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

- International Protocol -

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SaNDMAN has been endorsed by the following ESICM sections:

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

Amendment history

Protocol version	Date	Authors	Content
V1.0	04.03.2018	SM	Draft Protocol
V1.1	01.05.2018	Steering Committee	Edit of draft protocol
V2.0	09.02.2019	Statistician (JMP)	Statistical plan revision
V2.1	20.02.2019	Executive Committee	Amendment to draft protocol
V3.0	19.03.2019	Executive Committee	Final version for OUH R&D review
V3.1	20.07.2019	Executive Committee	Research assistants & Authorship
V3.1	20.07.2019	Executive Committee	Final version for R&D/Ethics review
V3.2	11.04.2020	Executive Committee	Amendments: Main study recruitment period, inclusion criteria, and details of COVID-19 Sub-study.
V3.3	15.12.2020	Principal Investigators	Amendments: Main study recruitment period, Change of Sponsor Institution
V3.4	12.08.2021	Principal Investigators	Amendments: Main study data collection period, Change of sponsor institution.

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SUMMARY

Title	**S**edation, **AN**algesia and **D**elirium **MAN**agement: an international audit of medical, surgical, trauma, and neuro-intensive care patients.
Abbreviation	SAnDMAN (Sub-study: SAnDMAN COVID-19)
Study design	Main study: Multicentre retrospective observational single cohort study COVID-19 sub-study: Multicentre retrospective observational two cohort study
Sponsor	University of Oxford, Clinical Trials and Research Governance, Joint Research Office, 1st Floor, Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7GB
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	***Sample Size:*** We aim to collect data from >2000 patients internationally from a minimum of 100 ICUs. ***Inclusion criteria:*** *Main study:* 1. "Standard ICU arm": Adults (≥18 years) admitted to a participating ICU from the 1st October 2019 until the 1st January 2020, 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. *COVID-19 sub-study:* 1. "COVID-19 ICU arm": Adults (≥18 years) admitted to a participating ICU from the 1st January 2020 until the 1st January 2021 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 1st January 2021 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. ***Exclusion criteria:*** none. ***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.
Planned Study Period	Participating ICUs will screen and collect data for the mechanically ventilated patients admitted to their ICU during the timeframe described below. We recognize that all ICUs may not be able to start on the same day, so **data from those defined periods will be collected from the institutional approval at each local site until the 1st June 2022.** 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 2020 to 1st January 2021). The date of the COVID-19 surge is exploratory and for data collection purposes it is defined as the date of the 1st COVID-19 patient admitted to ICU.
Study Registration	The study will be registered on Clinicaltrials.gov
Funder	European Society of Intensive Care Medicine Division of Scientific Affairs - Research Rue Belliard 19 – _1040 Brussels (Belgium) research@esicm.org Tel. 003225590353

Objectives		**Outcome Measures**	**Timepoint(s)**
Primary	A) ***Main study:*** To describe international practice in ICU, and practice variation in the use of drugs, and monitoring for Pain, Agitation and Delirium (PAD). B) ***COVID-19 sub-study:*** To describe the variation of sedation, analgesia, and delirium management during the COVID-19 pandemic in patients with confirmed or suspected SARS-CoV2 infection.	Variation of practice will be assessed as the number of patient/days for each sedative, analgesic, and anti-delirium drug (propofol, benzodiazepines, opioids, etc.) for both the main and COVID-19 sub-study. Monitoring for PAD will be assessed as the number of patient/days when a PAD scale has been used for both the main and COVID-19 sub-study.	Type of drug, administration method and dose will be recorded for the first 7 days of MV in ICU for each patient. Scales used to monitor PAD for the first 7 days of MV in ICU for each patient.

Secondary	A) ***Main study and COVID-19 sub-study:*** To quantify the adherence to the PAD clinical guidelines. B) ***Main study:*** 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 C) ***COVID-19 sub-study:*** To describe and compare management between COVID-19 negative ICU patient groups before and during the pandemic.	Sedation, analgesia, and delirium management will be compared to existing PAD guidelines and assessed for compliance. Sedation, analgesia, and delirium management in each subgroup will be assessed as: • the number of patient/days for each sedative/analgesic drug (propofol, benzodiazepines, opioids, etc.). • the type and number of assessments for delirium as well as the treatment of delirium symptoms Sedation, analgesia, and delirium management in the non-COVID-19 patients before and during the pandemic will be assessed as: • the number of patient/days for each sedative/analgesic drug (propofol, benzodiazepines, opioids, etc.). • the type and number of assessments for delirium as well as the treatment of delirium symptoms	Outcome measures will be assessed daily for the first 7 days of MV in ICU in each patient.

LAY ABSTRACT

Patients with acute severe health problems often need to be admitted to specialised hospital wards called Intensive Care Units (ICUs) where they can receive emergency treatment such as mechanical ventilation to support their breathing function via a machine, and sedative medications to reduce pain and anxiety associated with the severity of their condition. Although these interventions and treatments are often necessary to support patients' vital functions, they also carry the risk of important side effects. n

Sedative drugs use has a significant impact on short- and long-term outcomes. Despite international guidelines to help clinicians in the use of these drugs, there appears to be large variability in their use around the world such as use of different types of drugs, variable doses, or rate of continuous infusions, etc.

Despite this known variable practice across the world, there are no large-scale international studies looking at the use of sedative drugs, pain-relief medications, and drugs to control agitation and restlessness in ICUs.

Therefore, we propose a multinational study to better understand how different ICUs use these drugs and if they follow the guidance published by expert clinicians. We will collect data in more than 100 ICUs across the world and include more than 2000 adult patients admitted to ICU and needing mechanical breathing. Data will be obtained retrospectively from medical records and there are no active interventions on patients that are part of this research study. All patients included will receive the standard of care as per their local intensive care unit.

We will collect data retrospectively from medical records of patients previously admitted to ICU before and during the COVID-19 pandemic to explore how practice has changed during this exceptional timeframe.

The information we will obtain from this study will hopefully inform more research, education, and quality improvement initiatives to optimise care of these vulnerable patients.

This protocol refers to the study being conducted in the internationally and is based on the UK protocol sponsored by the University of Oxford. The results will be combined with those from all countries.

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).

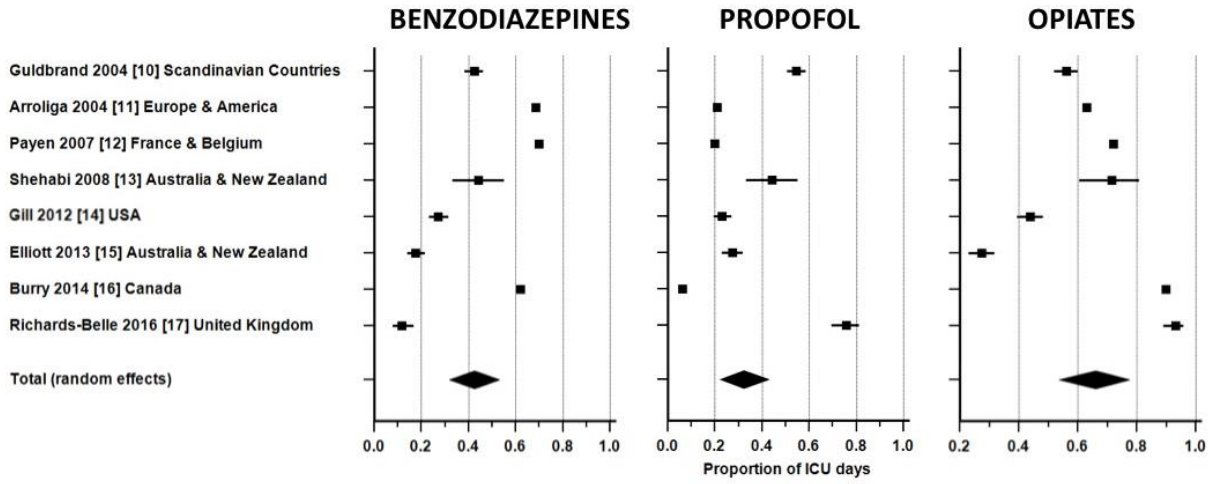
Table 1: Point of prevalence studies published between 1999-2018 evaluating the use of sedation and analgesia.

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]	Autralia 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 Random effects	BENZODIAZEPINES	PROPOFOL	OPIATES
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 of 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 of 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 of 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, Hypotheses and Outcome measures

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.

In this study/sub-study 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) 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.

Objectives		**Outcome Measures**	**Timepoint(s)**
Primary	A) ***Main study:*** To describe international practice in ICU, and practice variation in the use of drugs, and monitoring for Pain, Agitation and Delirium (PAD). B) ***COVID-19 sub-study:*** To describe the variation of sedation, analgesia, and delirium management during the COVID-19 pandemic in patients with confirmed or suspected SARS-CoV2 infection.	Variation of practice will be assessed as the number of patient/days for each sedative, analgesic, and anti-delirium drug (propofol, benzodiazepines, opioids, etc.) for both the main and COVID-19 sub-study. Monitoring for PAD will be assessed as the number of patient/days when a PAD scale has been used for both the main and COVID-19 sub-study.	Type of drug, administration method and dose will be recorded for the first 7 days of MV in ICU for each patient. Scales used to monitor PAD for the first 7 days of MV in ICU for each patient.

Secondary	A) ***Main study and COVID-19 sub-study:*** To quantify the adherence to the PAD clinical guidelines. B) ***Main study:*** 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 C) ***COVID-19 sub-study:*** To describe and compare management between COVID-19 negative ICU patient groups before and during the pandemic.	Sedation, analgesia, and delirium management will be compared to existing PAD guidelines and assessed for compliance. Sedation, analgesia, and delirium management in each subgroup will be assessed as: • the number of patient/days for each sedative/analgesic drug (propofol, benzodiazepines, opioids, etc.). • the type and number of assessments for delirium as well as the treatment of delirium symptoms Sedation, analgesia, and delirium management in the non-COVID-19 patients before and during the pandemic will be assessed as: • the number of patient/days for each sedative/analgesic drug (propofol, benzodiazepines, opioids, etc.). • the type and number of assessments for delirium as well as the treatment of delirium symptoms	Outcome measures will be assessed daily for the first 7 days of MV in ICU in each patient.

METHODS

Study Design

We will conduct a retrospective observational international study to collect anonymised data to gain a comprehensive picture of ICU practices regarding sedation, analgesia, and delirium management, and evaluate if practice patterns adhere to the Pain, Agitation and Delirium (PAD) guidelines (5). This research will be led by the Chief Investigator and the Executive Committee. Each site investigator (local Principal Investigator, PI) will collect data for the up to the first 7 days of mechanical ventilation for up to 20 consecutive patients admitted into their respective ICU(s) before the date of the first admission of COVID-19 patients. We will collect anonymised data about patients from both academic and community hospitals internationally. Data collection will remain open until the 1st of June 2022 to allow centres to participate and input data on the eCRF on flexible start dates.
This is a retrospective observational study, therefore there will be only no study visit and patients are not required to actively interact with the research.

COVID-19 sub-study

In this sub-study, the same design will be used (retrospective observational international study) with the aim to explore the differences in the sedation, analgesia and delirium management of COVID-19 and non-COVID-19 patients admitted to ICU during the SARS-CoV2 pandemic. In this two-arm sub-study, each site investigator (local Principal Investigator, PI) will collect data for up to the first 7 days of mechanical ventilation for up to 20 patients with a diagnosis of COVID-19 pneumonia and/or respiratory failure admitted during the COVID-19 pandemic, and up to 20 patients with no diagnosis of COVID-19 (admitted during the same timeframe, see eligibility criteria). The date of the COVID-19 surge is exploratory and for data collection purposes it is defined as the date of the 1st COVID-19 patient admitted to ICU.
This is a retrospective observational study, therefore there will be only one study visit and patients will not be required to participate.

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

Main study:

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

- Patients admitted to non-acute care units

COVID-19 sub-study

Data will not be collected from patients who fulfil the following exclusion criteria:

1. COVID-19 ICU arm:

• Patients with confirmed diagnosis of COVID-19 but admitted to ICU for indications different than pneumonia and/or acute respiratory failure (incidental positive COVID-19)

• Patients admitted to non-acute care units

2. Non-COVID-19 ICU arm:

• Patients admitted to non-acute care units

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.

Summary of study timeline

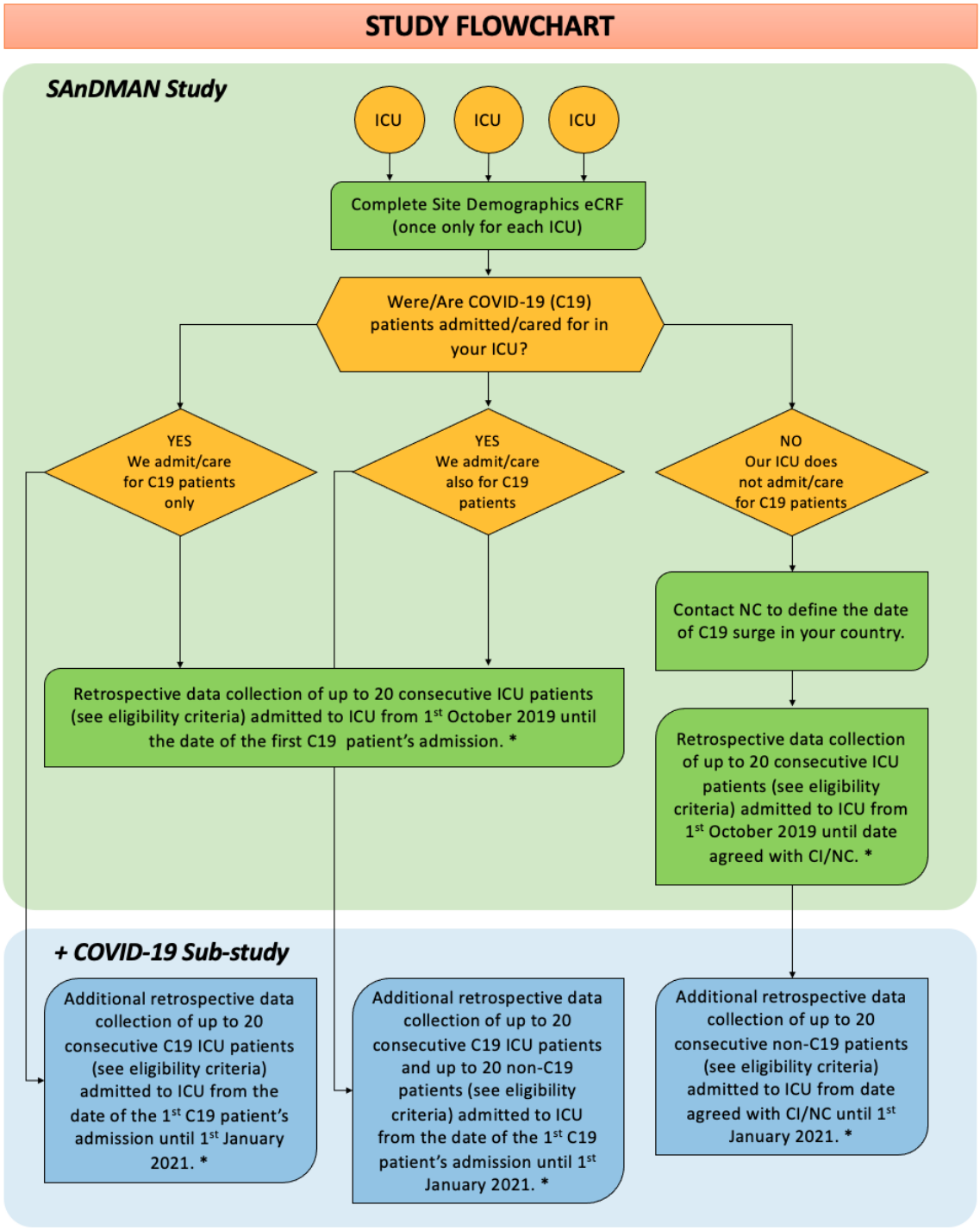


Figure 2. International Study Flowchart

Data Collection (input into eCRF by local research staff):

→ **From Ethics/Institutional Approval at each centre until 1st January 2022**. Data entry will open for few sites at the time to allow more accurate study coordination during the phase of data entry.

Participating ICUs will screen and collect data for the mechanically ventilated patients admitted to their ICU during the timeframe described Above. We recognize that all ICUs may not be able to start on the same day and 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 2020 to 1st January 2021).

The date of the COVID-19 surge is exploratory and for data collection purposes it is defined as the date of the 1st COVID-19 patient admitted to ICU.

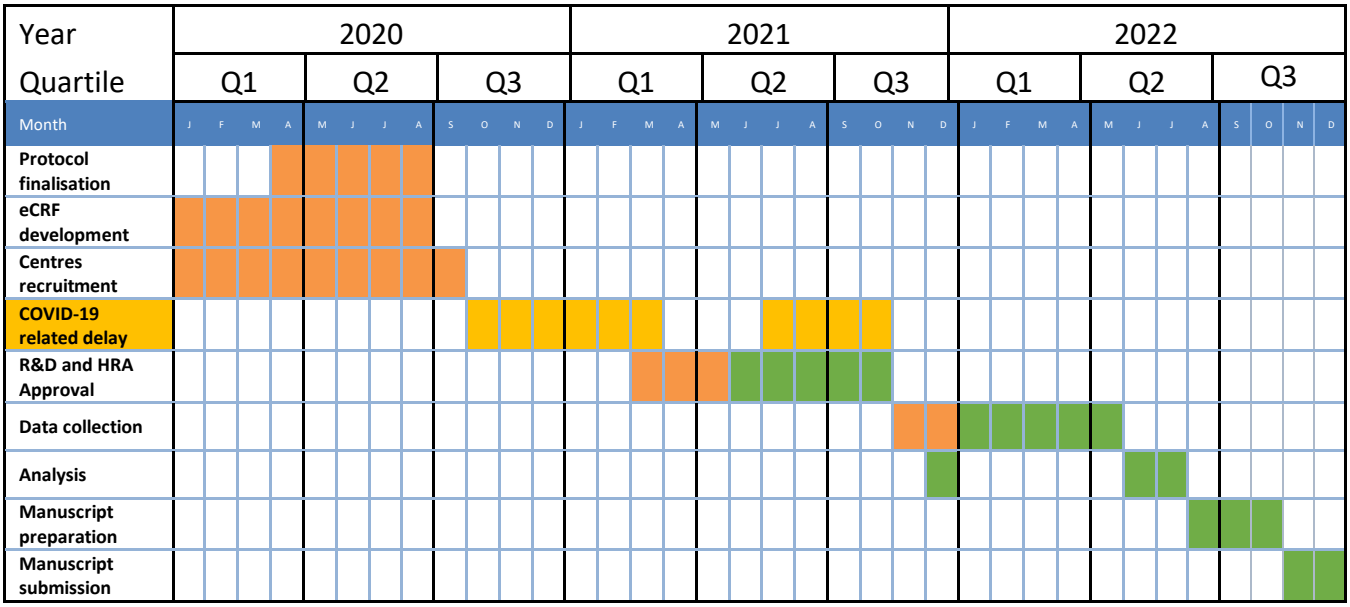


Figure 2. Proposed study timeline

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.

Protocol procedures

The study does not include any procedure or comparator. Given the observational retrospective nature of the study and COVID-19 sub-study, we will include data collection from medical notes (data sources) from previously collected clinical data.

The study (and COVID-19 sub-study) will include:

1. Recruitment of participating centres/ICUs in the United Kingdom and worldwide.

2. Screening and collection of participant data (retrospective) admitted to ICU.

3. Data collection as per eCRF provided by the study investigators (retrospective).

4. End of study, statistical analysis, and reporting/publication of results.

Methods Centre

The Methods Centre will be located at the 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.

Once HRA Approval in the United Kingdom is obtained and the study has been approved to start, each direct care team will review the admissions to ICU from the 1st of October until the 1st of January 2021 (or prior to the COVID-19 surge in the specific country). In the COVID-19 sub-study each direct team will review the admissions to ICU from the COVID surge until the 1st of January 2021.

All patients admitted to ICU and requiring mechanical ventilation for longer than 12 hours will be screened. Data from patients fulfilling the eligibility criteria will be collected.

Screening and Eligibility assessment

Querying of local electronic health records systems will be performed to extract the relevant data. All data will be extracted and anonymised at source, by members of the clinical care or research team (where appropriate approval for the research team to access patients' information is granted) who would process patient data as part of their role. All data will be anonymised at source and the study will be conducted exclusively with anonymised data. The investigators would have no way of de-anonymising these data and will not have access to protected health information.

Strict application of the inclusion and exclusion criteria will be performed by the providing hospital through the querying interface for their existing electronic health records system. There is no maximum duration allowed between screening and start of data collection. Each participant must satisfy all the approved inclusion and exclusion criteria of the protocol.

Members of the direct care team or research team (where appropriate approval for the research team to access patients' information is granted) will screen ICU admission registries and identify eligible patients by screening the following: date of admission to ICU, requirement for mechanical ventilation for more than 12 hours, COVID-19 status and date of birth. Research team members ideally will access only anonymised data. Analysis and reporting will be carried out by the study investigators.

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 and limit missing data. 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 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

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 ensures 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

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

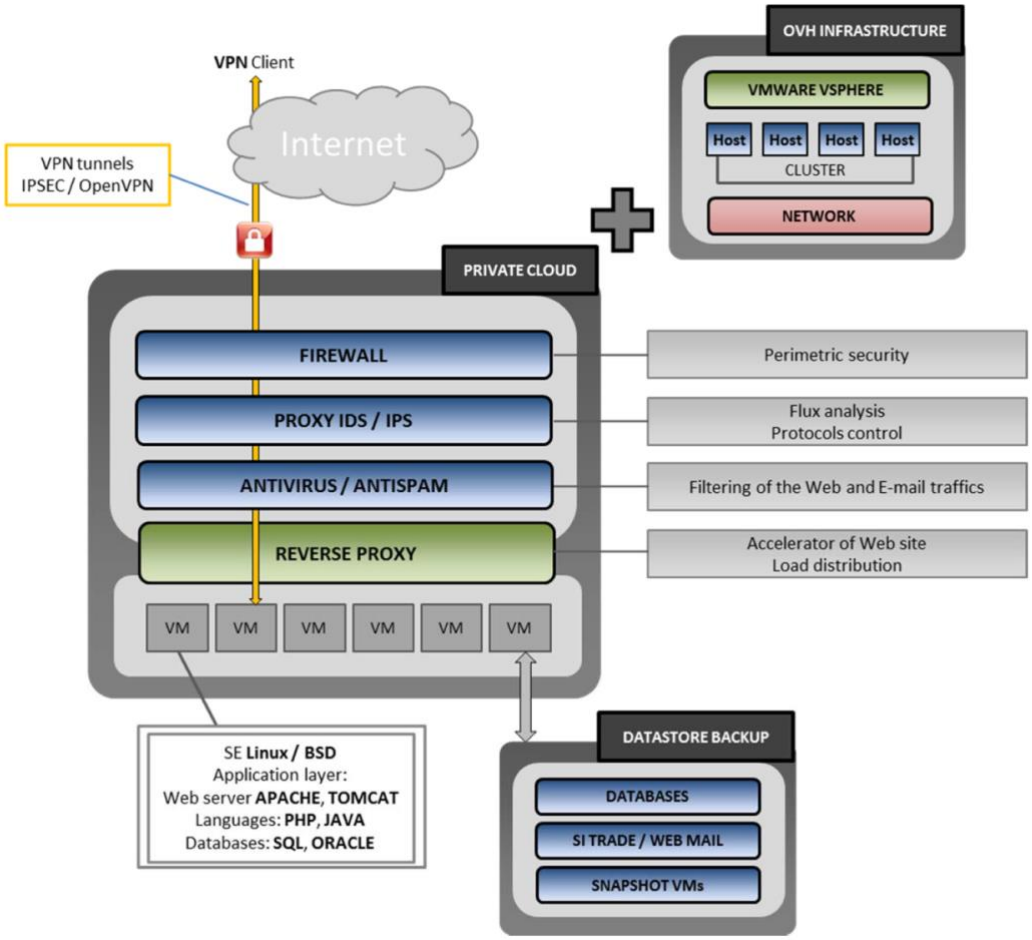


Figure 3. Data hosting and security features

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.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to the Statistician of the study. For this purpose, data will be anonymised at input into the eCRF by the local centres.

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.

Although no personal data will be shared, a Data Collaboration Agreement between local sites and the University of Oxford will be prepared and signed by the parties involved in data management.

Anonymised data will be retained in electronic form for a minimum of 10 years on encrypted hard drives at locked offices at the John Radcliffe Hospital on NHS/University premises (locked University offices at the Nuffield Department of Clinical Neurosciences on password-protected computer in encrypted folders).

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, Consultee 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-intervention 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 electroencephalography signatures of delirium after traumatic brain injury and is funded by a National Institute for Health Research Doctoral Research Fellowship (NIHR300741).

Sherihane Bensemmane MSc holds a master's degree in neuroscience, and in public health. She currently works as a researcher at the Scientific Institute for public health of the federal Belgian state, Sciensano. Previously, she worked as a scientific advisor at the European Society of Intensive Care Medicine and as a researcher at the Laboratory for Neuro- and Psychophysiology, a joint research group at the KU Leuven Medical School.

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 Hopital Erasme in Brussels (Belgium). Dr Taccone has a large area of interest in critical care medicine, with 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 several 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 taskforce 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.

REFERENCES

1. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, McArthur C, Seppelt IM, Webb S, Weisbrodt L; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators; ANZICS Clinical Trials Group. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med. 2012 Oct 15;186(8):724-31. doi: 10.1164/rccm.201203-0522OC. Epub 2012 Aug 2.

2. Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MA, Khoo TM, Ali SB, Saman MA, Shaltut A, Tan CC, Yong CY, Bailey M; Sedation Practice in Intensive Care Evaluation (SPICE) Study Group investigators. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med. 2013 May;39(5):910-8. doi: 10.1007/s00134-013-2830-2. Epub 2013 Jan 24.

3. Balzer F, Weiß B, Kumpf O, Treskatsch S, Spies C, Wernecke KD, Krannich A, Kastrup M. Early deep sedation is associated with decreased in-hospital and two-year follow-up survival. Crit Care. 2015 Apr 28; 19:197. doi: 10.1186/s13054-015-0929-2.

4. Tanaka LM, Azevedo LC, Park M, Schettino G, Nassar AP, Réa-Neto A, Tannous L, de Souza-Dantas VC, Torelly A, Lisboa T, Piras C, Carvalho FB, Maia Mde O, Giannini FP, Machado FR, Dal-Pizzol F, de Carvalho AG, dos Santos RB, Tierno PF, Soares M, Salluh JI; ERICC study investigators. Early sedation and clinical outcomes of mechanically ventilated patients: a prospective multicenter cohort study. Crit Care. 2014 Jul 21;18(4):R156. doi: 10.1186/cc13995.

5. Lonardo NW, Mone MC, Nirula R, Kimball EJ, Ludwig K, Zhou X, Sauer BC, Nechodom K, Teng C, Barton RG. Propofol is associated with favorable outcomes compared with benzodiazepines in ventilated intensive care unit patients. Am J Respir Crit Care Med. 2014 Jun 1;189(11):1383-94. doi: 10.1164/rccm.201312-2291OC. Erratum in: Am J Respir Crit Care Med. 2014 Jun 1;189(11):e70.

6. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013 Jan;41(1):263-306. doi: 10.1097/CCM.0b013e3182783b72.

7. DAS-Taskforce 2015, Baron R, Binder A, Biniek R, Braune S, Buerkle H, Dall P, Demirakca S, Eckardt R, Eggers V, Eichler I, Fietze I, Freys S, Fründ A, Garten L, Gohrbandt B, Harth I, Hartl W, Heppner HJ, Horter J, Huth R, Janssens U, Jungk C, Kaeuper KM, Kessler P, Kleinschmidt S, Kochanek M, Kumpf M, Meiser A, Mueller A, Orth M, Putensen C, Roth B, Schaefer M, Schaefers R, Schellongowski P, Schindler M, Schmitt R, Scholz J, Schroeder S, Schwarzmann G, Spies C, Stingele R, Tonner P, Trieschmann U, Tryba M, Wappler F, Waydhas C, Weiss B, Weisshaar G. Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) - short version. Ger Med Sci. 2015 Nov 12;13:Doc19. doi: 10.3205/000223. eCollection 2015.

8. Sauder P, Andreoletti M, Cambonie G, Capellier G, Feissel M, Gall O, Goldran-Toledano D, Kierzek G, Mateo J, Mentec H, Mion G, Rigaud JP, Seguin P. Sedation and analgesia in intensive care (with the exception of new-born babies). French Society of Anesthesia and Resuscitation. Ann Fr Anesth Reanim. 2008 Jul-Aug;27(7-8):541-51. doi: 10.1016/j.annfar.2008.04.021. Epub 2008 Jun 24.

9. Kotfis K, Zegan-Barańska M, Żukowski M, Kusza K, Kaczmarczyk M, Ely EW. Multicenter assessment of sedation and delirium practices in the intensive care units in Poland - is this common practice in Eastern Europe? BMC Anesthesiol. 2017 Sep 2;17(1):120. doi: 10.1186/s12871-017-0415-2.

10. Guldbrand P, Berggren L, Brattebö G, Mälstam J, Rönholm E, Winsö O; Scandinavian Critical Care Trials Group. Survey of routines for sedation of patients on controlled ventilation in Nordic intensive care units. Acta Anaesthesiol Scand. 2004 Sep;48(8):944-50.

11. Arroliga A, Frutos-Vivar F, Hall J, Esteban A, Apezteguía C, Soto L, Anzueto A; International Mechanical Ventilation Study Group. Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. Chest. 2005 Aug;128(2):496-506.

12. Payen JF, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou JL, Binhas M, Genty C, Rolland C, Bosson JL. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicentre patient-based study. Anesthesiology. 2007 Apr;106(4):687-95.

13. Shehabi Y, Botha JA, Boyle MS, Ernest D, Freebairn RC, Jenkins IR, Roberts BL, Seppelt IM. Sedation and delirium in the intensive care unit: an Australian and New Zealand perspective. Anaesth Intensive Care. 2008 Jul;36(4):570-8.

14. Gill KV, Voils SA, Chenault GA, Brophy GM. Perceived versus actual sedation practices in adult intensive care unit patients receiving mechanical ventilation. Ann Pharmacother. 2012 Oct;46(10):1331-9.

15. Elliott D, Aitken LM, Bucknall TK, Seppelt IM, Webb SA, Weisbrodt L, McKinley S; Australian and New Zealand Intensive Care Society Clinical Trials Group; George Institute for Global Health. Patient comfort in the intensive care unit: a multicentre, binational point prevalence study of analgesia, sedation and delirium management. Crit Care Resusc. 2013 Sep;15(3):213-9.

16. Burry LD, Williamson DR, Perreault MM, Rose L, Cook DJ, Ferguson ND, Lapinsky SC, Mehta S. Analgesic, sedative, antipsychotic, and neuromuscular blocker use in Canadian intensive care units: a prospective, multicentre, observational study. Can J Anaesth. 2014 Jul;61(7):619-30.

17. Richards-Belle A, Canter RR, Power GS, Robinson EJ, Reschreiter H, Wunsch H, Harvey SE. National survey and point prevalence study of sedation practice in UK critical care. Crit Care. 2016 Oct 27;20(1):355.

18. Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguía C, Nightingale P, Arroliga AC, Tobin MJ; Mechanical Ventilation International Study Group.

Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA. 2002 Jan 16;287(3):345-55.

19. Morandi A, Piva S, Ely EW, Myatra SN, Salluh JIF, Amare D, Azoulay E, Bellelli G, Csomos A, Fan E, Fagoni N, Girard TD, Heras La Calle G, Inoue S, Lim CM, Kaps R, Kotfis K, Koh Y, Misango D, Pandharipande PP, Permpikul C, Cheng Tan C, Wang DX, Sharshar T, Shehabi Y, Skrobik Y, Singh JM, Slooter A, Smith M, Tsuruta R, Latronico N. Worldwide Survey of the "Assessing Pain, Both Spontaneous Awakening and Breathing Trials, Choice of Drugs, Delirium Monitoring/Management, Early Exercise/Mobility, and Family Empowerment" (ABCDEF) Bundle. Crit Care Med. 2017 Nov;45(11):e1111-e1122. doi: 10.1097/CCM.0000000000002640.

20. Borkowska M, Labeau S, Blot S. Nurses' practice concerning sedation during weaning from mechanical ventilation. Intensive Care Medicine Experimental 2015, 3(Suppl 1):A925.

21. Burry LD, Williamson DR, Perreault MM, Rose L, Cook DJ, Ferguson ND, Lapinsky SC, Mehta S. Analgesic, sedative, antipsychotic, and neuromuscular blocker use in Canadian intensive care units: a prospective, multicentre, observational study. Can J Anaesth. 2014 Jul;61(7):619-30. doi: 10.1007/s12630-014-0174-1.

22. Burry LD, Williamson DR, Mehta S, Perreault MM, Mantas I, Mallick R, Fergusson DA, Smith O, Fan E, Dupuis S, Herridge M, Rose L. Delirium and exposure to psychoactive medications in critically ill adults: A multi-centre observational study. J Crit Care. 2017 Dec;42:268-274. doi: 10.1016/j.jcrc.2017.08.003.

23. deBacker J, Tamberg E, Munshi L, Burry L, Fan E, Mehta S. Sedation Practice in Extracorporeal Membrane Oxygenation-Treated Patients with Acute Respiratory Distress Syndrome: A Retrospective Study. ASAIO J. 2017 Oct 18. doi: 10.1097/MAT.0000000000000658.

24. Gill KV, Voils SA, Chenault GA, Brophy GM. Perceived versus actual sedation practices in adult intensive care unit patients receiving mechanical ventilation. Ann Pharmacother. 2012 Oct;46(10):1331-9. doi: 10.1345/aph.1R037. Epub 2012 Sep 18.

25. Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, Kress JP, Davidson JE, Spencer FA. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. Crit Care Med. 2013 Sep;41(9 Suppl 1):S30-8. doi: 10.1097/CCM.0b013e3182a16898.

26. Luetz A, Balzer F, Radtke FM, et al. Delirium, Sedation and Analgesia in the Intensive Care Unit: A Multinational, Two-Part Survey among Intensivists. Mazza M, ed. *PLoS ONE*. 2014;9(11):e110935. doi:10.1371/journal.pone.0110935.

27. Kotfis K, Zegan-Barańska M, Żukowski M, Kusza K, Kaczmarczyk M, Ely EW. Multicenter assessment of sedation and delirium practices in the intensive care units in Poland - is this common practice in Eastern Europe? *BMC Anesthesiology*. 2017;17:120. doi:10.1186/s12871-017-0415-2.

28. Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, Herridge M, Ferguson N, Devlin J, Tanios M, Dodek P, Fowler R, Burns K, Jacka M, Olafson K, Skrobik Y, Hébert P, Sabri E, Meade M; SLEAP Investigators; Canadian Critical Care Trials Group. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA. 2012 Nov 21;308(19):1985-92. Erratum in: JAMA. 2013 Jan 16;309(3):237

Data Analytics References:

- Aha, D. W., & Bankert, R. L. (1996). A comparative evaluation of sequential feature selection algorithms. In Learning from data (pp. 199-206). Springer, New York, NY.
- Breiman, L. (2001). Random forests. Machine learning, 45(1), 5-32.
- Chang, C. C., & Lin, C. J. (2011). LIBSVM: a library for support vector machines. ACM transactions on intelligent systems and technology (TIST), 2(3), 27.
- Chen, T., & Guestrin, C. (2016, August). Xgboost: A scalable tree boosting system. In Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining (pp. 785-794). ACM.
- Freund, Y. & Schapire, R. E. (1997). A decision-theoretic generalization of on-line learning and an application to boosting. Journal of computer and system sciences, 55(1), 119-139.
- Gallinari, P., Thiria, S., Badran, F., & Fogelman-Soulie, F. (1991). On the relations between discriminant analysis and multilayer perceptrons. neural networks, 4(3), 349-360.
- Guyon, I., & Elisseeff, A. (2003). An introduction to variable and feature selection. Journal of machine learning research, 3(Mar), 1157-1182.
- Kursa, M. B., & Rudnicki, W. R. (2010). Feature selection with the Boruta package. J Stat Softw, 36(11), 1-13.
- Oh, I. S., Lee, J. S., & Moon, B. R. (2004). Hybrid genetic algorithms for feature selection. IEEE Transactions on Pattern Analysis & Machine Intelligence, (11), 1424-1437.
- Rish, I. (2001, August). An empirical study of the naive Bayes classifier. In IJCAI 2001 workshop on empirical methods in artificial intelligence (Vol. 3, No. 22, pp. 41-46). New York: IB.
- Saeys, Y., Inza, I., & Larrañaga, P. (2007). A review of feature selection techniques in bioinformatics. bioinformatics, 23(19), 2507-2517.
- Tibshirani, R. (1996). Regression shrinkage and selection via the lasso. Journal of the Royal Statistical Society. Series B (Methodological), 267-288.

COVID-19 References/Resources:

- https://www.who.int/emergencies/diseases/novel-coronavirus-2019
- https://www.worldometers.info/coronavirus/
- https://jamanetwork.com/journals/jama/pages/coronavirus-alert
- https://www.thelancet.com/coronavirus