ventilation, and survival).

C. Daily Patient Data (Appendix C)

Core data includes medications received (analgesics, sedatives, anti-psychotics, paralytics) and route (continuous infusion, intermittent dosing, etc.), objective assessment of pain, sedation and delirium, daily sedative interruption, use of paralysis, physical restraint use, and mobilization.

Data Sources/Measurements

Source data include all information, original records of clinical findings, observations, or other documents necessary for the completion of the study. Examples of these original documents and data records include but are not limited to: patient paper and electronic records, nursing flowsheets, ventilation records, pharmacy records, and medication administration records.

Bias

There are limitations to this study. First, there is potential for bias, in that participating hospitals may have a greater interest in ICU practice quality improvement and will be less likely to deviate from PAD

guidelines. In addition, the results may be driven by disproportionate participation from academic centers, and higher income countries. Therefore, in our recruitment of participating sites, we will ensure a wide distribution and adequate representation of academic and community hospitals, as well as geographic regions.

Study Size

Our plan is to recruit as many centres as possible, aiming at a minimum sample size of at least 2000 patients and a minimum of 100 ICUs. There will be no upper limit to the number of patients or recruiting centres. Our intention is to have a realistic and feasible sample size. This should include an adequate number of ICUs from each geographic location, as well as patients, to make the results generalizable.

Due to the current knowledge on the size of variation of practice in different geographic regions and the combined hypotheses tested in the study, an exploratory sample comparable to previous large observational studies is acceptable (reference ARDS and ABCDEF surveys). Statistical models will be adapted to the event rates (e.g. benzodiazepine use) provided by the recruited samples.

Outcome Measures

The data gathered by this study will provide insight into current ICU practices and the variability of practice across Europe. The use of electronic data entry will minimize errors and site workload. This information will identify areas of knowledge gaps and help direct and focus resources to provide additional support or research to optimize care for critically ill patient in ICU.

Safety considerations

SAnDMAN is an observational study only, and participation will not alter the local standard of care. Data will be extracted from the patients' medical records, and participation in the study does not impose any risks for patients. Confidentiality breach is a not a potential risk which as data collected will be completely anonymised.

The SAnDMAN eCRF is compliant with European General Data Protection Regulation (GDPR). The GDPR (Regulation (EU) 2016/679) is a regulation by which the European Parliament, the Council of the European Union and the European Commission intend to strengthen and unify data protection for all individuals within the European Union (EU). It also addresses the export of personal data outside the EU. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) required the Secretary of the U.S. Department of Health and Human Services (HHS) to develop regulations protecting the privacy and security of certain health information. For eCRF security considerations please refer to the ClinFile Data Hosting and Security.

Follow-up

For each patient, we will collect clinical data retrospectively until the end of the hospital stay. We will not collect long-term follow-up data beyond the candidate admission.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data entry and checks

All sites will be provided with a Manual of operations which includes responses to frequently asked questions (FAQ), relevant study personnel contact information, and a data dictionary which provides information about completion of the electronic case report forms (eCRF).

All data will be collected using eCRF. No patient identifying information will be collected. Each site will be assigned a sequential number (e.g., 01, 02, 03, etc), and patients will be assigned consecutive unique identifiers, so that patients will be labelled as: Site number - Patient number (e.g., 01-01, 01-02, etc.).

Range edits and value checks will be incorporated into the software to reduce the potential for data entry errors. Data queries will be automatically generated and sent to participating sites. Site investigators will be required to answer all queries before they can electronically finalize a patient data set.

Centres not able to complete an eCRF will be offered the use of a paper CRF. When complete, these de-identified records will be shipped to the University of Oxford via signed post and entered into the eCRF by methods centre staff.

Statistical analysis

We aim to recruit >2000 within a minimum of 100 ICUs (no upper limit for the total number of patients) and anticipate that this will provide an accurate indication of worldwide practices.

Preliminary descriptive statistics will be used to report baseline demographic and clinical variables. Continuous variables will be described using measures of central tendency and spread (means and standard deviations (SD) or median and interquartile ranges dependent on data distribution). Frequencies, proportions and their 95% confidence intervals will be used to describe categorical variables. Interventions and outcomes for different groups of patients will be compared using the Wilcoxon rank sum test for continuous variables, Pearson Chi-square test or Fisher exact tests for categorical variables.

Predictive analytics will be performed on treatment analysis (including as targets drug selection, clinical protocols, assessment tools, treatment outcomes). This predictive analysis will include the following steps:

1. Feature subset selection (Guyon & Elisseeff, 2003; Saeys, et al. 2007) will be performed in this sequence:
 - a. Preliminary selection: features selected based on clinical significance or biological plausibility.
 - b. Correlation filtering: Filtering out features with absolute correlation or information gain measure less than a selected threshold as well as the less informative feature for those pairs with higher absolute cross-correlation.
 - c. Wrapper filtering: Three different wrapper filtering methods will be applied:
 - i. Beam search subset selection (Aha, et al. 1996)
 - ii. Boruta feature subset selection (Kursa & Rudnicki, 2010)

- iii. Hybrid genetic algorithm-based feature selection (Oh, et al. 2004)
2. Supervised learning model: The following methods will be applied:
 - a. Logistic regression (standard and regularised: Lasso, Ridge, and ElasticNet) (Tibshirani & 1996)
 - b. Support Vector Machines (Chang & Lin, 2011)
 - c. Random Forests (Breiman, 2001)
 - d. Naïve Bayes (Rish, 2001)
 - e. Multilayer Perceptron (Gallinari, et al. 1991)
 - f. Boosting: Adaboost (Freund & Schapire, 1997) and XGBoost (Chen & Guestrin, 2016)

The predictive analytics will be evaluated using a multi-fold cross validation or bootstrapping, saving an out-of-sample dataset for the final validation process.

We will describe practice variation among participating ICUs and across countries. We will use regression methods to address possible patient and setting determinants of use of:

- a) Specific medications or strategies (e.g. size of hospital, type of ICU, type of patient);
- b) Assessment with a validated sedation/pain assessment tool;
- c) Delirium assessment;
- d) Use of a sedation protocol.

We may find that there is appreciable under-utilization of some interventions for which there is strong evidence of efficacy, or over-utilization of interventions that lack evidence of efficacy. If regression methods show associations between these observations and practice setting (academic versus community hospital), or size of ICU, for example, we will target educational interventions accordingly.

Missing data will be minimal, as completion of all fields in the eCRF will be mandatory. For each question, we will provide response options of “unknown” and “not applicable” or “data/information not available”. Complete data collection will be further encouraged by a user-friendly eCRF, a manual of operations with a data dictionary, and prompt queries about incorrect data.

Quality assurance and Data protection

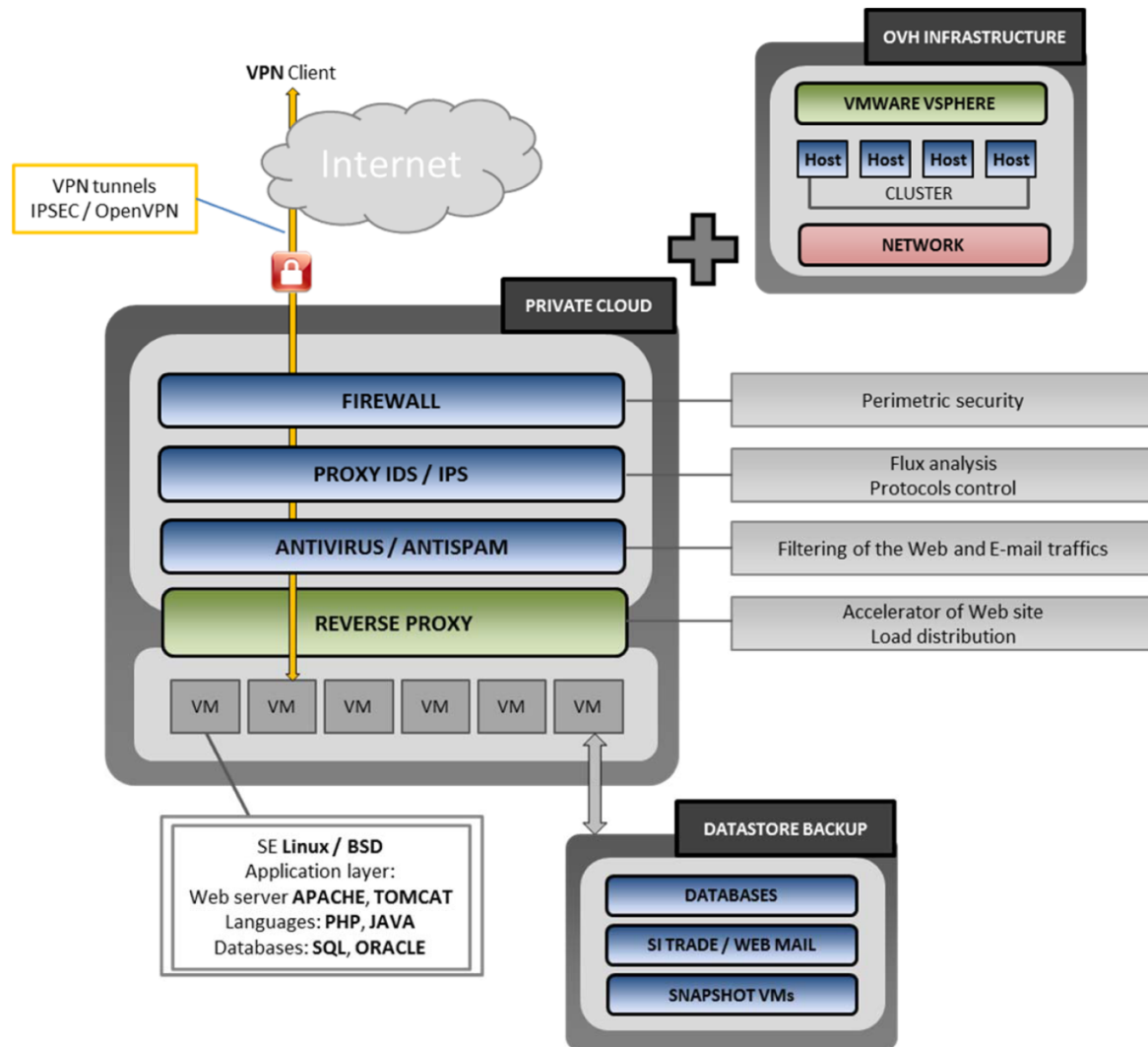
The eCRF platform to support data collection for the study will be developed by ClinFile in collaboration with ESICM. Here below we report an example of quality assurance and data protection based on the ClinFile reports (<http://www.clinfile.com/en/>). ClinFile is the platform of choice of the European Society of Intensive Care Medicine.

Data hosting and security (see Figure below)

Clinfile uses OVH PRIVATE CLOUD service. OVH society, European leader in hosting service provider, awarded ISO / IEC 27001 certification for the provision and operation of dedicated cloud infrastructure. OVH insures an exclusive space to create, host, maintain and secure a set of virtual servers. Guarantees of security and optimal performance:

- Secure administration: login and password encrypted and reset every month

- Infrastructure totally duplicated: network connection, inverter, power supply, routing, storage
- Preserved Data: backup every hour in RAID 10 (disk cloning)
- Reliable Data centres: reinforced buildings against intrusions and other physical security hazard
- 24-hour monitoring: technical team on all sites
- Optimal quality network: optimal transfer speed of data



Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators and their staff. All medical or administrative staff with access to the data are subject to a duty of confidentiality and data protection. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidentiality agreement protocols.

The study sponsor and representatives of local authorities may inspect all documents and records required to be maintained by the local investigator for the participants in this study. The clinical study site will permit access to such records.

De-identified data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to the Data Manager and the Statistician of the study. For this purpose, data will be de-identified and anonymized at input into the eCRF by the local centres.

DISSEMINATION OF RESULTS AND PUBLICATION POLICY

Knowledge translation

The findings of this study will be communicated with participating sites and with the intensive care community through presentation at professional practice conferences and ultimately disseminated via peer-reviewed abstracts and manuscripts. Participating sites will be able to contrast their own management with other ICUs in their geographic regions and across Europe.

Following publication of the planned SAnDMAN manuscripts, the Steering committee will invite submissions of proposals for secondary analyses from contributing investigators. Following approval of the proposals by the Executive committee, the data will be available for these approved secondary analyses.

Data sharing policy

Any requests for the use of the data will be submitted in writing to the SAnDMAN Executive Committee, and decisions will be made in relation to these requests. SAnDMAN investigators will have priority in requests to use the data set for subsequent secondary analyses.

Publication and Authorship

Results will be made available to ESICM members and to the scientific community by means of abstracts submitted to the ESICM annual conference and by scientific papers submitted to peer-reviewed journals. Authorship of the main manuscript will follow the International Committee of Medical Journal Editors (ICMJE) recommendations that base authorship on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authorship of the principal study report will be listed as the individual members of the writing committee, who will take responsibility for the content of the paper, on behalf of the SANDMAN Study Group, i.e. 'Jane Smith *for* the SANDMAN Study Group.' The writing committee will include members of the steering committee, as well as other members of the SANDMAN Study Group co-opted at the discretion of the Executive committee. It is anticipated that the 2 co-principal investigators will be the first and last authors. Members of the SANDMAN Study Group, including a maximum of 2 local research staff, will be listed in an appendix to the manuscript or in a supplementary file. All national coordinators and site investigators

who recruit 20 patients with less than 20% missing data will be listed as collaborators. For further information about authorship please refer to the 'Authorship and publication' document.

ESICM support and endorsement will be acknowledged on all SAnDMAN publications.

DURATION OF THE PROJECT

We will permit staggered start times to accommodate site-specific processes including research ethics board approval, completion of data sharing agreements, and personnel needs. If the recruitment is slower than forecasted, the Executive Committee will discuss the possibility to amend the data collection period and concede longer recruitment time to centres who will make the case for this.

ANTICIPATED CHALLENGES

One expected challenge is to generate generalizable data: to address this challenge we will ensure diverse representation of countries, academic versus community ICUs, and patient populations. Another challenge is complete and accurate data: the user-friendly eCRF will include range checks, with mandatory responses to each question, and site personnel will receive queries in real time for missing or incorrect data. A potential risk is that ICU clinicians may change their management because they are aware that their practice is being audited. Finally, the audit will provide a snapshot of practice over 7 days, which may not be reflective of other time-points.

PROJECT MANAGEMENT

Principal investigators and Steering Committee

The roles and responsibilities of the Principal Investigators and SC are to:

- Coordinate the study and identify participating countries and country coordinators.
- Ensure that the study is conducted in accordance with the protocol and in compliance with Ethics and Legal regulations in all participating sites and countries.
- Apply for regulatory approval at a national level in the coordinating countries (United Kingdom and Canada) and ensure that regulatory authorities' approvals are obtained for most participating sites in their country prior to the initiation of the study.
- Ensure application for regulatory approval from a local Data Protection Authority (DPA) in the coordinating country.
- Assist with the translation of the study documents according to local regulations.
- Ensure good communication with the participating country coordinators, including monitoring and encouraging to achieve optimal recruitment and follow-up during the study period.
- Assist the research assistant and Executive Committee in communicating with sites regarding data queries.
- Take responsibility for the collected data, statistical analysis, communication and all publications.

Country coordinators

The roles and responsibilities of the country coordinators are to:

- Liaise with National Intensive Care Societies and advertise the study in the individual countries and identify participating sites and local PIs in their country.
- Apply for regulatory approval at a national level where applicable and ensure that ethical committee (EC) approvals, or waivers of EC approvals, are obtained for all the participating sites in their country prior to the initiation of the study.
- Apply for regulatory approval from a local Data Protection Authority (DPA), where applicable.
- Assist with the translation of the study protocol, Patient Information Sheet, Consent form or equivalent according to local regulations.
- Ensure good communication with the participating sites in their country, including monitoring and encouraging to achieve optimal recruitment and follow-up during the study period.
- Assist the research assistant and Executive Committee in communicating with sites regarding data queries.

Site Investigators

For each participating ICU, one local investigator will be identified. The roles and responsibilities of the local investigators are to:

- Lead the study at their site.
- Inform the respective country coordinator of their interest to participate in the study.
- Apply for research ethics board approval and/or local site approvals in collaboration with the country coordinator and ensure that local approvals are in place prior to the initiation of the study.
- Notify and send verification of local site approval to the country coordinator.
- Ensure accurate and timely data collection and entry in the eCRF.
- Reply promptly to data queries from the country coordinator.
- Maintain effective communication with the country coordinator and coordinating centre.
- If applicable, inform patients about their enrolment in the study and to acquire patients' non-opposition according to local regulations.

Advertisement and ICU recruitment

The study will be advertised at the annual ESICM LIVES 2018 conference and through the ESICM press/media via the Society Communication Committee. An invitation email will be sent to all ESICM members. To expand the visibility of the study internationally the SAnDMAN Steering Committee will contact other societies and networks for endorsement and support (WFSICCM, SCCM, ANZICS, ATS, etc). National Co-ordinators will be appointed to facilitate recruitment of ICUs and to assist with identification of site investigators in each ICU.

Premature termination or suspension of the study

This study may be suspended or prematurely terminated for reasonable cause agreed by the SAnDMAN Steering Committee. Written notification, documenting the reason for study suspension or termination

will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the National Coordinators/Local PIs will promptly inform the Ethics Committees or other local authorities according to local legislation and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination could be: low recruitment or insufficient compliance with the protocol. The study may resume when the Steering Committee agree the concerns have been addressed and issues resolved.

ETHICS

Ethics committee

Each NC/PI will notify the relevant ethics committee, in compliance with the local legislation and rules. The national coordinators will facilitate this process. The approval of the protocol (if required by local authorities) must be obtained before any participant is enrolled. Any amendments to the protocol will require review and approval by the SC, as well as ethics committees, before the changes are implemented to the study.

A waived consent model will be used

As SAnDMAN is an observational, no-risk study, we will request approval from research ethics boards to collect data retrospectively with a waiver of informed consent, for the following reasons:

1. It is impracticable to obtain consent from all patients or substitute decision makers (SDM) for a retrospective practice audit because some patients might have been discharged or have died, or do not have an SDM or the SDM cannot be located.
2. All data entered in the database is de-identified. There is no risk of associating individual patients with outcomes, as only summary statistics will be used for presentation of data.
3. Waiving the need for consent for these studies ensures that ALL patients with the condition that is being evaluated contribute their data, leading to a comprehensive, unselected, generalizable, unbiased dataset.

Posters explaining the study and providing investigator contact information will be posted in each participating ICU, in a location visible to SDMs. This model has been used successfully by the Canadian Critical Care Trials Group and in other large-scale international audits. While waived consent will be our preferred approach, each center will obtain authorization to perform the study according to their national regulations. Centers will abide by regulations within their country, including obtaining informed consent from patients/SDMs, if required.

Medical care related to the study

The medical care of the participant in the study is performed as per local standard of care, without any deviation from usual clinical protocols.

STUDY FUNDING

The study was submitted for competitive assessment by the Trials Group of the European Society of Intensive Care for the Trials Group Award 2018 and received a grant of €25,000.

COLLABORATION WITH OTHER SCIENTISTS OR RESEARCH INSTITUTIONS

The investigators and ESICM endorsement

SAnDMAN investigators are uniquely positioned to complete this study, which represents collaboration across professions, disciplines, institutions, and countries. Each of the investigators has expertise in the management of diverse critically ill patients, and all are productive investigators. The steering committee includes members ranging from early career investigators to senior investigators. The study will be led by PI Dr. Sangeeta Mehta and co-PI Dr. Lara Prisco. Dr Lara Prisco is lead for the SAnDMAN COVID-19 sub-study. Members of our team have experience in systematic reviews (SM, LB, LP, MC, IH, FST, GC), multi-center practice audits (SM, LB, LP, BW, MC, GC), randomized trials (SM, LB, MC, FST, GC, GM), and large neuro-intensive care multicentre observational studies (GM, LP, FST, GC). The study statistician (JMP) has a longstanding experience in big-data, machine-learning statistics and previous experience in healthcare data analysis.

The study has received endorsement from three ESICM sections: Health Services Research and Outcome (HSRO), Neuro-intensive Care (NIC), and Peri-operative Intensive Care (POIC) sections. The study investigators include representation from each of these groups; which is ideal because the clinical management of sedation, analgesia and delirium are relevant to all 3 of these sections.

There is no overlap between SAnDMAN and the ongoing EuMAS study (European Management of Analgesia, Sedation and Delirium), which is led by Dr. Bjorn Weiss and was awarded an ESICM startup grant. EuMAS is a one-day prevalence study evaluating perceived practice and especially the diagnostic validity of delirium-screening. SAnDMAN and EuMAS will provide complementary data regarding sedation management.

SaNDMAN INVESTIGATORS

Sangeeta Mehta MD is a critical care physician, Professor of Medicine and a Clinician Scientist. She has more than twenty years of experience in clinical ICU research, including surveys, practice audits, observational studies, systematic reviews, and RTCs. She led the large multicentre RCT, SLEAP (28).

Lara Prisco MD, AFRCA, AFFICM, MSc is a Consultant Neurointensivist and Neuroanaesthetist (John Radcliffe Hospital, Oxford) and Senior Clinical Research Fellow at the Nuffield Department of Clinical Neurosciences (University of Oxford). Dr Prisco is currently exploring the mechanisms of anaesthesia-induced unconsciousness (PI. Dr Katie Warnaby). She is Co-Investigator of the large multicentre observational study Synapse-ICU (PI. Dr Giuseppe Citerio). She is the past Deputy Chair of the

Neurointensive Care Section of the ESICM and member of the Women in NeuroCritical Care Committee of the NeuroCritical Care Society.

Geert Meyfroidt MD, PhD (NIC) is Associate Professor of Medicine at University of Leuven (KU Leuven) and Consultant Intensivist at the University Hospitals Leuven, Belgium. He is funded by the Flemish Government as Senior Clinical Investigator (2012-2017 and 2017-2022). Current research projects include: the use of data mining and predictive modeling in neuro-intensive care and acute kidney injury; the Brain Injury and Ketamine (BIKe) study (awarded the ESICM established investigator award 2016); cerebrovascular autoregulation; Synapse-ICU (national coordinator and steering committee). In ESICM, he was country representative for Belgium (2012-2015), and is now active in the Neuro-Intensive Care section. He is president-elect of the Belgian Society of Intensive Care Medicine (SIZ).

Lisa Burry PharmD, FCCM, FCCP is an Assistant Professor and Clinician Scientist at the Leslie Dan Faculty of Pharmacy, University of Toronto and Clinical Pharmacy Specialist at Mount Sinai Hospital Toronto, Canada. Dr. Burry is currently investigating melatonin for prevention of ICU delirium in a multicentre randomized controlled trial. Dr. Burry has led systematic reviews and observational studies investigating sedation and delirium in the ICU.

Fabio Silvio Taccone MD, PhD is Professor at the Department of Intensive Care of Hospital Erasme in Brussels (Belgium). Dr Taccone has a large area of interest in critical care medicine, with a particular research in antibiotic pharmacokinetics, brain injury after cardiac arrest, cerebral perfusion and microcirculation during severe infections and therapeutic hypothermia as a neuro-protective strategy. Dr Taccone has authored more than 190 scientific publications in peer-reviewed journals and is currently one of the supervisors of the Experimental Laboratory of Critical Care Medicine of the Hopital Erasme in Brussels (Belgium). He is also Deputy of the Neuro-Intensive Care section of the European Society of Intensive Care Medicine (ESICM) since 2013 and member of the Advisory Board of the International Symposium of Intensive Care and Emergency Medicine (ISICEM) since 2011. He is also co-investigator for the SHOCKOMICS study, endorsed by the European Community (FP7 Project – 2013) and the PI for the TRAIN Study (TRansfusion strategies in Acute brain INjured patients – endorsed by the ESICM Clinical Trials Group) and PRINCESS Study (intra-arrest hypothermia after cardiac arrest).

Giuseppe Citerio MD is Professor of Anesthesia and Intensive Care at the Milano Bicocca University, School of Medicine and Surgery and Director of Anesthesia and Neurosurgical Intensive Care, San Gerardo Hospital and Desio Hospital, ASST-Monza. He is the PI of the SYNAPSE-ICU study, and has actively participated in national and international collaborations, such as BrainIT and CenterTBI. He has contributed to the development of international guidelines on subarachnoid hemorrhage and neuromonitoring. At present he is Senior Deputy Editor of Intensive Care Medicine and will be the next Editor-in-Chief. Dr. Citerio has been Chair of the Division of Scientific Affairs of the ESICM, Executive Committee member, and Chair of the Annual ESICM Meeting and regional congresses.

Dylan deLange is an intensivist at the University Medical Center Utrecht. He is full professor in Clinical Toxicology and the chair of the Dutch National Poisons Information Center since 2017. He is a board member of the National Intensive Care Evaluation (NICE) Foundation. Part of his current research is

derived from this large national database: (long term) outcome after intensive care treatment. Since 2017 he is the chair of the scientific section on "Health Safety Research and Outcome" (HSRO) of the European Society of Intensive Care Medicine (ESICM). His research interests focus on "predicting outcome" in critically ill intoxicated patient, pharmacokinetics and toxicokinetics of antimicrobials and immunosuppressants, and biomarkers.

Michelle Chew MBBS PhD EDA EDIC, is the academic chair of the Department of Anesthesiology and Intensive Care at Linköping University Hospital and Deputy Chair for the HSRO section. Her research interests include the heart in sepsis and perioperative outcomes. She has been the national coordinator for a number of studies including EuSOS, ISOS, PRISM and NONSEDA and is the research lead for the MINSS study.

Ib Jammer is the current Chair of the ESICM POIC section. He is the national lead for international observational studies such as EuSOS, LAS VEGAS. Dr Jammer is recruiting local investigators for participating in ESA initiated studies (ETPOS, APRICOT). He is first author of the ESA/ESICM joint taskforce on perioperative outcome measures and main investigator in local interventional clinical trials and international observational studies. He is Co-chief investigator of Squeeze, an ESICM-ESA coordinated observational trial on postoperative vasoplegia.

Björn Weiss MD is Chair of ESICM NEXT, an intensive care consultant at Charité - Berlin University Hospital. Dr Björn Weiss' research interest focuses on ICU sedation and effects of sedatives and he is part of the Charité, Berlin group on delirium and long-term outcomes. He is co-investigator in several multicenter clinical trials (e.g., LoveMi, IDeAS) and is member of the German evidence- and consensus-based guideline task-force for sedation, analgesia, and delirium and has been member of the advisory board for the European Guidelines on Postoperative Delirium. Dr Weiss' clinical interests comprise ARDS and extracorporeal lung assists. He is currently leading the EuMAS study, a multi-centre one-day prevalence study evaluating the diagnostic utility of delirium screening.

Jorge Salluh MD is a senior researcher at the critical care department of the D' OR institute for research and education. He is Professor of the Postgraduate program at the Federal University of Rio de Janeiro. Dr. Salluh is a member of the scientific committee of BRICNet (Brazilian research in intensive care Network).

Jose M. Peña PhD is a data science expert, director of Lurtis Ltd. Former Professor at the Universidad Politécnica de Madrid and Deputy Director of the Madrid Supercomputing Centre (CeSViMa). He has 150+ journal papers and peer-reviewed conferences in the areas of data science, machine learning, and soft computing both theoretical and applied to health care, neuroscience, engineering, logistics, and finance.

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