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

Principal Investigator: **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
erupt@muv.ac.at

Steering Committee

Prof.	Manfred	Blobner	Anaesthesiologist & Intensivist	University Hospital Ulm
Prof.	Bronwen	Connolly	Physiotherapist	Queen's University Belfast
Prof	Frantisek	Duska	Intensivist	Charles University in Prague
Prof.	Lauren	Ferrante	Intensivist	Yale School of Medicine
Prof.	Rik	Gosselink	Rehabilitation Science	KU Leuven
Dr.	Sabrina	Eggmann	Physiotherapist	Inselspital Bern
Prof.	Carol	Hodgson	Deputy Director ANZICS Physiotherapist	ANZIC-RC, Monash University
Dr.	Keibun	Liu	Intensivist	ICU Collaboration Network (ICON), Tokyo
Prof.	Michelle	Kho	Physiotherapist	School of Rehabilitation Science, McMaster University
Prof.	David	McWilliams	Physiotherapist	University Hospitals Birmingham NHS Foundation Trust
Prof.	Dale	Needham	Intensivist	Johns Hopkins University
Dr.	Peter	Nydahl	Nurse scientist	UKSH, Kiel
Prof.	Bhakti	Patel	Intensivist	The University of Chicago
Prof.	Zudin	Puthucheary	Intensivist	Royal London Hospital
Prof.	Stefan	Schaller	Anaesthesiologist & Intensivist	Medical University of Vienna

Research Coordinator

Vera Karner, Medical University of Vienna (vera.karner@muv.ac.at)

Statisticians

1. Prof. Georg Heinze, Medical University of Vienna
2. Bernhard Ulm, University Hospital Ulm
3. Machine Learning: Lorenz Kapral, MSc, Medical University of Vienna

This study is currently funded solely by institutional funds and is endorsed by the European Society of Intensive Care Medicine (ESICM).

Electronic signature PI:

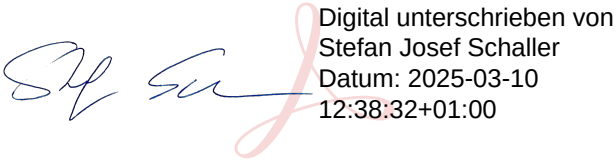


Table of Contents

1 Synopsis

Title	Early rehabilitation of intensive care unit patients - a multinational prospective observational study on dosage and outcome
Abbreviation	ERUPT Study
Study design	Prospective, multicentre observational study
Background and Rationale	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.
Objectives	The main objectives of the study are: 1. Assessment of the variety of different mobilisation practices worldwide 2. The analysis of the association of mobilisation dosage on patient outcomes 3. The evaluation of the association of the prehospital functional status or invasive mechanical ventilation on patient outcomes
Methods	***Sample Size:*** We aim to recruit > 6000 patients internationally from a minimum of 200 ICUs including at least 30 consecutive patients each (20 mechanically ventilated (10 functionally independent, 10 functionally dependent before hospital admission) and 10 without invasive mechanical ventilation independent of functional status at study inclusion) ***Inclusion criteria:*** Adults (≥ 18 years) who are expected to stay > 24 hours in the ICU, within 48 hours of ICU admission ***Exclusion criteria:*** 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 or patients whose functional status is unlikely to be obtainable. ***Data collection:*** 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.
Outcomes	***Primary outcome*** will be the functional status at ICU discharge. ***Secondary outcomes***: ICU mortality, hospital mortality, ICU length of stay, hospital length of stay, and 90 day follow up for mortality, global function using WHODAS 2.0 and functional status, as well as the trajectory of functional status over time.
Duration of study	***Screening and recruitment*****:** Participating ICUs will screen and collect data for all newly admitted patients with the aim of sets of 30 (10 consecutive functionally dependent, 10 functionally independent patients, 10 patients without invasive

	mechanical ventilation). Per ICU a maximum of 3 complete sets (90 patients) will be allowed. ***Follow up*** will be collected at 90 days. ***Duration:*** 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.
Study registration	The study will be registered in advance.

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.[1] 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.[2,3] 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.[4,5] 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.[5] Globally, the quality of survival following an ICU stay has been identified as one of the most significant health challenges for these patients.[6,7]

3.2 Variation of practice and definitions worldwide

A currently recommended intervention is early mobilisation.[8-10] 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.[11] Consequently, people consider providing early mobilisation if surveyed.[12] However, this result contradicts the prevalence studies, where early mobilisation or mobilising intubated patients is still rare.[13-16] Importantly, any intervention started late, i.e. 72 hours after intensive care admission, failed to show improvement in patient outcome.[17] Such early intervention, however, seems necessary to prevent muscle atrophy[18] and improve functional outcomes.[19-22]

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.[23,24] 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.[25] 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.[18] 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.[26] Furthermore, existing randomised trials only included functionally independent patients before ICU admission.[17]

A secondary analysis of the Team RCT revealed that patients with diabetes demonstrated increased mortality at 180 days with early active mobilisation.[27]

Lastly, in a secondary analysis using cluster analysis, different patient cohorts benefited from different mobilisation components.[28]

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) and unpleasant patient experiences (e.g., vulnerability, intense stress on the body system, negative emotional situation).[29,30] Modern critical care uses non-invasive ventilation (NIV) and high-flow oxygen therapy to reduce the need for mechanical ventilation.[31-33]

Consequently, this group will also be included and observed in the study. Patients who will be non-invasively ventilated at the time of the study enrolment or must be intubated later 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 of mobilisation dosage (frequency, duration and level of mobilisation) on outcomes of critically ill patients?
2. Is there an association of the prehospital status or invasive mechanical ventilation at ICU admission with outcomes of critically ill patients?

4.2 Aims and Objectives with hypotheses

The main objectives of the study are:

1. The assessment of the variety of different mobilisation practices worldwide
    a. The frequency of early mobilisation differs between countries or regions worldwide. (Endpoint: Frequency of early mobilisation)
    b. Mobilisation provided on 7 days per week differs between countries or regions worldwide. (Endpoint: Frequency of daily mobilisation per week)

   c. The duration of mobilisation per day differs between countries or regions worldwide. (Endpoint: Duration of mobilisation per day)
   d. There is a geographical variation in minutes spent with the patient on active or passive mobilisation activities. (Endpoint: % active mobilisation)
2. The analysis of the association of mobilisation dosage on outcomes of critically ill patients to define a minimum mobilisation dosage necessary to provide a clinically meaningful treatment effect on outcomes of critically ill patients
   a. There is a minimum daily mobilisation dosage providing a clinically meaningful treatment effect on outcomes of critically ill patients (H0: No minimum mobilisation dosage can be identified providing a clinically meaningful treatment effect on outcomes of critically ill patients.) → Main outcome set
   b. There is an association between the number of staff (staff resources) involved in mobilisation and patient outcomes. (H0: There is no association between the number of staff (staff resources) involved in mobilisation and patient outcomes.) → Main outcome set
   c. There is an association between the involvement of physiotherapists in mobilisation and patient outcomes. (H0: There is no association between the involvement of physiotherapists in mobilisation and patient outcomes.) → Main outcome set
3. The evaluation of the association of the prehospital functional status or invasive mechanical ventilation on outcomes of critically ill patients
   a. The prehospital functional status influences the effect of mobilisation on the patient outcome. (H0: The prehospital functional status does not influence the effect of mobilisation on the patient outcome.) → Main outcome set
   b. Invasive mechanical ventilation at the time of study inclusion (< 48h of ICU admission) influences the effect of mobilisation on the patient outcome. (H0: An invasive mechanical ventilation at the time of study inclusion (< 48h of ICU admission) does not influence the effect of mobilisation on patient outcome.) → Main outcome set

5 Study Endpoints

The primary outcome is physical function measured at ICU discharge using the Functional Status Score for the Intensive Care Unit (FSS-ICU)[34], the total score ranges from 0-35

Secondary endpoints (obligatory) are:

1. ICU Mobility Scale (IMS)[14] at ICU discharge
2. ICU length of stay
3. Hospital length of stay
4. Clinical Frailty Scale (CFS) [35] at ICU discharge and 90 days
5. ICU-, hospital and 90-day mortality
6. WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)[36] at 90 days
7. Barthel Score[37] at ICU discharge and 90 days

8. IMS at 90 days
9. FSS-ICU at 90 days

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

1st stage:

1. Chelsea Critical Care Physical Assessment Tool (CPAx[38]) at ICU discharge
2. Medical Research Council (MRC) Score[39] 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

2nd stage:

1. Physical Function ICU Test-scored (PFIT-s)[40] at ICU discharge
2. 30-second sit-to-stand test at ICU discharge

6 Overall study design

6.1 Patient Population

6.1.1 Inclusion criteria

The inclusion criteria are:

1. Adult (≥ 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 obtainable
- or they have language barriers

6.2 Procedures

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

6.3 Data collection

6.3.1 Patient data

The functional baseline will be obtained retrospectively by interviewing the responsive and oriented patient or a proxy/relatives regarding the status 2 weeks before hospital admission: (1) The FSS-ICU, as described earlier, will

be used to classify patients as prior independent and dependent. (2) The Barthel Score measures 10 activities of daily living.[37] (3) The maximal ICU Mobility Scale (IMS[14]) will provide the patient's general characterisation and prehospital mobility level. (4) The Clinical Frailty Scale (CFS)[35] will be used to screen for frailty and determine its level.

Table 1. Overview of collected obligatory variables.

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

a) Pre-ICU Status: Status 2 weeks before hospital admission 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.[41] The severity of the disease will be documented by the daily SOFA score.[42]

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,[14] 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.

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. Table 1 and Table 2 provide an overview of obligatory and facultative study data.

Table 2. Overview of facultative assessments

		Baseline ICU admission	Daily in ICU	ICU discharge	Hospital discharge	90 Day Follow up
1st stage of facultative assessments	**Delirium**		X			
	CPAx[a]			X		
	MRC Score			X		
	EQ-5D-5L					X
2nd stage of facultative assessments	**Detailed nutritional information**		X			
	PFIT-s			X		
	30s STS			X		

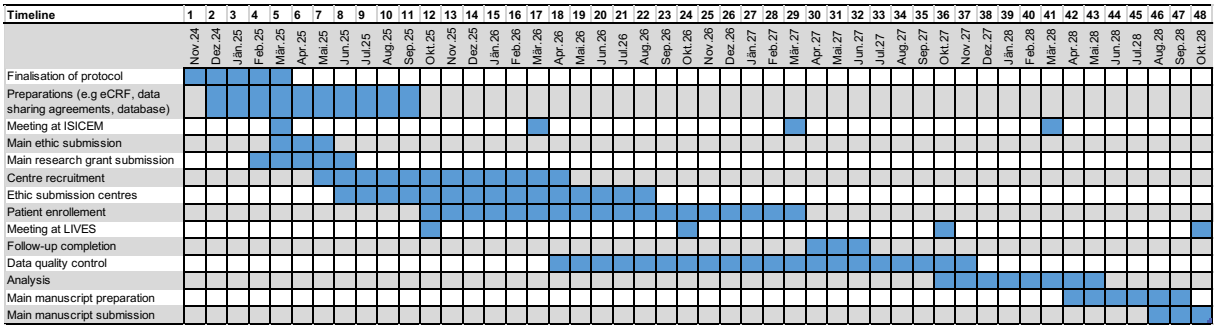
a) In the CPAx all sub-elements shall be collected since not all centres can do hand grip strength tests.

6.3.2 Centre data

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

6.4 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 ethic submission at later time points.



7 Data management

7.1 Data entry and checks

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

All data will be collected using the eCRF provided by the Medical University of Vienna via Clincase. No patient-identifying information will be collected. Each site will be assigned a number (e.g., 001, 002, 003, etc.), and

patients will be assigned consecutive unique identifiers, so patients will be labelled as Study identifier (ERU) + Site number + Patient number (e.g., ERU001-001, ERU001-002, etc.).
Range edits and value checks will be incorporated into the software to reduce the potential for data entry errors. Data queries will be automatically generated and sent to participating sites. Site investigators will be required to answer all queries before they can electronically finalise a patient data set.

7.2 Quality assurance and Data protection

Clincase (https://www.clincase.com/) by the company Quadratek will be used to provide the eCRFs. The Medical University of Vienna provides the aforementioned electronic data collection system for quality-assured documentation of multicentre studies. The system complies with the regulations of the Food and Drug Administration (FDA) - Regulation 21 CRF 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.

7.3 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.).

7.4 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 described visually and in tables for reporting and publication purposes. Continuous variables will be described as means ± SD or median and IQR, as appropriate. Frequencies and proportions will be used for categorical variables.
For main objective 1, the proportion of early mobilisation and mobilisation provided seven days per week will be reported and descriptively compared between countries and regions. The distributions of the duration of

mobilisation per day and the percentage of active mobilisation will be reported using appropriate statistical measures by country and region.

For the second main objective, the association of mobilisation dosage, number of staff, and the involvement of physiotherapists with each (quasi-)metric outcome will be examined as follows: Scatterplots will be used to represent the dependence of each outcome on its respective baseline value and on mobilisation dosage. Local polynomial regression (LOESS) will be used to reveal non-linear associations. Linear mixed models will be used to adjust the effect of mobilisation dosage on each outcome at the respective post-treatment time point by its baseline value, while accounting for clustering. Mobilisation dosage will be modelled flexibly using splines. The nested clustering induced by region, country, and centre will be represented by appropriate covariance structures (nested block diagonal).

After defining clinically meaningful treatment effects for each outcome, the minimum mobilisation dosage required to achieve this level will be estimated from the corresponding linear mixed model with a 95% confidence interval.

To account for deaths, length of stay and mortality outcomes will be investigated as ICU- or hospital-free days alive until day 90, respectively.

For main objective 3, the modification of the effect of mobilisation dosage on each outcome will be graphically investigated by using a dichotomous factor (prehospital functional dependence; invasive mechanical ventilation), with the scatterplots being coloured accordingly. The aforementioned linear mixed models will be extended to include an interaction between mobilisation dosage and the relevant dichotomous factor.

A p-value of less than 0.05 will be regarded as statistically significant. The p-values of model results for secondary outcomes will be adjusted for multiple outcome testing using the Bonferroni-Holm method within each hypothesis. A detailed statistical analysis plan will be published before the database is closed.

8.2 Sample Size

The anticipated sample size of > 6000 patients (min. 30 pt/centre, > 200 centres) will provide a sufficient number of different mobilisation dosages for fitting the statistical models described above. To avoid an overrepresentation of some centres, we ceil the data collection to 90 patients/ICU and 600 patients/centre. This number of enrolled patients and ICUs reflects an adequate sample size to capture a range of variations in practice and therapy. We also aim to include LMICs, who usually do not participate in these studies, to represent worldwide variability.

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.[43]

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.[44]
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 a 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
Waehringer Guertel 18-20
1090 Vienna
Austria
Email: aai@meduniwien.ac.at

12.4.2 Project Coordinator

Vera Karner
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
erupt@meduniwien.ac.at
Phone: +43-1-4040041290

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.

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 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 one collaborator per ICU for a complete subset of 10 patients (prior functionally dependent or independent, without invasive mechanical ventilation), i.e. three collaborators for each complete set of 30 patients (10 prior functionally dependent and independent each, 10 without invasive mechanical ventilation) of an ICU with complete obligatory data collection set in the eCRF, consent where applicable, and all answered queries named in the group authorship list. Two additional collaborators per complete facultative stage of a complete set of 30 patients can be named. 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).

16 References

1. Hodgson CL, Udy AA, Bailey M, et al. The impact of disability in survivors of critical illness. Intensive care medicine 2017;43(7):992-1001. DOI: 10.1007/s00134-017-4830-0.
2. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in ANZ, 2000-2012. JAMA : the journal of the American Medical Association 2014;311(13):1308-16. (Observational Study) (In eng). DOI: 10.1001/jama.2014.2637.
3. Farhan H, Moreno-Duarte I, Latronico N, Zafonte R, Eikermann M. Acquired Muscle Weakness in the Surgical Intensive Care Unit: Nosology, Epidemiology, Diagnosis, and Prevention. Anesthesiology 2016;124(1):207-34. DOI: 10.1097/ALN.0000000000000874.
4. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. The New England journal of medicine 2011;364(14):1293-304. DOI: 10.1056/NEJMoa1011802.
5. Investigators TS, Hodgson C, Bellomo R, et al. Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. Crit Care 2015;19:81. DOI: 10.1186/s13054-015-0765-4.
6. Iwashyna TJ. Survivorship will be the defining challenge of critical care in the 21st century. Ann Intern Med 2010;153(3):204-5. DOI: 10.7326/0003-4819-153-3-201008030-00013.
7. Iwashyna TJ, Netzer G. The burdens of survivorship: an approach to thinking about long-term outcomes after critical illness. Semin Respir Crit Care Med 2012;33(4):327-38. (Research Support, N.I.H., Extramural) (In eng). DOI: 10.1055/s-0032-1321982.
8. Bein T, Bischoff M, Bruckner U, et al. S2e guideline: positioning and early mobilisation in prophylaxis or therapy of pulmonary disorders : Revision 2015: S2e guideline of the German Society of Anaesthesiology and Intensive Care Medicine (DGAI). Anaesthesist 2015;64 Suppl 1:1-26. DOI: 10.1007/s00101-015-0071-1.
9. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Critical care medicine 2018;46(9):e825-e873. DOI: 10.1097/CCM.0000000000003299.
10. Schaller SJ, Scheffenbichler FT, Bein T, et al. Guideline on positioning and early mobilisation in the critically ill by an expert panel. Intensive care medicine 2024;50(8):1211-1227. DOI: 10.1007/s00134-024-07532-2.
11. Clarissa C, Salisbury L, Rodgers S, Kean S. Early mobilisation in mechanically ventilated patients: a systematic integrative review of definitions and activities. Journal of intensive care 2019;7:3. DOI: 10.1186/s40560-018-0355-z.
12. Morandi A, Piva S, Ely EW, et al. 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. Critical care medicine 2017;45(11):e1111-e1122. DOI: 10.1097/CCM.0000000000002640.
13. Sibilla A, Nydahl P, Greco N, et al. Mobilization of Mechanically Ventilated Patients in Switzerland. J Intensive Care Med 2017:885066617728486. DOI: 10.1177/0885066617728486.
14. Hodgson CL, Bailey M, Bellomo R, et al. A Binational Multicenter Pilot Feasibility Randomized Controlled Trial of Early Goal-Directed Mobilization in the ICU. Critical care medicine 2016;44(6):1145-52. DOI: 10.1097/CCM.0000000000001643.
15. Nydahl P, Ruhl AP, Bartoszek G, et al. Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany. Critical care medicine 2014;42(5):1178-86. DOI: 10.1097/CCM.0000000000000149.
16. Berney SC, Harrold M, Webb SA, et al. Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine 2013;15(4):260-5. (https://www.ncbi.nlm.nih.gov/pubmed/24289506).
17. Fuest K, Schaller SJ. Recent evidence on early mobilization in critical-Ill patients. Curr Opin Anaesthesiol 2018;31(2):144-150. DOI: 10.1097/ACO.0000000000000568.
18. Wollersheim T, Grunow JJ, Carbon NM, et al. Muscle wasting and function after muscle activation and early protocol-based physiotherapy: an explorative trial. J Cachexia Sarcopenia Muscle 2019. DOI: 10.1002/jcsm.12428.
19. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373(9678):1874-82. DOI: 10.1016/S0140-6736(09)60658-9.
20. Schaller SJ, Anstey M, Blobner M, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet 2016;388(10052):1377-1388. DOI: 10.1016/S0140-6736(16)31637-3.
21. Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. Intensive care medicine 2015;41(5):865-74. DOI: 10.1007/s00134-015-3763-8.
22. Morris PE, Berry MJ, Files DC, et al. Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial. Jama 2016;315(24):2694-702. DOI: 10.1001/jama.2016.7201.
23. group ATC, Bernhardt J, Langhorne P, et al. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet 2015;386(9988):46-55. DOI: 10.1016/S0140-6736(15)60690-0.
24. Bernhardt J, Churilov L, Ellery F, et al. Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). Neurology 2016;86(23):2138-45. DOI: 10.1212/WNL.0000000000002459.
25. Hodgson CL, Bailey M, Bellomo R, et al. Early Active Mobilization during Mechanical Ventilation in the ICU. N Engl J Med 2022;387(19):1747-1758. (In eng). DOI: 10.1056/NEJMoa2209083.
26. Titsworth WL, Hester J, Correia T, et al. The effect of increased mobility on morbidity in the neurointensive care unit. J Neurosurg 2012;116(6):1379-88. DOI: 10.3171/2012.2.JNS111881.
27. Serpa Neto A, Bailey M, Seller D, et al. Impact of High-Dose Early Mobilization on Outcomes for Patients with Diabetes: A Secondary Analysis of the TEAM Trial. Am J Respir Crit Care Med 2024;210(6):779-787. DOI: 10.1164/rccm.202312-2289OC.
28. Fuest KE, Ulm B, Daum N, et al. Clustering of critically ill patients using an individualized learning approach enables dose optimization of mobilization in the ICU. Crit Care 2023;27(1):1. DOI: 10.1186/s13054-022-04291-8.
29. von During S, Parhar KKS, Adhikari NKJ, et al. Understanding ventilator-induced lung injury: The role of mechanical power. Journal of critical care 2025;85:154902. DOI: 10.1016/j.jcrc.2024.154902.
30. Danielis M, Povoli A, Mattiussi E, Palese A. Understanding patients' experiences of being mechanically ventilated in the Intensive Care Unit: Findings from a meta-synthesis and meta-summary. J Clin Nurs 2020;29(13-14):2107-2124. DOI: 10.1111/jocn.15259.
31. Criner GJ, Gayen S, Zantah M, et al. Clinical review of non-invasive ventilation. Eur Respir J 2024;64(5). DOI: 10.1183/13993003.00396-2024.
32. Lewis SR, Baker PE, Parker R, Smith AF. High-flow nasal cannulae for respiratory support in adult intensive care patients. The Cochrane database of systematic reviews 2021;3(3):CD010172. DOI: 10.1002/14651858.CD010172.pub3.
33. Grasselli G, Calfee CS, Camporota L, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive care medicine 2023;49(7):727-759. DOI: 10.1007/s00134-023-07050-7.

34. Huang M, Chan KS, Zanni JM, et al. Functional Status Score for the ICU: An International Clinimetric Analysis of Validity, Responsiveness, and Minimal Important Difference. Critical care medicine 2016;44(12):e1155-e1164. DOI: 10.1097/CCM.0000000000001949.
35. Flaatten H, De Lange DW, Morandi A, et al. The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (>/= 80 years). Intensive care medicine 2017;43(12):1820-1828. DOI: 10.1007/s00134-017-4940-8.
36. Rehabilitation UDSfM. The FIM instrument: Its background, structure, and usefulness. Uniform Data System for Medical Rehabilitation.
37. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Maryland state medical journal 1965;14:61-5. (https://www.ncbi.nlm.nih.gov/pubmed/14258950).
38. Corner EJ, Wood H, Englebretsen C, et al. The Chelsea critical care physical assessment tool (CPAx): validation of an innovative new tool to measure physical morbidity in the general adult critical care population; an observational proof-of-concept pilot study. Physiotherapy 2013;99(1):33-41. DOI: 10.1016/j.physio.2012.01.003.
39. Compston A. Aids to the investigation of peripheral nerve injuries. Medical Research Council: Nerve Injuries Research Committee. His Majesty's Stationery Office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous system. By Michael O'Brien for the Guarantors of Brain. Saunders Elsevier: 2010; pp. [8] 64 and 94 Figures. Brain 2010;133(10):2838-44. DOI: 10.1093/brain/awq270.
40. Denehy L, de Morton NA, Skinner EH, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). Phys Ther 2013;93(12):1636-45. DOI: 10.2522/ptj.20120310.
41. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100(6):1619-36. (https://doi.org/10.1378/chest.100.6.1619).
42. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive care medicine 1996;22(7):707-10. (https://www.ncbi.nlm.nih.gov/pubmed/8844239).
43. Sutton RS, Barto AG. Reinforcement learning: An introduction: MIT press Cambridge, 1998.
44. Thomas P, Brunskill E. Data-Efficient Off-Policy Policy Evaluation for Reinforcement Learning. In: Maria Florina B, Kilian QW, eds. Proceedings of The 33rd International Conference on Machine Learning. Proceedings of Machine Learning Research: PMLR; 2016:2139--2148.