STUDY TITLE

Evaluation of the effect of robot-assisted early mobilization on critically ill patients, on the mobilization behaviour and experience of the mobilizing professionals and the organizational processes in an intensive care unit - a clinical intervention study.

Project MobiStaR

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Table of Content

1. EXECUTIVE SUMMARY

Early mobilization stands for the mobilization in the early course of critically ill patients after admission to the intensive care unit. The positive impact of early mobilization of critically ill patients on various patient outcomes has already been demonstrated. However, the implementation of early mobilization in clinical practice is challenging. Especially the high personnel effort constitutes a barrier.

The Munich-based SME Reactive Robotics (RR) is currently developing the world's first adaptive robotic assistance system VEMO©, which has CE approval for the planned indication and aims to be used in the medium term for mobilizing intensive care patients.

Within the MobiStaR project, the adaptation of procedures in an intensive care unit combined with the use of this robotic system will create the conditions to significantly increase the mobilization rate of critically ill intensive care patients, possibly thereby increasing the rehabilitation outcomes for these patients and developing a new standard of care for robot-assisted early mobilization. The robotic system will be used in anesthesiological intensive care units of the LMU hospital. The protocol of the preliminary study to identify relevant problems, barriers and facilitating factors in the use of mobilization robots in the clinical setting and to record the current status of early mobilization with consideration of the professional groups involved has already been submitted to the Ethics Committee (Clearing 20-883).

In project module four, the effects of robot-assisted early mobilization shall now be evaluated. This study contains three study arms, in which (1) the feasibility and practicability of robot-assisted early mobilization, (2) the behavior and experience of the mobilizing professionals and (3) the effect on patient outcomes will be evaluated.

The study is monocentric, prospective and interventional. It does not include invasive measures or blood sampling and has multiple data collection time points.

(1) The feasibility study of robot-assisted early mobilization collects data on how many VEM therapies can be performed in how many patients and whether and which adverse events occur. This will be collected by project staff during the VEM therapies.

(2) The behavior and experience of the mobilizing professionals will be evaluated using episodic interviews as well as standardized observations. Nurses with specialized training in anesthesia and intensive care, nurses and physiotherapists who have at least three years of professional experience in an intensive care unit as well as medical specialists who have completed their training as medical specialists or who have a leading position in an intensive care unit are included. In addition, the individuals have an employment contract at LMU Klinikum. Furthermore, the secondment to the anesthesiological intensive care units is an inclusion criterion.

(3) The effects on patient outcomes, primarily duration of ventilation, muscle mass (sonographic examination) and physical activity (measured by established scores such as FSS-ICU and MRC classification), will be measured at different points in time and compared with a historical patient population. Secondary outcomes such as delirium incidence, hemodynamic parameters, respiratory parameters but also longitudinal parameters such as intensive care and hospital length of stay will be analyzed from routine data/patient records. Included are informed consenting patients who will undergo a planned surgical procedure that involves postoperative intensive treatment and an anticipated duration of ventilation of more than 48 hours. These patients will receive standardized early mobilization using the robotic system at either ten frequencies or for seven days. No invasive procedures such as blood sampling will be performed as part of the study. To evaluate the effect of robot-assisted VEM, the outcomes

will be compared with a historical comparison group. Approximately 30 patients shall be included. The results will be compared to a historical group (n=30) with conventional early mobilization.

The intervention is planned for a duration of five to six months starting in August 2021.

2. BACKGROUND AND RATIONALE

Many studies have shown that early mobilization of ICU (intensive care units) patients improves functional and cognitive health (1-7). The best possible rehabilitation is achieved (8) and the length of stay in the ICU and hospital is shortened (3). It has also been described that functional disorders can be prevented (9, 10). However, studies show mixed results regarding this (11-14).

The definition of early mobilization is not consistent across the literature (15). Many studies talk about early mobilization if it starts within 72 hours after admission to the ICU. Early mobilization of ventilated ICU patients is only feasible with an extraordinarily high level of personnel effort (16). Other factors such as sedation or unconsciousness of the patients or the period of treatment (e.g. at the weekend) also lead to the fact that only about 25% of the patients in the intensive care unit are mobilized (17). This has considerable consequences for the healing process of the patients as well as for the costs of treatment (9).

Currently, there are several devices on the market that allow automated robotic early mobilization therapy. Compared to manual early mobilization, robotic support has the advantage that mobilization in bed can reduce the risk of falls for patients. In addition, the physical strain for mobilizing professionals is reduced, as the robotic device takes over the verticalization and leg movement. Some models verticalize and mobilize patients. However, this requires the patient to be transferred from their bed to the training device and then back to the bed. Another product is a modern tilting intensive care bed, which allows passive movement of the legs.

The early mobilization robot used in our study design is able to verticalize the patients in their bed without transfer and generate a movement of the legs that measures and supports the patients' own movement. The device fulfills the requirements for mobilizing critically ill patients in an intensive care unit, maintaining hygiene standards and providing the best possible support for the patient's own movement.

The process of the overall project is based on the development model of complex interventions of the Medical Research Council (MRC) (18): In a cycle of piloting, evaluation, implementation and (further) development, the framework conditions for the use of the early mobilization device are created within the overall duration of the project (see Fig. 1).
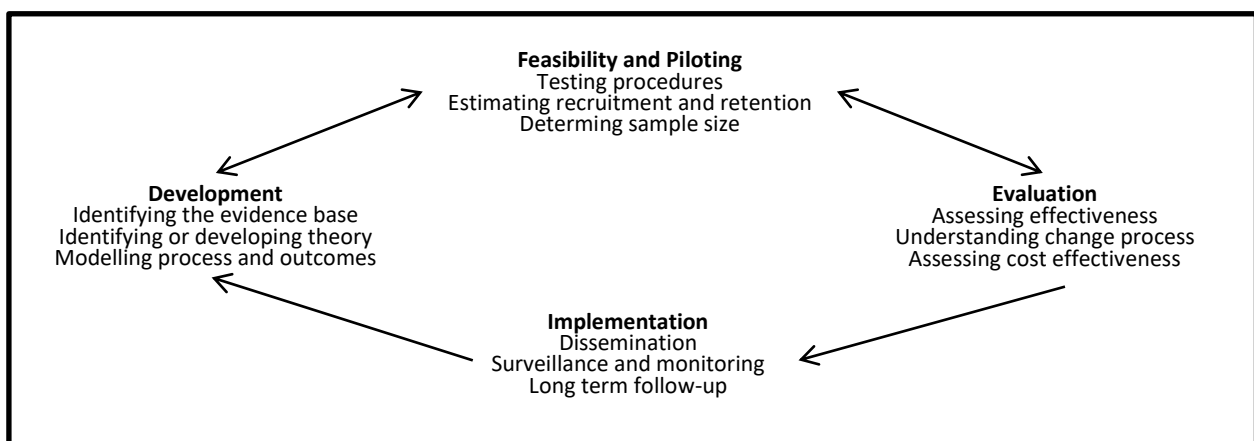

Abb. 1: Medical Research Council: Key elements of the development and evaluation process (18)

As part of the preliminary study (Ethics Vote 20-883), support factors and barriers for integrating a robotic system into the clinical setting were evaluated using the following study components:

- Identification of relevant problems, barriers and facilitating factors in the use of mobilization robots in the clinical setting - The perspective of clinical experts and developers,
- Assessment of the Current Status of Early Mobilization in Intensive Care Units - The Perspective of the Professional Groups Involved and of Science

Based on the results of this study, robot-assisted early mobilization in intensive care units will now be investigated.

Evidence-based data on whether the use of robot-assisted early mobilization can improve patient outcomes, what the experience of users is like, and whether the implementation can be embebbed organizationally and structurally in the daily routine of an intensive care unit are currently lacking.

The aim of the study is to investigate whether (1) robot-assisted early mobilization in intensive care units is feasible according to previously considered support factors/barriers, (2) which effect the integration of the device and the treatment has on the patient's outcomes, and (3) how the behavior and experience of the mobilizing professionals as well as the medical and nursing processes change. The three overall objectives will be considered in more detail under point five.

2.1.1. STATUS QUO OF EARLY MOBILIZATION IN GERMANY

In Germany, 2.1 million patients receive intensive care treatment every year. About 18% of them need artificial respiration temporarily (19). 20 - 30% of those affected are considered seriously ill patients who require artificial respiration over a longer period of time. About 20% of all patients in intensive care are considered to be critically ill, and the tendency is increasing.

Regular mobilization, meaning all forms and processes of mobilization aiming at the rehabilitation of intensive care patients, leads to a multitude of important positive healing processes and consequently to an overall faster recovery (20) (see Figure 2).
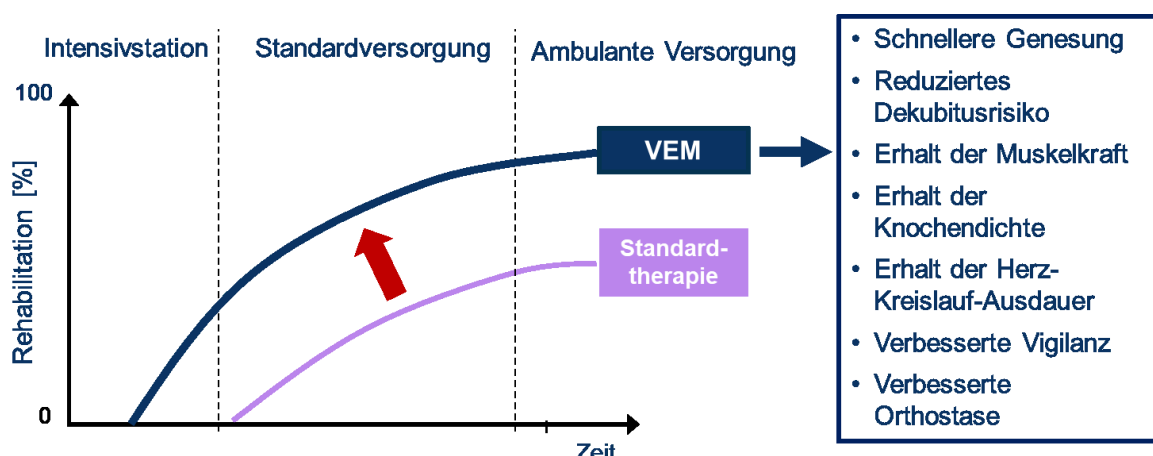
Figure 2: Comparison of rehabilitation duration with standard treatment and with early mobilization as therapy (21, 5, 22, 3, 23-27).

Regular mobilization, especially through assisted walking movements, reduces the risk of decubitus ulcers, maintains mobility and cardiac function, as well as facilitating bowel movements. In intensive

Clinical intervention study – Project MobiStaR
Study protocol Version 2.0 from 27.05.2021
Page **6** of

care units, these mobilizing measures are already part of the therapy program of less heavily affected patients (9, 28).

Clinical studies show that critically ill ICU patients who receive very early mobilization (VEM), i.e., mobilization performed within 72 hours of ICU admission, achieve the best possible rehabilitation (10). However, optimal VEM therapy requires daily mobilization of patients for at least 20 minutes, combining the verticalization of patients and the movement of their legs, according to a normal gait pattern.

Due to the critical physical condition of intensive care patients, VEM therapy can therefore only be carried out with an extraordinarily high level of personnel effort. Often, critically ill patients cannot stand on their own feet due to their severe limitations and have to be "exercised" on a therapy device. The transfer of intensive care patients from bed to a separate therapy device is time-consuming and not without risk for patients and is therefore not often performed in clinical practice. Active mobilization should be performed by at least two qualified staff members, as described in the current S2 guideline (S2e guideline: "Positioning therapy and early mobilization for prophylaxis or therapy of pulmonary dysfunctions [1]" (29)).

For these and many other reasons, such as sedation/paralysis of the patients concerned (46%), unconsciousness (4%), staff shortage (17%), weekend (8%), etc. (30), only a quarter of the eligible patients are currently early mobilized (8, 17). This has considerable consequences for the healing process, the burden on relatives, and not least for the costs incurred by health insurances and the people insured.

2.1.2. ROBOT-ASSISTED EARLY MOBILIZATION IN THE INTENSIVE CARE UNIT

The Munich-based SME Reactive Robotics (RR) is currently developing the world's first adaptive robotic assistance system for mobilizing intensive care patients. However, the path towards

- a nursing robot that can be used in a standardized manner for all eligible, critically ill patients,
- that sustains the quality of care,
- significantly improves the outcomes for patients and their chances of recovery,
- thereby relieving the personnel,
- that is economically attractive
- and is easily integrated into the processes of an intensive care unit

strongly depends on the environment, the processes and organizational procedures in which the robot is integrated.

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[1] Bein T, Bischoff M, Brückner U. *et al.* Kurzversion S2e-Leitlinie – „Lagerungstherapie und Frühmobilisation zur Prophylaxe oder Therapie von pulmonalen Funktionsstörungen". *Anaesthesist* **64,** 596–611 (2015).

The vision of integrating robot-assisted early mobilization into the daily routine of an intensive care unit is shown in Figure 3.

Figure 3: MobiStaR Vision: Verticalization and exercise of patients in their intensive care bed.

There is currently no adequate evidence for the benefit of the use of robotics in the early mobilization of ICU patients.

3. OBJECTIVES

The aim of this interventional study is to determine whether robot-assisted early mobilization of critically ill patients is feasible. In addition, it is intended to identify the effects of this form of VEM compared to conventional, manual VEM on the experience of the users and the outcomes of the patients.

To achieve this purpose of the study, the following research questions will be examined in the context of (1) organizational feasibility, (2) evaluation of effects on patient* outcomes, and (3) evaluation of the mobilizing professionals' experience:

3.1. ORGANISATIONAL FEASIBILITY

- How many patients are suitable for robot-assisted VEM and how many are actually early mobilized with the robotic device? (Number of patients treated / number of suitable patients)
- In how many cases the conventional/robotic VEM could be performed completely? In how many cases did the robotic VEM have to be discontinued? (Number of completely performed VEMs in patients/ Number of treated patients/ Reasons for discontinuation)
- How was the early mobilization performed? (Duration of VEM and set-up times, frequency of VEM, intensity of VEM (number of steps per minute/ total number/ degree of verticalization).
- Could the planned procedure of the VEM be performed? (Number of aborted/ cancelled VEMs, number of VEMs carried out)
- Could the VEM become part of the daily routine of the ICU? And if not, what factors are influencing this? (Free text)
- Are the technical requirements for complete rehabilitative therapy using a robotic device available or have there been failures? (Number of failures)

Primary target criteria	Feasibility of early mobilization	Suitability of patients for robotic VEM (number)
		Frequency of treatment (completed number of treatments)
		Duration of treatment and set-up times (in min)
		Frequency of treatment
		Intensity of treatment (comparison group using ICU Mobility Scale (31)
		Number of failures of the technical system
	Adverse Events	The following adverse events are defined as long as they occur during mobilization and up to 15 minutes afterwards:
		New cardiocirculatory insufficiency (hypotension, hypertension, arrhythmia).
		New respiratory insufficiency (drop in saturation, asynchrony with ventilator).
		Accidental removal/dislocation of devices such as tubes, drains, catheters
		Injury and fall
		All serious adverse events will be analyzed and evaluated by the investigator to determine whether they occurred as a result of the study.

4.2 EVALUATION OF THE BEHAVIOUR AND EXPERIENCE OF THE MOBILIZING PROFESSIONALS

- How do professionals involved in early mobilization and positioning of ICU patients experience the use of a robotic system for early mobilization?
- How do the mobilizing specialists in nursing, physiotherapy and medicine rate the robotic system for early mobilization of patients in the intensive care unit regarding the burden and relief during the mobilization?
- What consequences does the implementation of a robotic system for the early mobilization of patients in intensive care units have on the mobilization and positioning behavior of the nursing, physiotherapy and medical staff involved?

Episodic interviews	Subjectively perceived emotions (such as stress) of the mobilizing professionals during positioning and mobilization without (T1) and with (T2 and T3) the robotic system.
	Recording of the motivating and challenging factors of the mobilizing professionals during positioning and mobilization without (T1) and with (T2 and T3) the robotic system.
	Subjectively perceived physical strain of the mobilizing professionals during positioning and mobilization without (T1) and with (T2 and T3) the robotic system.
Standardized observation	Behavior of the mobilizing professionals during positioning and mobilization without (T1) and with (T2 and T3) the robotic system
	Body posture of the mobilizing professionals during positioning and mobilization without (T1) and with (T2 and T3) the robotic system
	Personnel effort during positioning and mobilization without (T1) and with (T2 and T3) the robotic system
	Secondary data of patients (T2 and T3) who are mobilized (from the study arm effects on patient outcomes).

4.3 EVALUATION OF THE EFFECTS ON PATIENT OUTCOMES

- Can robot-assisted early mobilization improve muscle strength and reduce muscle loss compared with the historical collective?
- Can robot-assisted early mobilization reduce the duration of ventilation?
  In addition, further questions will be addressed:
- Does robotic-assisted early mobilization result in changes in consciousness, pain, cognition, health perception, cardiocirculatory and respiratory function, other factors such as pressure ulcers, bowel emptying, insulin requirements, and duration of treatment?

For this purpose, the following outcome criteria of the patients are examined.

Primary outcome criteria	**Physical function/muscle strength**	Surveyed according to the MRC (Medical Research Council) classification on upper and lower extremity and using the FSS-ICU (32, 33) at discharge ICU.
	Parameters for the assessment of muscle deterioration	Muscle thickness of quadriceps femoris muscle (thickness quadriceps femoris muscle and cross sectional area rectus femoris muscle)
		Muscle thickness of the diaphragm / Thickening fraction diaphragm
		Diaphragm mobility at discharge ICU
	Ventilation time	Duration (d) of invasive ventilation

Secondary outcome criteria	**Consciousness/ cognition/ pain/ health perception**	Pain using the Visual Analog Scale (VAS) (before and after mobilization).
		Delirium incidence using the CAM ICU (34): number of days without delirium.
		Sedation level using the Richmond Agitation Sedation Scale (RASS)(35)
		level of consciousness using the Glasgow Coma Scale (GCS) (36)
		Health-related quality of life after 3 months using the SF-36 questionnaire (37)
	Hemodynamics	Blood pressure / catecholamine demand / heart rate / cardiac output / oxygen consumption
	Respiration	CPAx-respiratory function(38) / oxygenation index / lung ultrasound parameter
	Others	Intestinal evacuation (yes/no)
		Decubitus (grade classification 1-4 according to Shea (39)
		Lactate level before and after mobilization (if laboratory value available)
		Insulin requirement
	ICU Scores	SOFA [39] / Apache II (40) / SAPS II (41)
		Intensive care unit treatment duration / inpatient treatment duration

5. TIMELINE OF THE STUDY

The study includes the period of early mobilization by robotic system of patients who meet the inclusion and exclusion criteria. These will be mobilized using the robotic early mobilization device twice a day for 20 minutes, at least ten times or within seven days. The data collection is planned for five to six months.

Within the study period, the following topics will be covered in three study lines (cf. fig. 4):

(1) Feasibility of robot-assisted VEM in the Intensive Care Unit.

(2) Behavior and experience of the mobilizing professionals
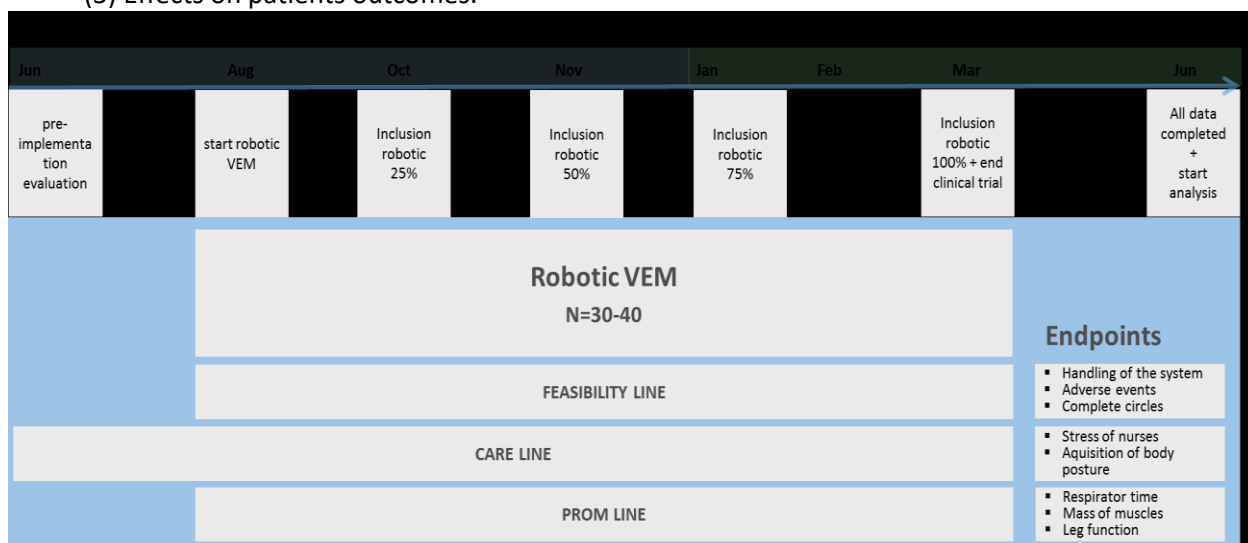
(3) Effects on patients outcomes.

Figure 4: Overview of the time courses of the study arms.

6. STUDY DESIGN

The present study is a monocentric, prospective intervention study, designed to

- evaluate the feasibility and integration in the setting of an Intensive Care Unit.
- evaluate the behavior and experience of the mobilizing specialists of the robot-assisted VEM in a longitudinal section (three data collection points).
- compare robot-assisted VEM in critically ill intensive care patients with non-robot-assisted early mobilization according to the standard of care of a historical patient population.

7. STUDY POPULATION

The study population consists of adult patients undergoing surgical procedures and scheduled for postoperative treatment in the anesthesiological intensive care units at LMU Klinikum, with an

anticipated postoperative ventilation duration of > 48 hours. All patients will be included in the prospective intervention study according to inclusion and exclusion criteria.

Feasibility surveys will be conducted by project staff and will refer to the study populations of patients and mobilizing professionals.

The mobilizing professionals consist of physicians, nurses and physiotherapists working in anesthesiological intensive care units, who are regularly involved in mobilization. Physicians, nurses and physiotherapists will be included according to inclusion and exclusion criteria.

7.1 INCLUSION AND EXCLUSION CRITERIA FOR PROFESSIONALS INVOLVED

Inclusion Criteria

Nurses with advanced training in anesthesia and intensive care and/or nurses who have at least three years of professional experience in an intensive care unit will be included. In addition, these persons have an employment contract at LMU Hospital.

Similarly, specialists in leading positions in intensive care units with completed residency training and an employment contract at LMU-Klinikum as well as physiotherapists with at least three years of professional experience in an intensive care unit and an employment contract at LMU-Klinikum are included.

For T_2 and T_3, all specialists should also be assigned to the anesthesiological intensive care units.

Specialists will only be included if they agree to participate in the study.

Exclusion criteria

Persons who are members of the MobiStaR project team, have less than three years of professional experience as a nurse or specialist in an ICU, or are still in residency training are excluded. Physiotherapists with less than three years of professional experience in intensive care units are also excluded. Individuals who are not employed at LMU Hospital are also excluded. In T_2 and T_3, specialists who are not assigned to the anesthesiological intensive care units according to the duty schedule are excluded.

7.2 INCLUSION AND EXCLUSION CRITERIA FOR PATIENTS

Inclusion criteria

- planned surgical intervention
- postoperative intensive care and therapeutic treatment
- expected duration of ventilation > 48 hours
- age ≥ 18 years
- preoperative patient consent for the study
- weight >45 kg and <135 kg

- Body height >1.50 m and <1.95 m

Exclusion criteria

- Patients refusal to participate in the study
- unable to give informed consent
- chronically bedridden before inclusion
- clinical frailty scale ≥ 7 (42)
- chronic ventilation (more than 24 hours) before admission to the intensive care unit
- Elevated intracranial pressure / risk for elevated intracranial pressure / recent cerebral hemorrhage
- Pregnancy
- Pre-existing neuromuscular disease resulting in chronic limitation of strength and performance
- Sternotomy / Sternectomy during a surgical procedure

Patients meeting the following criteria will be retrospectively selected for the historical comparison group:

- planned surgical procedure
- Postoperative intensive care and therapeutic treatment
- Duration of ventilation > 48 hours
- age ≥ 18 years
- Weight >45 kg and <135 kg
- Body height >1.50 m and <1.95 m
- Patients who met any of the exclusion criteria during their intensive care unit stay will not be included in the historical group.

No matching is planned.

7.3. NUMBER OF PATIENTS

In order to test correlations using multiple-variate models (multiple linear regressions) with a statistical power of 80% on approximately 8 independent variables (UV) compared to the dependent variable (AV), an approximate total sample size of 50 subjects is required.

Thus, with an expected drop-out of 10%, 55 patients (robotic intervention and historical comparison group) should be included in the study. A sample size of 20 subjects is considered a lower limit with moderately strong associations between UVs and AV and inclusion of a maximum of 5 UVs, with alpha=5% and power=80% (43, 44). In this regard, if 30-35 patients are included in the robot-assisted intervention and a maximum of 6 UVs, meaningful results can be expected to be obtained in a manageable period of time.

All patients will be included in the intervention only if written informed consent is obtained. Due to the expected patients' recruitment (6-8 patients/month) with a given number of cases (30-35 patients in the intervention), the study is expected to last five to six months from the start. The recruitment rate depends on the number of patients.

In general, all patients meeting the above-mentioned criteria will be included in the study. The study is completed as soon as the required number of patients has been recruited for the intervention. The corresponding number of cases for the historical group will be taken from the routine data.

7.4. TERMINATION CRITERIA FOR PATIENTS

All patients included in the study are free to withdraw their consent to participate in the study, in whole or in part, at any time and without giving reasons. In such a case, patients will be asked to state the reason for withdrawal but will be informed that they are not required to do so. Time and reasons for withdrawal (if given) will be documented. Patients can be excluded from the study if a violation of inclusion or exclusion criteria is subsequently determined or if the data collection is incomplete.

7.5. TERMINATION CRITERIA FOR PERFORMING PROFESSIONALS

All professionals included in the study are free to withdraw their consent to participate in the study, in whole or in part, at any time and without giving reasons. In such a case, professionals will be asked to state the reason for discontinuation but will be informed that they are not required to do so. Time and reasons for withdrawal (if given) will be documented. Professionals may be excluded from the study if a violation of inclusion or exclusion criteria is subsequently identified or if data collection is incomplete.

7.6. TERMINATION CRITERIA FOR THE ENTIRE STUDY

Termination of the study is not foreseen in general. An interim evaluation is not planned for short study durations.

If less than half of the patients have been recruited after three months, an interim evaluation will take place. The study can be discontinued if the interim evaluation shows that the recruitment rate is not sufficient to achieve the objectives mentioned under 4. as the number of patients is too low and an increase in the recruitment rate is not possible.

The decision to discontinue the study is made by the project management together with the study physicians. All patients included in the study up to the point of discontinuation should be evaluated in any case in order to be able to evaluate the early mobilization in this patient group, the previous implementation and the experience of the mobilizing specialists.

8. METHOD AND PROCEDURE

Patients of the LMU Hospital will be included according to the inclusion and exclusion criteria (see 5.2. and 5.3.). All patients who are to be treated surgically and whose postoperative care is planned in the anesthesiological intensive care units will be screened according to the inclusion and exclusion criteria. If the expected duration of postoperative ventilation exceeds 48 hours and there are no contraindications, the patient is given an information session. This should be done preoperatively with awake patients who are able of giving consent. In case of consent, the patient will be included in the study.

In addition, within the scope of the experience of the mobilizing specialists, nurses, physiotherapists, and physicians will be included according to inclusion and exclusion criteria, who are predominantly assigned to the intensive care units of the LMU Hospital and from T_2 onwards to the anesthesiological intensive care units.

With the start of robot-assisted early mobilization, the survey will be conducted within the framework of organizational feasibility. This is carried out by project staff and ward staff. The survey ends with the last robot-assisted mobilization.
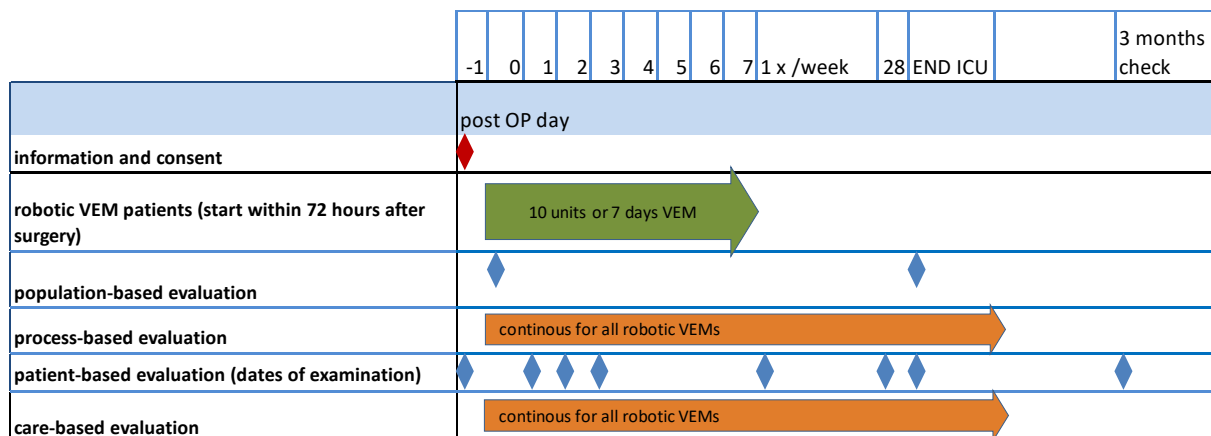

Fig. 5: Detailed procedure of the study with examination times of the patients

All patients will receive a physical examination at different time points to assess physical functionality and muscle strength, as well as a sonographic examination of leg muscles, diaphragm, and lungs. These examinations should be performed on day -1 (preoperatively), on postoperative days 1,2,3, then once a week if the patient remains in the Intensive Care Unit, on day 28, on the day of discharge from the Intensive Care Unit, and on a follow-up examination approximately 3 months after discharge from the Intensive Care Unit. The follow-up examination should only take place if the patients present themselves at the LMU Hospital anyway due to medically indicated follow-up examinations (not study-related). Alternatively, patients can be asked about their condition by telephone (see Fig. 5).

Conventional early mobilization

The comparison group is a historical collective, which also meets the inclusion and exclusion criteria of the study. These patients were early mobilized following the ward routine of the intensive care units conventional early mobilization according to the instructions of the treatment team, consisting of physicians, nurses, and physiotherapists. Conventional early mobilization cannot be precisely defined on the basis of a retrospective study (45, 15). The information used for the study regarding early mobilization and the defined outcome criteria of the patients is taken from the routinely collected data.

Robot-assisted early mobilization

Patients included in the study according to the inclusion and exclusion criteria will be mobilized using the robotic system. The aim is to perform a standardized mobilization with verticalization within the first 72 hours after admission to the Intensive Care Unit. If possible, this should be performed twice every day for 20 minutes, with a minimum of ten treatment cycles or for seven days. Treatment characteristics such as timing, intensity, duration, and complications will be documented.

As part of the study, routinely collected personal data and laboratory chemistry data will also be documented. There will be no blood sampling or other invasive procedure as part of the study. The study period begins for the patients after their informed consent shortly before the surgical procedure and ends approximately 3 months after study inclusion with the planned follow-up examination, with the end of the recording period of the study or the death of the patient.

LIST OF THE DATA TO BE COLLECTED

All required information collected in routine clinical practice is to be obtained from the patient documentation system (electronic patient record).

8.1. DATA COLLECTION ORGANIZATIONAL FEASIBILITY

As part of organizational feasibility, population-based data will be collected on a weekly basis. These include the following characteristics:

Characteristic	Expression
Number of newly admitted and eligible patients on the anesthesiological intensive care units per week	Count value
Number of patients enrolled in the study per week	Count value
Number of eligible patients not included in the study	Count value
Number of patients for whom the intervention was discontinued - **from patient side** - **from clinical side**	Count value / rate
Adverse events (46) - **patient-related** - **user-related** - **technique-related**	Count value

In addition, intervention-related data should be collected daily or on each day that early mobilization is performed.

A unique three-digit ID will be assigned to each patient, under which all data will be recorded pseudonymously. The following data is collected for each mobilization:

Patient-related data

Three-digit ID	postoperative day
Date	
Consecutive number of mobilizations	
Duration of mobilization	start - end (number of minutes)
Set-up time preparation	Number of minutes
Set-up time postprocessing	Number of minutes
Number of mobilizing professionals	Number
Intervention related data	
Degree of verticalization	Degree between 0 and 70
Number of minutes in the highest degree of verticalization	Number of minutes
Steps per minute	Number
Total steps	Number
Adverse event / premature termination	yes /no (If yes, type of event)
Feasibility assessment by mobilizing professional	7 point Likert scale
Assessment of the mobilizing professional's own physical stress	7 point Likert scale

8.2. DATA COLLECTION BEHAVIOUR AND EXPERIENCE OF MOBILIZING PROFESSIONALS

1. Survey of stress/motivation and physical strain
- Episodic interviews (47) at least four people per professional group (until data saturation occurs).
  o Analysis by means of qualitative content analysis (48)
  o The mobilizing professionals are interviewed about their emotions in the mobilization situation (see appendix for topics of observation)
- Distress thermometer (49) in conjunction with each interview.
  o Analysis by means of descriptive statistics (49)

2. Survey of positioning and mobilization behavior
- Standardized observations (50) with n= 30-50
    - Analysis by means of descriptive statistics (51)
    - Behavior and attitude of mobilizing professionals will be observed (see appendix for topics of observation)
    - In addition, the following data will be included in T2 and T3, which will be collected in the study arm "effects on patient outcomes":
        - Ventilation (Yes / No)
        - Medication (in Weaning → Yes / No; Analgosedation → Yes / No; Catecholamines → Yes / No)
        - Gender
        - Weight/ Height

Observation will only occur during mobilization of patients who have given consent to participate in the study.

Additionally, only mobilizing professionals who have given consent to participate in the study will be included in the observations and interviews. Should consent to the study be subsequently withdrawn at a later date, the study participants will be asked whether the data obtained up to that point may still be used. Otherwise, all the data collected up to that point will be destroyed.

8.3. DATA COLLECTION EFFECTS ON PATIENT OUTCOMES

In this study, various interventions will be performed on patients. All invasive procedures performed on patients will be performed as routine procedures independently of the study in the Intensive Care Unit (ICU) according to medical indication. The following study-related procedures will be performed on the patients beyond the informed consent and documentation of patient-related data:

Patients will receive robot-assisted mobilization within the first 72 hours after admission to the Intensive Care Unit ≥2 x / day for 20 minutes, for a minimum of ten treatment cycles or seven days. Clinical-functional examination with collection of clinical scores and ultrasound parameters on day -1, 1,2,3, then once a week if continued in the Intensive Care Unit, day 28, day of discharge from the Intensive Care Unit, 3 months after study inclusion (within the data collection period) (39).

No other study-related burdens or risks arise for patients.

An overview of clinical and study-related measures is provided below:

Measure	Measure performed	Specification/ Invasiveness
Education and informed consent	Study-related	Noninvasive
Clinical examination to determine physical function	Study-related	Noninvasive

Sonographic examination of the lungs, diaphragm, and M. quadriceps femoris	Study-related	Noninvasive
Early mobilization, robot-assisted	Study-related	Non-invasive within the framework of the CE-certified indication for approval
Documentation of patient-related data	Study-related	Noninvasive

In addition, personal data, laboratory values from clinical routine and clinical data are recorded:

Domain	Parameters
1. Personal Data	
	Age, sex, height, weight
Diagnosis	Admission and progressive diagnoses
Therapy	Medications, infusion solutions
2. Laboratory diagnostic data	
	Parameters determined from the routine
3. Clinical data	
SOFA score (52) Apache II score (41) SAPS II score (40) RASS(31) VAS GCS (36) Decubitus score according to Shea (37)	Temperature, mean arterial pressure, heart rate, respiratory rate, Oxygenation index, Blood pH, Lactate, Bicarbonate, Operative status, Glasgow Coma Score Chronic conditions, export urine See Scores
Acute renal failure	AKIN-Stadium
Data Organ replacement	Renal replacement procedures, ECMO therapy
Advanced hemodynamic monitoring	Cardiac index, zvO2... (if advanced hemodynamic monitoring such as pulmonary catheter or PICCO is established)
Invasive ventilation	Duration, ventilation parameters, CPAx-respiratory function (39)

Individual measures during study procedure

Education and Informed consent

Only patients who are capable of giving consent and can be informed preoperatively will be included. Informed consent will be obtained from all patients who meet the other inclusion criteria. If the patients withdraw their consent to the study at a later point in time, they will be asked whether the data collected up to this point in time may still be used. Otherwise, all data collected up to that point will be destroyed. There is no intention to include persons from the group of persons in need of special protection.

Clinical examination to determine physical function/ health-related quality of life.

To assess physical function and muscle strength, the following non-invasive examinations will be performed and/or scores will be collected as required by the study:

FSS-ICU (53): the FSS-ICU assesses the patients "Physical Performance" based on 5 factors. For each of the 5 tasks, a minimum of 0 to a maximum of 7 points can be assigned. The following table summarizes the individual tasks.

Task	Score
1. Turning	
2. Transition from lying to sitting	
3. Transition from sitting to standing	
4. Sitting at the edge of the bed	
5. Walking	
Total score	

MRC (Medical Research Council) classification on upper and lower extremity:

Assessment of the degree of strength using the MRC classification is widely used and follows the well-known classification (see table below):

	Degree of Strength
Absence of muscle contraction	0
Visible muscle contraction	1
Movement with elimination of gravity	2
Active movement against gravity	3
Active movement against resistance	4
Normal force	5

At the follow-up examination approximately 3 months after discharge from the intensive care unit, the health-related quality of life will also be assessed using the SF-36 questionnaire (34).

Sonographic examination of the lungs, diaphragm and Musculus quadriceps femoris

Part of the examination is the sonographic evaluation of the diaphragm, lungs and Musculus quadriceps femoris.

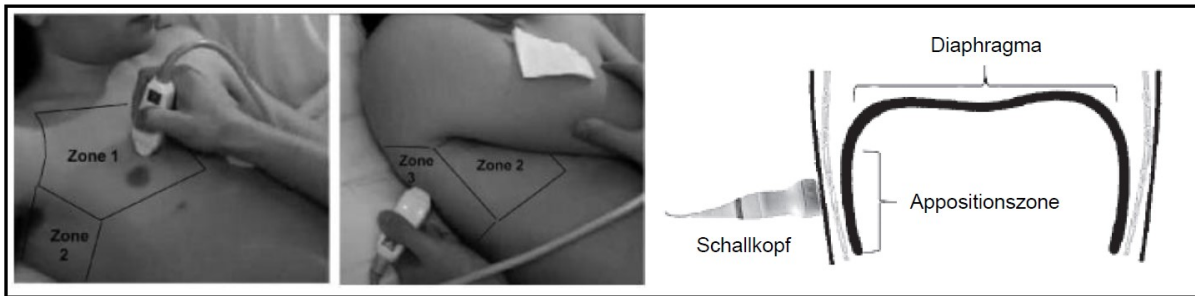These will be briefly illustrated with reference to Figures 6-8.

Figure 6: Landing points sonography lung: quantification of diaphragm thickness is performed on the right side of the body, where the diaphragm approaches the thoracic wall in the region of the liver (so-called apposition zone) (38, 54).

To determine the thickening fraction, the diaphragm thickness is determined in inspiration and in expiration (55).
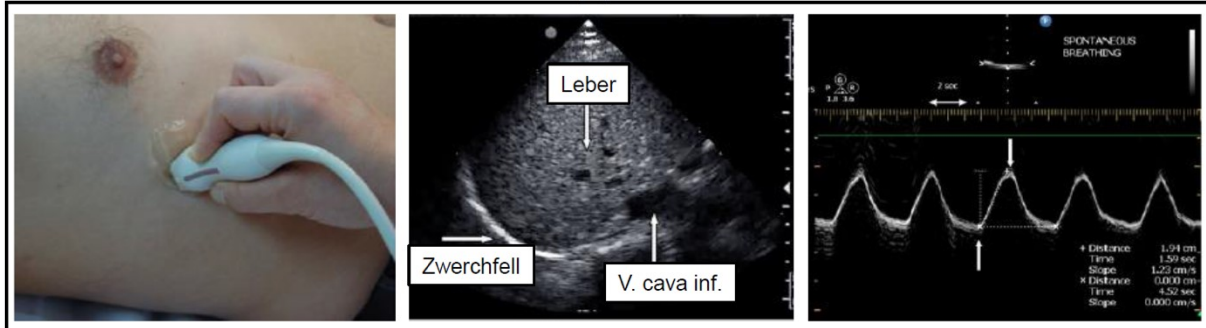

Fig. 7: Assessment of diaphragmatic excursions: Using a submammary plumb line (left image), the liver is first visited on the right side of the body as a sonic window (middle image). The diaphragmatic excursions are quantified using the M-mode (right image). On the left side of the body, the spleen is used as a sonic window (not shown).

The Musculus quadriceps femoris will be quantified using cross sectional area and thickness (56, 57). The principle of the examination is shown in Figure 8.
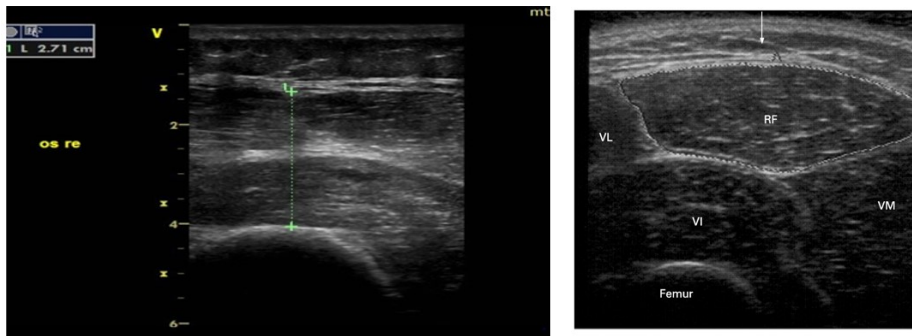
Fig. 8: left: Sonographically determined thickness of the M.quadriceps femoris on the right thigh in B-mode. Measurement points: Femur bone (+) and the posterior border of the Fascia Lata (+1). Right: Sonographically determined cross sectional area of the Musculus rectus femoris. RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; VI, vastus intermedius (57).

Robot-assisted early mobilization

The patient group will be early mobilized using robot-assisted therapy. Robot-assisted early mobilization is performed only if it is deemed safe to perform according to the criteria and recommendations of the Consensus Conference (58). This Consensus Manuscript provides recommendations on the conditions under which safe active mobilization is feasible in ventilated patients. It considers four categories (respiratory, cardiovascular, neurological, other). In this study, patients should only be robot-assisted if this is in accordance with the recommendations - level green or yellow - (see Fig. 7). Since transferring to a therapy device as described is not required for mobilization with the VEMO© system, the mobilization is categorized as "in-bed-exercise" (versus out-of-bed mobilization). The criteria are discussed with the ward team prior to each robot-assisted mobilization.


Figure 9: Traffic light system (59): In the patient group, robot-assisted mobilization is only performed if the risk assessment is green; if the risk assessment is yellow, a critical risk-benefit assessment is performed with the ward team and a graduated mobilization is performed. In the case of a red risk assessment, no active robot-assisted mobilization takes place.

The adaptive robotic system VEMO© enables early mobilization of even the most severely ill patients (see Fig. 10). These can be verticalized with the bed up to 70° degrees. Here, a leg movement can be generated according to gait patterns.

The treatment team does not differ for the individual patients: it usually consists of nurses from the corresponding intensive care units, assigned physiotherapists and the corresponding ward physicians. For the duration of the study, an additional study team will be established, consisting of study physicians, study nurses and technical support from the manufacturer.

Robotic-assisted early mobilization should be performed within the first 72 hours postoperatively, if possible, and should be performed at least twice a day for 20 minutes until the seventh postoperative day or at least ten cycles of treatment during the intensive care unit stay.

Frequency of treatment, treatment duration and intensity are recorded. Treatment-associated events will be recorded.

In case of hemodynamic, respiratory or other instability during treatment, the therapy session can be discontinued at any time. The decision to discontinue mobilization rests solely with the treatment team. The study team can advise.

Fig. 10: Robot-assisted verticalization with VEMO©.

9. BIOMETRY

In the context of organizational feasibility, descriptive data is reported and visualized for robot-assisted VEM. Subsequently, regression analyses are used to contextualize and quantify the data. Depending on the variables and the type of distribution, they are quantified after calculating degrees of freedom and correlations are tested using applicable analysis methods.

Descriptive data on stress experience and physical behavior will be collected within a robot-assisted mobilization situation and analyzed and visualized using descriptive statistics.

Within the study population, conventional early mobilization of critically ill intensive care patients (historical comparison group) will be compared with robot-assisted early mobilization. The data will be evaluated by graphical representations of the individual parameters in the course by means of box plots and scatter diagrams. Associations between parameters are quantified using appropriate (depending on scale level and distribution) correlation coefficients. For comparison between conventional and robot-assisted VEM, commonly used robust statistical methods are applied.

10. Ethical Consideration from the Perspective of the Study Team

The study itself is designed as a clinical intervention study with comparison to a historical patient population. Patient participation is voluntary. The value of early mobilization in critically ill patients has been proven, as has the safety of early mobilization. Harmful events occurred very rarely in comparable studies, and serious adverse events seen in association with the study did not occur (5, 16). The use of the VEMO© system has also been studied and found to be safe. Thus, participating patients have no a priori disadvantage. The VEMO© system has a CE certificate and is approved for the early mobilization of critically ill patients. It is categorized as a class 2a medical device and is in regular use in several German and international hospitals, such as the Berufsgenossenschaftliche Unfallklinik Murnau, the Schön Klinik Bad Aibling or the Universitätsmedizin Charité Berlin. The system is only used for the approved indication (early mobilization of critically ill patients). A hygiene concept for the application of the system was developed in cooperation with the hospital hygiene department. The surveys within the scope of organizational feasibility accompany the interventions and pose no risk to patients through the observational function.

Otherwise, the study team has no influence on the treatment of the patients.

The primary benefit in terms of effects on patient outcomes is to determine whether robot-assisted mobilization differs from conventional early mobilization in its ability to reduce ventilation time, muscle atrophy, and intensive care unit (ICU)-acquired weakness.

Individual patients could benefit from intensive robot-assisted early mobilization in terms of shorter ventilation, less muscle atrophy, and better physical functionality. A lasting negative impact in the patient group is not expected if treatment with a safe, non-invasive medical device and intensive physiotherapeutic exercise is performed. Serious adverse events associated with the medical device are not known. Possible adverse events such as short-lasting changes in blood pressure and heart rate, the accidental removal of drains or the development of skin lesions due to the mobilization cuffs could occur.

From the data obtained, improved therapy concepts can be developed and the use of robot-assisted mobilization can be established as part of a new standard of care. This study makes a significant contribution to a future improvement of therapy for critically ill patients. If the measures of robot-assisted VEM prove to be superior to the measures of historical, conventional VEM, the new treatment technique could be quickly implemented in the clinical routine of intensive care units on the basis of the project presented here.

The data collected during the study are not available to the treating physicians during the patient recruitment phase. This way, in particular, no negative influence on the therapy of the individual patient can arise. Even if conclusions regarding the treatment of future patients or patients from other intensive care units cannot be drawn from the data obtained in an unlimited and uncritical manner, the study presented here provides a valuable gain in knowledge with the aim of comparatively examining different forms of early mobilization of the effect on a specific patients population. By simultaneously surveying the experience and behavior of the mobilizing professionals, it is also possible to record their workload when using the new therapy. Given the high workload in intensive care units, a feasibility study is essential, so the focus of this study is on users, patients, and structures.

In summary, this study makes an important and necessary contribution to improving the therapy of critically ill patients. There are no study-related burdens for the individual patients and participation in the study is without risks for the patients.

11. Data Management (Data Protection, Anonymization, Data Storage)

For the entire project, an overarching data protection statement Art 6 DSGVO of the data protection officer of the LMU Hospital is available. (Procedure number 1582 of 26.02.2020/ Procedure Number 1582a of 13.07.2021).

The data will be collected by means of digital questionnaires. The patients receive a three-digit pseudonymized ID after giving their consent. Target criteria collected in routine clinical practice will be recorded with the routine case number and transferred to the research database created specifically for the project. After completion of the documentation, the case number will be replaced by the above-mentioned ID. All personal data will be recorded under this ID. The data from the survey forms are promptly stored electronically in a secure folder. These are secured by the network of the participating institutions and the restricted access to the data.

Only the research team has access to the research database. Access to personal data (effects on patient outcomes) is restricted to the study physicians, who are bound by medical confidentiality. After completion of the study for the individual patients, the personal reference is removed and the encryption code is only kept in a written document in a lockable cabinet on the anesthesiological intensive care unit, to which only the clinical study director has access. Decoding is only done for the safety of the patients (= medical reasons) or in case of a change of the scientific question (= scientific reasons). The regulations of medical confidentiality and data protection are observed in this study. Patients will be informed in detail about data protection during the patient education. Access to study-related data is only possible via the respective study directors. All data will be destroyed according to the usual retention periods (Federal Data Protection Act).

Only the study team of the LMU Hospital and the Catholic University of Eichstätt-Ingolstadt (experience and behavior of the users) has access to the collected data.

The names of the participants and all other confidential information are subject to confidentiality and the regulations of the General Data Protection Regulation (DSGVO) and the Federal/State Data Protection Act (BDSG/BayDSG). Data of the study participants will not be passed on. Third parties will not be given access to the original documents. The data collected during the study will be kept until the data analysis is completed and then destroyed. Pseudonymized data may be shared with scientific project partners as part of the discourse on the study.

OBLIGATION OF THE STUDY MANAGEMENT ACCORDING TO STUDY PROTOCOL

The study directors as well as all participating scientists commit themselves to conduct the study described here according to the study protocol. Changes of the study protocol are only possible after consultation with the ethics committee, if necessary a new evaluation will be obtained.

BIOBANKING

Biobanking will not be performed in this study.

12. DISSEMINATION

The results of the study as well as results from the respective surveys will be made available to the public subsequently. This will be done in the form of publications.

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