

## Early rehabilitation of intensive care unit patients - a multinational prospective observational study on dosage and outcome (ERUPT Study)

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### Overview of changes to the protocol

Version	Date	Description
1.0	10 March 2025	Initial version (Initial ethics vote 1272/2025 from Medical University of Vienna from 30 April 2025)
2.0	24 October 2025	Changes made (Approval of the proposed amendment to the protocol by the Ethics Committee of the Medical University of Vienna on 5 November 2025): <ul style="list-style-type: none"><li>• Affiliations and professions of the members of the Steering Committee adjusted</li><li>• Current professional societies endorsing ERUPT added</li><li>• Table “Overview of changes to the protocol” added</li><li>• Clarifications and language adaptations, especially statistical description</li><li>• Change of the targeted strata sizes for recruiting</li><li>• Classification of facultative assessments (first and second stage) changed; Secondary outcome driving capability added</li></ul>
2.1	15 December 2025	Change made (not subject to approval): <ul style="list-style-type: none"><li>• Affiliation of one Steering Committee member adjusted</li></ul>

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## 1 Synopsis

<b>Title</b>	Early rehabilitation of intensive care unit patients - a multinational prospective observational study on dosage and outcome
<b>Abbreviation</b>	ERUPT Study
<b>Study design</b>	Prospective, multicentre observational study
<b>Background and Rationale</b>	Early mobilisation is generally recommended in recent guidelines although its evidence according to meta-analysis is weak and its realization personnel-intensive. Randomized controlled trials have only investigated patients who were functionally independent before intensive care unit admission and the TEAM RCT demonstrated the importance of dosing.
<b>Objectives</b>	<p>The main objectives of the study are:</p> <ol style="list-style-type: none"> <li>1. The description of the variety of different mobilisation practices worldwide</li> <li>2. The analysis of the association between mobilisation dosage and patient outcomes</li> <li>3. The evaluation of the association between prehospital functional status or invasive mechanical ventilation and patient outcomes</li> <li>4. The development of a model for decision support using reinforcement learning.</li> </ol>
<b>Methods</b>	<p><b>Sample Size:</b> We aim to recruit &gt; 6000 patients internationally from a minimum of 200 ICUs including at least 30 consecutive patients each (strata: (1) mechanically ventilated functionally independent, (2) mechanically ventilated functionally dependent before hospital admission and (3) without invasive mechanical ventilation independent of functional status at study inclusion)</p> <p><b>Inclusion criteria:</b> Adults (<math>\geq 18</math> years) who are expected to stay &gt; 24 hours in the ICU, within 48 hours of ICU admission</p> <p><b>Exclusion criteria:</b> Patients who receive end-of-life care at the time of screening, patients with language barriers, patients whose treatment plans are still under discussion and/or not all team members are committed to full active treatment, patients who had been enrolled in the ERUPT study before or patients whose functional status is unlikely to be obtainable.</p> <p><b>Data collection:</b> Baseline data will be collected after study inclusion. Mobilisation data (frequency, duration, level) together with organ support, interventions (e.g., tracheostomy) and sedation will be recorded daily until ICU discharge, day 28 or death.</p>
<b>Outcomes</b>	<p><b>Primary outcome</b> will be physical function at ICU discharge.</p> <p><b>Secondary outcomes:</b> ICU mortality, hospital mortality, ICU length of stay, hospital length of stay, and 90 day follow up for mortality, global function using</p>

	WHODAS 2.0 and driving capability as well as and functional status including the trajectory of functional status over time.
<b>Duration of study</b>	<p><b>Screening and recruitment:</b> Participating ICUs will screen and collect data for all newly admitted patients with the aim of sets of 30 (targeted strata: 5 consecutive functionally dependent, 15 functionally independent patients, 10 patients without invasive mechanical ventilation). Per ICU a maximum of 3 complete sets (90 patients) will be allowed.</p> <p><b>Follow up</b> will be collected at 90 days.</p> <p><b>Duration:</b> Not all ICUs may be able to start on the same day, so given the large number of ICUs, we aim to collect data over a 21-month period.</p>
<b>Study registration</b>	The study was prospectively registered on Clinicaltrials.gov (NCT06960642).

## 2 Plain English Summary

Critically ill patients require substantial resources and multiple interventions. Some die, and many of those who survive have delayed and compromised functional recovery long after their treatment has been completed. Mobilisation in critically ill patients significantly impacts the short- and long-term functional outcomes. There is evidence that the cognitive outcome may also be improved by mobilisation. However, there is tremendous variability in frequency, duration and level of mobilisation, without any large-scale multinational data describing mobilisation practice in the intensive care unit. Patients who have been limited in their walking abilities or with low reserves (frail) before their hospital admission have been excluded from interventional mobilisation trials. It is, therefore, essential to understand the optimal dosage of mobilisation necessary to promote a favourable functional outcome and to understand if and how we can maintain functionality in prior dependent patients.

Furthermore, we want to investigate differences between ventilated and non-ventilated critically ill patients. We will collect data worldwide in academic and non-academic ICUs on heterogeneous populations of critically ill adult patients, including medical, surgical, trauma and neuro-intensive care patients. The data generated from this study will promote research and clinical care for a diverse patient population.

### **3 Background**

#### **3.1 *Incomplete recovery after critical illness***

Incomplete recovery following critical illness is a major public health problem worldwide.<sup>1</sup> More than 5.7 million patients in the USA, more than 2 million in Germany, and around 150,000 patients in Australia are treated annually in intensive care units.<sup>2,3</sup> These critically ill patients require substantial resources and multiple interventions. Some die, and many of those who survive and are without pre-existing neuromuscular impairment have delayed and compromised functional recovery long after their treatment has been completed.<sup>4,5</sup> As many as 25% of the ICU survivors who were living at home prior to ICU admission are unable to return home due to impaired physical function.<sup>5</sup> Globally, the quality of survival following an ICU stay has been identified as one of the most significant health challenges for these patients.<sup>6,7</sup>

#### **3.2 *Variation of practice and definitions worldwide***

A currently recommended intervention is early mobilisation.<sup>8-10</sup> There is no uniform definition of early mobilisation worldwide. Some define early mobilisation within 72 hours of ICU admission, others if started during mechanical ventilation and others if started during the ICU.<sup>11</sup> Consequently, people consider providing early mobilisation if surveyed.<sup>12</sup> However, this result contradicts the prevalence studies, where early mobilisation or mobilising intubated patients is still rare.<sup>13-16</sup> Importantly, any intervention started late, i.e. 72 hours after intensive care admission, failed to show improvement in patient outcome.<sup>17</sup> Such early intervention, however, seems necessary to prevent muscle atrophy<sup>18</sup> and improve functional outcomes.<sup>19-22</sup>

#### **3.3 *The influence of mobilisation dosage***

In 2015, it became evident that dosage might have essential effects on the outcomes of our patients and that this should be considered. This insight came from data on stroke patients but not ICU patients, indicating that dosage, i.e. frequency, duration, and level, influenced the outcome of those patients.<sup>23,24</sup> In mechanically ventilated adult ICU patients, the randomised controlled TEAM trial demonstrated that early mobilisation at the highest level possible and for the longest duration possible did not significantly increase the days patients were alive or out of the hospital compared to mobilisation according to current standards. Instead, adverse events increased.<sup>25</sup> Additionally, a high dosage affects the necessary personnel resources tremendously. Without knowing the optimal mobilisation dosage, it is not known what mobilisation concept should be provided and how much (personnel) resources are necessary and valuable to improve patient outcomes.

By collecting data on staff resources involved in mobilisation, the study also aims to identify associations between staff resources and patient outcomes. This should provide initial evidence-based information on the staff resources required for optimal mobilisation care.

#### **3.4 *Patient population and the influence of the functional status before hospital admission***

While some patients might need extensive resources to maintain their functional status, others might not benefit. One example is very sick (SOFA  $\geq 9$ ) septic patients: early mobilisation seems to prevent muscle mass loss but does not improve functional outcomes.<sup>18</sup> In the neurocritical care population, no randomised controlled trial is

available. The best evidence for this cohort comes from a large observational study that lacks any information on mobilisation dosage.<sup>26</sup> Furthermore, existing randomised trials only included functionally independent patients before ICU admission.<sup>17</sup>

A secondary analysis of the Team RCT revealed that patients with diabetes demonstrated increased mortality at 180 days with early active mobilisation.<sup>27</sup>

Lastly, in a secondary analysis using cluster analysis, different patient cohorts benefited from different mobilisation components.<sup>28</sup>

Consequently, it remains unclear whether (1) the functional status of patients who were functionally dependent prior to ICU admission can be maintained or restored by mobilisation, (2) whether the required mobilisation dosage for these patients differs significantly, and (3) what the optimal mobilisation dosage and risks are in different patient cohorts.

In summary, this study addresses the burden of long-term morbidity among all patients admitted to the ICU, including patients who have been functionally dependent prior to the hospital admission and have not been investigated so far. There is an urgent and unmet need to better understand and improve health outcomes for this cohort of patients.

### **3.5 Patients not invasively ventilated**

Invasive mechanical ventilation is a widely used intervention in intensive care medicine. However, it is also associated with health risks (e.g., ventilator-induced lung injury)<sup>29</sup> and unpleasant patient experiences (e.g., vulnerability, intense stress on the body system, negative emotional situation).<sup>30</sup> Modern critical care uses non-invasive ventilation (NIV) and high-flow oxygen therapy to reduce the need for mechanical ventilation.<sup>31-33</sup>

Consequently, this group will also be included in and observed as part of the study. Patients who will not require invasive ventilation at the time of study enrollment will constitute a subgroup.

## **4 Research Questions and Objectives**

### **4.1 Research Questions**

The main research questions of this study are:

1. What is the association between mobilisation dosage (frequency, duration and level of mobilisation) and outcomes of critically ill patients?
2. Is there an association between the prehospital status or invasive mechanical ventilation at ICU admission and outcomes of critically ill patients?

### **4.2 Aims and Objectives with hypotheses**

The aims and objectives of the study are:

1. The description of the variety of different mobilisation practices worldwide using a harmonised scheme of data collection. We hypothesise that
  - a. the frequency of early mobilisation differs between countries or regions worldwide.
  - b. mobilisation provided on 7 days per week differs between countries or regions worldwide.
  - c. the duration of mobilisation per day differs between countries or regions worldwide.

- d. there is a geographical variation in minutes spent with the patient on active or passive mobilisation activities.
2. The analysis of the association between mobilisation dosage and outcomes in critically ill patients aims to define a minimum mobilisation dosage necessary to achieve a clinically meaningful treatment effect on these patients' outcomes. We hypothesise that
  - a. there is a minimum daily mobilisation dosage providing a clinically meaningful treatment effect on outcomes of critically ill patients.
  - b. there is an association between the number of staff (staff resources) involved in mobilisation and patient outcomes.
  - c. there is an association between the involvement of physiotherapists in mobilisation and patient outcomes.
3. The evaluation of the association between prehospital functional status or invasive mechanical ventilation and outcomes in critically ill patients. We hypothesise that
  - a. the prehospital functional status influences the effect of mobilisation on the patient outcome.
  - b. invasive mechanical ventilation at the time of study inclusion (< 48h of ICU admission) influences the effect of mobilisation on the patient outcome.
4. The development of a model for decision support using reinforcement learning.

## 5 Study Endpoints

The primary endpoint is physical function at ICU discharge, measured using the Functional Status Score for the Intensive Care Unit (FSS-ICU)<sup>34</sup>. The total score ranges from 0-35, with higher scores indicating better physical function.

Secondary endpoints (obligatory) are:

1. ICU Mobility Scale (IMS)<sup>14</sup> at ICU discharge and 90 days
2. ICU length of stay
3. Hospital length of stay
4. Clinical Frailty Scale (CFS)<sup>35</sup> at ICU discharge and 90 days
5. ICU-, hospital and 90-day mortality
6. WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)<sup>36</sup> at 90 days
7. Barthel Score<sup>37</sup> at ICU discharge and 90 days
8. FSS-ICU at 90 days
9. Driving capability (part 1) at 90 days

Exploratory endpoints (facultative assessments in centres that are interested in additional scientific questions and able to conduct these assessments):

1<sup>st</sup> stage:

1. Chelsea Critical Care Physical Assessment Tool (CPAx<sup>38</sup>) at ICU discharge
2. Medical Research Council (MRC) Score<sup>39</sup> at ICU discharge

3. 5-level EQ-5D version (EQ-5D-5L) at 90 days
4. Delirium- and coma-free days during the ICU stay
5. Physical Function ICU Test-scored (PFIT-s)<sup>40</sup> at ICU discharge
6. 30-second sit-to-stand test at ICU discharge
7. Driving capability (part 2) at 90 days

## 6 Overall study design

### 6.1 Patient Population

#### 6.1.1 Inclusion criteria

The inclusion criteria are:

1. Adult ( $\geq 18$  years old) within 48 hours of ICU admission
2. Expected to stay  $> 24$  hours in the ICU

#### 6.1.2 Exclusion criteria

Patients are excluded if, at the time of screening,

- they receive end-of-life care
- their treatment plans are still under discussion and/or not all team members are committed to full active treatment
- their functional status is unlikely to be obtained
- they have language barriers
- they were already enrolled in the study.

### 6.2 Procedures

This is a multinational observational study without intervention. Exposure is the standard mobilisation therapy each ICU provides.

### 6.3 Patient recruitment

An international, multicentre stratified recruitment of patients will be implemented, with the aim that each ICU recruits at least 30 consecutive patients. The stratified recruitment will seek to include the various ICU cohorts outlined in Table 1.

*Table 1. Targeted strata per ICU.*

No	Strata
1	Patients with invasive mechanical ventilation, functionally independent before hospital admission
2	Patients with invasive mechanical ventilation, functionally dependent before hospital admission
3	Patients without invasive mechanical ventilation independent of their functional status at study inclusion

## 6.4 Data collection

### 6.4.1 Patient data

The functional baseline will be obtained retrospectively by interviewing the responsive and oriented patient or a proxy/relatives regarding the status before the onset of illness that led to hospital admission: (1) The FSS-ICU, as described earlier, will be used to assess patients' prehospital physical function. (2) The Barthel Score measures 10 activities of daily living.<sup>37</sup> (3) The maximal ICU Mobility Scale (IMS<sup>14</sup>) will provide the patient's general characterisation and prehospital mobility level, and will be used to classify patients as prior independent and dependent. (4) The Clinical Frailty Scale (CFS)<sup>35</sup> will be used to screen for frailty and determine its level. (5) The patients' driving capability will be assessed.

*Table 2. Overview of collected obligatory variables.*

	Baseline ICU admission	Daily in ICU	ICU discharge	Hospital discharge	90 Day Follow up
ICU Mobility Scale	X <sup>a</sup>	X	X		X
FSS-ICU	X <sup>a</sup>		X		X
Barthel Score	X <sup>a</sup>		X		X
CFS	X <sup>a</sup>		X		X
Driving capability I	X <sup>a</sup>				X
SOFA Score	X	X	X		
Patient characteristics <sup>b</sup>	X				
Basic nutritional information	X	X			
Organ support <sup>c</sup>		X			
Interventions and sedation <sup>d</sup>		X			
Mobilisation Dose <sup>e</sup>		X			
ICU Length of stay			X		
Hospital Length of stay				X	
Mortality			X	X	X
WHODAS 2.0					X

a) Pre-ICU Status: Status before the onset of illness that led to hospital admission reported by responsive and oriented patient or proxy/relatives

b) These include, e.g. age, sex, comorbidities, and admission category

c) This includes the requirement of e.g. vasopressors, mechanical ventilation

d) Interventions each day which might limit mobilisation, like surgery

e) Levels, frequency, timing and duration of mobilisation

The admission category will be classified using the APACHE III ICU Diagnoses Code.<sup>41</sup> The severity of the disease will be documented by the daily SOFA score.<sup>42</sup>

Focus is the mobilisation dosage provided during the ICU stay, including documentation of (1) time, (2) duration, (3) level using an extended version of the IMS,<sup>14</sup> which documents not only active but also passive forms of mobilisation, and (4) provider(s) (e.g. nurse, physical therapist) of each mobilisation the patient receives. To standardise the documentation of mobilisation, the participating ICUs will be provided with a corresponding documentation form, a manual explaining its use, and FAQs.

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Organ support documentation will include a daily assessment of mechanical ventilation (including airway type, e.g., endotracheal tube), haemodialysis (including localisation neck vs. groin), ECMO, and simple information about vasopressors.

Interventions or sedation which might limit mobilisation will be documented. This will include the type and duration of intervention or sedation. Basic nutritional information will also be captured, with the option for detailed documentation facultatively.

Baseline data will be collected after study inclusion. Mobilisation data, together with the SOFA score, organ support, interventions, sedation and basic nutritional information, will be recorded daily until ICU discharge, day 28 or death. Performance-based standardised tests and questionnaires will be conducted to measure physical function and quality of life. Patients' participation in the study will conclude with the follow-up examination (telephone interview) scheduled at 90 days after enrolment.

Study centres can also collect optional data on mobilisation, physical function, quality of life, nutrition and the patient's driving capability. A distinction is made here between the first and second stages of facultative assessments. Tables 2 and 3 provide an overview of obligatory and facultative study data.

**Table 3. Overview of facultative assessments**

		Baseline ICU admission	Daily in ICU	ICU discharge	Hospital discharge	90 Day Follow up
1 <sup>st</sup> stage of facultative assessments	<b>WHODAS 2.0</b>	X <sup>a</sup>				
	<b>Driving capability II</b>	X <sup>a</sup>				X
	<b>Delirium</b>		X			
	<b>Additional mobilisation information</b>		X			
	<b>CPAx<sup>b</sup></b>			X		
	<b>MRC Score</b>			X		
	<b>PFIT-s</b>			X		
	<b>30s STS</b>			X		
	<b>EQ-5D-5L</b>					X
2 <sup>nd</sup> stage of facultative assessments	<b>Detailed nutritional information</b>		X			

a) Pre-ICU Status: Status before the onset of illness that led to hospital admission reported by responsive and oriented patient or proxy/relatives

b) In the CPAx all sub-elements shall be collected since not all centres can do hand grip strength tests.

#### 6.4.2 Centre data

Eligible ICUs willing to participate will complete the Centre Data Characteristics Form once at the study's beginning, including, e.g., the number of beds, admissions, and the existence of mobilisation protocols.

#### 6.5 Workflow of the study

Here, we present the workflow/timeline of the complete project. As in earlier studies endorsed by the ESICM, we will allow centres to enter until a defined time point and, therefore, also allow ethics submission at later time points.



Administration (FDA) - Regulation 21 CFR Part 11 and the Good Clinical Practice (GCP) criteria. The university's IT service stores and secures data according to current technical standards and GDPR against unauthorised access.

#### **7.4 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 documentation, data and all other information generated will be held in strict confidentiality agreement protocols.

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

Study participant research data, which is for statistical analysis and scientific reporting, will be transmitted to the statistician(s) of the study. For this purpose, data is deidentified at input into the eCRF by the local centres. Only the local study centres have identified data and are responsible for adequate data safety.

Data may be anonymised (removal of pseudonyms) to be published at a public scientific repository or aggregated for scientific presentations (posters, talks, manuscripts, etc.).

#### **7.5 Data Archiving**

Essential study documents will be retained for 10 years after completion or termination of the study. If a longer period is required by law in some study centres, they will follow their regulations. Anonymised data (i.e., pseudonymisation removed) has no restriction on archiving time.

## **8 Statistical Considerations**

### **8.1 Statistical Analysis**

Descriptive statistics will summarise patient characteristics at the individual, ICU, and country aggregation levels. Data will be presented visually and in tables for reporting and publication purposes. Continuous variables will be described as means  $\pm$  SD or as medians and IQR, as appropriate. Frequencies and proportions will be applied for categorical variables.

For the main objective 1, the proportion of early mobilisation and the distribution of other measures of mobilisation (duration, dosage, cumulative dosage) provided per day per patient will be reported and descriptively compared using summary statistics and graphics. These descriptions will also inform how to parametrise mobilisation dosage (day-by-day or cumulative, e.g., over the first week) for the second aim.

For the second main objective, the association between mobilisation dosage, the number of staff, and the involvement of physiotherapists with each (quasi-)metric outcome will be examined as follows: Scatterplots will be used to graphically describe the association of each outcome with its respective baseline value and mobilisation dosage. Locally estimated scatterplot smoothing (LOESS) will be used to reveal non-linear associations. Mixed models will be used to estimate the association between each outcome and mobilisation dosage, adjusted for its baseline value, while accounting for clustering. The functional form of mobilisation dosage in its association with outcomes will be modelled flexibly using splines. The nested clustering induced by region, country, and centre

will be accounted for by the corresponding variance components and random effects. Length of stay and mortality outcomes will be investigated in combination as ICU- or hospital-free days alive until day 90.

Depending on the scale level of each outcome, we will use ordinal mixed models for FSS-ICU, IMS, and other scales, negative binomial mixed models for length of stay, and logistic mixed models for binary outcomes, such as ICU mortality, hospital mortality, or 90-day mortality. Appropriate residual diagnostics and posterior predictive checks (comparing model-based simulated outcomes vs. observed outcomes) will be used to verify distributional assumptions of each model.

After defining clinically meaningful treatment targets for each outcome, the minimum mobilisation dosage required to achieve a target will be estimated from the corresponding mixed model with a 95% confidence interval. For main objective 3, the modification of the effect of mobilisation dosage by prehospital functional dependence and invasive mechanical ventilation will be graphically and numerically investigated by introducing corresponding interaction (product) terms to the models.

All estimated associations will be described by appropriate effect size measures with 95% confidence intervals. Particular emphasis will be given to the possibility of nonlinear associations, which will be identified by modelling mobilisation dosage using appropriate methodology (restricted cubic splines). Moreover, the set of adjustment variables for each model will be carefully chosen to reflect temporal dependencies of dosage on these variables. Still, to avoid collider bias, we will not adjust for variables that may already depend on mobilisation or outcomes. A detailed statistical analysis plan will be published prior to the database's closure.

## **8.2 Sample Size**

A target sample size of 6,000 patients (with a minimum of 30 patients per centre, across more than 200 centres) has been selected to ensure sufficient statistical precision and representativeness for the study's primary descriptive aims. To avoid overrepresentation of specific centres, we limit the data collection to 90 patients per ICU and 600 patients per centre. We also aim to include low- and middle-income countries (LMICs), which typically do not participate in these studies, to capture worldwide variability. This large and diverse sample will facilitate accurate estimation of the prevalence and variability of early mobilisation practices across countries and regions, including subgroup analyses by ICU type, geography, and patient characteristics. Additionally, the sample size will enable robust modelling of associations between mobilisation dosage and key patient outcomes such as physical function at discharge, ICU and hospital length of stay, and mortality. The sample is expected to provide adequate power to describe clinically relevant patterns and potential effect modifications (e.g., by prehospital functional status or mechanical ventilation) related to the study aims.

## **8.3 Reinforcement learning**

Reinforcement learning (RL) is based on modelling a virtual decision-making 'agent' (the algorithm) interacting with its environment described by a set of states; the interaction between the agent and the environment is limited to a finite number of actions (treatment choices). At each step, the agent chooses an action, and the environment changes its state depending on the action. Each transition to a new state returns a reward. Unlike supervised learning, which relies on labelled data sets, RL optimises decisions through the cumulative reward signal over time, often balancing exploration (seeking new actions to improve future outcomes) and exploitation (using what

has already been learned). This framework has proven successful in a variety of domains, from game playing to robotics and clinical decision support.<sup>45</sup>

We will apply reinforcement learning in the context of intensive care to optimise the timing of the mobilisation dose (action), where the reward is defined by functional status at ICU discharge or the secondary outcomes of ICU mortality, hospital mortality, ICU length of stay, hospital length of stay, and 90-day mortality. For this study, patient data are aggregated and assigned unique IDs. Complete patient trajectories are then randomly distributed across the training, validation, and test sets. During training, the validation set is used to assess the performance of the algorithm, while the test set evaluates the final performance of the algorithm on previously unseen data.

Each patient's condition at any given moment reflects the state of the environment and is characterised by a vector that includes both continuous and categorical variables (over a 24-hour period). The RL algorithm will learn a mapping from the patient's current state to a recommended mobilisation dosage. These dosages are standardised to equivalent amounts of mobilisation and categorised into meaningful groups. We intend to evaluate and compare the performance of various RL algorithms (e.g., PPO). Additionally, we remain open to different modelling strategies—both clustering-based and non-clustering methods—to address the heterogeneity present in ICU populations.

### *8.3.1 Evaluation of the RL algorithm*

A critical step is verifying that a newly proposed treatment strategy is beneficial and safe. An established method for this verification is off-policy evaluation, which estimates how a strategy would have performed by analysing previously collected patient data.<sup>46</sup>

Following the development of our RL model, we will conduct an off-policy evaluation using importance sampling. By retrospectively examining historical ICU data, this approach enables us to estimate how recommended treatments might have impacted patient outcomes had they been implemented in the past. This method offers insights into both efficacy and safety.

## **9 Potential risks and benefits**

### **9.1 Potential Risks**

The ERUPT study is observational. It does not introduce any interventional procedure. The data is extracted from the patient's medical records and does not affect the local standard of care. Performance-based standardised tests are used to measure physical function, which are also used in routine treatment in many ICUs. Hence, the study does not lead to an increased medical risk. If the tests are not performed as standard, the study has an extremely low risk due to injuries or falls of patients during the tests. The tests are only carried out by trained medical personnel to prevent this risk.

Confidentiality breaches are potential risks that will be addressed by deidentifying data and pseudonymisation.

## **9.2 Benefits**

The patients enrolled in the study will not directly benefit from the research. However, the study's potential benefits include improving knowledge for better medical management of similar patients in the future and generating hypotheses for further collaborative research.

## **10 Ethics**

### **10.1 Ethical Standards**

The PI and Steering Committee will ensure that this study is conducted in full conformity with the Declaration of Helsinki and Good Scientific Practices.

### **10.2 Ethics Committee**

Each national coordinator or local PI will notify the responsible 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 and ethics committees before the changes are implemented in the study.

### **10.3 Consent procedure: Initial waiver with oral consent at follow-up**

Each centre must follow the rules according to their local regulation.

#### **10.3.1 Consent Procedure Option 1 - Waiver**

As ERUPT is an observational study, we will request approval from research ethics boards to collect data prospectively 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) because:
  - a. Some patients do not have an SDM, or the SDM cannot be located.
  - b. Obtaining informed consent from the SDM can take more than an hour, which can distract the research coordinator from other research activities.
2. It is impracticable to collect data retrospectively because of missing or unclear documentation in the patient record.
3. Critical illness and ICU admission are stressful for patients and their families. Approaching them for consent to collect data for an observational study may further unnecessarily increase the stress for patients and families.
4. Unique identifiers will be assigned locally; thus, all data entered in the database will be de-identified.
5. Waiving the need for consent for these studies ensures that ALL patients with the condition being evaluated contribute their data, leading to a comprehensive, unselected, generalisable, unbiased dataset.

Posters that explain the study and provide investigator contact information will be displayed in each participating ICU, positioned in a spot visible to SDMs. The Canadian Critical Care Trials Group and other large-scale international studies have effectively employed this model.

### ***10.3.2 Consent Procedure Option 2 – Deferred consent with oral consent at follow-up***

This consent model resembles model 1 (waiver), yet it is founded on a different legal argument. Nevertheless, it shares the same rationale as above to minimise the workload. Like model 1, posters and flyers in the intensive care unit present information about the study, as does a website where all information is made accessible, including the option to download written patient information.

Patients are included at the time of intensive care admission, as this is an extremely low-risk observational study, by means of assumed consent. Consent is requested verbally during the follow-up to minimise the effort as described in model 1.

At the 90-day follow-up, patients who have regained capacity will be asked to provide informed consent verbally and will be given the option to:

- provide informed consent for the acute data and follow-up.
- decline participation in the follow-up assessment but allow usage of the collected data.
- deny research participation and request the destruction of all data collected.

If the data does not have to be destroyed, this oral consent (with the date, time, and name of the researcher gaining consent) will be documented in paper form and stored at each centre.

### ***10.3.3 Consent Procedure Option 3 – Deferred consent***

If the law permits only written consent as informed consent, the following procedure should be adhered to:

1. If a legal representative or proxy is involved, their written consent must be obtained.
2. If no legal representative or proxy is present, the deferred consent model will be used for this low-risk study.
3. Once the patient is able to understand the study and sign the consent form, they will be asked for informed consent. If they refuse, they will be asked whether the data already collected may be used or destroyed.

### ***10.3.4 General statement – local regulations***

While consent models 1 or 2 will be our preferred approach, each centre will obtain authorisation to perform the study according to its local regulations. Centres will abide by regulations within their country, including obtaining informed consent from patients/SDMs if required.

## ***10.4 Medical care related to the study***

The medical care of the study participant is performed according to the local standard of care without any deviation from usual clinical protocols.

## **11 Funding**

Institutional funds will be used. An application for public funding to cover study costs (e.g., database, research coordinator, statistical analysis, and machine learning approaches) is planned.

## **12 Study administration structure**

### **12.1 Principal Investigator and Steering Committee (PI and SC)**

The roles and responsibilities of the Principal Investigators supported by the Steering Committee are:

- to coordinate the study and identify participating countries and national coordinators
- to ensure that the study is conducted according to the protocol and in compliance with Good Scientific Practice in all participating sites and countries
- to help the national coordinators to apply for all necessary approvals (ethical or data protection) in their countries
- to assist with the translation of the study documents according to local regulations
- to ensure good communication with the participating national coordinators, including monitoring and encouraging to achieve optimal recruitment and follow-up during the period of the study
- to assist in communicating with sites regarding data queries
- to take responsibility for the collected data, statistical analysis, communication and publications
- to organise investigator meetings

### **12.2 National Coordinators (NC)**

The roles and responsibilities of the national coordinators are:

- to liaise with National Intensive Care Societies, advertise the study in the individual countries and identify participating sites and local PIs in their country.
- to 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.
- to apply for regulatory approval from a local Data Protection Authority (DPA), where applicable.
- to assist with translating the study protocol and documents according to local regulations where required.
- to 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.
- to assist in communicating with sites regarding data queries.

### **12.3 Local Investigators (LI)**

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
- to inform the respective national coordinator of their interest in participating in the study.
- to 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
- to notify and send verification of local site approval to the national coordinator and PI
- to ensure accurate and timely data collection and entry in the eCRF
- to reply promptly to data queries

- to maintain effective communication with the national coordinator and coordinating centre.
- if applicable, to inform patients about their enrolment in the study and to acquire patients' non-opposition according to local regulations

## **12.4 Contact details**

### **12.4.1 Coordinating Centre**

Medical University of Vienna

Department of Anaesthesia, Intensive Care Medicine and Pain Medicine

Clinical Division of General Anaesthesia and Intensive Care Medicine

Währinger Gürtel 18-20

1090 Vienna

Austria

Email: [aai@meduniwien.ac.at](mailto:aai@meduniwien.ac.at)

### **12.4.2 Project Coordinator**

Vera Karner

[erupt@meduniwien.ac.at](mailto:erupt@meduniwien.ac.at)

### **12.4.3 PI and Chair Steering Committee**

Prof Dr. Stefan J Schaller

Medical University of Vienna

Department of Anaesthesia, Intensive Care Medicine and Pain Medicine

Clinical Division of General Anaesthesia and Intensive Care Medicine

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## **13 Advertisement and ICU recruitment**

The study will be advertised via ESICM and social media. To expand the visibility of the study internationally, the ERUPT Steering Committee will contact other societies and networks for endorsement and support (WFSICCM, SCCM, ANZICS, etc). National Coordinators will be appointed to facilitate the recruitment of ICUs and assist with identifying site investigators in each ICU. All details are available at [www.erupt-study.eu](http://www.erupt-study.eu) or in German at [www.erupt.at](http://www.erupt.at).

## **14 Premature termination or suspension of the study**

This study may be suspended or prematurely terminated for reasonable cause agreed upon by the ERUPT Steering Committee. The suspending or terminating party will provide written notification documenting the reason for

study suspension or termination. Suppose the study is prematurely terminated or suspended. In that case, the National Coordinators/Local PIs will promptly inform the ethics committees or other local authorities according to local legislation and provide the reason(s) for the termination or suspension. Circumstances that may warrant termination could be low recruitment, insufficient compliance with the protocol, or a pandemic. The study may resume when the Steering Committee agrees that the concerns have been addressed and the issues resolved.

## **15 Dissemination of results and publication policy**

### **15.1 Knowledge translation**

The findings of this study will be communicated to participating sites and within the scientific community through presentations at professional scientific conferences (e.g., ESICM LIVES meeting) and ultimately disseminated via peer-reviewed abstracts and manuscripts. Participating sites can contrast their management with other ICUs in their geographic regions.

Following the publication of our planned manuscripts, all site investigators interested in further analyses and manuscripts can apply to the Steering Committee. Subsequently, applications will be open for non-study investigators for further secondary analyses 3 years after it was opened to participating investigators.

### **15.2 Data sharing policy**

The ERUPT investigators own the data collectively. The ERUPT investigators consist of:

- The Steering Committee
- The national coordinators and
- The local investigators

Individual site data will be co-owned by each participating centre, and they will be given access to local data for any scientific purpose upon request after publication of the primary manuscript. National will be given access to their country-specific data upon request. By entering data into the ERUPT database, each centre agrees that the ERUPT Steering Committee can use these data for scientific purposes.

Any requests to use the data will be submitted in writing to the ERUPT Steering Committee, and decisions will be made concerning these requests. ERUPT investigators will have priority in requests to use the data set for subsequent secondary analyses as described above.

### **15.3 Publications, authorship and collaborators**

Results will be made available to ESICM members and the scientific community through abstracts submitted to the ESICM annual conference and scientific papers submitted to peer-reviewed journals. The authorship of the main manuscript will follow the ICMJE recommendations.

A writing committee that includes the Principal Investigators, the Study Coordinator, and members of the Steering Committee will draft the work. Steering Committee members will be authors of the manuscript if they have a participating site or support the inclusion of centres in their countries, and fulfil the ICMJE criteria.

National coordinators will be considered authors if they meet the ICMJE criteria and have facilitated the enrolment of at least 500 patients with complete data collection in their country. Local investigators who successfully recruit

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three complete sets of patients with full data collection, along with consent where applicable and with all queries answered, will be invited to be authors if they satisfy the ICMJE criteria.

Suppose the number of authors, as planned above, is too high for the agreed journal. In that case, the national coordinators with the highest number of included patients, followed by the sites with the highest number of included patients, will be preferred for the first manuscript. In contrast, the remaining ones will be selected for the subsequent manuscripts, moving down in the order of included patients for each publication if necessary.

All participating centres will be mentioned in the acknowledgement section of all ERUPT publications (of the obligatory data) and labelled as the “ERUPT investigators”. The corresponding author will specify the group name and will identify the group members who can take credit and responsibility for their work as collaborators. We will allow three collaborators for each complete set of 30 patients of an ICU with a complete obligatory data collection set in the eCRF, consent where applicable, and all answered queries listed in the group authorship list. Two additional collaborators per complete facultative stage of a complete set of 30 patients can be listed. In publications from facultative data, the process will be similar; however, only for centres with appropriate facultative data provided.

All ERUPT publications will acknowledge support and endorsements (e.g., ESICM).

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