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Algorithmic **S**urveillance of **IC**U patients with acute respiratory distress syndrome (ASIC): Manual for a multicentre stepped-wedge cluster-randomized quality improvement strategy.

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ABSTRACT

Introduction

The acute respiratory distress syndrome (ARDS) is a highly relevant entity in critical care with mortality rates of 40%. Despite extensive scientific efforts, outcome-relevant therapeutic measures are still insufficiently practiced at the bedside. Thus, there is a clear need to adhere to early diagnosis and sufficient therapy in ARDS, assuring lower mortality and multiple organ failure.

Methods and analysis

In this quality improvement strategy (QIS), a decision support system as a mobile application (ASIC app), which uses available clinical real-time data, is implemented to support physicians in timely diagnosis and improvement of adherence to established guidelines in the treatment of ARDS.

ASIC is conducted on 31 intensive care units (ICU) at 8 German university hospitals. It is designed as a multicentre stepped-wedge cluster randomized QIS. ICUs are combined into 12 clusters which are randomized in 12 steps. After preparation (18 months) and a control phase of 8 months for all clusters, the first cluster enter a *roll-in* phase (3 months) that is followed by the actual QIS phase. The remaining clusters follow in month wise steps.

The co-primary key-performance-indicators (KPIs) consist of the ARDS diagnostic rate and guideline-adherence regarding lung-protective ventilation. Secondary KPIs include the prevalence of organ dysfunction within 28 days after diagnosis or ICU discharge, the treatment duration on ICU and the hospital-mortality. Furthermore, the user acceptance and usability of new technologies in medicine are examined. To show improvements in health care of ARDS patients, differences in primary and secondary KPIs between control phase and QIS will be tested.

Ethics and dissemination

Ethical approval was obtained from the independent Ethics Committee (EC) at the RWTH Aachen Faculty of Medicine (local EC reference number: EK 102/19) and the respective data protection officer in March 2019. The results of the ASIC QIS will be presented at conferences and published in peer-reviewed journals.

Trial registration number: DRKS00014330

Keywords: Acute respiratory distress syndrome, ICU, algorithmic surveillance, mobile device, quality improvement, decision support system, quality improvement strategy

STRENGTHS AND LIMITATIONS

- The project aims to improve the timely diagnosis in ARDS, especially of frequently underdiagnosed mild stages as well as to increase guideline-adherent therapy.

- Usage of mobile devices on ICUs to shorten response time onto clinically relevant events in critical care medicine.
- Realisation of interoperability of heterogeneous medical routine data to improve its use for research and improvement of care and to enable cross-site data exchange.
- There are no mandatory changes in clinical care, as treatment remains in the full responsibility of the physician in charge.
- To prove feasibility and means of implementation, a QIS was chosen, thus a confirmatory trial building on the experiences gained within this project will be necessary prior to a more profound clinical implementation.

INTRODUCTION

ARDS is a life-threatening medical condition associated with mortality rates ranging approximately from 25% to 46% across all severities and can be even higher when associated with dysfunction of other organs (1, 2). Depending on the severity of hypoxia which is defined by the p_aO_2/F_iO_2 ratio (Horovitz quotient), moderate ARDS (with a p_aO_2/F_iO_2 ratio 101 - 200) has been reported to occur in 16 to 23 and severe ARDS (with a p_aO_2/F_iO_2 ratio ≤ 100) in 58 to 79 per 100,000 inhabitants per year (3). Lung-protective ventilation, i.e. the use of low tidal volumes and the limitation of airway pressures, has been shown to improve outcomes compared to mechanical ventilation with high tidal volumes and airway pressures. Despite this outcome-improving strategy, the large multicentre, observational “LUNG SAFE”-trial observed a low adherence to lung-protective ventilatory strategies and guidelines associated with a high mortality rates up to 46% in severe ARDS (1). An additional finding of the LUNG SAFE-trial was that up to 39% of the ARDS cases were not diagnosed by the physicians, which suggests procedural and infrastructural deficits. Particularly early and mild or moderate ARDS often remains unrecognized until respiratory dysfunction of the patient has deteriorated further and severe hypoxia is present. By implementing consistent lung-protective ventilation, as described in the German guideline "Invasive ventilation and use of extracorporeal procedures in acute respiratory insufficiency" (4), significant improvement in the prognosis of this disease entity should be achieved (5, 6). However, implementation of these therapy principles cannot be achieved when ARDS is not or not early enough diagnosed. Hence, improvements in both ARDS-screening as well as in implementation of evidence-based therapeutic measures are urgently needed. Improvements of procedural and infrastructural deficits might be provided by intelligent technical solutions (7, 8). A software approach pre-processing data from electronic health records (EHRs) and providing diagnostic data and treatment recommendations on a mobile device might be such a solution. This approach has been taken by the use case ‘Algorithmic Surveillance of ICU patients with acute respiratory distress syndrome’ (ASIC). ASIC is an integral part of the ‘Smart Medical Information Technology for Healthcare’ (SMITH) project (9). SMITH is one of four consortia funded by the ‘Medical Informatics Initiative’ of the German Federal Ministry of Education and Research (10).

The objective of our quality improvement project is to improve ARDS detection and guideline adherence in the treatment of mechanically ventilated ARDS-patients by implementing an application software (app) provided on a mobile device and consecutively improve outcome in this patient population.

METHODS AND ANALYSIS

ASIC app

The ASIC app is a mobile, technical support system to facilitate diagnosis and therapy of ARDS and has been specifically developed for this project. It operates system-independently on different devices. As part of the ASIC project, it is intended to be used on a mobile device (e.g. tablet, smartphone). The data used by the ASIC app is obtained from the local EHR. According to these data, a diagnosis of ARDS can be made by the physician according to the Berlin Criteria (11). Manual entries are required for the findings, which are not documented automatically,

like radiographic reports. Due to these functions, the ASIC app only displays a compilation of already existing and documented clinical routine data.

ARDS is suspected in mechanically ventilated patients (≥24 hours duration) by automated ASIC app dependent positive screening of respiratory dysfunction. The duration of mechanical ventilation, the p_aO_2/FiO_2 ratio and the positive endexpiratory pressure (PEEP) are extracted and screened by the ASIC app automatically. An ARDS suspicion is defined as deterioration of the p_aO_2/FiO_2 ratio ≤ 300 mmHg that occurs under a PEEP ≥ 5 cmH_2O. In case of ARDS suspicion, the physician will be informed and has to evaluate a potential diagnosis by checking the non-automated criteria of ARDS. These include a) an acute onset of lung injury within 1 week of an apparent clinical insult and with progression of respiratory symptoms, b) presence of bilateral opacities on chest imaging (chest radiograph or CT) not explained by other lung pathology (e.g. effusion, lobar/lung collapse, or nodules) and c) respiratory failure not explained by heart failure or volume overload. According to the Berlin Definition, 3 severity stages of ARDS (mild, moderate, severe) are categorized based on the degree of hypoxemia using the p_aO_2/F_iO_2 ratio (11). If the diagnosis has been made by the physician, the ASIC app displays the relevant recommendations of the German S3 guideline "Invasive ventilation and use of extracorporeal procedures in acute respiratory insufficiency" (4) and requests the physician to evaluate applicability of these recommendations for the individual patient. Responsibilities for diagnostic and therapeutic decisions remain with the physicians in charge. If the ARDS-diagnosis is not verified, a 24-hour blocking period follows, in which the app does not issue any further notifications. If screening for ARDS remains positive, the app will ask the physician for re-evaluation after 24 hours.

Project design

This paragraph describes the initial design of the project as it was planned before the start of control phase. The project is designed as a multicentre stepped-wedge cluster randomized QIS (12). It will be conducted at 8 German university hospitals: Aachen (8 ICUs/96 beds), Bonn (4/58), Duesseldorf (1/16), Halle a. d. Saale (2/30), Hamburg-Eppendorf (10/116), Jena (2/50), Leipzig (3/78) and Rostock (1/23). Since not all of these 31 ICUs are technically and organisationally independent, the dependent ICUs will be summarised into clusters. This results in a total of 12 clusters available for randomisation, of which each will be randomised to one of the 12 steps. After a preparation phase of 18 months, all participating clusters start with a control phase (standard of care) simultaneously. After 8 months, the first clusters enter the roll-In phase (3 months) that is followed by the actual QIS phase. The remaining clusters follow in a stepwise fashion with 1 month between each step (Figure 1). During the control phase, the status quo in diagnosis and therapy of ARDS is recorded without any interventions and change in clinical routine. According to the randomization scheme, the ASIC app will be implemented on the participating ICUs during the roll-in phase to ensure clinical and technical functionality and adequate training of the ICU staff. 3 months later, the QIS phase will start, using the ASIC app in clinical routine. In this phase, the physicians will be assisted to optimize diagnosis and guideline-adherent therapy of ARDS by the ASIC app. Except for the app-usage, there are no further changes in routine caregiving. The final evaluation of primary and secondary KPIs (see below) will take place in the evaluation phase.

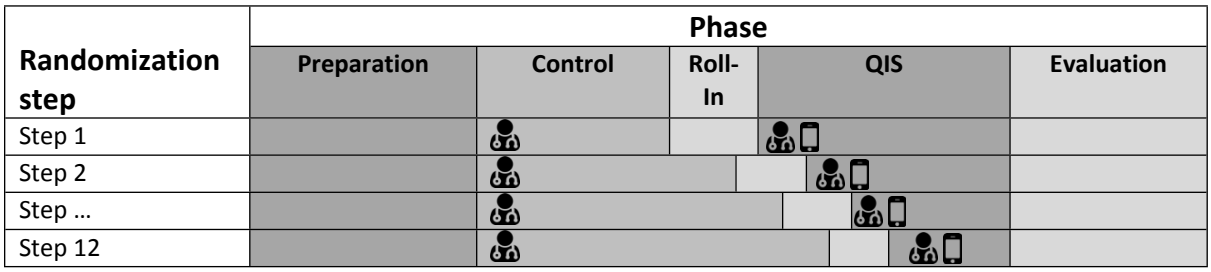

Figure 1: Stepped-wedge design. During the Control phase, ARDS detection is performed according to local standard by the physician in charge. With beginning of the QIS phase, physician´s ARDS diagnosis is supported by the ASIC app.

Population under Surveillance

All patients ≥ 18 years of age in the participating ICUs, who are mechanically ventilated for at least 24 hours, will be admitted to the project. According to pre-existing data from the local EHRs, we expect approximately 5000 patients per year to be surveyed within the project.

Key Performance Indicators

The co-primary KPIs of the project consist of the diagnostic rate, defined as the proportion of patients diagnosed with ARDS out of all monitored patients, and guideline-adherence regarding lung-protective ventilation, defined as shown below (see table 1).

Table 1: Co-Primary and secondary key-performance-indicators of ASIC.

Co-Primary key-performance-indicators	Secondary key-performance-indicators
Diagnostic rate, defined as the proportion of patients diagnosed with ARDS out of all monitored patients	Prevalence of **organ dysfunction** within 28 days after diagnosis of ARDS or ICU discharge (whatever occurs first), defined as days without need of following measures: ○ Mechanical ventilation ○ Vasopressor use ○ Renal replacement therapy
Guideline-adherence regarding **lung-protective ventilation**, defined as the percentage of time within 28 days after ARDS diagnosis or ICU discharge (whatever occurs first), during which the mechanical ventilation parameters fulfil the following criteria: ○ Tidal volume (V_t): ≤ 6 ml/kg KG (ideal) ○ Endinspiratory pressure (P_{EI}): ≤ 30 cmH_2O ○ Positive endexpiratory pressure (PEEP) ≥ 5 cmH_2O ○ Driving pressure (Δ P = P_{EI} - PEEP) ≤ 15 cmH_2O	**Treatment-duration on ICU** after ARDS-diagnosis **Hospital-mortality** after ARDS-diagnosis **Acceptance and usability** of the ASIC app and the mobile device: a) Pre-Roll-In of the ASIC app b) Post-Roll-In (6 months) of the ASIC app

Secondary KPIs include the prevalence of organ dysfunction within 28 days after ARDS-diagnosis or ICU discharge (whatever occurs first). The treatment duration on ICU and the hospital-mortality after ARDS-diagnosis will be assessed at hospital discharge, irrespective of length of stay.

Furthermore, the user acceptance and usability of new technologies in medicine, such as mobile devices or clinical decision support systems will be examined. Therefore, a survey

among the app users will be conducted before and after the ASIC app-implementation, in order to investigate user acceptance of mobile technical support systems within clinical routine.

Clinical Data Collection and Data Protection

The total data collection started in July 2019 and is scheduled to be completed in December 2021. All data used by the ASIC app or included in the analysis are primarily displayed and stored in the local EHR (tables 1-3). At admission to the ICU, the body height of the patients will be measured using disposable measuring tape in order to determine the ideal body weight for calculating the tidal volume according to ARDS network (13). Ideal body weight is computed in men as 50 + (0.91 × [height in centimetres − 152.4]) and in women as 45.5 + (0.91 × [height in centimetres − 152.4]). The diagnosis of ARDS is assumed to be made when the ICD-10 code J80.x is documented, depending on severity of disease. The onset of ARDS in the control phase is defined as the time, when the p_aO_2/F_iO_2 ratio decreases consistently ≤300 mmHg, i. e. during a period of 2 hours or in 2 consecutive arterial blood gas analyses, if the time interval between them is longer than 2 hours. During the QIS, the onset of ARDS is assumed, when the physician diagnoses an ARDS using the app. Data are collected from admission to the project until discharge from hospital. Patients who develop ARDS will be assessed for their outcomes when discharged from ICU or 28 days after diagnosis (whatever occurs first) and at hospital discharge depending on the outcome parameter. For a detailed summary, which parameter is collected at which time point, please refer to table 1.

Table 2: Patient-related data-acquisition.

Data acquired at inclusion	
Demographic data	Age, sex, height, weight, body mass index, ideal bodyweight (according to the ARDS-network)
Acquired data at diagnosis of ARDS	
Therapeutic interventions	Prone-positioning
Acquired data 28 days after diagnosis of ARDS or ICU discharge (whatever occurs first)	
Guideline-adherence	Time fraction of guideline-adherent therapy. Included parameters: ○ Tidal volume (V_t): ≤ 6 ml/kg ideal bodyweight ○ Endinspiratory pressure (P_{EI}): ≤ 30 cmH_2O ○ Positive endexpiratory pressure (PEEP) ≥ 5 cmH_2O ○ Driving pressure (Δ P = P_{EI}-PEEP): ≤ 15 cmH_2O
Days without organ dysfunction	Full days without organ replacement therapy: ○ Mechanical ventilation (excluding atelectasis-prophylaxis) ○ Use of vasopressors ○ Renal replacement therapy
Acquired data at hospital discharge	
Duration of treatments	Duration of hospital treatment, duration of ICU treatment, duration of hospital treatment until ARDS-diagnosis
Mechanical ventilation	Duration of mechanical ventilation (excluding atelectasis-prophylaxis)
Mortality	In-hospital mortality of ARDS, ICU-mortality of ARDS

Table 3: Clinical data collected during the project.

Scores	Glasgow coma scale (GCS), Sequential organ failure assessment-Score (SOFA)
Vital parameters	Heart rate, oxygen saturation, arterial blood pressure (systolic, diastolic, mean pressure), central venous pressure, body temperature, 24h-fluidbalance
Hemodynamic monitoring	Pulmonary artery pressure (systolic, diastolic, mean pressure), Pulmonary artery wedge pressure, extravascular lung water-index (EVLWI), global enddiastolic volume-index (GEDVI), cardiac output, cardiac index, stroke volume, stroke volume-index, systemic vascular resistance-index (SVRI), pulmonary vascular resistance-index (PVRI)
Parameters of mechanical ventilation	Respiratory rate (measured, spontaneous), I:E-ratio, tidal volume per ideal bodyweight, inspiratory oxygen-fraction, expiratory oxygen-fraction, end-inspiratory-pressure (p_{EI}), positive endexpiratory pressure (PEEP), driving pressure ($\Delta P = p_{EI}$ - PEEP), lung compliance, endexpiratory CO_2
Laboratory parameters	Leucocytes, hemoglobin, hematocrit, platelets, CRP, PCT, urea, creatinine, brain natriuretic peptide, bilirubin, albumin, AST, ALT, troponin, creatinkinase, creatinkinase isoform MB (CK-MB), amylase, lipase, international normalized ratio (INR), activated partial thromboplastin time (aPTT)
Blood gas analysis	pH, p_aO_2, p_aCO_2, S_aO_2, lactate, bicarbonate, $S_{cv}O_2$, base excess (BE), p_aO_2/F_iO ratio
Medication	Nitric oxide (NO) inhal., iloprost inhal., dobutamine iv, adrenaline iv, noradrenaline iv, vasopressin iv, milrinone iv, levosimendan iv, propofol iv, midazolam iv, clonidine iv, dexmedetomidine iv, S-ketamine iv, isoflurane inhal., sevoflurane inhal., sufentanil iv, fentanyl iv, morphine iv, rocuronium iv, furosemide iv, hydrocortisone iv, prednisolone iv, dexamethasone iv, terlipressin iv, fludrocortisone iv
Extracorporeal membrane oxygenator (ECMO)	Veno-venous ECMO (VV-ECMO), Veno-arterial ECMO (VA-ECMO), extracorporeal bloodflow, extracorporeal gasflow, oxygenfraction of extracorporeal gasflow

The data usage takes place within the secure networks of the participating hospitals. When the patient has been discharged, the collected data are transferred to the local Data Integration Centre (DIC), where they are anonymised. The DIC of each location enables medical data sharing across institutional boarders to improve patient care and clinical research. The establishment of these DICs is intended to create a sufficiently large database to allow further analyses. This could help to identify further risk factors with diagnostic or prognostic relevance for ARDS in the future, using e.g. current methods of data science.

Comprehensive validation of data protection issues was carried out by external legal consultants. Furthermore, a data protection concept was developed by external data protection experts for the concrete data protection processes in accordance with the local data protection commissioners (e.g. data transfer, anonymization, data storage).

Proposed Sample Size

To check whether the size of the sample we expect to collect in the 12 clusters will suffice to detect a difference in ARDS diagnosis rates with 80% power, we did a power calculation as proposed by Hussey and Hughes (14) using the R package swCRTdesign (15) in R (version 3.5.1)

(16). This package implements power calculations that take into account the particular characteristics of stepped-wedge cluster-randomized trials such as within-cluster correlations as shown in the article by Hussey and Hughes (14)

Based on the expected case numbers of 5000 Patients/year, we assumed a mean of 1041 patients per cluster for the study duration of 2.5 years. For the ARDS diagnosis rate in the control phase we used incidences from Brun-Buisson et al. (17)and Bellani et al. (1) which suggest a rate of 16.1% and 23.4 %, respectively. Under both of these baseline rates an increase as small as 1% (e.g. from 16.1% to 17.1%) could be detected with at least 80% power.

Statistical Analysis

To provide explorative evidence of improvement in health care of ARDS patients, differences in primary and secondary KPIs between control phase and QIS will be tested using generalised linear mixed models, where the level of clustering is the 12 clusters. The hypotheses tested for the coprimary KPIs are:

A) The ARDS diagnosis rate in the QIS phase (p_{QIS}) is higher than the rate in the control phase ($p_{control}$):
$H_0^A: p_{QIS} = p_{control}$ vs. $H_1^A: p_{QIS} \neq p_{control}$

B) The percentage of lung protective ventilation time in the QI phase (p_{QIS}) is higher than the percentage in the control phase ($p_{control}$):
$H_0^B: p_{QIS} = p_{control}$ vs. $H_1^B: p_{QIS} \neq p_{control}$

We will conduct two-sided significance tests with a significance level of 5% and also use point estimates and their 95% confidence interval to judge the effect. Secondary KPIs will be analyzed descriptively and if feasible with exploratory hypothesis tests following the modelling approach of the primary KPIs.

Patient and public involvement

ASIC is carried out in the routine care of critically ill patients. It fosters the timely diagnose and the adherence to existing guidelines and does not introduce new therapeutic measure. Due to that fact, patients were not included into the planning of the project. During the development of the ASIC app, physicians, who were supposed to use the app, contributed to a user-friendly design of the app. Additionally, surveys among the using physicians will be carried out to evaluate the physician´s view onto the app. At last, patient and public involvement will be reached by the SMITH Congresses 2019 and 2021 (https://www.digital-health-2019.de/) and the activities of the German 'Medical Informatics Initiative' (https://www.medizininformatik-initiative.de/).

ETHICS AND DISSEMINATION

Ethics Review, Registration and Informed consent

Ethical approval was obtained from the independent EC at the RWTH Aachen Faculty of Medicine (local EC reference number: EK 102/19) as well as the respective data commissioner in March 2019. ASIC is registered at the German Clinical Trials Register (DRKS00014330) and will be conducted according to the current version of the *Declaration of Helsinki*. The collection of routine documentation upon which the ASIC app operates does not require an informed consent because the app merely serves as a supplement to the existing EHR, which will remain the main resource in patient data management.

Access to Data and Dissemination

The results of the ASIC QIS will be presented at scientific and medical conferences and published in peer-reviewed journals. ASIC was created to demonstrate the possibilities offered by advanced digital services and infrastructure in healthcare and therefore serves as an exemplary use case with clinical benefit in order to prove the functionality of the DIC infrastructure within the SMITH consortium. One of the main objectives of establishing DIC at the local sites is to facilitate the exchange and use of medical data across the borders of institutions and geographical locations in interoperable data formats for medical research while meeting the data protection and security laws and requirements.

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AUTHOR´S CONTRIBUTIONS

GM and ASchu developed the concept and design of the ASIC use case. OM, SD and JKi worked as project managers for the SMITH project and coordinated the use case. SFr, JKu, OM, SD and JB wrote the manuscript. GM, JB, SFr, JKu, CP, SZ, FE, RK, KK, FS, SK, SG, LH, FB, PS, NJ and TS were responsible for the extraction and summary of the guideline recommendations for the ASIC app. VL and NV developed the technical architecture of the ASIC app and supervised the programming of the ASIC app. SH, IL, SZ, FE, DG, SB, JG, PJ, DT, EW, DA, SM, TW and PG worked on the technical implementation of the DIC at their respective centers and the data extraction for the ASIC app. ASchu, RP, KS, HM, LK, WS, RB, JL, MR, CB, ASto and SFo worked on the identification of unknown risk factors with diagnostic and prognostic relevance for ARDS. ASche and JG provided feedback regarding the study design and the statistical analysis. GM and VL worked on legal issues concerning the implementation of the ASIC App. VL, NV, SH, IL worked on technical issues concerning the implementation of the ASIC App. All Authors read and approved the final manuscript.

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COMPETING INTERESTS

None reported

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Algorithmic **S**urveillance of **IC**U patients with acute respiratory distress syndrome (ASIC): Protocol for a multicentre stepped-wedge cluster-randomized quality improvement strategy.

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ABSTRACT

Introduction

The acute respiratory distress syndrome (ARDS) is a highly relevant entity in critical care with mortality rates of 40%. Despite extensive scientific efforts, outcome-relevant therapeutic measures are still insufficiently practiced at the bedside. Thus, there is a clear need to adhere to early diagnosis and sufficient therapy in ARDS, assuring lower mortality and multiple organ failure.

Methods and analysis

In this quality improvement strategy (QIS), a decision support system as a mobile application (ASIC app), which uses available clinical real-time data, is implemented to support physicians in timely diagnosis and improvement of adherence to established guidelines in the treatment of ARDS.

ASIC is conducted on 31 intensive care units (ICU) at 8 German university hospitals. It is designed as a multicentre stepped-wedge cluster randomized QIS. ICUs are combined into 12 clusters which are randomized in 12 steps. After preparation (18 months) and a control phase of 8 months for all clusters, the first cluster enter a *roll-in* phase (3 months) that is followed by the actual QIS phase. The remaining clusters follow in month wise steps.

The co-primary key-performance-indicators (KPIs) consist of the ARDS diagnostic rate and guideline-adherence regarding lung-protective ventilation. Secondary KPIs include the prevalence of organ dysfunction within 28 days after diagnosis or ICU discharge, the treatment duration on ICU and the hospital-mortality. Furthermore, the user acceptance and usability of new technologies in medicine are examined. To show improvements in health care of ARDS patients, differences in primary and secondary KPIs between control phase and QIS will be tested.

Ethics and dissemination

Ethical approval was obtained from the independent Ethics Committee (EC) at the RWTH Aachen Faculty of Medicine (local EC reference number: EK 102/19) and the respective data protection officer in March 2019. The results of the ASIC QIS will be presented at conferences and published in peer-reviewed journals.

Trial registration number: DRKS00014330

Keywords: Acute respiratory distress syndrome, ICU, algorithmic surveillance, mobile device, quality improvement, decision support system, quality improvement strategy

STRENGTHS AND LIMITATIONS

- Continuous monitoring of routinely collected parameters to improve the timely diagnosis in ARDS, especially of frequently underdiagnosed mild stages as well as to increase guideline-adherent therapy.

- Usage of mobile devices on ICUs to shorten response time onto clinically relevant events in critical care medicine.
- Realisation of interoperability of heterogeneous medical routine data to improve its use for research and improvement of care and to enable cross-site data exchange.
- No mandatory changes in clinical care, as treatment remains in the full responsibility of the physician in charge.
- Statistic analysis will not comply with the standards of a regular clinical trial, since a quality improvement strategy was chosen to prove feasibility and means of implementation

INTRODUCTION

ARDS is a life-threatening medical condition associated with mortality rates ranging approximately from 25% to 46% across all severities and can be even higher when associated with dysfunction of other organs (1, 2). Depending on the severity of hypoxia which is defined by the p_aO_2/F_iO_2 ratio (Horovitz quotient), moderate ARDS (with a p_aO_2/F_iO_2 ratio 101 - 200) has been reported to occur in 16 to 23 and severe ARDS (with a p_aO_2/F_iO_2 ratio ≤ 100) in 58 to 79 per 100,000 inhabitants per year (3). Lung-protective ventilation, i.e. the use of low tidal volumes and the limitation of airway pressures, has been shown to improve outcomes compared to mechanical ventilation with high tidal volumes and airway pressures. Despite this outcome-improving strategy, the large multicentre, observational “LUNG SAFE”-trial observed a low adherence to lung-protective ventilatory strategies and guidelines associated with a high mortality rates up to 46% in severe ARDS (1). An additional finding of the LUNG SAFE-trial was that up to 39% of the ARDS cases were not diagnosed by the physicians, which suggests procedural and infrastructural deficits. Particularly early and mild or moderate ARDS often remains unrecognized until respiratory dysfunction of the patient has deteriorated further and severe hypoxia is present. By implementing consistent lung-protective ventilation, as described in the German guideline "Invasive ventilation and use of extracorporeal procedures in acute respiratory insufficiency" (4), significant improvement in the prognosis of this disease entity should be achieved (5, 6). However, implementation of these therapy principles cannot be achieved when ARDS is not or not early enough diagnosed. Hence, improvements in both ARDS-screening as well as in implementation of evidence-based therapeutic measures are urgently needed. Improvements of procedural and infrastructural deficits might be provided by intelligent technical solutions (7, 8). A software approach pre-processing data from electronic health records (EHRs) and providing diagnostic data and treatment recommendations on a mobile device might be such a solution. This approach has been taken by the use case ‘Algorithmic Surveillance of ICU patients with acute respiratory distress syndrome’ (ASIC). ASIC is an integral part of the ‘Smart Medical Information Technology for Healthcare’ (SMITH) project (9). SMITH is one of four consortia funded by the ‘Medical Informatics Initiative’ of the German Federal Ministry of Education and Research (10).

The objective of our quality improvement project is to improve ARDS detection and guideline adherence in the treatment of mechanically ventilated ARDS-patients by implementing an application software (app) provided on a mobile device and consecutively improve outcome in this patient population.

METHODS AND ANALYSIS

ASIC app

The ASIC app is a mobile, technical support system to facilitate diagnosis and therapy of ARDS and has been specifically developed for this project. It operates system-independently on different devices. As part of the ASIC project, it is intended to be used on a mobile device (e.g. tablet, smartphone). The data used by the ASIC app is obtained from the local EHR. According to these data, a diagnosis of ARDS can be made by the physician according to the Berlin Criteria (11). Manual entries are required for the findings, which are not documented automatically,

like radiographic reports. Due to these functions, the ASIC app only displays a compilation of already existing and documented clinical routine data.

ARDS is suspected in mechanically ventilated patients (≥24 hours duration) by automated ASIC app dependent positive screening of respiratory dysfunction. The duration of mechanical ventilation, the p_aO_2/FiO_2 ratio and the positive endexpiratory pressure (PEEP) are extracted and screened by the ASIC app automatically. An ARDS suspicion is defined as deterioration of the p_aO_2/FiO_2 ratio ≤ 300 mmHg that occurs under a PEEP ≥ 5 cmH_2O. In case of ARDS suspicion, the physician will be informed and has to evaluate a potential diagnosis by checking the non-automated criteria of ARDS. These include a) an acute onset of lung injury within 1 week of an apparent clinical insult and with progression of respiratory symptoms, b) presence of bilateral opacities on chest imaging (chest radiograph or CT) not explained by other lung pathology (e.g. effusion, lobar/lung collapse, or nodules) and c) respiratory failure not explained by heart failure or volume overload. According to the Berlin Definition, 3 severity stages of ARDS (mild, moderate, severe) are categorized based on the degree of hypoxemia using the p_aO_2/F_iO_2 ratio (11). If the diagnosis has been made by the physician, the ASIC app displays the relevant recommendations of the German S3 guideline "Invasive ventilation and use of extracorporeal procedures in acute respiratory insufficiency" (4) and requests the physician to evaluate applicability of these recommendations for the individual patient. Responsibilities for diagnostic and therapeutic decisions remain with the physicians in charge. If the ARDS-diagnosis is not verified, a 24-hour blocking period follows, in which the app does not issue any further notifications. If screening for ARDS remains positive, the app will ask the physician for re-evaluation after 24 hours.

Project design

This paragraph describes the initial design of the project as it was planned before the start of control phase. The project is designed as a multicentre stepped-wedge cluster randomized QIS (12). It will be conducted at 8 German university hospitals: Aachen (8 ICUs/96 beds), Bonn (4/58), Duesseldorf (1/16), Halle a. d. Saale (2/30), Hamburg-Eppendorf (10/116), Jena (2/50), Leipzig (3/78) and Rostock (1/23). Since not all of these 31 ICUs are technically and organisationally independent, the dependent ICUs will be summarised into clusters. This results in a total of 12 clusters available for randomisation, of which each will be randomised to one of the 12 steps. After a preparation phase of 18 months, all participating clusters start with a control phase (standard of care) simultaneously. After 8 months, the first clusters enter the roll-In phase (3 months) that is followed by the actual QIS phase. The remaining clusters follow in a stepwise fashion with 1 month between each step (Figure 1). During the control phase, the status quo in diagnosis and therapy of ARDS is recorded without any interventions and change in clinical routine. According to the randomization scheme, the ASIC app will be implemented on the participating ICUs during the roll-in phase to ensure clinical and technical functionality and adequate training of the ICU staff. 3 months later, the QIS phase will start, using the ASIC app in clinical routine. In this phase, the physicians will be assisted to optimize diagnosis and guideline-adherent therapy of ARDS by the ASIC app. Except for the app-usage, there are no further changes in routine caregiving. The final evaluation of primary and secondary KPIs (see below) will take place in the evaluation phase.

Population under Surveillance

All patients ≥ 18 years of age in the participating ICUs, who are mechanically ventilated for at least 24 hours, will be admitted to the project. According to pre-existing data from the local EHRs, we expect approximately 5000 patients per year to be surveyed within the project.

Key Performance Indicators

The co-primary KPIs of the project consist of the diagnostic rate, defined as the proportion of patients diagnosed with ARDS out of all monitored patients, and guideline-adherence regarding lung-protective ventilation, defined as shown below (see table 1).

Table 1: Co-Primary and secondary key-performance-indicators of ASIC.

Co-Primary key-performance-indicators	Secondary key-performance-indicators
Diagnostic rate, defined as the proportion of patients diagnosed with ARDS out of all monitored patients	Prevalence of **organ dysfunction** within 28 days after diagnosis of ARDS or ICU discharge (whatever occurs first), defined as days without need of following measures: ○ Mechanical ventilation ○ Vasopressor use ○ Renal replacement therapy
Guideline-adherence regarding **lung-protective ventilation**, defined as the percentage of time within 28 days after ARDS diagnosis or ICU discharge (whatever occurs first), during which the mechanical ventilation parameters fulfil the following criteria: ○ Tidal volume (V_t): ≤ 6 ml/kg KG (predicted) ○ Endinspiratory pressure (P_{EI}): ≤ 30 cmH_2O ○ Positive endexpiratory pressure (PEEP) ≥ 5 cmH_2O ○ Driving pressure (Δ P = P_{EI} - PEEP) ≤ 15 cmH_2O	**Treatment-duration on ICU** after ARDS-diagnosis **Hospital-mortality** after ARDS-diagnosis **Acceptance and usability** of the ASIC app and the mobile device: a) Pre-Roll-In of the ASIC app b) Post-Roll-In (6 months) of the ASIC app

Secondary KPIs include the prevalence of organ dysfunction within 28 days after ARDS-diagnosis or ICU discharge (whatever occurs first). The treatment duration on ICU and the hospital-mortality after ARDS-diagnosis will be assessed at hospital discharge, irrespective of length of stay.

Furthermore, the user acceptance and usability of new technologies in medicine, such as mobile devices or clinical decision support systems will be examined. Therefore, a survey among the app users will be conducted before and after the ASIC app-implementation, in order to investigate user acceptance of mobile technical support systems within clinical routine.

Clinical Data Collection and Data Protection

The total data collection started in July 2019 and is scheduled to be completed in December 2021. All data used by the ASIC app or included in the analysis are primarily displayed and stored in the local EHR (tables 1-3). At admission to the ICU, the body height of the patients will be measured using disposable measuring tape in order to determine the predicted body weight for calculating the tidal volume according to ARDS network (13). Predicted body weight

is computed in men as 50 + (0.91 × [height in centimetres − 152.4]) and in women as 45.5 + (0.91 × [height in centimetres − 152.4]). The diagnosis of ARDS is assumed to be made when the ICD-10 code J80.x is documented, depending on severity of disease. The onset of ARDS in the control phase is defined as the time, when the p_aO_2/F_iO_2 ratio decreases consistently ≤300 mmHg, i. e. during a period of 2 hours or in 2 consecutive arterial blood gas analyses, if the time interval between them is longer than 2 hours. During the QIS, the onset of ARDS is assumed, when the physician diagnoses an ARDS using the app. Data are collected from admission to the project until discharge from hospital. Patients who develop ARDS will be assessed for their outcomes when discharged from ICU or 28 days after diagnosis (whatever occurs first) and at hospital discharge depending on the outcome parameter. For a detailed summary, which parameter is collected at which time point, please refer to table 1.

Table 2: Patient-related data-acquisition.

Data acquired at inclusion	
Demographic data	Age, sex, height, weight, body mass index, predicted bodyweight (according to the ARDS-network)
Acquired data at diagnosis of ARDS	
Therapeutic interventions	Prone-positioning
Acquired data 28 days after diagnosis of ARDS or ICU discharge (whatever occurs first)	
Guideline-adherence	Time fraction of guideline-adherent therapy. Included parameters: ○ Tidal volume (V_t): ≤ 6 ml/kg predicted bodyweight ○ Endinspiratory pressure (P_{EI}): ≤ 30 cmH_2O ○ Positive endexpiratory pressure (PEEP) ≥ 5 cmH_2O ○ Driving pressure (Δ P = P_{EI}-PEEP): ≤ 15 cmH_2O
Days without organ dysfunction	Full days without organ replacement therapy: ○ Mechanical ventilation (excluding atelectasis-prophylaxis) ○ Use of vasopressors ○ Renal replacement therapy
Acquired data at hospital discharge	
Duration of treatments	Duration of hospital treatment, duration of ICU treatment, duration of hospital treatment until ARDS-diagnosis
Mechanical ventilation	Duration of mechanical ventilation (excluding atelectasis-prophylaxis)
Mortality	In-hospital mortality of ARDS, ICU-mortality of ARDS

Table 3: Clinical data collected during the project.

Scores	Glasgow coma scale (GCS), Sequential organ failure assessment-Score (SOFA)
Vital parameters	Heart rate, oxygen saturation, arterial blood pressure (systolic, diastolic, mean pressure), central venous pressure, body temperature, 24h-fluidbalance
Hemodynamic monitoring	Pulmonary artery pressure (systolic, diastolic, mean pressure), Pulmonary artery wedge pressure, extravascular lung water-index (EVLWI), global enddiastolic volume-index (GEDVI), cardiac output, cardiac index, stroke volume, stroke volume-index, systemic vascular resistance-index (SVRI), pulmonary vascular resistance-index (PVRI)
Parameters of mechanical ventilation	Respiratory rate (measured, spontaneous), I:E-ratio, tidal volume per predicted bodyweight, inspiratory oxygen-fraction, expiratory oxygen-fraction,

	end-inspiratory-pressure (p_{EI}), positive endexpiratory pressure (PEEP), driving pressure ($\Delta P = p_{EI}$ - PEEP), lung compliance, endexpiratory CO_2
Laboratory parameters	Leucocytes, hemoglobin, hematocrit, platelets, CRP, PCT, urea, creatinine, brain natriuretic peptide, bilirubin, albumin, AST, ALT, troponin, creatinkinase, creatinkinase isoform MB (CK-MB), amylase, lipase, international normalized ratio (INR), activated partial thromboplastin time (aPTT)
Blood gas analysis	pH, p_aO_2, p_aCO_2, S_aO_2, lactate, bicarbonate, $S_{cv}O_2$, base excess (BE), p_aO_2/F_iO ratio
Medication	Nitric oxide (NO) inhal., iloprost inhal., dobutamine iv, adrenaline iv, noradrenaline iv, vasopressin iv, milrinone iv, levosimendan iv, propofol iv, midazolam iv, clonidine iv, dexmedetomidine iv, S-ketamine iv, isoflurane inhal., sevoflurane inhal., sufentanil iv, fentanyl iv, morphine iv, rocuronium iv, furosemide iv, hydrocortisone iv, prednisolone iv, dexamethasone iv, terlipressin iv, fludrocortisone iv
Extracorporeal membrane oxygenator (ECMO)	Veno-venous ECMO (VV-ECMO), Veno-arterial ECMO (VA-ECMO), extracorporeal bloodflow, extracorporeal gasflow, oxygenfraction of extracorporeal gasflow

The data usage takes place within the secure networks of the participating hospitals. When the patient has been discharged, the collected data are transferred to the local Data Integration Centre (DIC), where they are anonymised. The DIC of each location enables medical data sharing across institutional boarders to improve patient care and clinical research. The establishment of these DICs is intended to create a sufficiently large database to allow further analyses. This could help to identify further risk factors with diagnostic or prognostic relevance for ARDS in the future, using e.g. current methods of data science.

Comprehensive validation of data protection issues was carried out by external legal consultants. Furthermore, a data protection concept was developed by external data protection experts for the concrete data protection processes in accordance with the local data protection commissioners (e.g. data transfer, anonymization, data storage).

Proposed Sample Size

To check whether the size of the sample we expect to collect in the 12 clusters will suffice to detect a difference in ARDS diagnosis rates with 80% power, we did a power calculation as proposed by Hussey and Hughes (14) using the R package swCRTdesign (15) in R (version 3.5.1) (16). This package implements power calculations that take into account the particular characteristics of stepped-wedge cluster-randomized trials such as within-cluster correlations as shown in the article by Hussey and Hughes (14)

Based on the expected case numbers of 5000 Patients/year, we assumed a mean of 1041 patients per cluster for the study duration of 2.5 years. For the ARDS diagnosis rate in the control phase we used incidences from Brun-Buisson et al. (17)and Bellani et al. (1) which suggest a rate of 16.1% and 23.4 %, respectively. Under both of these baseline rates an increase as small as 1% (e.g. from 16.1% to 17.1%) could be detected with at least 80% power.

Statistical Analysis

To provide explorative evidence of improvement in health care of ARDS patients, differences in primary and secondary KPIs between control phase and QIS will be tested using generalised linear mixed models, where the level of clustering is the 12 clusters. The hypotheses tested for the coprimary KPIs are:

A) The ARDS diagnosis rate in the QIS phase (p_{QIS}) is higher than the rate in the control phase ($p_{control}$):
$H_0^A: p_{QIS} = p_{control}$ vs. $H_1^A: p_{QIS} \neq p_{control}$

B) The percentage of lung protective ventilation time in the QI phase (p_{QIS}) is higher than the percentage in the control phase ($p_{control}$):
$H_0^B: p_{QIS} = p_{control}$ vs. $H_1^B: p_{QIS} \neq p_{control}$

We will conduct two-sided significance tests with a significance level of 5% and also use point estimates and their 95% confidence interval to judge the effect. Secondary KPIs will be analyzed descriptively and if feasible with exploratory hypothesis tests following the modelling approach of the primary KPIs.

Patient and public involvement

ASIC is carried out in the routine care of critically ill patients. It fosters the timely diagnose and the adherence to existing guidelines and does not introduce new therapeutic measure. Due to that fact, patients were not included into the planning of the project. During the development of the ASIC app, physicians, who were supposed to use the app, contributed to a user-friendly design of the app. Additionally, surveys among the using physicians will be carried out to evaluate the physician´s view onto the app. At last, patient and public involvement will be reached by the SMITH Congresses 2019 and 2021 (https://www.digital-health-2019.de/) and the activities of the German 'Medical Informatics Initiative' (https://www.medizininformatik-initiative.de/).

ETHICS AND DISSEMINATION

Ethics Review, Registration and Informed consent

Ethical approval was obtained from the independent EC at the RWTH Aachen Faculty of Medicine (local EC reference number: EK 102/19) as well as the respective data commissioner in March 2019. ASIC is registered at the German Clinical Trials Register (DRKS00014330) and will be conducted according to the current version of the *Declaration of Helsinki*. The collection of routine documentation upon which the ASIC app operates does not require an informed consent because the app merely serves as a supplement to the existing EHR, which will remain the main resource in patient data management.

Access to Data and Dissemination

The results of the ASIC QIS will be presented at scientific and medical conferences and published in peer-reviewed journals. ASIC was created to demonstrate the possibilities offered by advanced digital services and infrastructure in healthcare and therefore serves as an exemplary use case with clinical benefit in order to prove the functionality of the DIC infrastructure within the SMITH consortium. One of the main objectives of establishing DIC at the local sites is to facilitate the exchange and use of medical data across the borders of institutions and geographical locations in interoperable data formats for medical research while meeting the data protection and security laws and requirements.

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FIGURE LEGENDS

Figure 1: Stepped-wedge design. During the Control phase, ARDS detection is performed according to local standard by the physician in charge. With beginning of the QIS phase, physician´s ARDS diagnosis is supported by the ASIC app.

AUTHOR´S CONTRIBUTIONS

GM and ASchu developed the concept and design of the ASIC use case. OM, SD and JKi worked as project managers for the SMITH project and coordinated the use case. SFr, JKu, OM, SD and JB wrote the manuscript. GM, JB, SFr, JKu, CP, SZ, FE, RK, KK, FS, SK, SG, LH, FB, PS, NJ and TS were responsible for the extraction and summary of the guideline recommendations for the ASIC app. VL and NV developed the technical architecture of the ASIC app and supervised the programming of the ASIC app. SH, IL, SZ, FE, DG, SB, JG, PJ, DT, EW, DA, SM, TW and PG worked on the technical implementation of the DIC at their respective centers and the data extraction for the ASIC app. ASchu, RP, KS, HM, LK, WS, RB, JL, MR, CB, ASto and SFo worked on the identification of unknown risk factors with diagnostic and prognostic relevance for ARDS. ASche, JG and ML provided feedback regarding the study design and the statistical analysis. GM and VL worked on legal issues concerning the implementation of the ASIC App. VL, NV, SH, IL worked on technical issues concerning the implementation of the ASIC App. All Authors read and approved the final manuscript.

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COMPETING INTERESTS

None reported

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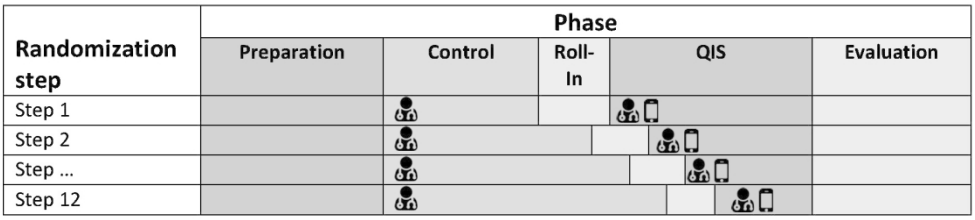

Figure 1: Stepped-wedge design. During the Control phase, ARDS detection is performed according to local standard by the physician in charge. With beginning of the QIS phase, physician´s ARDS diagnosis is supported by the ASIC app.

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