

BMJ Open Enhanced Recovery after Intensive Care (ERIC): study protocol for a German stepped wedge cluster randomised controlled trial to evaluate the effectiveness of a critical care telehealth program on process quality and functional outcomes

Christine Adrion ¹, Bjoern Weiss ², Nicolas Paul ², Elke Berger,³ Reinhard Busse ³, Ursula Marschall,⁴ Jörg Caumanns,⁵ Simone Rosseau,⁶ Ulrich Mansmann ¹, Claudia Spies ² on behalf of the ERIC study group

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CA and BW contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Claudia Spies;
claudia.spies@charite.de

ABSTRACT

Introduction Survival after critical illness has noticeably improved over the last decades due to advances in critical care medicine. Besides, there is an increasing number of elderly patients with chronic diseases being treated in the intensive care unit (ICU). More than half of the survivors of critical illness suffer from medium-term or long-term cognitive, psychological and/or physical impairments after ICU discharge, which is recognised as post-intensive care syndrome (PICS). There are evidence-based and consensus-based quality indicators (QIs) in intensive care medicine, which have a positive influence on patients' long-term outcomes if adhered to.

Methods and analysis The protocol of a multicentre, pragmatic, stepped wedge cluster randomised controlled, quality improvement trial is presented. During 3 predefined steps, 12 academic hospitals in Berlin and Brandenburg, Germany, are randomly selected to move in a one-way crossover from the control to the intervention condition. After a multifactorial training programme on QIs and clinical outcomes for site personnel, ICUs will receive an adapted, interprofessional protocol for a complex telehealth intervention comprising of daily telemedical rounds at ICU. The targeted sample size is 1431 patients. The primary objective of this trial is to evaluate the effectiveness of the intervention on the adherence to eight QIs daily measured during the patient's ICU stay, compared with standard of care. Furthermore, the impact on long-term recovery such as PICS-related, patient-centred outcomes including health-related quality of life, mental health, clinical assessments of cognition and physical function, all-cause mortality and cost-effectiveness 3 and 6 months after ICU discharge will be evaluated.

Ethics and dissemination This protocol was approved by the ethics committee of the Charité—Universitätsmedizin, Berlin, Germany (EA1/006/18). The results will be published in a peer-reviewed scientific journal and presented at international conferences. Study findings will

Strengths and limitations of this study

- Telemedicine-based care potentially improves the adherence to quality indicators in intensive care medicine, which accelerate patient recovery and improve long-term outcomes after critical illness.
- Enhanced Recovery after Intensive Care (ERIC) is the first large-scale cluster randomised controlled trial to be carried out in intensive care units (ICUs) in Berlin and Brandenburg, Germany, comparing the clinical and cost-effectiveness of a telehealth-based quality improvement intervention to standard of care.
- By employing a stepped wedge design, this quality improvement study will allow each cluster to act as its own control preserving the internal validity of the study, and has a potential for confounding by underlying secular trends.
- The nature of the intervention does not allow blinding of study personnel and eligible patients at ICUs.
- ERIC allows for a comprehensive evaluation from the patient's perspective, healthcare staff and health economics and to assess its suitability to become standard of care.

also be disseminated via the website (www.eric-projekt.net).

Trial registration number ClinicalTrials.gov Registry (NCT03671447).

INTRODUCTION

There is substantial heterogeneity in the process of critical care worldwide.¹ With more than 2.1 million critical care cases (25/1000) per year, Germany has one of

the most dense critical care environments in developed countries.² Over the last two decades, increased life expectancy, demographic changes and progress in treatment have resulted in increased survival, thus, resulting in trajectories typical for this new cohort of intensive care unit (ICU) survivors.³ These trajectories are characterised by impairments including mental illness (ie, anxiety, post-traumatic stress disorder and depression), neurocognitive degeneration and neuromuscular end organ failure resulting in conditions such as long-term ventilation.^{4–8} These long-term consequences are summarised as post-intensive care syndrome (PICS).^{9–10} Aside from PICS, a subcohort of ICU patients shows ‘chronic critical illness’ (CCI), characterised as a state of chronic dependence on organ support. Nowadays, these patients receive care in very heterogeneous settings, from rehabilitation centres to long-term acute care facilities or nursing homes. There are evidence-based strategies to reduce the PICS/CCI burden. These include, for example, the prevention of delirium, the preference of no or light sedation over heavy sedation, the conduction of spontaneous breathing trials for timely liberation from the ventilator^{4 11–17} and the use of quality indicators (QIs).

The German Interdisciplinary Association of Intensive Care and Emergency Medicine (DIVI) has summarised 10 QIs for intensive care treatment as the ‘German QIs of intensive care’, with the first version established in 2010.¹⁸ This set of 10 QIs reflects consensus-based strategies to improve quality of acute ICU care and, thus, can reduce PICS/CCI burden. For instance, if patients are frequently assessed and consequently treated for delirium, cognitive outcomes might improve.⁴ Yet, the adherence to these QIs is comparatively low and comprehensive implementation strategies are often lacking.^{19–20} QIs pertain to one or more of the three domains structure, process or outcome of quality of care.²¹ In QI development, areas of clinical practice need to be identified where evidence-based, best practice deviates from what is actually delivered to patients. Then, measurable key performance indicators are defined serving as surrogates for the level of implementation of the respective single QI. These must be accepted by the clinical team and, in the next step, implemented in daily practice to ultimately improve patient outcomes.¹⁸ As such, QIs can be used to align the allocation of healthcare resources for the improvement of patient outcomes within acute care as well as in the post-ICU period.

Telemedicine in critical care can be used as a vehicle to transport content and quality to medical settings and has already become a cornerstone in care settings with reduced access to intensive care specialists.^{22–23} It typically consists of a telemedical cockpit and a remote site, which share an audiovisual connection and health data to various degrees (depending on the applied care model).²⁴ Several studies and meta-analyses revealed a

significant reduction in ICU mortality and lengths of stay at ICU by telemedicine applications.^{25–27} Nevertheless, data on alternative aspects of the effectiveness of ICU telemedicine programmes are limited and conflicting.^{28–29} Building on this evidence, there exists, to our best knowledge, no randomised controlled trial investigating whether a virtual care network is capable of increasing quality of care and decreasing functional impairment of ICU survivors.

To fill this evidence gap, the quality improvement trial Enhanced Recovery after Intensive Care (ERIC) was initiated. This project is funded by the German Innovation Fund (‘New Forms of Care’) coordinated by the Innovation Committee of the Federal Joint Committee (grant number 01NVF16011; <https://www.g-ba.de/english/>).³⁰

METHODS AND ANALYSIS

This trial protocol is presented in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement^{31–32} (see online supplemental file 1) and also considers the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for stepped wedge cluster randomised trials (SW-CRT),^{33–34} the Standards for Quality Improvement Reporting Excellence (SQUIRE) reporting guideline³⁵ and the Template for Intervention Description and Replication (TIDieR) checklist.³⁶ The project’s webpage (www.eric-projekt.net; in German) provides an overview for clinicians, patients and their relatives.³⁷

Aim and objectives

This trial aims to demonstrate the clinical effectiveness of a multifaceted quality improvement intervention mediated by a critical care telemedicine service at ICU. The project with a target recruitment goal of 1431 patients in total has the following primary objective:

- ▶ To evaluate the benefit of a complex behavioural and telemedicine-based intervention on the adherence to evidence-based, national QIs daily assessed during the patient’s ICU stay.³⁸

Secondary objectives are:

- ▶ To evaluate whether the intervention improves long-term core outcomes including overall survival, health-related quality of life, and other (PICS-related) patient-centred outcomes concerning mental health, cognition and physical function of ICU survivors 3 and 6 months post-ICU discharge when compared with standard care.
- ▶ To estimate, in a health economic analysis alongside the main trial, the cost-effectiveness during the 6 month post-ICU follow-up for patients exposed to the intervention versus to the control condition at ICU. We aim to assess whether the intervention imposes lower costs and care needs than routine practice, for example, by reducing the proportion of patients discharged ventilated from ICU.

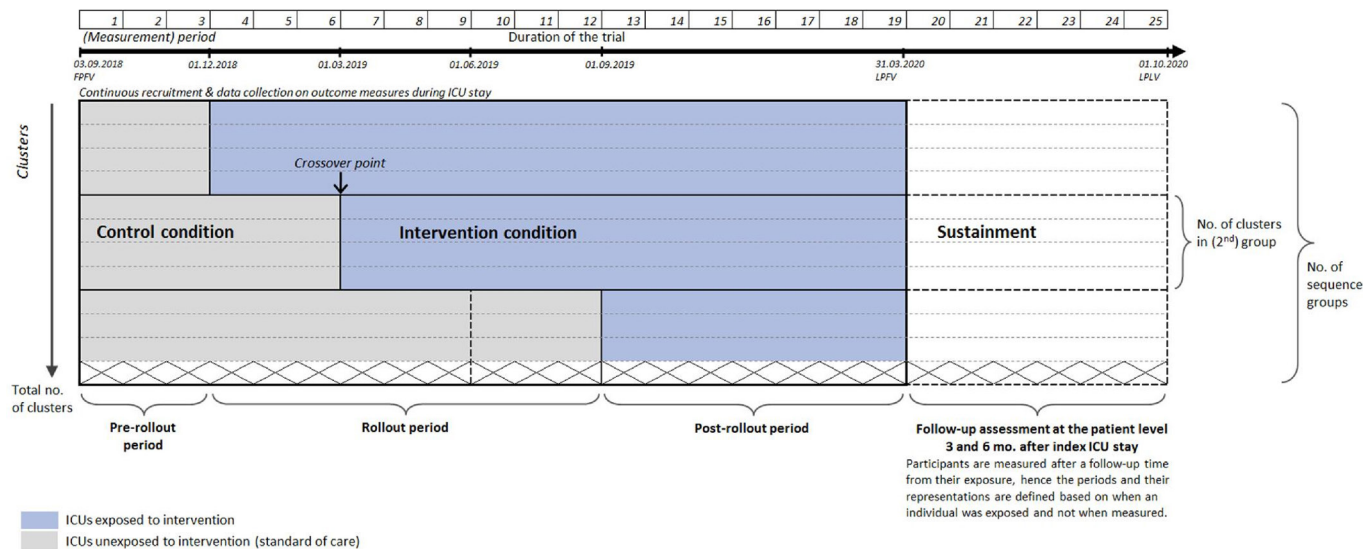


Figure 1 Schematic illustration of the staggered rollout process and timeline applied in the ERIC project (after the decision to extend recruitment, including postponement of third crossover date (indicated as vertical dashed line)). Blue areas indicate intervention stage (telemedicine), grey areas control stage and the unshaded area indicates the post-ICU phase (displayed after LPFV). In each sequence group, a 3-month transition period at the end of the control condition is defined. Follow-up assessments (secondary outcomes) on the patient level 3 and 6 months after index ICU stay. Randomisation of 12 units occurred at a single time point prior to patient enrolment; one cluster of sequence group 3 withdrew informed consent prior to start of recruitment. ERIC, Enhanced Recovery after Intensive Care; FPFV, first patient first visit; ICU, intensive care unit; LPF(L) V, last patient first (last) visit.

Study design and setting

ERIC is a national, large-scale, multicentre, pragmatic, cluster randomised controlled trial with an open cohort stepped wedge design with continuous recruitment.³⁹ The study will be conducted in adult critical care units of hospitals located in the metropolitan area of Berlin and the rural area of the surrounding federal state Brandenburg with a population of about 6 million inhabitants in total. The study area has approximately 150 000 ICU admissions per year (Gesundheitsberichterstattung (GBE)–Bund health data⁴⁰). During three predefined steps over the study period of 25 months (first patient in to last patient out), which includes a 6 month post-ICU follow-up at the patient level, participating hospital facilities are randomly selected to transition from the control to the multicomponent intervention condition. Once a cluster crosses over to the intervention, it will remain exposed to the intervention for the remaining duration of the study. After the last cluster has crossed over and has fully transitioned to the intervention, there will be a final 7-month period during which all ICUs will be fully exposed (see figure 1). This trial requires that all participating hospitals begin the control phase of the trial when the data collection period begins.

Site selection

Hospitals defined as study sites are eligible to participate if they are able to commit to the following criteria at the institutional level:

- ▶ Providing adult critical care units.

- ▶ Located in the Berlin/Brandenburg metropolitan region.
- ▶ Adherence to general legal obligations to participate in the study funded by the German Innovation Fund and participation in the respective contracts (which includes a cooperation agreement with Charité—Universitätsmedizin Berlin).
- ▶ Adherence to cluster randomisation.

Trial sites were recruited from the set of hospital facilities according to their letter-of-intent written during the project application ensuring that recruitment, data collection and delivery of the telemedicine-based intervention are feasible. The defined randomisation units, that is, clusters comprising of one to three ICUs, are geographically and organisationally separated, which prevents workforce movements between clusters, and thus, intervention contamination.

Patient population and eligibility criteria

Patients admitted to the ICU at the participating site will be routinely screened against the following eligibility criteria:

Inclusion criteria at the participant level

- ▶ Age 18 years or greater.
- ▶ Expected to receive treatment in a mixed, medical or surgical ICU connected to the project for more than 24 hours.
- ▶ Coverage by a German statutory health insurance company.

- ▶ Written informed consent of patient or legal representative.

Exclusion criteria at the participant level

- ▶ Age less than 18 years.

If a study patient is readmitted to a participating ICU at a later date, the same eligibility criteria will be applied and the patient can be enrolled on multiple occasions.

Patient recruitment and informed consent model

Prior to trial commencement, participating sites have to provide informed consent on an institutional level. Due to the open cohort design, patients are recruited in continuous time as they become eligible, that is, usually at ICU admission, and most of them are exposed for a short time.⁴¹ Patients will be identified and screened for eligibility by the local team in the ICU, which has been trained by the central study coordination team of the Charité (consortium leader; for details concerning the structure of the ERIC consortium see online supplemental file 2). Written informed consent is obtained by the patient or the legal representative if the patient is unable to consent.

Randomisation, allocation concealment and masking

Due to the stepped wedge design, hospitals defined as clusters are randomised to receive the experimental intervention at different preplanned crossover dates ('steps'), and all clusters receive it (figure 1). Prior to trial commencement, 12 sites that have provided a letter of intent to be involved in the study will be randomised. The independent trial statistician contemporaneously randomised the hospital sites to one of three sequence groups using a computer-generated algorithm (nQuery Advisor V.7; simple unrestricted allocation and fixed block size). Concealment of the crossover date assignment from sites and the research team is not possible

due to the inevitable planning of the preceding training period for ICU personnel. Patients will generally be aware of the condition they are exposed to (depending on their health condition during ICU stay). However, patients (and their proxies) will be unaware of the allocation sequence, that is, those not yet receiving the intervention will not be aware of the time at which the intervention is implemented at the treating ICU. By nature of the trial design and the intervention, it is not possible to blind the study personnel at ICUs. After ICU discharge, interviewer staff, healthcare providers (eg, at rehabilitation facilities) and general practitioners conducting follow-up assessments may be aware of the treatment condition (due to access to medical records), and therefore cannot be kept blinded. Independent data analysts are not involved in outcome assessment; they will be handed the final datasets for evaluation by the consortium leader in order to perform preplanned statistical analyses.

Although several outcome assessors including data analysts will not be blinded, we do not expect a high risk of ascertainment bias to influence the treatment effect for objective outcomes.

Treatment conditions and implementation of the intervention

Figure 2 displays a schematic representation of the pillars of the ERIC intervention and underlying mechanisms to improve quality of critical care.

Intervention condition: telemedicine

A health-related behavioural, quality improvement intervention comprising of the following two core components will be implemented at the institutional level:

1. Structured daily, telemedical cart-based ward rounds will be conducted, guided by QIs in intensive care medicine (V.2017 published by the DIVI³⁸) in order to

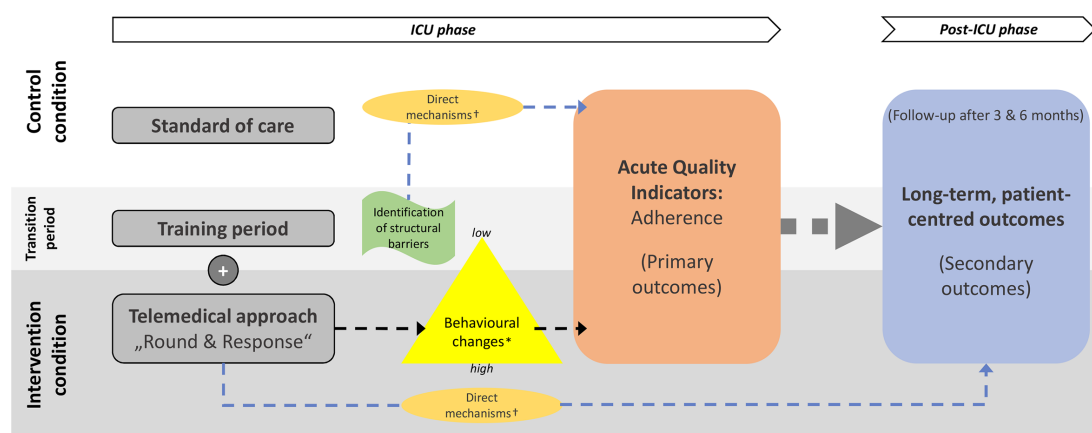


Figure 2 The pillars of the ERIC intervention: an integrated approach to critical care and causal pathways. Due to the complexity of the comprehensive ICU telemedicine intervention with multiple co-dependent components, all pillars need to be effectively implemented to be successful. *Behavioural changes include process-related factors: planning and coordination of measures, risk-benefit evaluation, responsibilities and roles. Cultural barriers: lack of mobility culture, staff knowledge and critical care expertise, or prioritisation of therapeutic concepts. †Direct mechanisms are the mechanisms that might influence the QI adherence without a behavioural change; the identification of structural barriers that result in limitations (eg, no availability of an electronic medical record so far) might have an influence on the QI documentation and, thus, QI adherence. ERIC, Enhanced Recovery after Intensive Care; ICU, intensive care unit; QI, quality indicator.

Table 1 Consensus-based set of quality indicators in intensive care for Germany (third edition 2017, see Kumpf *et al*³⁸) applied for the definition of the binary primary outcomes

Indicator no.	Description of QIs	Criteria for QI adherence
QI I	Daily multiprofessional and interdisciplinary clinical visits with documentation of daily goals	Daily medical round with a multiprofessional team and specified goals
QI II	Management of sedation, analgesia and delirium	Assessment of (1) level of sedation, (2) delirium and (3) level of pain with appropriate scoring tools
QI III	Patient-adapted ventilation	In case of mechanical ventilation, application of low tidal volume, adequate ventilation pressures
QI IV	Early weaning from invasive ventilation	Daily evaluation of weaning potential and standardised spontaneous breathing trials
QI V*	Monitoring the measures for the prevention of infection	N/A
QI VI	Measures for infection management	Early, empirical anti-infective therapy; early microbiological testing; avoidance of unnecessary anti-infective therapy; therapeutic drug monitoring
QI VII	Early enteral nutrition	Early feeding with patient-specific calorie goals; application of 50% of set calorie goal within first 48 hours of ICU admission
QI VIII	Documentation of structured patient and family communication	Documented communication with patient's family or proxy; adequate content including patient's personal preferences
QI IX	Early mobilisation	Early mobilisation within first 72 hours of ICU admission and then daily physiotherapy
QI X*	Direction of the intensive care unit	N/A

*Quality indicator (QI) V and QI X are not specified as primary efficacy outcomes since they are not assessed on a patient-level during daily QI visits and do not enable estimation of an interpretable effect of the intervention. ICU, intensive care unit; N/A, not applicable.

assess patient-individual QI-related performance measures. QI visits will be led by a specialised ICU consultant and a critical care-trained nurse working in the telemedical cockpit (tele-ICU, located at the cluster Charité at the site of the consortium leader) and attended by the concomitant treating physician and the bedside nurse at the remote ICU. This telehealth approach involves an interactive and secure two-way audiovisual communication at the bedside of the patient and face-to-face dialogue during delivery of healthcare between the tele-ICU and local care provider. This procedure is based on remote video visualisation of the patient and their monitoring devices by means of the telemedical cart serving as access device.

Each round entails the discussion of all QIs (table 1) in a step-by-step approach discussion, for example, sedation, ventilator settings and antibiotics. QI-related criteria are subsequently assessed based on information obtained and documented by the tele-ICU consultant during daily telemedical ward rounds and on medical records at the remote ICU. Beyond mere QI assessment, the tele-ICU consultant can provide additional advice concerning treatment plans to remote ICU physicians.

2. A 24/7 on-call service staffed with a board-certified critical care specialist will be provided by the telemedical cockpit to ensure the coverage of acute medical issues on demand and easy access to high-quality 'virtual care' in the local treating ICU.

The main features of the tele-ICU and its equipment together with a photograph of the telemedical cart (manufacturer: InTouch Technologies, USA) used in the local patient rooms are provided in the online supplemental file 3 following the TIDieR checklist.³⁶

Control condition: usual ICU care

While delivering the control condition, ICUs are provided with no special instruction in the care of their patients and treatment is considered to be 'usual care' according to local standards, that is, the status quo provided by the cluster's ICU before the randomised start of the intervention, with treatment at the discretion of the treating clinician. In particular, no telemedicine-based support will be provided during the daily bedside ward rounds. Hence, assessment of QI adherence in the control phase is based on examination of medical records regarding QI-related parameters (table 1).

Preceding training activities and implementation of the intervention

A structured multicomponent training programme will be provided to all hospitals within a sequence group taking place during the last 3 months before the cross-over date representing a transition phase.

The training is delivered as a blended-learning concept with (1) an e-learning course for each QI (ERIC e-learning platform accessible at <https://best-edx.charite.de>), (2) a simulation-based training and (3) an on-the-job training to make sure the local ICU staff is trained in the use of the telemedical cart. Not the whole ICU team at



the participating site will be trained, but local experts (physicians and nurses) can operate as multipliers within the team. Prior to the training period, ICUs are highly encouraged to consider a medical peer review as a standardised tool for continuous quality improvement in intensive care medicine, which was developed by the German Medical Association (based on the conceptual framework of the Plan-Do-Study-Act cycle)⁴². These peer reviews conducted during multiple visits by colleagues promote the exchange of experience between professions and disciplines at ICU and focus on the systematic evaluation of the quality of an ICU's structure, its processes and outcome to secure the sustainability of the planned change processes in patient care.^{43–45}

Adherence to the intervention

After the crossover date, the adherence to the intervention condition delivered by the ICU is monitored by the tele-ICU team. Tele-ICU consultants will ensure that every patient treated on intervention condition is rounded on daily. The login times to the audiovisual communication are monitored by a distinct fleet management system resulting in an anonymous monthly performance report and show the connection times that enable to draw conclusions about the compliance of the caregivers both at the remote as well as at the tele-ICU. Unusual durations or timings of telemedical ward rounds will be reported to the clinical lead of the tele-ICU. In case of problems, tele-ICU consultants will contact remote ICU physicians via telephone.

Study outcomes and data collection schedule

Primary outcomes

To evaluate whether the intervention has a beneficial effect compared with usual care in at least one of the eight patient-level QIs in intensive care medicine (definition according to Kumpf *et al*³⁸), eight co-primary binary efficacy outcome measures derived from several QI-related performance parameters are prespecified (table 1), with each one of these defined as follows:

- ▶ Adherence (fulfilled yes/no) to a single intrahospital QI being daily assessed on a patient level starting from date of enrolment (after ICU admission) until ICU discharge, within a 24-hour time window.

Whether a single QI for patient *i* on day *t* is fulfilled or not is subsequently assessed by an intensive care specialist at the tele-ICU cockpit rating the underlying electronic QI documentation recorded by the remote site physician. This central endpoint adjudication process is used irrespective of whether the ICU delivers care on control or intervention condition.

Secondary outcomes

Secondary outcomes will be assessed during the sustainment phase with time points scheduled 3 and 6 months after the patient's exposure during index ICU stay. In particular, several key secondary outcomes are defined following the conceptual framework of core outcome sets

with respect to PICS-related domains.^{10 46} Besides, some measures related to healthcare utilisation and socioeconomic status will be assessed. A list of secondary outcomes and corresponding measurement instruments is provided in table 2.

Data collection and trial procedures during ICU stay and follow-up Table 3 shows the patient data collection schedule.

ICU stay

Data documented by local research teams for all patients while at ICU include:

- ▶ Patient details (distinct identifiers, sociodemographics, statutory health insurance status).
- ▶ Baseline data and critical illness characteristics (eg, date and mode of hospital or ICU admission or transfer from general ward care, eligibility criteria, vital signs, laboratory findings, documented preexisting conditions/medical history, illness severity scores).
- ▶ QI-related performance parameters assessed during daily QI visits.
- ▶ Hospital discharge data (discharge status (intermediate care/normal care/death), date of discharge/death).

Follow-up procedures and post-acute care

In providing written informed consent, all patients assent to the study team having access to their medical records for data collection and to be contacted in order to arrange two follow-up visits. These are scheduled 3 and 6 months after index ICU discharge including an enhanced patient monitoring with the opportunity for on-demand counselling sessions between the treating GP or the rehabilitation facility and investigators of the Charité experienced in ICU aftercare including PICS. These investigators of the Charité cannot be blinded regarding the treatment condition as they need to assess the electronic medical record data, which might be a potential source of bias. Locating of patients will contemporaneously be supported by contacting the patient's GP starting after 1 month, providing information about the ERIC project and relevant post-ICU follow-up procedures. If no GP is available or if the patient's GP does not support the project, site personnel affiliated to the Charité (consortium leader) or to a consortium partner (Ernst von Bergmann hospital in Bad Belzig, Brandenburg) will conduct the follow-up assessments. The latter one is specialised for out-of-hospital mechanical ventilation and prolonged weaning in the case the patient stays at a rehabilitation facility, weaning unit or a hospital at the time of the follow-up visits. Depending on the patient's health status, follow-up visits can be performed as home visits by clinicians of the study team.

Post-ICU follow-up data include health service and resource use assessed by means of medical records and will be documented by paper-based case report forms (CRFs) delivered to the patient's GP or filled by the study team. Additionally, validated tests and patient

Table 2 Key secondary outcomes

Domain/outcome	Timepoint	Measurement instrument
All-cause mortality	Up to 6 months after index ICU admission	Number of deaths from any cause including in-hospital mortality (using hospital administrative records, electronic medical records, municipal personal records database and the 3-month and 6-month follow-up with surrogates)
Mental health condition Subdomains: anxiety and depression	At month 3 and 6	Patient-reported symptom burden on anxiety and depression assessed by the paper-based Patient Health Questionnaire-4 (screening tool). Higher scores indicate higher impairment ⁶⁰
Mental health condition Subdomain: post-traumatic stress disorder (PTSD)	At month 6	Patient-reported symptom burden on PTSD assessed by the paper-based questionnaire Impact of Event Scale—Revised. Higher scores indicate greater distress ⁶¹
Cognition Subdomains: memory, visuospatial and visuoconstructional skills	At month 3 and 6	Functional outcome assessed by the MiniCog test (two tests: three-item recall task; clock-drawing task). Higher scores indicate better cognitive functioning ^{62 63}
Cognition Subdomain: verbal fluency	At month 3 and 6	Functional outcome assessed by the Animal Naming Test. Higher scores indicate better cognitive functioning ⁶⁴
Physical function Subdomain: mobility	At month 3 and 6	Patient's walking ability and risk of fall assessed by the Timed Up and Go Test. Higher scores indicate higher impairment ⁶⁵
Physical function Subdomain: muscle strength	At month 3 and 6	Patient's muscle and nerve function assessed by the Hand-Grip-Strength Test measured with a dynamometer (average strength (in kg) of three trials for the dominant hand) ⁶⁶
Health-related quality of life (HRQoL)	At month 3 and 6	Patient's self-reported HRQoL assessed by the EuroQol—5 dimensions—5 level descriptive system (items: mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and the Visual Analogue Scale, a thermometer-like rating scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Higher scores indicate better HRQoL ^{67 68}
Organ dysfunction	At month 3 and 6	Number of patients with organ dysfunction as assessed by general practitioner or study personnel/ investigator
Pulmonary function and symptoms—dyspnoea	At month 6	Self-perceived breathlessness during daily activities graded by the Modified British Medical Research Council Dyspnea Scale (range 0–4). Higher score indicate higher impairment ^{69 70}
Outpatient ventilation	Up to 6 months after index ICU discharge	Total duration (in days) of mechanical ventilation
Functioning and disability	At month 6	Patient-reported General Disability Score, as measured by the WHO Disability Assessment Schedule V.2.0 for activity limitation and participation restriction, 12-item short version, self-administered questionnaire. The raw score is calculated by summing the values for each item. Higher scores indicate greater disability ^{71 72}
ICU and hospital length of stay	At month 6	Total number of days spent at ICU, and in hospital
Employment status	At month 3 and 6	Return to work, or change in employment status

ICU, intensive care unit.

questionnaires with a focus to screen for PICS-related symptoms will be used (see [table 2](#) for measurement instruments). Survival status at 3 and 6 months will be ascertained through the patient's surrogates, the GP or caregivers, or municipal personal records database.

Data management, data security and quality control

Patient-level study data documented during the ICU stay will be collected and managed using Research Electronic Data Capture (REDCap) hosted at Charité at the site of the coordinating investigator. REDCap is a secure, web-based research data management platform providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for importing data from external sources.⁴⁷ Follow-up data at month 3 and 6 are

initially collected via paper-based CRFs and questionnaires before being entered into a separate REDCap CRF. All installations have been made in compliance with EU General Data Protection Regulation (GDPR) and are continuously monitored by the data protection officers.

Data quality control will be assured by automated data entry plausibility checks, and on-site monitoring to ensure accuracy and enquire implausible or missing data on a regular basis.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for participant recruitment, or the design and implementation of the study. A patient representative is a member of the trial oversight committee (independent advisory board).



Table 3 Schedule of enrolment, interventions and assessments in the Enhanced Recovery after Intensive Care Trial from the patient's perspective. Randomisation of all clusters to a transition step was done before the start of the trial

Timeline	Study period				
	Admission (or transfer from ward)	Treatment period		Post-ICU follow-up*	
	To ICU	ICU stay	ICU discharge	3 months after T0	6 months after T0
Timepoint	T-1†	Tx	T0	T1	T2
Randomisation—institutional level	X				
Enrolment					
Eligibility screen	X				
Patient's informed consent‡	X				
Patient demographics	X				
Medical history, comorbidities at admission	X				
Critical illness characteristics (eg, admission diagnosis, physiological and illness severity scores)	(X)	X	(X)		
Intervention					
Intervention condition					
Control condition (usual care)					
Assessments (in-person, by GP or site personnel)					
Quality measurements (QI-related performance parameters, QI adherence (see table 1))	(X)	X (daily)	(X)		
Mental health (Patient Health Questionnaire-4, Impact of Event Scale—Revised)§				X	X
Cognition (MiniCog test, Animal Naming Test)§				X	X
Physical and muscle function and symptoms (Timed Up and Go Test, Hand Grip Strength Test)§				X	X
Health-related quality of life (EuroQol—5 dimensions—5 level)				X	X
Organ dysfunction				X	X
Pulmonary function (Modified British Medical Research Council)					X
Outpatient ventilation				X	X
Functioning and disability (WHO Disability Assessment Schedule V.2.0)					X
All-cause mortality		X	X	X	X
Socioeconomic data (including educational background, current employment status/working ability)				X	
Healthcare utilisation, including concomitant (drug and non-drug) therapies, readmission, outpatient care				X	X

(X) depicts an optional measurement.

*Follow-up visits (at the GP's practice, or at the patient's home, or at a rehabilitation or nursing facility with assessments performed by site personnel) scheduled 3 and 6 months after the first study-related ICU discharge (index ICU stay).

†Time of admission to the hospital and to the ICU can be identical (depending on the patient's health condition). Otherwise, transferral from hospital's general ward to the participating ICU and recruitment happens at a later date.

‡If applicable, by authorised representative.

§Assessments are part of the outpatient post-intensive care syndrome screening.

GP, general practitioner; ICU, intensive care unit; QI, quality indicator.

Public involvement is achieved through the active role of the German statutory health insurance company BARMER that represents the interests of its members. The results of the study will be disseminated to the patients through public information such as the BARMER customer magazine and by the dedicated project's website, which has a section for patients and relatives. Furthermore, our aim is to include patients in the interpretation of the study results if possible.

Clinical evaluation: statistical methodology and planned analyses

Power considerations and pretrial sample size calculation

Following the cluster-randomised design, a pragmatic power calculation was performed on a per hospital facility basis assuming equal cluster sizes and considering a limited number of potential sites and resources. To allow for eight binary co-primary outcomes with all of them having equal importance from a clinical perspective, a Bonferroni correction for multiple testings was applied for sample size calculation based on an overall one-sided type I error rate of $\alpha=5\%$ (resulting in an $\alpha/8=0.625\%$ significance level for confirmatory testing for a single QI). A minimum clinically relevant difference of 10% in QI adherence was specified; this target difference between both treatment conditions was guided by values in the literature.^{19 48}

A two group χ^2 test with a 0.625% one-sided significance level will have 82% power to detect the difference between a group 1 proportion (control condition), p_1 , of 60% and a group 2 proportion (intervention condition), p_2 , of 70% (OR of 1.556) when the sample size on each treatment condition is 530 patients in the case of independent observations (nQuery Advisor V.7.0). To deal with the correlation between individuals from the same cluster, a design effect (variance inflation factor) of 1.35 was estimated, together with an intracluster correlation coefficient of 0.117 (derived from unpublished data available for site Charité only) which measures the correlation between observations within the same cluster.^{49 50} The total study sample size required for the CRT design is then obtained as 1431 patients. Considering practical aspects of admission and capacities results in a total setting of 12 clusters with approximately 163 cases per cluster and a total sample size of 1956 cases (12·163). Further details are given in the online supplemental file 4.

No transition period was included in the sample size calculation. Besides, there has been no allowance for varying cluster sizes since these methodological issues still need development for studies with stepped wedge design. Altogether, we expect the underlying assumptions used for the initial sample size calculation being rather conservative to detect an absolute increase in adherence of 10% in at least one of eight QIs.

Statistical methods: clinical effectiveness

The analyses of primary outcomes will be conducted according to intention-to treat and clusters will be considered exposed to the intervention post randomised crossover date. All patients from a randomised medical facility defined as a unit of randomisation (one cluster comprising of one to three ICUs) who are recorded in the database and for whom at least one QI measurement has been obtained will be included in the analyses with respect to the treatment specified by the allocated randomisation order. The eight co-primary outcomes will be compared using Bonferroni-adjusted two-sided confirmatory testing at a 0.625% significance level.

Medical facilities who initially agreed to participate but subsequently withdraw before trial start date but after randomisation (without recruiting any patients) will be excluded. Several protocol deviations at the cluster level may occur: Departures from the randomisation at a cluster level are defined as any cluster, which does not switch to the intervention at the assigned intervention implementation time point according to the randomisation schedule determined prior to trial commencement. Depending on the relevance and number of the deviations, a per-protocol analysis, which will exclude departures from the randomisation schedule (including the affected patients), will be completed for the primary efficacy outcomes only.

Most patients experience either the control or intervention condition during their index ICU stay (defined as the first study-related ICU stay at one of the participating medical facilities). 'Crossover patients', that is, patients being exposed to both conditions, should be avoided in the case they are admitted to the ICU shortly before the allocated crossover date. If a patient will be readmitted to the ICU at a later time—documented as a new case—he or she will be exposed to the condition delivered at the respective time point which might be different from the one during index ICU stay.

To avoid (within cluster) contamination, patients who will be enrolled before the ICU's crossover with set-up and activation of the tele-ICU will remain being treated on control condition according to the protocol. Therefore, patients who will nevertheless be exposed to both conditions due to being enrolled immediately before the ICU's crossover will be excluded from the analyses (ie, from the primary comparison of control and intervention condition).³⁹ Likewise, patients who are admitted on control and later readmitted on intervention condition after a site's crossover, thus, being exposed to both conditions, will also be excluded from the principal analysis to assess telemedicine effectiveness.

A generalised linear mixed effects modelling approach is chosen that allows to model intervention-by-time interactions as well as to consider assumptions on effects regarding the transition periods. Related sensitivity analyses will be described in the upcoming statistical analysis plan (SAP). More details on the models for primary and

secondary outcomes are described in the online supplemental file 4. There, we also discuss methodological issues related to death truncation and informative missings for functional patient outcomes.

Statistical analyses will be performed using the software package R V.3.6.1 or higher.⁵¹ A full SAP will be written ahead of the final database lock.

Process evaluation

To ensure that the intervention is delivered as expected and successfully implemented, selected key components will be evaluated. There will be a nested qualitative study embedded within this SW-CRT to assess the acceptability of e-learning courses during the training phase. For telemedical ward rounds (QI visits), data on the connection failure rate and overall connection quality between the tele-ICU and remote ICUs are closely monitored to avoid inadequate implementation of the intervention.

Health economic evaluation

Alongside the main trial, a health economic evaluation will be performed to assess the economic impact of the ERIC intervention compared with standard of care.^{52 53} This evaluation consists of cost-effectiveness analyses and a cost-utility analysis,⁵⁴ and the perspective of the health, long-term and retirement insurances will be taken into account.⁵⁵ Direct medical and non-medical costs as well as indirect costs and outcomes will be assessed for the ICU and post-ICU period up to 12 months (by extrapolation).⁵⁶ Further, all costs and consequences will be discounted by 3%, as recommended by the Institute for Quality and Efficiency in Healthcare (IQWiG).^{57 58} Health economic outcomes include mortality rate, rate of long-term mechanically ventilated patients, QoL as measured by EuroQol—5 dimensions—5 level and quality-adjusted life years gained.^{56 59}

The following data sources will be used, among others, to estimate costs and outcomes: clinical data collected during ICU stay, hospital claims data, statutory health insurance expenditures data (BARMER) and data captured from the CRF used for follow-up assessments. The results will be reported as mean costs, mean outcomes and incremental cost-effectiveness ratios, where appropriate. Robustness will be addressed in sensitivity analyses, as suggested by IQWiG.⁵⁸ ERIC will be shown to be cost-effective if costs are lower and outcomes are the same or better, or if costs are the same and outcomes are clearly better as compared standard of care.

DISCUSSION AND PRACTICAL IMPLICATIONS

Study impact and importance

ERIC is a German large-scale cluster randomised trial with a stepped wedge design evaluating whether the phased implementation of a 'round and response' telehealth programme is effective. In doing so, it is hypothesised that daily telemedicine-based, structured ward rounds being one of the core interventional components can

be a successful performance-improvement strategy not only on the institutional level (clinician-led QIs as surrogates for quality of care at ICUs), but also on the level of the critically ill patient (benefit on patient-centred core outcomes, in particular with respect to PICS).

Given the significant financial and personnel resources required for the installation and upkeep of telemedicine systems at ICUs, a thorough evaluation of the impact of a tele-ICU coverage leading to improved intensivist coverage at off-site hospitals is vital. Assessing the process quality at ICU imposes the risk of an inadequate choice of QIs. The QIs chosen for this trial were established by the DIVI in 2010, and are evidence-based, clinical-practice guideline derived, and operationalised ensuring that they can be measured on a daily basis. Eight (out of ten) consensus-based QIs are specified as binary primary outcomes, which can be reliably assessed on the patient level. However, this results in eight possible trial outcomes increasing the possibility of an equivocal rather than a definitive result.

PICS-related, patient-centred outcomes such as quality of life will be assessed 3 and 6 months but not at baseline, that is, before ICU admission. However, given the large sample size, we assume that randomisation will balance the baseline levels of these secondary outcomes.

Conclusion

ERIC is one of the first projects of the German Innovation Fund's 'New Forms of Care' programme. The project was assessed as evidence based and regionally viable. The evaluation concept is robust and has been developed with clinicians, biometricians and health economists. It will allow a comprehensive assessment from the patient's, clinical and health economic perspective after about 3 years.

If this trial demonstrates a beneficial impact on evidence-based QIs at ICU, alongside a favourable health economic assessment, then there would be a strong case for incorporating this telemedicine programme into clinical routine throughout Germany—leading to a system change in critical care medicine by improving patient care pathways.

TRIAL STATUS

At the time of first manuscript submission, research ethics approval has been obtained for the trial. Data collection with enrolment of the first patient commenced on 04 September 2018. Last patient last visit (including a 6-month follow-up period) is expected in October 2020.

Progress of the study and extension of the study duration

Before the transition of the last sequence group from control to intervention status, we realised that the preplanned target sample size could not be reached since the recruitment rate was far lower than anticipated. Additionally, barriers with respect to data protection rules were identified leading to a delayed cooperation agreement between several participating sites and the consortium leader. This in particular affected the number of patients recruited under control condition. One cluster of sequence

group three withdrew informed consent prior to start of recruitment. In May 2019, all consortium partners agreed to extend the duration of the recruitment (first patient in to last patient in) from 12 to 19 months and postponed the prespecified third crossover date (while extending the rollout period) by 3 months to further enhance the number of patients treated on control condition.

ETHICS AND DISSEMINATION

Ethical considerations

This study is being conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and is consistent with Good Clinical Practice (GCP). Enrolment of patients at the participating ICUs did not start until the written and unrestricted positive vote of the local ethics committee (EC) was obtained. The protocol is based on the underlying project application which received previous independent peer review as part of the grant funding process. Together with the patient information sheets and consent forms, the protocol was first approved by the EC of the Charité—Universitätsmedizin Berlin on 26 January 2018 (approval number EA1/006/18), and the EC of the Brandenburg Medical School Theodor Fontane joined (approval number Z-01-20180828). Amendments to the protocol will be submitted to the EC for review. Individual written informed consent including consent to data collection will be obtained from all eligible patients in the trial. Consent forms for the trial include consent for publication of results in peer-reviewed journals. Relevant data protection rules for all analysed data will be enforced.

By implementing a quality improvement intervention based on evidence-based QIs, no additional risks to patients are expected relative to standard of care. Outcome data are routinely collected health data together with post-ICU data. Therefore, adverse events will not be monitored or reported. An independent Advisory Board has been appointed to ensure that ethical, legal and social aspects and responsibilities are carried out according to GCP.

Dissemination plan

The success of the trial will depend entirely on the collaboration of clinicians in the participating ICUs and those who hold key responsibilities at the study sites. The main results of the evaluation will be reported to trial collaborators and subsequently be published in peer-reviewed scientific journals and at national and international conferences. Additionally, study findings will be disseminated via a press release that will also be available on social media after publication to reach out to patients and surrogates as well as healthcare professionals. Authors and collaborators will be involved in reviewing drafts of the manuscripts, press releases and any other publication format arising from this project.

Author affiliations

¹Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-University, Munich, Germany

²Department of Anesthesiology and Operative Intensive Care Medicine, Charité—Universitätsmedizin Berlin, Berlin, Germany

³Department of Health Care Management, Technical University of Berlin, Berlin, Germany

⁴BARMER, Wuppertal, Germany

⁵Fraunhofer Institute for Open Communication Systems, Berlin, Germany

⁶Weaning and Ventilation Centre, Ernst von Bergmann Klinikum, Bad Belzig, Germany

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Collaborators ERIC study group (see online supplemental file 2).

Contributors CS, BW and SR did the clinical conceptual planning of the Enhanced Recovery after Intensive Care project. UMan designed the trial and has oversight for the statistical analyses. As trial statisticians of the project, CA and UMan were responsible for the independent clinical evaluation. EB and RB designed the health economic evaluation; RB has oversight for the health economic analyses. BW, UMan and RB contributed to the preceding research proposal leading to the funding of the trial. CS led the grant application and, as principal investigator and consortium leader, has oversight for the trial. BW was the study project manager, responsible for the study's quality assessment and was in charge of the overall study management. NP was responsible for post-intensive care unit follow-up procedures and contributed to project management issues at the site of the consortium leader. UMar supervised the project from the perspective of the statutory health insurance company BARMER. JC designed the IT-infrastructure. CA and BW drafted the manuscript (joint first authorship). All authors have critically read, contributed with inputs and revisions and approved the final manuscript.

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ORCID iDs

Christine Adrion <http://orcid.org/0000-0003-2408-2533>

Bjoern Weiss <http://orcid.org/0000-0003-3139-595X>

Nicolas Paul <http://orcid.org/0000-0003-2228-3980>

Reinhard Busse <http://orcid.org/0000-0003-4961-9130>

Ulrich Mansmann <http://orcid.org/0000-0002-9955-8906>

Claudia Spies <http://orcid.org/0000-0002-1062-0495>

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