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Algorithmic Surveillance of ICU patients with acute respiratory distress syndrome (ASIC): Manual for a multicentre stepped-wedge clusterrandomized quality improvement strategy.

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49 ABSTRACT

50 Introduction

51 The acute respiratory distress syndrome (ARDS) is a highly relevant entity in critical care with 52 mortality rates of 40%. Despite extensive scientific efforts, outcome-relevant therapeutic 53 measures are still insufficiently practiced at the bedside. Thus, there is a clear need to adhere 54 to early diagnosis and sufficient therapy in ARDS, assuring lower mortality and multiple organ 55 failure.

56 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. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

⁰ 73 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.

78 **Trial registration number:** DRKS00014330

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

82 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.

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- 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 ٠ confirmatory trial building on the experiences gained within this project will be necessary prior to a more profound clinical implementation.

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95 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 \leq 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.

⁵⁰ 129 **METHODS AND ANALYSIS**

53 130 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, 137 like radiographic reports. Due to these functions, the ASIC app only displays a compilation of
 138 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_aO₂/FiO₂ 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 \leq 300 mmHg that occurs under a PEEP \geq 5 cmH₂O. 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.

33 34 159 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.

	Phase				
Randomization	Preparation	Control	Roll-	QIS	Evaluation
step			In		
Step 1		B		& []	
Step 2		B		.	
Step		B			
Step 12					

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.

16182Population under Surveillance

18 All patients ≥ 18 years of age in the participating ICUs, who are mechanically ventilated for at
 184 least 24 hours, will be admitted to the project. According to pre-existing data from the local
 21 185 EHRs, we expect approximately 5000 patients per year to be surveyed within the project.

186 Key Performance Indicators 24

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).

Co-Primary key-performance-indicators	Secondary key-performance-indicators	
Diagnostic rate, defined as the proportion of	Prevalence of organ dysfunction within 28 days	
patients diagnosed with ARDS out of all monitored	after diagnosis of ARDS or ICU discharge (whatever occurs first), defined as days without need of	
patients		
	following measures:	
	 Mechanical ventilation 	
	 Vasopressor use 	
	 Renal replacement therapy 	
Guideline-adherence regarding lung-protective	Treatment-duration on ICU after ARDS-diagnosis	
ventilation, defined as the percentage of time	Hospital-mortality after ARDS-diagnosis	
within 28 days after ARDS diagnosis or ICU discharge	Tospital-mortality arter Altos-diagnosis	
(whatever occurs first), during which the mechanical	Acceptance and usability of the ASIC app and the	
ventilation parameters fulfil the following criteria:	mobile device:	
◦ Tidal volume (V_t): ≤ 6 ml/kg KG (ideal)	a) Pre-Roll-In of the ASIC app	
• Endinspiratory pressure (P_{EI}): $\leq 30 \text{ cmH}_2O$	b) Post-Roll-In (6 months) of the ASIC app	
• Positive endexpiratory pressure (PEEP) \geq 5		
cmH₂O		
• Driving pressure ($\Delta P = P_{EI} - PEEP$) $\leq 15 \text{ cmH}_2O$		

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

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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.

8 201 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 $45.5 + (0.91 \times [height in centimetres - 152.4])$. 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.

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}): $\leq 30 \text{ cmH}_2\text{O}$		
	◦ Positive endexpiratory pressure (PEEP) \ge 5 cmH ₂ O		
	◦ Driving pressure (Δ P = P_{EI} -PEEP): ≤ 15 cmH ₂ O		
Days without organ	Full days without organ replacement therapy:		
dysfunction	 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		

218 Table 2: Patient-related data-acquisition.

221	Table 3: Clinical data collected during the project.
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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	Respiratory rate (measured, spontaneous), I:E-ratio, tidal volume per ideal		
ventilation	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	Veno-venous ECMO (VV-ECMO), Veno-arterial ECMO (VA-ECMO),		
oxygenator (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) **BMJ** Open

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(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_{OIS}) is higher than the rate in the control phase (*p*_{control}):

 $H_1^A: p_{QIS} \neq p_{control}$

vs.

 $H_0^A: p_{QIS} = p_{control}$

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

> 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

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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

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12 13 284 Access to Data and Dissemination

15 The results of the ASIC QIS will be presented at scientific and medical conferences and 285 16 286 published in peer-reviewed journals. ASIC was created to demonstrate the possibilities offered 17 287 by advanced digital services and infrastructure in healthcare and therefore serves as an 18 19 exemplary use case with clinical benefit in order to prove the functionality of the DIC 288 20 289 infrastructure within the SMITH consortium. One of the main objectives of establishing DIC at 21 290 the local sites is to facilitate the exchange and use of medical data across the borders of 22 23 291 institutions and geographical locations in interoperable data formats for medical research 24 while meeting the data protection and security laws and requirements. 292 25

will remain the main resource in patient data management.

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COMPETING INTERESTS

None reported

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4	-	sundrama (ASIC)
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7	3	Protocol for a multicentre stepped-wedge cluster-randomized quality
8	Δ	improvement strategy
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48 ABSTRACT

49 Introduction

50 The acute respiratory distress syndrome (ARDS) is a highly relevant entity in critical care with 51 mortality rates of 40%. Despite extensive scientific efforts, outcome-relevant therapeutic 52 measures are still insufficiently practiced at the bedside. Thus, there is a clear need to adhere 53 to early diagnosis and sufficient therapy in ARDS, assuring lower mortality and multiple organ 54 failure.

55 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. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

⁰ 72 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.

77 Trial registration number: DRKS00014330

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

81 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.

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- 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 ٠ of the physician in charge.
- Statistic analysis will not comply with the standards of a regular clinical trial, since a ٠ to be the way of the second seco 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 \leq 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, 137 like radiographic reports. Due to these functions, the ASIC app only displays a compilation of
 138 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_aO₂/FiO₂ 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 \leq 300 mmHg that occurs under a PEEP \geq 5 cmH₂O. 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.

33 34 159 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.

179 **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.

183 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).

187 Table 1: Co-Primary and secondary key-performance-indicators of ASIC. **Co-Primary key-performance-indicators** Secondary key-performance-indicators Prevalence of organ dysfunction within 28 days Diagnostic rate, defined as the proportion of patients diagnosed with ARDS out of all monitored after diagnosis of ARDS or ICU discharge (whatever occurs first), defined as days without need of patients following measures: Mechanical ventilation 0 Vasopressor use 0 Renal replacement therapy 0 Treatment-duration on ICU after ARDS-diagnosis Guideline-adherence regarding lung-protective ventilation, defined as the percentage of time Hospital-mortality after ARDS-diagnosis within 28 days after ARDS diagnosis or ICU discharge Acceptance and usability of the ASIC app and the (whatever occurs first), during which the mechanical ventilation parameters fulfil the following criteria: mobile device: a) Pre-Roll-In of the ASIC app Tidal volume (V_t): $\leq 6 \text{ ml/kg KG}$ (predicted) 0 b) Post-Roll-In (6 months) of the ASIC app Endinspiratory pressure (P_{EI}) : $\leq 30 \text{ cmH}_2\text{O}$ 0 Positive endexpiratory pressure (PEEP) \geq 5 0 cmH_2O Driving pressure ($\Delta P = P_{EI} - PEEP$) $\leq 15 \text{ cmH}_2\text{O}$ 0

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Secondary KPIs include the prevalence of organ dysfunction within 28 days after ARDSdiagnosis 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.

⁵³ 198 Clinical Data Collection and Data Protection

The total data collection started in July 2019 and is scheduled to be completed in December
 200 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 $50 + (0.91 \times [height in centimetres - 152.4])$ 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-acauisition.

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}): $\leq 30 \text{ cmH}_2O$	
	• Positive endexpiratory pressure (PEEP) \geq 5 cmH ₂ O	
	• Driving pressure ($\Delta P = P_{EI}$ -PEEP): $\leq 15 \text{ cmH}_2\text{O}$	
Days without organ	Full days without organ replacement therapy:	
dysfunction	 Mechanical ventilation (excluding atelectasis-prophylaxis) 	
	 Use of vasopressors 	
	 Renal replacement therapy 	
Acquired data at hospital discharge		
Duration of treatments	s 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	namic 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	Respiratory rate (measured, spontaneous), I:E-ratio, tidal volume per	
ventilation	predicted bodyweight, inspiratory oxygen-fraction, expiratory oxygen-fraction,	

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	end-inspiratory-pressure (p _{EI}), positive endexpiratory pressure (PEEP), driving		
	pressure ($\Delta P = p_{EI} - PEEP$), lung compliance, endexpiratory CO ₂		
Laboratory parameters	arameters 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_2		
	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	Veno-venous ECMO (VV-ECMO), Veno-arterial ECMO (VA-ECMO),		
oxygenator (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).

3 232 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)

53 239 Based on the expected case numbers of 5000 Patients/year, we assumed a mean of 1041 54 240 patients per cluster for the study duration of 2.5 years. For the ARDS diagnosis rate in the 55 56 241 control phase we used incidences from Brun-Buisson et al. (17) and Bellani et al. (1) which 57 suggest a rate of 16.1% and 23.4 %, respectively. Under both of these baseline rates an 242 58 increase as small as 1% (e.g. from 16.1% to 17.1%) could be detected with at least 80% power. 243 59

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245 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 $(p_{control})$: $H_0^A: p_{OIS} = p_{control}$ vs. $H_1^A: p_{OIS} \neq p_{control}$

- 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.
- 2930 262 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/).

45 272 ETHICS AND DISSEMINATION

47 273 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.

- ⁵⁸⁵⁹ 281 Access to Data and Dissemination

BMJ Open

282 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 283 284 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 285 infrastructure within the SMITH consortium. One of the main objectives of establishing DIC at 286 287 the local sites is to facilitate the exchange and use of medical data across the borders of 288 institutions and geographical locations in interoperable data formats for medical research while meeting the data protection and security laws and requirements. 289

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332 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.

13 336

14337AUTHOR'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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47 359 **COMPETING INTERESTS**

49 360 None reported

51 361 License Statement

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Phase Randomization Roll-QIS Preparation Control Evaluation In step Step 1 £. **&** Step 2 ß Step ... £.[] £ Step 12 £ []

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.

165x52mm (300 x 300 DPI)