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# Automated control of inspired oxygen fraction in mechanically ventilated patients – a single center randomized controlled trial



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| Keywords: | INTENSIVE & CRITICAL CARE, ANAESTHETICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE |
| | |

# Title

Automated control of inspired oxygen fraction in mechanically ventilated patients – a single center randomized controlled trial

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## Abstract

**Background**: A novel automated system for the control of the inspired fraction of oxygen named LeoClac was implemented on a mechanical ventilator. The system uses a separate sensor for the measurement of the peripheral oxygen saturation which is connected directly to the ventilator. We hypothesize that LeoClac will be superior to manual control in keeping critically ill and mechanically ventilated patients in a $SpO_2$-target zone.

**Methods**: This is a randomized controlled, single-center superiority study with two parallel groups including 2x 20 patients. Mechanically ventilated patients treated on the intensive care unit will be screened for eligibility and included in the study after written informed consent. Patients in the intervention group will be treated with LeoClac. In the control group, oxygen demand will be controlled manually by the intensive care team. The primary endpoint of the study is the proportion of time in target zone for peripheral oxygen saturation within the first 24 hours following randomization. Secondary endpoints include the analysis of hyperoxia and hypoxia, number of changes in gas fraction, number, and reasons of self- and user-aborts of the automated system, proportion of time in target zone for peripheral oxygen saturation in the subgroups of patients with hypoxemic respiratory failure and acute hypercapnic respiratory failure. Furthermore, ventilator-free days at day 28 and ICU mortality will be analyzed.

**Analysis:** The precise control of oxygen demand with the aim of avoiding both hyperoxia and hypoxia are central challenges in the highly technical field of mechanical ventilation. Incorporation of patient heterogeneity, the benefits of reduced manual intervention, and the potential to optimize treatment outcomes underscore the importance of this research. By addressing the complexities of precise oxygen control in adults, this study contributes to the advancement of critical care practices and may improve patient outcomes.

**Ethics:** The study protocol was approved by the ethics committee of the Christian-Albrechts-University Kiel, Germany, on 17th May 2023.

## Trial registration & status:

German Clinical Trials Register (DRKS); registration number: DRKS00032113; (https://drks.de/search/en/trial/DRLS00032113), date of registry 20th June 2023. Recruitment will begin in December 2023 and is expected to end in September 2024.


### Strengths and limitations of this study

- This study aims to evaluate whether an automated system can effectively optimize oxygen therapy in critically ill, invasively ventilated patients.
- This study investigates the benefits and limitations of an automated oxygen control in a very heterogenous sample of adult intensive care patients.

- The novel system will be used for up to 28 days per patient to evaluate feasibility of the sensors in daily routine.


## Keywords

Liberal oxygen therapy, Intellivent-ASV, automated control of $FiO_2$, closed loop automatic oxygen control, $SpO_2$ target zone, LeoClac


# Administrative information

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|---|---|
| Title {1} | Automated control of inspired oxygen fraction in mechanically ventilated patients – a single center randomized controlled trial |
| Trial registration {2a and 2b}. | DRKS: 00032113, https://drks.de/search/en/trial/DRKS00032113<br>All items from the WHO Trial Registration dataset can be found within the study protocol or on the DRKS website. |
| Protocol version {3} | Study protocol 2.0 (02.02.2024) |
| Funding {4} | Löwenstein Medical provided single-use peripheral oxygen sensors free of charge during the study period. No further funding was received. |
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| Role of sponsor {5c} | Löwenstein Medical played no role in study planning, execution, analysis, interpretation writing and submission of the manuscript. |


## Funding {4}

Provision of Study Materials (Löwenstein Medical Innovation, Steinbach, Germany); provision of $SpO_2$ sensors.


## Composition of the coordinating centre and trial steering committee {5d}

Not applicable. Study is a monocentric study.

# Introduction

## Background and rationale {6a}

Oxygen therapy plays a crucial role in the therapy of critically ill patients, ensuring adequate oxygen delivery while avoiding hypo- and hyperoxia. Nevertheless, overdosing oxygen may be harmful, as both excessively high and low arterial partial pressure of oxygen ($PaO_2$) are associated with increased mortality (1). A recent meta-analysis highlighted the risks of liberal oxygen therapy, showing increased mortality compared to conservative oxygen therapy (2). The current German guideline recommends titrating peripheral oxygen saturation ($SpO_2$) between 92% to 96% in mechanically ventilated patients (3).

Currently, manual oxygen ($FiO_2$) control based on $SpO_2$ and $PaO_2$ measurements is the standard in clinical practice. However, compliance to peripheral oxygen targets is poor (4, 5), which carries the risk of unrecognized hypoxia or hyperoxia. Additionally, health care professionals often prioritize avoiding desaturation over avoiding hyperoxia, potentially leading to oxygen oversupply (6). Therefore, it is crucial to carefully monitor patients' response to therapy and adjust oxygen delivery accordingly.

To address the limitations of manual control, an automated system for $FiO_2$ control would be desirable. Its aim is to continuously modulate oxygen supply, ensure normoxemia and prevent desaturation. Intellivent-ASV (fully automated closed loop ventilation) has been the sole available system for automated $FiO_2$ control in invasively ventilated adult patients. The algorithm in Intellivent-ASV compares $SpO_2$ values with the target range and automatically adjusts the $FiO_2$ to maintain desired saturation levels (6). However, access to Intellivent-ASV is limited, available only on selected ventilators. A new alternative, the Loewenstein closed-loop automatic oxygen control (LeoClac), offers rapid modulation of $FiO_2$ based on a separate $SpO_2$ measurement attached to the ventilator. Recent publications suggest that closed-loop control devices maintain higher saturation levels, spend less time below the target saturation, and save oxygen resources (6-8). Moreover, an automated system may contribute to maintaining sufficient oxygenation during exercise and physiotherapy when oxygen consumption rises (9).

While automated closed-loop systems have been well evaluated in infants to prevent hyperoxia and

retinal damage, longterm evaluation in adults is lacking (6, 10, 11). However, Bialais et al. were able to demonstrate, that Intellivent-ASV provides a safe ventilation with optimized oxygenation and reduced workload on caregivers over a time period of 48 hours (12). The aim of this study is to further investigate the benefits and limitations of automated control of inspired $FiO_2$ in invasively ventilated critically ill adults. The primary endpoint of this trial is the proportion of time in target zone for peripheral oxygen saturation within the first 24h hours following randomization. This also includes the analysis of blood gas samples, self- and user-aborts of the automated system and the number of changes in $FiO_2$. Furthermore, proportion of time in peripheral oxygen target zone in patients with acute hypoxemic resp. acute hypercapnic respiratory failure will be further analyzed.

### Explanation for the choice of comparators {6b}

The primary objective is to examine the compliance with the target zone for peripheral oxygen saturation (SpO2) using the LeoClac automated system compared to manual control. Thus, the comparators in this trial are manual and automated $F_iO_2$ control. Manual control refers to the standard practice of manually adjusting the inspired fraction of oxygen ($F_iO_2$) based on clinical judgment and periodic assessments of the patient's condition. It represents the current approach used in clinical practice.

The use of manual control as a comparator allows for a direct comparison with the LeoClac automated system. By assessing the efficacy of LeoClac in maintaining $SpO_2$ within the target zone, it can be determined whether the automated system provides improved control and adherence to the desired oxygen saturation levels compared to standard manual control methods.

By comparing the performance of the LeoClac system to manual control, the trial aims to evaluate whether the automated system can effectively optimize oxygen therapy and improve patient outcomes in critically ill, invasively ventilated patients.

### Objectives {7}

The primary objective of this study is to investigate compliance within the predefined $SpO_2$-target zone of 92 to 96% in critically ill and invasively ventilated patients comparing LeoClac to manual control.

### Trial design {8}

This trial is a randomized, controlled, single-center superiority trial with two parallel groups. The study aims to assess the proportion of time spent in the target zone for peripheral oxygen saturation within the first 24 hours following randomization as the primary endpoint. Randomization is conducted using random permuted block randomization with a 1:1 allocation ratio. Blinding is not feasible in this study.

## Methods: Participants, interventions, and outcomes

### Study setting {9}

The study will be performed on all interdisciplinary surgical intensive care units of the Department of

Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel.

## Eligibility criteria {10}

To be considered eligible for the study, patients must meet the following inclusion criteria: (1) Intubated or tracheotomized patients requiring mechanical ventilation for a duration of at least 9 hours as of 9:00 am, (2) participants must be at least 18 years old, and (13) written informed consent must be obtained. Potential patients will be excluded from the study if any of the following exclusion criteria are met: (1) Inability to measure peripheral oxygen saturation, (2) absence of a detectable pulsatile plethysmography curve, (13) clinical indication for hyperoxia ($SpO_2$ target >96%), (4) expected extubation within the next 24 hours, or (5) negative presumed will regarding study participation.

Patient and Public involvement section

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## Intervention description {11a}

After obtaining written informed consent, patients will be included in the study. Patients randomized to the intervention group will be mechanically ventilated with an automated control of the inspired oxygen fraction. Therefore, the ventilator will automatically adjust the amount of oxygen required based on oxygen saturation, with the goal of always maintaining oxygen saturation between 93 and 96%. Due to technical reasons, patients in the intervention group will need an additional measurement system for oxygen saturation. LeoClac will be used from the start of the study period until the end of invasive ventilation (extubation, decannulation, dismission or death) or day 28.

## Criteria for discontinuing or modifying allocated interventions {11b}

If instances of uncontrollable respiratory instability occur during the intervention, or if the patient experiences acute pulmonary decompensation, the intervention will be discontinued. Treating physicians (who are not part of the study team) can suspend the study at any time. LeoClac can be deactivated at any time and for any reasons. The reason will be documented in the case report form. Furthermore, participants/representatives may withdraw from the study without citing a reason at any time. There is no provision for modifying the assigned intervention.

## Strategies to improve adherence to interventions {11c}

Adherence to the study protocol is ensured by staff training courses and information leaflets, which are attached to the patient's ventilator.

## Relevant concomitant care permitted or prohibited during the trial {11d}

All procedures and interventions in this study adhere to established internal standard procedures

required for optimal patient treatment.

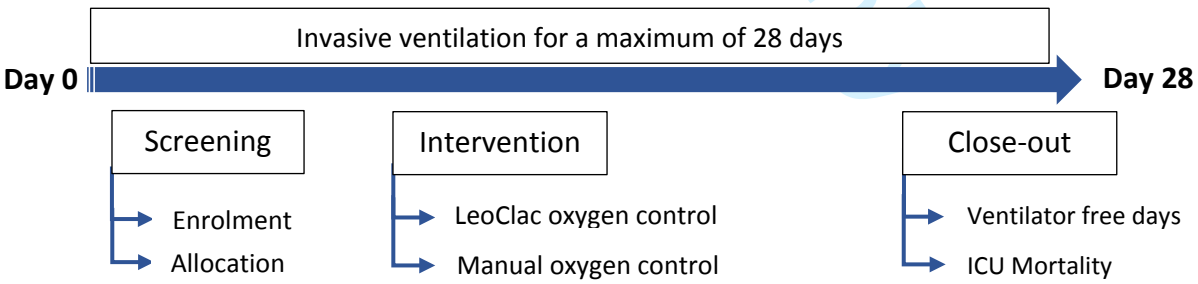
## Outcomes {12}

The primary endpoint of this trial is the proportion of time in target zone for peripheral oxygen saturation within the first 24h hours following randomization.

Secondary endpoints include:

- Proportion of time with automated control of inspired fraction of oxygen in intervention group
- Cumulative duration of episodes with hypoxia according to pulse oximetry ($SpO_2$ <90%)
- Cumulative duration of episodes with hyperoxia according to pulse oximetry ($SpO_2$ >98%)
- Number of blood gas samples with hypoxia ($PaO_2$ <60 mmHg)
- Number of blood gas samples with hyperoxia ($PaO_2$ >110 mmHg)
- Number of changes of inspired fraction of oxygen
- Number and reasons of self-aborts of the automated system
- Number and reasons of user-aborts of the automated system
- Proportion of time in target zone for peripheral oxygen saturation in the subgroup of patients with acute hypoxemic respiratory failure
- Proportion of time in target zone for peripheral oxygen saturation in the subgroup of patients with acute hypercapnic respiratory failure
- Ventilator-free days alive at day 28d
- ICU mortality

## Participant timeline {13}




## Sample size {14}

Based on data with other automated systems and on our clinical experience with manual oxygen control, we expect a time within $SpO_2$ target range of 80% (SD 20) with LeoClac and of 60% (SD 20) with manual control. For a two-sided Mann-Whitney-U-Test, power calculation with 1-Beta = 0.8 and alpha 0.05 yields a required sample size of 2x 20 patients to be sufficient.

### Recruitment {15}

Eligible patients will be screened for study participation every morning (Monday - Friday). Screening will be conducted by senior physicians. Recruitment will be continuously conducted by physicians of the research team until the target randomized sample size of 40 participants is achieved. Based on current clinical case numbers, this will take approximately six months.

## Assignment of interventions: allocation

### Sequence generation {16a}

Randomization is performed by random permuted block randomization with a 1:1 allocation ratio, Minimum Block Size: 4; Maximum Block Size: 8; Increment: 2. The randomization is performed electronically with using the www.studyrandomizer.com.

### Concealment mechanism {16b}

The randomization is performed electronically using www.studyrandomizer.com.

### Implementation {16c}

The allocation sequence is generated electronically.

### Who will be blinded {17a}

Blinding of the study team is not feasible due to the study concept.

### Procedure for unblinding if needed {17b}

n/a

## Data collection and management

### Plans for assessment and collection of outcomes {18a}

Demographic and clinical data are recorded on electronic based case report forms (eCRFs) by data collectors. Ventilator measurement data and oxygen saturation values are exported electronically from the ventilator and the monitoring unit. To determine the primary and further secondary outcome, ventilator data and monitoring data will be analyzed by the data analyzing team as described below (20a).

### Plans to promote participant retention and complete follow-up {18b}

N/a. No follow-up for clinically relevant outcome measurement needed.

### Data management {19}

All participant information will be stored on password-protected databases to which only research team members have access. Collected data are pseudonymized by a coded ID [identification] number. All records that contain names or other personal identifiers, such as informed consent forms, will be stored separately from study records. Demographic and clinical data will be stored on electronic case report forms (eCRFs). Log files containing ventilator data are exported from ventilators and saved on a password-secured network drive.

### Statistical methods for primary and secondary outcomes {20a}

Descriptive statistical analyses (mean +/- standard deviation, median and 95% confidence interval where appropriate) will be used. As we expect proportion of time in target zone for peripheral oxygen saturation within the first 24 hours following randomization to be non-normally distributed, the primary endpoint will be compared between study groups with a Mann-Whitney-U-Test. Categorial endpoints will be investigated using Fisher´s exact test. Other between-group comparisons of numerical endpoints will be conducted using a two-sided t-test or Mann-Whitney-U-test, as appropriate. Testing for normal distribution will be performed with Shapiro-Wilk test.

### Methods for additional analyses (e. g. subgroup analyses) {20b}

Not applicable, further analyses are not planned.

Proportion of time in target zone for peripheral oxygen saturation in subgroups regarding level of sedation (Richmond agitation and sedation scale) and septic shock (14) will be performed.

### Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Data sets will be excluded if the study intervention was not performed, or if the primary endpoint cannot be evaluated.

## Methods: Monitoring

### Composition of the data monitoring committee, its role and reporting structure {21a}

As no interim analyses are planned or will be performed, a data monitoring committee has not been organised for this study.

### Interim analyses {21b}

Not applicable, there will be no interim analyses.

### Adverse event reporting and harms {22}

Adverse events and other unintended effects of the trial will be collected, assessed, and immediately reported to the principal investigator.

### Frequency and plans for auditing trial conduct {23}

Not applicable, an auditing trail conduct is not required.

## Ethics and Dissemination

### Ethics approval and consent to participate {24}

The local review board of the Medical Faculty of the Christian-Albrecht University approved the study, reference number D 449/22. Written, informed consent to participate will be obtained from all patients.

### Plans for communicating important protocol amendments to relevant parties (e. g. trial participants, ethical committees) {25}

Any changes in protocol will be submitted to the local ethics committee for approval, all changes will be communicated to the study team via E-Mail and during the regular study group meetings. The trial record on DRKS will be updated accordingly.

### Who will take informed consent? {26a}

In this randomized controlled trial investigating a novel system for automated $F_iO_2$ control in critically ill, mechanically ventilated patients, the process of obtaining informed consent will be multistep based due to the patients' critical condition. Since most patients will be unable to provide written consent themselves, the patient's presumed will regarding study participation will be determined in consultation with their relatives or representatives. Written informed consent will then be obtained from the patient's legal representatives prior to their participation in the study.

Patients will be assessed for potential study inclusion daily (Monday-Friday). As soon as a patient regains consciousness, their written informed consent will be sought. It is important to note that in accordance with the principles outlined in the Declaration of Helsinki and national regulations, consent can be withdrawn at any time, without the need to specify reasons, and without compromising the patient's future medical care.

### Additional consent provisions for collection and use of participant data and biological specimens {26b}

n/a. No additional data will be collected.

### Confidentiality {27}

Data are handled confidentially, and the storage of patient-related medical data is pseudonymized. No

features are transferred that allow direct identification of specific participants. The subject identification code list to personal data is accessible only to the principal investigator. All further records containing names or other personal identifiers, such as informed consent forms are kept separate from the study data identified by code number. Data collection, coding, security, and storage will comply with the provisions of the German Federal Data Protection Act (BDSG) and the EU General Data Protection Regulation (EU-GPDR). Accordingly records and documents related to the clinical trial will be kept for at least 15 years.

## Competing interests {28}

Provision of Study Materials ($SpO_s$ sensors) (Löwenstein Medical Innovation, Steinbach, Germany). The authors declare that they have no other competing interests.

## Availability of data and materials {29}

Following publication of the trial, datasets containing pseudonymized patient data will be made accessible upon reasonable request to the corresponding author.

## Provisions for post-trial care {30}

All patients will receive a standard monitoring of oxygen saturation with a separate pulse oximeter in addition to monitoring pulse oximetry with the ventilator for automated control with LeoClac. Due to this redundancy, there is no additional risk, and a patient insurance is not needed.

## Dissemination plans {31a}

Once the study has been completed, the results will be published in a peer-reviewed scientific journal and presented on national and international conferences for anaesthesiology and intensive care medicine.

## Authors' contributions {31b}

All authors were involved in the design of the study and have contributed and approved publication of the study protocol. CE: formal analysis, writing and editing the manuscript, HS: data acquisition, writing and editing the manuscript; LH: screening of patients, data acquisition, reviewing of the manuscript; AS: screening of patients, data acquisition, reviewing of the manuscript; ML gave important intellectual input and critically reviewed the study protocol TB: conceived the LeoClac controller, drafted and reviewed the study protocol, screening of patients, data acquisition DS: original idea for study, first draft of study protocol, principal investigator; all authors read and approved the final manuscript. All authors contributed to the study according to the criteria of the ICMJE.

## Plans to give access to the full protocol, participant level-data and statistical code {31c}

Datasets containing anonymized patient data will be made accessible upon reasonable request to the corresponding author, in compliance with European data protection regulations (EU-GDPR).

### Consent for publication {32}

Not applicable.

### Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/a. No biological specimens will be collected.

## Discussion

This study aims to evaluate the efficacy of an automated closed-loop oxygen control system to examine compliance with the $SpO_2$-target zone in critically ill and invasively ventilated adult patients. The precise control of oxygen demand with the aim of avoiding both hyperoxia and hypoxia are central challenges in the highly technical field of mechanical ventilation. From the pediatric and neonatal point of view, automatic oxygen control has already been able to demonstrate significant success in numerous studies (10, 15-17). In adult patients, the sensitivity to oxygen is not as pronounced, yet neither the consequences of hypoxia and hyperoxia nor the economic follow-up costs should be underestimated (18-20). With the novel LeoClac function, the oxygen demand is continuously monitored and checked several times per minute. Increases in oxygen demand are therefore immediately detected, for instance, when the patient is more active or mobilized. This real-time adaptability may significantly reduce the likelihood of sudden fluctuations in oxygen saturations.

It is imperative to acknowledge the patient heterogeneity observed in critically ill patients. Understanding how different patients respond to automated oxygen control is vital for tailoring treatment strategies to individual needs. The reduction of manual intervention could become a significant advantage of automated oxygen control. The current standard often requires manual adjustment and monitoring of oxygen supply, placing a significant burden on medical staff especially in patients with high oxygen demand. The automation of this process holds promise, especially in high-workload situations or when multiple patients are being cared for simultaneously, where the system can increase efficiency and reduce the burden on medical staff. In addition, the precise and controlled delivery of oxygen holds the potential to optimize treatment outcomes.

Incorporation of patient heterogeneity, the benefits of reduced manual intervention, and the potential to optimize treatment outcomes underscore the paramount importance of this research. By addressing the complexities of precise oxygen control in adults, this study contributes to the advancement of critical care practices and may improve patient outcomes.

### Trial status

The study protocol was approved by the ethics committee of the Christian-Albrechts-University Kiel,

Germany, on 01 February 2023. Recruitment has begun in December 2023 and is expected to end in September 2024.

## Abbreviations

ASV, Adaptive support ventilation

BDSG, German Federal Data Protection Act

CRF, case report form

EU-GDPR, European Union General Data Protection Regulation

$FiO_2$, inspired oxygen fraction

LeoClac, Closed loop automatic oxygen control

Intellivent-ASV, fully automated closed loop ventilation

$PaO_2$, arterial oxygen partial pressure

$SpO_2$, oxygen saturation

## Declarations

### Acknowledgements

Not applicable.

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## Authors' contributions

All authors were involved in the design of the study and have contributed and approved publication of the study protocol. CE: formal analysis, writing and editing the manuscript, HS: data acquisition, writing and editing the manuscript; TB: screening of patients, data acquisition, reviewing of the manuscript; LH: screening of patients, data acquisition, reviewing of the manuscript; AS: screening of patients, data acquisition, reviewing of the manuscript; ML gave important intellectual input and critically reviewed the study protocol TB: conceived the LeoClac controller, drafted and reviewed the study protocol, screening of patients, data acquisition DS: original idea for study, first draft of study protocol, principal investigator; all authors read and approved the final manuscript.

## Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit-sectors.

## Competing interests statement

The authors have no relevant interests to disclose.

| | Screening | | Study period | |
|---|---|---|---|---|
| | **Enrolment** | **Allocation** | **Post-allocation** | **Close-out** |
| **TIMEPOINT:** | Day 0 | Day 0 | Day 0-28 | Day 28 |
| **ENROLMENT:** | X | | | |
| Eligibility Screen | X | | | |
| Written informed consent | X | | | |
| **ALLOCATION:** | | X | | |
| **INTERVENTIONS:** | | | | |
| LeoClac Oxygen control | | | X | |
| Manual oxygen control | | | X | |
| **ASSESSMENTS:** | | | | |
| Proportion of time of oxygen saturation in target zone | | | X | |
| Duration of time of hyperoxia and hypoxia (pulse oximetry; blood gas samples) | | | X | |
| Collection of self- and user-aborts of the automated system | | | X | |
| **CLOSE OUT:** Ventilator-free days | | | | X |
| ICU Mortality | | | | X |

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# Automated control of inspired oxygen fraction in mechanically ventilated patients – a study protocol for single center randomized controlled trial

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| | |

# Title

Automated control of inspired oxygen fraction in mechanically ventilated patients – A study protocol for a single center randomized controlled trial

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## Abstract

**Background**: A novel automated system for the control of the inspired fraction of oxygen named LeoClac has been implemented on a mechanical ventilator. The system uses a separate sensor for the measurement of the peripheral oxygen saturation which is connected directly to the ventilator. We hypothesize that LeoClac will be superior to manual control in keeping critically ill and mechanically ventilated patients in a $SpO_2$-target range (92-96%).

**Methods**: This is a randomized controlled, single-center superiority study with two parallel groups including 40 patients. Mechanically ventilated patients treated on the intensive care unit will be screened for eligibility and included in the study after written informed consent. Patients in the intervention group will be treated with LeoClac. In the control group, $FiO_2$ will be controlled manually by the intensive care team. The primary endpoint of the study is the proportion of time in target zone for peripheral oxygen saturation within the first 24 hours following randomization. Secondary endpoints include the analysis of hyperoxia and hypoxia, number of changes in $FiO_2$, number, and reasons of self-aborts and manual overrides of the automated system, proportion of time in target zone for peripheral oxygen saturation in the subgroups of patients with hypoxemic respiratory failure and acute hypercapnic respiratory failure. Furthermore, ventilator-free daysand ICU mortality at day 28 will be analyzed.

**Analysis:** The precise control of $FiO_2$ with the aim of avoiding both hyperoxia and hypoxia is a fundamental challenge in the highly technical field of mechanical ventilation. Incorporation of patient heterogeneity, the benefits of reduced manual intervention, and the potential to optimize treatment outcomes underscore the importance of this research. By addressing the complexities of precise oxygen control in adults, this study contributes to the advancement of critical care practices and may improve patient outcomes.

**Ethics:** The study protocol was approved by the ethics committee of the Christian-Albrechts-University Kiel, Germany, on 17th May 2023.

## Trial registration & status:

German Clinical Trials Register (DRKS); registration number: DRKS00032113; (https://drks.de/search/en/trial/DRKS00032113), date of registry 20th June 2023. Recruitment will begin in December 2023 and is expected to end in June 2025.


### Strengths and limitations of this study

- This study aims to evaluate whether an automated system can effectively optimize oxygen therapy in critically ill, invasively ventilated patients.
- This study plans to investigate the benefits and limitations of an automated oxygen control in a very heterogenous sample of adult intensive care patients.

- The novel system will be used for up to 28 days per patient to evaluate feasibility of the sensors in daily routine.


## Keywords

Liberal oxygen therapy, Intellivent-ASV, automated control of $FiO_2$, closed loop automatic oxygen control, $SpO_2$ target zone, LeoClac


# Administrative information

| | |
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| Title {1} | Automated control of inspired oxygen fraction in mechanically ventilated patients – A study protocol for a single center randomized controlled trial |
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| Protocol version {3} | Study protocol 2.0 (02.02.2024) |
| Funding {4} | Löwenstein Medical provided single-use peripheral oxygen sensors free of charge during the study period. No further funding has been received. |
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| Role of sponsor {5c} | Löwenstein Medical played no role in study planning, execution, analysis, interpretation writing and submission of the manuscript. |

## Funding {4}

Provision of Study Materials (Löwenstein Medical Innovation, Steinbach, Germany); provision of $SpO_2$ sensors.

## Composition of the coordinating centre and trial steering committee {5d}

Not applicable. Study is a single center study.

# Introduction

## Background and rationale {6a}

Oxygen therapy plays a crucial role in the therapy of critically ill patients, ensuring adequate oxygen delivery while avoiding hypo- and hyperoxia. Nevertheless, overdosing oxygen may be harmful, as both excessively high and low arterial partial pressure of oxygen ($PaO_2$) are associated with increased mortality [1, 2]. Stolmeijer et al. indicated that liberal oxygen therapy leads to hyperoxia and may also affect survival [3]. A recent meta-analysis also highlighted the risks of liberal oxygen therapy, showing increased mortality compared to conservative oxygen therapy [4]. The current German guideline recommends titrating peripheral oxygen saturation ($SpO_2$) between 92% to 96% in mechanically ventilated patients [5]. In adult patients, sensitivity to oxygen is not as pronounced; yet, neither the consequences of hypoxia or hyperoxia, nor the associated economic follow-up costs should be underestimated [6-8].

Currently, manual oxygen ($FiO_2$) control based on $SpO_2$ and $PaO_2$ measurements is the standard in clinical practice. However, based on neonatal studies compliance to peripheral oxygen targets is poor [9, 10] this finding might be also applicable to adults and carries the risk of unrecognized hypoxia or hyperoxia. Additionally, health care professionals often prioritize avoiding desaturation over avoiding hyperoxia, potentially leading to oxygen oversupply [11]. Therefore, it is crucial to carefully monitor patients' response to therapy and adjust oxygen delivery accordingly.

To address the limitations of manual control, an automated system for $FiO_2$ control would be desirable. Its aim is to continuously modulate oxygen supply, ensure normoxemia and prevent desaturation. In a study by Lellouche et al., automated oxygen flow titration was superior to constant oxygen flow in maintaining $SpO_2$ levels [12]. Saihi et al. demonstrated that an automated $FiO_2$ controller, based on continuous oxygen saturation, was capable in maintaining $SpO_2$ reliably within a predefined target range [13]. Intellivent-ASV (fully automated closed loop ventilation) has been the sole available ventilation mode including automated $FiO_2$ control in invasively ventilated adult patients. The algorithm in Intellivent-ASV compares $SpO_2$ values with the target range and automatically adjusts the $FiO_2$ to maintain desired saturation levels [11]. However, access to Intellivent-ASV is limited, available only on selected ventilators. A new alternative, the Loewenstein closed-loop automatic oxygen control (LeoClac), offers rapid modulation of $FiO_2$ based on a separate $SpO_2$ measurement attached to the ventilator. The user sets a target $SpO_2$ range to be maintained before starting the $FiO_2$ control. The user

also defines a $FiO_2$ threshold for receiving an alarm. An alarm is triggered, if the $FiO_2$ alarm threshold is exceeded, however, the automatic regulation continues until deactivation by the user ("manual override"). The $SpO_2$ measurement is based on a configurable number of pulse waves. $FiO_2$ reductions occur every two minutes, increases are limited to every 45 seconds to avoid "swinging" of the system.

Recent publications suggest that closed-loop control devices maintain higher saturation levels, spend less time below the target saturation, and save oxygen resources [11, 14, 15]. Moreover, an automated system may contribute to maintaining sufficient oxygenation during exercise and physiotherapy when oxygen consumption rises [16].

While automated closed-loop systems have been well evaluated in infants to prevent hyperoxia and retinal damage, longterm evaluation in adults is lacking [11, 17, 18]. However, Bialais et al. were able to demonstrate, that Intellivent-ASV provides a safe ventilation with optimized oxygenation and reduced workload on caregivers over a time period of 48 hours [19]. Nevertheless, the aim of this study is to further investigate the benefits and limitations of automated control of inspired $FiO_2$ in invasively ventilated critically ill adults. The SPIRIT figure provides an overview of the phases of the trial and data collection timepoints (Fig 1). The primary endpoint of this trial is the proportion of time in target zone for peripheral oxygen saturation within the first 24h hours following randomization, calculated based on all usable time with a valid $SpO_2$ signal. This also includes the analysis of blood gas samples, self-aborts and manual overrides of the automated system and the number of changes in $FiO_2$. Furthermore, proportion of time in peripheral oxygen target zone in patients with acute hypoxemic resp. acute hypercapnic respiratory failure will be further analyzed.

Figure 1: SPIRIT Figure

## Explanation for the choice of comparators {6b}

The primary objective is to examine the compliance with the target zone for peripheral oxygen saturation ($SpO_2$) using the LeoClac automated system compared to manual control. Thus, the comparators in this trial are manual and automated $FiO_2$ control. Manual control refers to the standard practice of manually adjusting the inspired fraction of oxygen ($FiO_2$) based on clinical judgement. periodic assessments of the patient's condition and reference to current and recent $SpO_2$ levels. It represents the current approach used in clinical practice.

The use of manual control as a comparator allows for a direct comparison with the LeoClac automated system. By assessing the efficacy of LeoClac in maintaining $SpO_2$ within the target zone, it can be determined whether the automated system provides improved control and adherence to the desired oxygen saturation levels compared to standard manual control methods.

By comparing the performance of the LeoClac system to manual control, the trial aims to evaluate whether the automated system can effectively optimize oxygen therapy and improve patient outcomes in critically ill, invasively ventilated patients.

## Objectives {7}

The primary objective of this study is to investigate compliance within the predefined $SpO_2$-target zone of 92 to 96% in critically ill and invasively ventilated patients comparing LeoClac to manual control.

### Trial design {8}

This trial is a randomized, controlled, single-center superiority trial with two parallel groups. The study aims to assess the proportion of time spent in the target zone for peripheral oxygen saturation within the first 24 hours following randomization as the primary endpoint. Randomization is conducted using random permuted block randomization with a 1:1 allocation ratio. Blinding is not feasible in this study.

## Methods: Participants, interventions, and outcomes

### Study setting {9}

The study will be performed on all interdisciplinary surgical intensive care units of the Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel.

### Eligibility criteria {10}

To be considered eligible for the study, patients must meet the following inclusion criteria: (1) Intubated or tracheotomized patients requiring mechanical ventilation for a duration of at least 9 hours as of 9:00 am, (2) participants must be at least 18 years old, and written informed consent must be obtained. Potential patients will be excluded from the study if any of the following exclusion criteria are met: (1) Inability to measure peripheral oxygen saturation, (2) absence of a detectable pulsatile plethysmography curve, (3) clinical indication for hyperoxia ($SpO_2$ target >96%), (4) expected extubation within the next 24 hours, or (5) negative presumed will regarding study participation, (6) known pregnancy.

Patient and Public involvement section

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of our research.

### Intervention description {11a}

After obtaining written informed consent, patients will be included in the study. Patients randomized to the intervention group will be mechanically ventilated with an automated control of the inspired oxygen fraction. Therefore, the ventilator will automatically adjust the amount of oxygen required based on oxygen saturation, with the goal of always maintaining oxygen saturation between 93 and 96%. Regardless of group assignment, all patients receive an additional oxygen sensor as part of the LeoClac system. If the two oxygen saturation sensors show different values, the measurements from the LeoClac device should be used. In case of uncertainty, an arterial blood gas analysis should be performed for verification. LeoClac will be used from the start of the study period until the end of invasive ventilation (extubation, decannulation, dismission or death) or day 28. Figure 2 shows the participant timeline and

provides an overview of screening, intervention and close-out.

## Criteria for discontinuing or modifying allocated interventions {11b}

If instances of uncontrollable respiratory instability occur during the intervention, the intervention will be discontinued. Treating physicians (who are not part of the study team) can suspend the study at any time. LeoClac can be deactivated at any time and for any reasons. The reason will be documented in the case report form. Furthermore, participants/representatives may withdraw from the study without citing a reason at any time. There is no provision for modifying the assigned intervention.

## Strategies to improve adherence to interventions {11c}

Adherence to the study protocol is ensured by staff training courses and information leaflets, which are attached to the patient's ventilator.

## Relevant concomitant care permitted or prohibited during the trial {11d}

All procedures and interventions in this study adhere to established internal standard procedures required for optimal patient treatment.

## Outcomes {12}

The primary endpoint of this trial is the proportion of time in target zone for peripheral oxygen saturation within the first 24h hours following randomization.

Secondary endpoints apply to the entire study period and include:

- Proportion of time with automated control of inspired fraction of oxygen activated
- Proportion of time with hypoxia according to pulse oximetry ($SpO_2$ <90%)
- Proportion of time with hyperoxia according to pulse oximetry ($SpO_2$ >98%)
- Number of blood gas samples with hypoxia (n/day; $PaO_2$ <60 mmHg)
- Number of blood gas samples with hyperoxia (n/day; $PaO_2$ >110 mmHg)
- Number of changes of inspired fraction of oxygen (n/day)
- Number and reasons of self-aborts of the automated system (n/day)
- Number and reasons of manual overrides of the automated system (n/day)
- Proportion of time in target zone for peripheral oxygen saturation in the subgroup of patients with acute hypoxemic respiratory failure
- Proportion of time in target zone for peripheral oxygen saturation in the subgroup of patients with acute hypercapnic respiratory failure
- Ventilator-free days alive at day 28d
- ICU mortality within 28 days

### Participant timeline {13}

Figure 2: Participant timeline

### Sample size {14}

Based on data with other automated systems and on our clinical experience with manual oxygen control, we expect a time within $SpO_2$ target range of 80% (SD 20) with LeoClac and of 60% (SD 20) with manual control. For a two-sided Mann-Whitney-U-Test, power calculation with 1-Beta = 0.8 and alpha 0.05 yields a required sample size of 2x 20 patients to be sufficient.

### Recruitment {15}

Eligible patients will be screened for study participation every morning (Monday - Friday). Screening will be conducted by senior physicians. Recruitment will be continuously conducted by physicians of the research team until the target randomized sample size of 40 participants is achieved. Based on current clinical case numbers, this will take approximately six months.

## Assignment of interventions: allocation

### Sequence generation {16a}

Randomization is performed by random permuted block randomization with a 1:1 allocation ratio, Minimum Block Size: 4; Maximum Block Size: 8; Increment: 2. The randomization is performed electronically with using the www.studyrandomizer.com.

### Concealment mechanism {16b}

The randomization is performed electronically using www.studyrandomizer.com.

### Implementation {16c}

The allocation sequence is generated electronically.

### Who will be blinded {17a}

Blinding of the study team is not feasible due to the study concept. Patients and their representatives will be blinded to the intervention.

### Procedure for unblinding if needed {17b}

n/a

# Data collection and management

## Plans for assessment and collection of outcomes {18a}

Demographic and clinical data are recorded on electronic based case report forms (eCRFs) by data collectors. Ventilator measurement data and oxygen saturation values are exported electronically from the ventilator and the monitoring unit. To determine the primary and further secondary outcome, ventilator data and monitoring data will be analyzed by the data analyzing team as described below (20a).

## Plans to promote participant retention and complete follow-up {18b}

N/a. No follow-up for clinically relevant outcome measurement needed.

## Data management {19}

All participant information will be stored on password-protected databases to which only research team members have access. Collected data are pseudonymized by a coded ID [identification] number. All records that contain names or other personal identifiers, such as informed consent forms, will be stored separately from study records. Demographic and clinical data will be stored on electronic case report forms (eCRFs). Log files containing ventilator data are exported from ventilators and saved on a password-secured network drive.

## Statistical methods for primary and secondary outcomes {20a}

Descriptive statistical analyses (mean +/- standard deviation, median and 95% confidence interval where appropriate) will be used. As we expect proportion of time in target zone for peripheral oxygen saturation within the first 24 hours following randomization to be non-normally distributed, the primary endpoint will be compared between study groups with a Mann-Whitney-U-Test. Categorial endpoints will be investigated using Fisher´s exact test. Other between-group comparisons of numerical endpoints will be conducted using a two-sided t-test or Mann-Whitney-U-test, as appropriate. Testing for normal distribution will be performed with Shapiro-Wilk test.

## Methods for additional analyses (e. g. subgroup analyses) {20b}

Not applicable, no further analyses planned.

## Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Data sets will be excluded if the study intervention was not performed, or if the primary endpoint cannot be evaluated.

# Methods: Monitoring

### Composition of the data monitoring committee, its role and reporting structure {21a}

As no interim analyses are planned or will be performed, a data monitoring committee has not been organised for this study.

### Interim analyses {21b}

Not applicable, there will be no interim analyses.

### Adverse event reporting and harms {22}

Adverse events and other unintended effects of the trial will be collected, assessed, and immediately reported to the principal investigator.

### Frequency and plans for auditing trial conduct {23}

Not applicable, an auditing trail conduct is not required.

## Ethics and Dissemination

### Ethics approval and consent to participate {24}

The local review board of the Medical Faculty of the Christian-Albrecht University approved the study, reference number D 449/22. The patient information has been included in the Supplement (S1). Written, informed consent to participate will be obtained from all patients.

### Plans for communicating important protocol amendments to relevant parties (e. g. trial participants, ethical committees) {25}

Any changes in protocol will be submitted to the local ethics committee for approval, all changes will be communicated to the study team via E-Mail and during the regular study group meetings. The trial record on DRKS will be updated accordingly.

### Who will take informed consent? {26a}

In this randomized controlled trial investigating a novel system for automated $F_iO_2$ control in critically ill, mechanically ventilated patients, the process of obtaining informed consent will be multistep based due to the patients' critical condition. Since most patients will be unable to provide written consent themselves, the patient's presumed will regarding study participation will be determined in consultation with their relatives or representatives. Written informed consent will then be obtained from the patient's legal representatives prior to their participation in the study.

Patients will be assessed for potential study inclusion daily (Monday-Friday). As soon as a patient regains consciousness, their written informed consent will be sought. It is important to note that in accordance with the principles outlined in the Declaration of Helsinki and national regulations, consent

can be withdrawn at any time, without the need to specify reasons, and without compromising the patient's future medical care.

## Additional consent provisions for collection and use of participant data and biological specimens {26b}

n/a. No additional data will be collected.

## Confidentiality {27}

Data are handled confidentially, and the storage of patient-related medical data is pseudonymized. No features are transferred that allow direct identification of specific participants. The subject identification code list to personal data is accessible only to the principal investigator. All further records containing names or other personal identifiers, such as informed consent forms are kept separate from the study data identified by code number. Data collection, coding, security, and storage will comply with the provisions of the German Federal Data Protection Act (BDSG) and the EU General Data Protection Regulation (EU-GPDR). Accordingly records and documents related to the clinical trial will be kept for at least 15 years.

## Competing interests {28}

We have received study material ($SpO_2$ sensors) from Löwenstein Medical Innovation, Steinbach, Germany. Tobias Becher and Dirk Schädler received grants from the Federal Ministry of Education and Research, Tobias Becher received consulting and lecture fees (Löwenstein Medical, Vyaire Medical), Dirk Schädler received lecture fees (Sedana, Aerogen, Löwenstein). All other authors have no competing interests to declare.

## Availability of data and materials {29}

Following publication of the trial, datasets containing pseudonymized patient data will be made accessible upon reasonable request to the corresponding author.

## Provisions for post-trial care {30}

After completion of the study, patients will continue to receive care in our intensive care unit until they reach a level of recovery that allows for transfer to a general ward or a rehabilitation clinic. Patients are encouraged to contact our clinic at any time if they have any concerns.

## Dissemination plans {31a}

Once the study has been completed, the results will be published in a peer-reviewed scientific journal and presented on national and international conferences for anaesthesiology and intensive care medicine.

## Authors' contributions {31b}

All authors were involved in the design of the study and have contributed and approved publication of the study protocol. CE: formal analysis, writing and editing the manuscript, HS: data acquisition, writing and editing the manuscript; LH: screening of patients, data acquisition, reviewing of the manuscript; AS: screening of patients, data acquisition, reviewing of the manuscript; ML gave important intellectual input and critically reviewed the study protocol TB: conceived the LeoClac controller, drafted and reviewed the study protocol, screening of patients, data acquisition DS: acted as guarantor, original idea for study, first draft of study protocol, principal investigator; all authors read and approved the final manuscript. All authors contributed to the study according to the criteria of the ICMJE.

### Plans to give access to the full protocol, participant level-data and statistical code {31c}

Datasets containing anonymized patient data will be made accessible upon reasonable request to the corresponding author, in compliance with European data protection regulations (EU-GDPR).

### Consent for publication {32}

Not applicable.

### Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/a. No biological specimens will be collected.

## Discussion

This study aims to evaluate the efficacy of an automated closed-loop oxygen control system to examine compliance with the $SpO_2$-target zone in critically ill and invasively ventilated adult patients. The precise control of oxygen demand with the aim of avoiding both hyperoxia and hypoxia are central challenges in the highly technical field of mechanical ventilation. From the pediatric and neonatal point of view, automatic oxygen control has already been able to demonstrate significant success in numerous studies [17, 20-22]. With the novel LeoClac function, the oxygen demand is continuously monitored and checked several times per minute. Increases in oxygen demand are therefore immediately detected, for instance, when the patient is more active or mobilized. This real-time adaptability may significantly reduce the likelihood of sudden fluctuations in oxygen saturations.

It is imperative to acknowledge the patient heterogeneity observed in critically ill patients. Understanding how different patients respond to automated oxygen control is vital for tailoring treatment strategies to individual needs. The reduction of manual intervention could become a significant advantage of automated oxygen control. The current standard often requires manual adjustment and monitoring of oxygen supply, placing a significant burden on medical staff especially in patients with high oxygen demand. The automation of this process holds promise, especially in high-workload situations or when multiple patients are being cared for simultaneously, where the system can increase efficiency and reduce the burden on medical staff. In addition, the precise and controlled delivery of oxygen holds the

potential to optimize treatment outcomes.

Incorporation of patient heterogeneity, the benefits of reduced manual intervention, and the potential to optimize treatment outcomes underscore the paramount importance of this research. By addressing the complexities of precise oxygen control in adults, this study contributes to the advancement of critical care practices and may improve patient outcomes.

### Trial status

The study protocol was approved by the ethics committee of the Christian-Albrechts-University Kiel, Germany, on 01 February 2023. Recruitment has begun in December 2023 and is expected to end in June 2025.

## Abbreviations

ASV, Adaptive support ventilation

BDSG, German Federal Data Protection Act

CRF, case report form

EU-GDPR, European Union General Data Protection Regulation

$FiO_2$, inspired oxygen fraction

LeoClac, Closed loop automatic oxygen control

Intellivent-ASV, fully automated closed loop ventilation

$PaO_2$, arterial oxygen partial pressure

$SpO_2$, oxygen saturation

## Declarations

### Acknowledgements

Not applicable.

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## Figure Legends

Figure 1: The Spirit Figure provides an overview on the different phases of the trial and outlines the data collection timepoints.

Figure 2: The participant timeline provides an overview of screening, intervention, and close-out.

## Authors' contributions

All authors were involved in the design of the study and have contributed and approved publication of the study protocol. CE: formal analysis, writing and editing the manuscript, HS: data acquisition, writing and editing the manuscript; LH: screening of patients, data acquisition, reviewing of the manuscript; AS: screening of patients, data acquisition, reviewing of the manuscript; ML gave important intellectual input and critically reviewed the study protocol TB: conceived the LeoClac controller, drafted and reviewed the study protocol, screening of patients, data acquisition DS: acted as guarantor, original idea for study, first draft of study protocol, principal investigator; all authors read and approved the final manuscript. All authors contributed to the study according to the criteria of the ICMJE.

## Funding statement

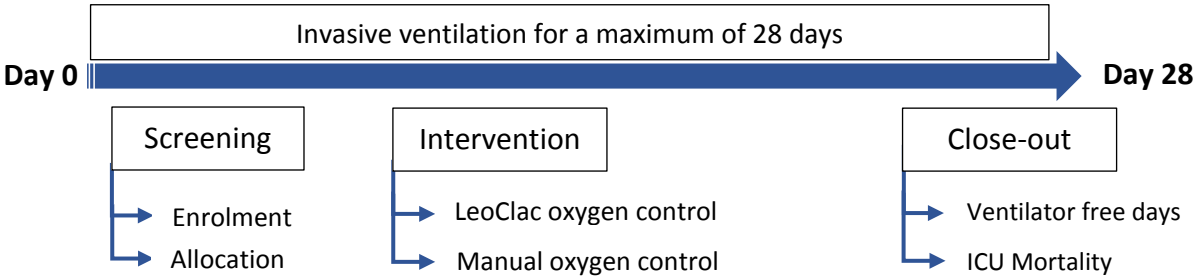
This research received no specific grant from any funding agency in the public, commercial or not-for-profit-sectors.

## Competing interests statement

We have received study material ($SpO_2$ sensors) from Löwenstein Medical Innovation, Steinbach, Germany. Tobias Becher and Dirk Schädler received grants from the Federal Ministry of Education and Research, Tobias Becher received consulting and lecture fees (Löwenstein Medical, Vyaire Medical), Dirk Schädler received lecture fees (Sedana, Aerogen, Löwenstein). All other authors have no competing interests to declare.

| | Screening | | Study period | |
|---|---|---|---|---|
| | **Enrolment** | **Allocation** | **Post-allocation** | **Close-out** |
| **TIMEPOINT:** | Day 0 | Day 0 | Day 0-28 | Day 28 |
| **ENROLMENT:** | X | | | |
| Eligibility Screen | X | | | |
| Written informed consent | X | | | |
| **ALLOCATION:** | | X | | |
| **INTERVENTIONS:** | | | | |
| LeoClac Oxygen control | | | X | |
| Manual oxygen control | | | X | |
| **ASSESSMENTS:** | | | | |
| Proportion of time of oxygen saturation in target zone | | | X | |
| Duration of time of hyperoxia and hypoxia (pulse oximetry; blood gas samples) | | | X | |
| Collection of self- and user-aborts of the automated system | | | X | |
| **CLOSE OUT:** Ventilator-free days | | | | X |
| ICU Mortality | | | | X |

Figure 2: Participant timeline



UNIVERSITY MEDICAL CENTER SCHLESWIG-HOLSTEIN

CAMPUS KIEL

DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE MEDICINE

DIRECTOR: PROF. DR. MED. STEINFATH

# Information for Patients
# Participation in the Clinical Study:

# Automatic Adjustment of Oxygen Concentration by the Ventilator

**Dear Patient,**

We would like to ask if you are willing to participate in the clinical study described below. Clinical studies are essential for gaining insights into the effectiveness of new therapies. Participation in such a study is entirely voluntary. You will only be included if you provide your written consent.

## What is the purpose of the planned study?

As part of your treatment at UKSH, mechanical ventilation in the intensive care unit is required. During this process, a ventilator pumps a mixture of oxygen and air into your lungs. Typically, the oxygen concentration on the ventilator is manually adjusted. However, the ventilators used at UKSH have a feature that allows the oxygen concentration to be automatically adjusted based on your oxygen saturation, measured with a finger clip (pulse oximetry).

This automatic adjustment aims to better match the oxygen concentration to your actual oxygen needs. The goal of the planned study is to investigate whether this automatic adjustment leads to fewer and shorter deviations of oxygen saturation levels outside the medically prescribed target range compared to manual adjustments.

## How does the study work?

If you agree to participate in the study, a random process will decide whether the oxygen concentration is adjusted manually or automatically by the ventilator's oxygen control system. This process is called "randomization" and is similar to flipping a coin.

During the study, data from the ventilator and other routine data collected as part of your intensive care treatment will be recorded for scientific analysis. Apart from the automatic adjustment of the oxygen concentration, no additional measures will be taken.

## When does the study end for me?

The study will end when mechanical ventilation is no longer required, or after 28 days at the latest. However, you have the right to withdraw your consent and stop participating in the study at any time. If you choose to withdraw, the study will end immediately for you.

## What potential benefit do I have from participating in the study?

You are unlikely to experience any personal benefit from participating in this study. However, by taking part, you may help contribute to scientific knowledge that could benefit the treatment of patients requiring mechanical ventilation in the future.

## What are the risks of the planned study?

Based on current scientific knowledge, we do not expect any additional risks from your participation in this study. This is primarily because, in addition to monitoring your blood oxygen levels via the ventilator, a separate monitoring device will continuously track your oxygen concentration. This ensures that the medical staff can respond to any changes at any time. If necessary, the automatic oxygen adjustment by the ventilator can be stopped or overridden by the medical or nursing staff at any time.

## Will I incur any costs or receive compensation for participating in the clinical study?

You will not incur any costs for participating in this clinical study, and you will not receive any financial compensation for your participation.

## What happens to my personal data?

The collected study findings and data will be recorded and then processed in a pseudonymized form. Pseudonymized means that no names or initials will be used; instead, a number or letter code along with your age in years will be assigned.

The processing of personal data of the patient you represent will be carried out for the purposes of scientific research by UKSH staff, who are bound by medical confidentiality.
If you have any questions regarding data protection, you can contact the study leadership (contact details below) as well as the data protection officer of UKSH, Dr. Stefan Reuschke (email: datenschutzbeauftrager@uksh.de; phone: +49 431 50014181). You have the right to request information about the data we store that pertains to you and, if necessary, request its deletion. Please contact the study leadership for this purpose.

## Contact Information of the Study Team

Principal Investigator and Responsible Person for Data Processing:

Priv.-Doz. Dr. med. Dirk Schädler

Klinik für Anästhesiologie und Operative Intensivmedizin

Universitätsklinikum Schleswig-Holstein, Campus Kiel

Arnold-Heller-Str. 3, Haus R3

D-24105 Kiel

Tel.: 0431/50020800

Fax: 0431/50020804

Email: dirk.schaedler@uksh.de

Additionally, in the case of unlawful data processing, you have the right to file a complaint with a supervisory authority. The competent supervisory authority for Schleswig-Holstein is:

Unabhängiges Landeszentrum für Datenschutz Schleswig-Holstein

Holstenstraße 98

24103 Kiel

Telefon: 0431/988-1200

Telefax: 0431/988-1223

E-Mail: mail@datenschutzzentrum.de

https://www.datenschutzzentrum.de

The pseudonymized data may also be shared with scientific collaborators of UKSH for scientific analysis. The results of the study will be published in a scientific journal. This will be done in full compliance with legal data protection regulations.

## Was the study reviewed by an ethics committee?

The conduct of the study has been reviewed by an independent ethics committee regarding ethical and legal concerns. The ethics committee raised no objections to the study being conducted.

## Can the decision to participate in the study be reversed?

Participation in the study is completely voluntary. **You can withdraw your participation at any time without facing any disadvantages.** If you have any questions, please contact the following doctors from the Department of Anesthesiology and Surgical Intensive Care Medicine:

Priv.-Doz. Dr. Dirk Schädler
Priv.-Doz. Dr. Tobias Becher
Dr. Matthias Lindner
Dr. Florian Roßkopf
Dr. Armin Sablewski
Dr. Christine Eimer
Dr. Phil Klose
Dr. Helene Selpien
Nina Schulz-Ruthenberg
Corinna Buchholz

If you decide to allow the patient you represent to participate in the study, we kindly ask for your signature on the consent form. A copy of the patient information and consent form provided to you is for your records.

We sincerely thank you for your cooperation.

„Automatic Adjustment of Oxygen Concentration by the Ventilator“

## Consent Form for Patients

Dr. [Name of Doctor] has provided me, [Patient's Name], with a detailed explanation about the nature, significance, and scope of this clinical study, as well as the procedures and implementation involved.

I have read and understood the written information for patients. I was given sufficient time and opportunity to ask questions. My questions have been answered thoroughly and to my satisfaction. I have been informed that if I have any further questions during the course of the study, I can contact the principal investigator, who will provide answers to the best of their knowledge and ability.

I consent to the collection of my medical and study data within the framework of this clinical study, both in paper form and on electronic storage devices, in pseudonymized form (without using my name). I understand that these data will be stored for 20 years and may be used for scientific publications. If necessary, the collected data may be shared in pseudonymized (encrypted) form with scientific collaborators of UKSH. I am aware that I can withdraw this consent at any time without giving a reason, and that no disadvantages will result from this. Upon withdrawal, all collected data will be deleted upon my request, unless complete anonymization has already been performed.

I, [First Name, Last Name], born on [Date of Birth], agree to participate in the above-mentioned study.

I have received the patient information and a copy of the consent form.

**Date and Signature of Patient**: _____

**Date and Signature of Doctor**: _____

BMJ Open

# Automated control of inspired oxygen fraction in mechanically ventilated patients – a study protocol for single center randomized controlled trial

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| Secondary Subject Heading: | Anaesthesia, Intensive care |
| Keywords: | ANAESTHETICS, Ventilators, Mechanical, Oxygen Saturation, INTENSIVE & CRITICAL CARE, Lung Diseases |
| | |

# Title

Automated control of inspired oxygen fraction in mechanically ventilated patients – A study protocol for a single center randomized controlled trial

## Names protocol contributors

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## Abstract

**Background**: A novel automated system for the control of the inspired fraction of oxygen named LeoClac has been implemented on a mechanical ventilator. The system uses a separate sensor for the measurement of the peripheral oxygen saturation which is connected directly to the ventilator. We hypothesize that LeoClac will be superior to manual control in keeping critically ill and mechanically ventilated patients in a $SpO_2$-target range (93-96%).

**Methods**: This is a randomized controlled, single-center superiority study with two parallel groups including 40 patients. Mechanically ventilated patients treated on the intensive care unit will be screened for eligibility and included in the study after written informed consent. Patients in the intervention group will be treated with LeoClac. In the control group, $FiO_2$ will be controlled manually by the intensive care team. The primary endpoint of the study is the proportion of time in target zone for peripheral oxygen saturation within the first 24 hours following randomization. Secondary endpoints include the analysis of hyperoxia and hypoxia, number of changes in $FiO_2$, number, and reasons of self-aborts and manual overrides of the automated system, proportion of time in target zone for peripheral oxygen saturation in the subgroups of patients with hypoxemic respiratory failure and acute hypercapnic respiratory failure. Furthermore, ventilator-free days and ICU mortality at day 28 will be analyzed.

**Analysis:** The precise control of $FiO_2$ with the aim of avoiding both hyperoxia and hypoxia is a fundamental challenge in the highly technical field of mechanical ventilation. Incorporation of patient heterogeneity, the benefits of reduced manual intervention, and the potential to optimize treatment outcomes underscore the importance of this research. By addressing the complexities of precise oxygen control in adults, this study contributes to the advancement of critical care practices and may improve patient outcomes.

**Ethics:** The study protocol was approved by the ethics committee of the Christian-Albrechts-University Kiel, Germany, on 17th May 2023.

## Trial registration & status:

German Clinical Trials Register (DRKS); registration number: DRKS00032113; (https://drks.de/search/en/trial/DRKS00032113), date of registry 20th June 2023. Recruitment will begin in December 2023 and is expected to end in June 2025.


### Strengths and limitations of this study

- This study aims to evaluate whether an automated system can effectively optimize oxygen therapy in critically ill, invasively ventilated patients.
- This study plans to investigate the benefits and limitations of an automated oxygen control in a very heterogenous sample of adult intensive care patients.

- The novel system will be used for up to 28 days per patient to evaluate feasibility of the sensors in daily routine.


## Keywords

Liberal oxygen therapy, Intellivent-ASV, automated control of $FiO_2$, closed loop automatic oxygen control, $SpO_2$ target zone, LeoClac


# Administrative information

| | |
|---|---|
| Title {1} | Automated control of inspired oxygen fraction in mechanically ventilated patients – A study protocol for a single center randomized controlled trial |
| Trial registration {2a and 2b}. | DRKS: 00032113, https://drks.de/search/en/trial/DRKS00032113<br>All items from the WHO Trial Registration dataset can be found within the study protocol or on the DRKS website. |
| Protocol version {3} | Study protocol 2.0 (02.02.2024) |
| Funding {4} | Löwenstein Medical provided single-use peripheral oxygen sensors free of charge during the study period. No further funding has been received. |
| Author details {5a} | Christine Eimer (christine.eimer@uksh.de)<br>Helene Selpien (helene.selpien@uksh.de)<br>Lara Hartmann (lara.hartmann@uksh.de)<br>Armin Sablewski (armin.sablewski@uksh.de)<br>Matthias Lindner (matthias.lindner@uksh.de)<br>Tobias Becher (tobias.becher@uksh.de)<br>Dirk Schädler (dirk.schaedler@uksh.de)<br>Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel<br>E-Mail: christine.eimer@uksh.de |
| Name and contact information for the trial sponsor {5b} | University Medical Center Schleswig-Holstein, Campus Kiel<br>Department for Anesthesiology and Intensive Care Medicine<br>Christine Eimer<br>Arnold-Heller Str. 3, 24105 Kiel, Germany<br>Tel: 0431 500 20801 |
| Role of sponsor {5c} | Löwenstein Medical played no role in study planning, execution, analysis, interpretation writing and submission of the manuscript. |

## Funding {4}

Provision of Study Materials (Löwenstein Medical Innovation, Steinbach, Germany); provision of $SpO_2$ sensors.

## Composition of the coordinating centre and trial steering committee {5d}

Not applicable. Study is a single center study.

# Introduction

## Background and rationale {6a}

Oxygen therapy plays a crucial role in the therapy of critically ill patients, ensuring adequate oxygen delivery while avoiding hypo- and hyperoxia. Nevertheless, overdosing oxygen may be harmful, as both excessively high and low arterial partial pressure of oxygen ($PaO_2$) are associated with increased mortality [1, 2]. Stolmeijer et al. indicated that liberal oxygen therapy leads to hyperoxia and may also affect survival [3]. A recent meta-analysis also highlighted the risks of liberal oxygen therapy, showing increased mortality compared to conservative oxygen therapy [4]. The current German guideline recommends titrating peripheral oxygen saturation ($SpO_2$) between 92% to 96% in mechanically ventilated patients [5]. In adult patients, sensitivity to oxygen is not as pronounced; yet, neither the consequences of hypoxia or hyperoxia, nor the associated economic follow-up costs should be underestimated [6-8].

Currently, manual oxygen ($FiO_2$) control based on $SpO_2$ and $PaO_2$ measurements is the standard in clinical practice. However, based on neonatal studies compliance to peripheral oxygen targets is poor [9, 10] this finding might be also applicable to adults and carries the risk of unrecognized hypoxia or hyperoxia. Additionally, health care professionals often prioritize avoiding desaturation over avoiding hyperoxia, potentially leading to oxygen oversupply [11]. Therefore, it is crucial to carefully monitor patients' response to therapy and adjust oxygen delivery accordingly.

To address the limitations of manual control, an automated system for $FiO_2$ control would be desirable. Its aim is to continuously modulate oxygen supply, ensure normoxemia and prevent desaturation. In a study by Lellouche et al., automated oxygen flow titration was superior to constant oxygen flow in maintaining $SpO_2$ levels [12]. Saihi et al. demonstrated that an automated $FiO_2$ controller, based on continuous oxygen saturation, was capable in maintaining $SpO_2$ reliably within a predefined target range [13]. Intellivent-ASV (fully automated closed loop ventilation) has been the sole available ventilation mode including automated $FiO_2$ control in invasively ventilated adult patients. The algorithm in Intellivent-ASV compares $SpO_2$ values with the target range and automatically adjusts the $FiO_2$ to maintain desired saturation levels [11]. However, access to Intellivent-ASV is limited, available only on selected ventilators. A new alternative, the Loewenstein closed-loop automatic oxygen control (LeoClac), offers rapid modulation of $FiO_2$ based on a separate $SpO_2$ measurement attached to the ventilator. The user sets a target $SpO_2$ range to be maintained before starting the $FiO_2$ control. The user

also defines a $FiO_2$ threshold for receiving an alarm. An alarm is triggered, if the $FiO_2$ alarm threshold is exceeded, however, the automatic regulation continues until deactivation by the user ("manual override"). The $SpO_2$ measurement is based on a configurable number of pulse waves. $FiO_2$ reductions occur every two minutes, increases are limited to every 45 seconds to avoid "swinging" of the system.

Recent publications suggest that closed-loop control devices maintain higher saturation levels, spend less time below the target saturation, and save oxygen resources [11, 14, 15]. Moreover, an automated system may contribute to maintaining sufficient oxygenation during exercise and physiotherapy when oxygen consumption rises [16].

While automated closed-loop systems have been well evaluated in infants to prevent hyperoxia and retinal damage, longterm evaluation in adults is lacking [11, 17, 18]. However, Bialais et al. were able to demonstrate, that Intellivent-ASV provides a safe ventilation with optimized oxygenation and reduced workload on caregivers over a time period of 48 hours [19]. Nevertheless, the aim of this study is to further investigate the benefits and limitations of automated control of inspired $FiO_2$ in invasively ventilated critically ill adults. The SPIRIT figure provides an overview of the phases of the trial and data collection timepoints (Fig 1). The primary endpoint of this trial is the proportion of time in target zone for peripheral oxygen saturation within the first 24h hours following randomization, calculated based on all usable time with a valid $SpO_2$ signal. This also includes the analysis of blood gas samples, self-aborts and manual overrides of the automated system and the number of changes in $FiO_2$. Furthermore, proportion of time in peripheral oxygen target zone in patients with acute hypoxemic resp. acute hypercapnic respiratory failure will be further analyzed.

Figure 1: SPIRIT Figure

## Explanation for the choice of comparators {6b}

The primary objective is to examine the compliance with the target zone for peripheral oxygen saturation ($SpO_2$) using the LeoClac automated system compared to manual control. Thus, the comparators in this trial are manual and automated $FiO_2$ control. Manual control refers to the standard practice of manually adjusting the inspired fraction of oxygen ($FiO_2$) based on clinical judgement. periodic assessments of the patient's condition and reference to current and recent $SpO_2$ levels. It represents the current approach used in clinical practice.

The use of manual control as a comparator allows for a direct comparison with the LeoClac automated system. By assessing the efficacy of LeoClac in maintaining $SpO_2$ within the target zone, it can be determined whether the automated system provides improved control and adherence to the desired oxygen saturation levels compared to standard manual control methods.

By comparing the performance of the LeoClac system to manual control, the trial aims to evaluate whether the automated system can effectively optimize oxygen therapy and improve patient outcomes in critically ill, invasively ventilated patients.

## Objectives {7}

The primary objective of this study is to investigate compliance within the predefined $SpO_2$-target zone of 93 to 96% in critically ill and invasively ventilated patients comparing the novel “LeoClac”-controller to manual control.

### Trial design {8}

This trial is a randomized, controlled, single-center superiority trial with two parallel groups. The study aims to assess the proportion of time spent in the target zone for peripheral oxygen saturation within the first 24 hours following randomization as the primary endpoint. Randomization is conducted using random permuted block randomization with a 1:1 allocation ratio. Blinding is not feasible in this study.

## Methods: Participants, interventions, and outcomes

### Study setting {9}

The study will be performed on all interdisciplinary surgical intensive care units of the Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel.

### Eligibility criteria {10}

To be considered eligible for the study, patients must meet the following inclusion criteria: (1) Intubated or tracheotomized patients requiring mechanical ventilation for a duration of at least 9 hours as of 9:00 am, (2) participants must be at least 18 years old, and written informed consent must be obtained. Potential patients will be excluded from the study if any of the following exclusion criteria are met: (1) Inability to measure peripheral oxygen saturation, (2) absence of a detectable pulsatile plethysmography curve, (3) clinical indication for hyperoxia ($SpO_2$ target >96%), (4) expected extubation within the next 24 hours, or (5) negative presumed will regarding study participation, (6) known pregnancy.

Patient and Public involvement section

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of our research.

### Intervention description {11a}

After obtaining written informed consent, patients will be included in the study. Patients randomized to the intervention group will be mechanically ventilated with an automated control of the inspired oxygen fraction. Therefore, the ventilator will automatically adjust the amount of oxygen required based on oxygen saturation, with the goal of always maintaining oxygen saturation between 93 and 96%. Regardless of group assignment, all patients receive an additional oxygen sensor as part of the LeoClac system. If the two oxygen saturation sensors show different values, the measurements from the LeoClac device should be used. In case of uncertainty, an arterial blood gas analysis should be performed for verification. LeoClac will be used from the start of the study period until the end of invasive ventilation

(extubation, decannulation, dismission or death) or day 28. Figure 2 shows the participant timeline and provides an overview of screening, intervention and close-out.

## Criteria for discontinuing or modifying allocated interventions {11b}

If instances of uncontrollable respiratory instability occur during the intervention, the intervention will be discontinued. Treating physicians (who are not part of the study team) can suspend the study at any time. LeoClac can be deactivated at any time and for any reasons. The reason will be documented in the case report form. Furthermore, participants/representatives may withdraw from the study without citing a reason at any time. There is no provision for modifying the assigned intervention.

## Strategies to improve adherence to interventions {11c}

Adherence to the study protocol is ensured by staff training courses and information leaflets, which are attached to the patient's ventilator.

## Relevant concomitant care permitted or prohibited during the trial {11d}

All procedures and interventions in this study adhere to established internal standard procedures required for optimal patient treatment.

## Outcomes {12}

The primary endpoint of this trial is the proportion of time in target zone for peripheral oxygen saturation within the first 24h hours following randomization.

Secondary endpoints apply to the entire study period and include:

- Proportion of time with automated control of inspired fraction of oxygen activated
- Proportion of time with hypoxia according to pulse oximetry ($SpO_2$ <90%)
- Proportion of time with hyperoxia according to pulse oximetry ($SpO_2$ >98%)
- Number of blood gas samples with hypoxia (n/day; $PaO_2$ <60 mmHg)
- Number of blood gas samples with hyperoxia (n/day; $PaO_2$ >110 mmHg)
- Number of changes of inspired fraction of oxygen (n/day)
- Number and reasons of self-aborts of the automated system (n/day)
- Number and reasons of manual overrides of the automated system (n/day)
- Proportion of time in target zone for peripheral oxygen saturation in the subgroup of patients with acute hypoxemic respiratory failure
- Proportion of time in target zone for peripheral oxygen saturation in the subgroup of patients with acute hypercapnic respiratory failure
- Ventilator-free days alive at day 28d
- ICU mortality within 28 days

### Participant timeline {13}

Figure 2: Participant timeline

### Sample size {14}

Based on data with other automated systems and on our clinical experience with manual oxygen control, we expect a time within $SpO_2$ target range of 80% (SD 20) with LeoClac and of 60% (SD 20) with manual control. For a two-sided Mann-Whitney-U-Test, power calculation with 1-Beta = 0.8 and alpha 0.05 yields a required sample size of 2x 20 patients to be sufficient.

### Recruitment {15}

Eligible patients will be screened for study participation every morning (Monday - Friday). Screening will be conducted by senior physicians. Recruitment will be continuously conducted by physicians of the research team until the target randomized sample size of 40 participants is achieved. Based on current clinical case numbers, this will take approximately six months.

## Assignment of interventions: allocation

### Sequence generation {16a}

Randomization is performed by random permuted block randomization with a 1:1 allocation ratio, Minimum Block Size: 4; Maximum Block Size: 8; Increment: 2. The randomization is performed electronically with using the www.studyrandomizer.com.

### Concealment mechanism {16b}

The randomization is performed electronically using www.studyrandomizer.com.

### Implementation {16c}

The allocation sequence is generated electronically.

### Who will be blinded {17a}

Blinding of the study team is not feasible due to the study concept. Patients and their representatives will be blinded to the intervention.

### Procedure for unblinding if needed {17b}

n/a

## Data collection and management

### Plans for assessment and collection of outcomes {18a}

Demographic and clinical data are recorded on electronic based case report forms (eCRFs) by data collectors. Ventilator measurement data and oxygen saturation values are exported electronically from the ventilator and the monitoring unit. To determine the primary and further secondary outcome, ventilator data and monitoring data will be analyzed by the data analyzing team as described below (20a).

### Plans to promote participant retention and complete follow-up {18b}

N/a. No follow-up for clinically relevant outcome measurement needed.

### Data management {19}

All participant information will be stored on password-protected databases to which only research team members have access. Collected data are pseudonymized by a coded ID [identification] number. All records that contain names or other personal identifiers, such as informed consent forms, will be stored separately from study records. Demographic and clinical data will be stored on electronic case report forms (eCRFs). Log files containing ventilator data are exported from ventilators and saved on a password-secured network drive.

### Statistical methods for primary and secondary outcomes {20a}

Descriptive statistical analyses (mean +/- standard deviation, median and 95% confidence interval where appropriate) will be used. As we expect proportion of time in target zone for peripheral oxygen saturation within the first 24 hours following randomization to be non-normally distributed, the primary endpoint will be compared between study groups with a Mann-Whitney-U-Test. Categorial endpoints will be investigated using Fisher´s exact test. Other between-group comparisons of numerical endpoints will be conducted using a two-sided t-test or Mann-Whitney-U-test, as appropriate. Testing for normal distribution will be performed with Shapiro-Wilk test.

### Methods for additional analyses (e. g. subgroup analyses) {20b}

Not applicable, no further analyses planned.

### Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Data sets will be excluded if the study intervention was not performed, or if the primary endpoint cannot be evaluated.

# Methods: Monitoring

## Composition of the data monitoring committee, its role and reporting structure {21a}

As no interim analyses are planned or will be performed, a data monitoring committee has not been organised for this study.

## Interim analyses {21b}

Not applicable, there will be no interim analyses.

## Adverse event reporting and harms {22}

Adverse events and other unintended effects of the trial will be collected, assessed, and immediately reported to the principal investigator.

## Frequency and plans for auditing trial conduct {23}

Not applicable, an auditing trail conduct is not required.

# Ethics and Dissemination

## Ethics approval and consent to participate {24}

The local review board of the Medical Faculty of the Christian-Albrecht University approved the study, reference number D 449/22. The patient information has been included in the Supplement (S1). Written, informed consent to participate will be obtained from all patients.

## Plans for communicating important protocol amendments to relevant parties (e. g. trial participants, ethical committees) {25}

Any changes in protocol will be submitted to the local ethics committee for approval, all changes will be communicated to the study team via E-Mail and during the regular study group meetings. The trial record on DRKS will be updated accordingly.

## Who will take informed consent? {26a}

In this randomized controlled trial investigating a novel system for automated $F_iO_2$ control in critically ill, mechanically ventilated patients, the process of obtaining informed consent will be multistep based due to the patients' critical condition. Since most patients will be unable to provide written consent themselves, the patient's presumed will regarding study participation will be determined in consultation with their relatives or representatives. Written informed consent will then be obtained from the patient's legal representatives prior to their participation in the study.

Patients will be assessed for potential study inclusion daily (Monday-Friday). As soon as a patient regains consciousness, their written informed consent will be sought. It is important to note that in

accordance with the principles outlined in the Declaration of Helsinki and national regulations, consent can be withdrawn at any time, without the need to specify reasons, and without compromising the patient's future medical care.

## Additional consent provisions for collection and use of participant data and biological specimens {26b}

n/a. No additional data will be collected.

## Confidentiality {27}

Data are handled confidentially, and the storage of patient-related medical data is pseudonymized. No features are transferred that allow direct identification of specific participants. The subject identification code list to personal data is accessible only to the principal investigator. All further records containing names or other personal identifiers, such as informed consent forms are kept separate from the study data identified by code number. Data collection, coding, security, and storage will comply with the provisions of the German Federal Data Protection Act (BDSG) and the EU General Data Protection Regulation (EU-GPDR). Accordingly records and documents related to the clinical trial will be kept for at least 15 years.

## Competing interests {28}

We have received study material ($SpO_2$ sensors) from Löwenstein Medical Innovation, Steinbach, Germany. Tobias Becher and Dirk Schädler received grants from the Federal Ministry of Education and Research, Tobias Becher received consulting and lecture fees (Löwenstein Medical, Vyaire Medical), Dirk Schädler received lecture fees (Sedana, Aerogen, Löwenstein). All other authors have no competing interests to declare.

## Availability of data and materials {29}

Following publication of the trial, datasets containing pseudonymized patient data will be made accessible upon reasonable request to the corresponding author.

## Provisions for post-trial care {30}

After completion of the study, patients will continue to receive care in our intensive care unit until they reach a level of recovery that allows for transfer to a general ward or a rehabilitation clinic. Patients are encouraged to contact our clinic at any time if they have any concerns.

## Dissemination plans {31a}

Once the study has been completed, the results will be published in a peer-reviewed scientific journal and presented on national and international conferences for anaesthesiology and intensive care medicine.

## Authors' contributions {31b}

All authors were involved in the design of the study and have contributed and approved publication of the study protocol. CE: formal analysis, writing and editing the manuscript, HS: data acquisition, writing and editing the manuscript; LH: screening of patients, data acquisition, reviewing of the manuscript; AS: screening of patients, data acquisition, reviewing of the manuscript; ML gave important intellectual input and critically reviewed the study protocol TB: conceived the LeoClac controller, drafted and reviewed the study protocol, screening of patients, data acquisition DS: acted as guarantor, original idea for study, first draft of study protocol, principal investigator; all authors read and approved the final manuscript. All authors contributed to the study according to the criteria of the ICMJE.

## Plans to give access to the full protocol, participant level-data and statistical code {31c}

Datasets containing anonymized patient data will be made accessible upon reasonable request to the corresponding author, in compliance with European data protection regulations (EU-GDPR).

## Consent for publication {32}

Not applicable.

## Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/a. No biological specimens will be collected.

# Discussion

This study aims to evaluate the efficacy of an automated closed-loop oxygen control system to examine compliance with the $SpO_2$-target zone in critically ill and invasively ventilated adult patients. The precise control of oxygen demand with the aim of avoiding both hyperoxia and hypoxia are central challenges in the highly technical field of mechanical ventilation. From the pediatric and neonatal point of view, automatic oxygen control has already been able to demonstrate significant success in numerous studies [17, 20-22]. With the novel LeoClac function, the oxygen demand is continuously monitored and checked several times per minute. Increases in oxygen demand are therefore immediately detected, for instance, when the patient is more active or mobilized. This real-time adaptability may significantly reduce the likelihood of sudden fluctuations in oxygen saturations.

It is imperative to acknowledge the patient heterogeneity observed in critically ill patients. Understanding how different patients respond to automated oxygen control is vital for tailoring treatment strategies to individual needs. The reduction of manual intervention could become a significant advantage of automated oxygen control. The current standard often requires manual adjustment and monitoring of oxygen supply, placing a significant burden on medical staff especially in patients with high oxygen demand. The automation of this process holds promise, especially in high-workload situations or when multiple patients are being cared for simultaneously, where the system can increase efficiency and

reduce the burden on medical staff. In addition, the precise and controlled delivery of oxygen holds the potential to optimize treatment outcomes.

Incorporation of patient heterogeneity, the benefits of reduced manual intervention, and the potential to optimize treatment outcomes underscore the paramount importance of this research. By addressing the complexities of precise oxygen control in adults, this study contributes to the advancement of critical care practices and may improve patient outcomes.

### Trial status

The study protocol was approved by the ethics committee of the Christian-Albrechts-University Kiel, Germany, on 01 February 2023. Recruitment has begun in December 2023 and is expected to end in June 2025.

## Abbreviations

ASV, Adaptive support ventilation
BDSG, German Federal Data Protection Act
CRF, case report form
EU-GDPR, European Union General Data Protection Regulation
$FiO_2$, inspired oxygen fraction
LeoClac, Closed loop automatic oxygen control
Intellivent-ASV, fully automated closed loop ventilation
$PaO_2$, arterial oxygen partial pressure
$SpO_2$, oxygen saturation

## Declarations

### Acknowledgements

Not applicable.

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## Figure Legends

Figure 1: The Spirit Figure provides an overview on the different phases of the trial and outlines the data collection timepoints.

Figure 2: The participant timeline provides an overview of screening, intervention, and close-out.

## Authors' contributions

All authors were involved in the design of the study and have contributed and approved publication of the study protocol. CE: formal analysis, writing and editing the manuscript, HS: data acquisition, writing and editing the manuscript; LH: screening of patients, data acquisition, reviewing of the manuscript; AS: screening of patients, data acquisition, reviewing of the manuscript; ML gave important intellectual input and critically reviewed the study protocol TB: conceived the LeoClac controller, drafted and reviewed the study protocol, screening of patients, data acquisition DS: acted as guarantor, original idea for study, first draft of study protocol, principal investigator; all authors read and approved the final manuscript. All authors contributed to the study according to the criteria of the ICMJE.

## Funding statement

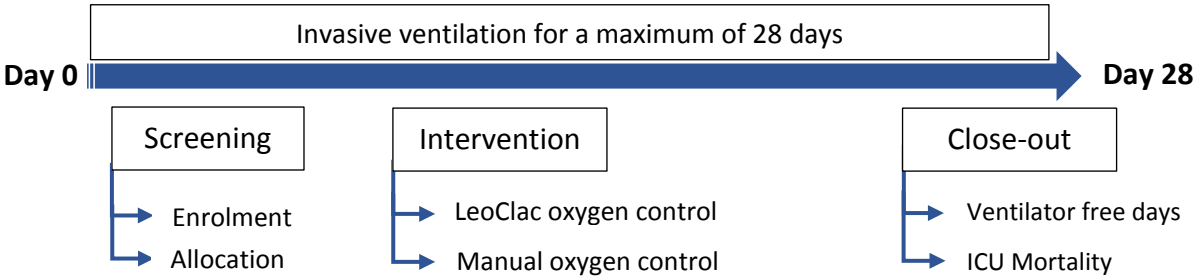
This research received no specific grant from any funding agency in the public, commercial or not-for-profit-sectors.

## Competing interests statement

We have received study material ($SpO_2$ sensors) from Löwenstein Medical Innovation, Steinbach, Germany. Tobias Becher and Dirk Schädler received grants from the Federal Ministry of Education and Research, Tobias Becher received consulting and lecture fees (Löwenstein Medical, Vyaire Medical), Dirk Schädler received lecture fees (Sedana, Aerogen, Löwenstein). All other authors have no competing interests to declare.

| | Screening | | Study period | |
|---|---|---|---|---|
| | **Enrolment** | **Allocation** | **Post-allocation** | **Close-out** |
| **TIMEPOINT:** | Day 0 | Day 0 | Day 0-28 | Day 28 |
| **ENROLMENT:** | X | | | |
| Eligibility Screen | X | | | |
| Written informed consent | X | | | |
| **ALLOCATION:** | | X | | |
| **INTERVENTIONS:** | | | | |
| LeoClac Oxygen control | | | X | |
| Manual oxygen control | | | X | |
| **ASSESSMENTS:** | | | | |
| Proportion of time of oxygen saturation in target zone | | | X | |
| Duration of time of hyperoxia and hypoxia (pulse oximetry; blood gas samples) | | | X | |
| Collection of self- and user-aborts of the automated system | | | X | |
| **CLOSE OUT:** Ventilator-free days | | | | X |
| ICU Mortality | | | | X |

Figure 2: Participant timeline



UNIVERSITY MEDICAL CENTER SCHLESWIG-HOLSTEIN

CAMPUS KIEL

DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE MEDICINE

DIRECTOR: PROF. DR. MED. STEINFATH

# Information for Patients
# Participation in the Clinical Study:

# Automatic Adjustment of Oxygen Concentration by the Ventilator

**Dear Patient,**

We would like to ask if you are willing to participate in the clinical study described below. Clinical studies are essential for gaining insights into the effectiveness of new therapies. Participation in such a study is entirely voluntary. You will only be included if you provide your written consent.

## What is the purpose of the planned study?

As part of your treatment at UKSH, mechanical ventilation in the intensive care unit is required. During this process, a ventilator pumps a mixture of oxygen and air into your lungs. Typically, the oxygen concentration on the ventilator is manually adjusted. However, the ventilators used at UKSH have a feature that allows the oxygen concentration to be automatically adjusted based on your oxygen saturation, measured with a finger clip (pulse oximetry).

This automatic adjustment aims to better match the oxygen concentration to your actual oxygen needs. The goal of the planned study is to investigate whether this automatic adjustment leads to fewer and shorter deviations of oxygen saturation levels outside the medically prescribed target range compared to manual adjustments.

## How does the study work?

If you agree to participate in the study, a random process will decide whether the oxygen concentration is adjusted manually or automatically by the ventilator's oxygen control system. This process is called "randomization" and is similar to flipping a coin.

During the study, data from the ventilator and other routine data collected as part of your intensive care treatment will be recorded for scientific analysis. Apart from the automatic adjustment of the oxygen concentration, no additional measures will be taken.

## When does the study end for me?

The study will end when mechanical ventilation is no longer required, or after 28 days at the latest. However, you have the right to withdraw your consent and stop participating in the study at any time. If you choose to withdraw, the study will end immediately for you.

## What potential benefit do I have from participating in the study?

You are unlikely to experience any personal benefit from participating in this study. However, by taking part, you may help contribute to scientific knowledge that could benefit the treatment of patients requiring mechanical ventilation in the future.

## What are the risks of the planned study?

Based on current scientific knowledge, we do not expect any additional risks from your participation in this study. This is primarily because, in addition to monitoring your blood oxygen levels via the ventilator, a separate monitoring device will continuously track your oxygen concentration. This ensures that the medical staff can respond to any changes at any time. If necessary, the automatic oxygen adjustment by the ventilator can be stopped or overridden by the medical or nursing staff at any time.

## Will I incur any costs or receive compensation for participating in the clinical study?

You will not incur any costs for participating in this clinical study, and you will not receive any financial compensation for your participation.

## What happens to my personal data?

The collected study findings and data will be recorded and then processed in a pseudonymized form. Pseudonymized means that no names or initials will be used; instead, a number or letter code along with your age in years will be assigned.

The processing of personal data of the patient you represent will be carried out for the purposes of scientific research by UKSH staff, who are bound by medical confidentiality.
If you have any questions regarding data protection, you can contact the study leadership (contact details below) as well as the data protection officer of UKSH, Dr. Stefan Reuschke (email: datenschutzbeauftrager@uksh.de; phone: +49 431 50014181). You have the right to request information about the data we store that pertains to you and, if necessary, request its deletion. Please contact the study leadership for this purpose.

## Contact Information of the Study Team

Principal Investigator and Responsible Person for Data Processing:

Priv.-Doz. Dr. med. Dirk Schädler

Klinik für Anästhesiologie und Operative Intensivmedizin

Universitätsklinikum Schleswig-Holstein, Campus Kiel

Arnold-Heller-Str. 3, Haus R3

D-24105 Kiel

Tel.: 0431/50020800

Fax: 0431/50020804

Email: dirk.schaedler@uksh.de

Additionally, in the case of unlawful data processing, you have the right to file a complaint with a supervisory authority. The competent supervisory authority for Schleswig-Holstein is:

Unabhängiges Landeszentrum für Datenschutz Schleswig-Holstein

Holstenstraße 98

24103 Kiel

Telefon: 0431/988-1200

Telefax: 0431/988-1223

E-Mail: mail@datenschutzzentrum.de

https://www.datenschutzzentrum.de

The pseudonymized data may also be shared with scientific collaborators of UKSH for scientific analysis. The results of the study will be published in a scientific journal. This will be done in full compliance with legal data protection regulations.

## Was the study reviewed by an ethics committee?

The conduct of the study has been reviewed by an independent ethics committee regarding ethical and legal concerns. The ethics committee raised no objections to the study being conducted.

## Can the decision to participate in the study be reversed?

Participation in the study is completely voluntary. **You can withdraw your participation at any time without facing any disadvantages.** If you have any questions, please contact the following doctors from the Department of Anesthesiology and Surgical Intensive Care Medicine:

Priv.-Doz. Dr. Dirk Schädler
Priv.-Doz. Dr. Tobias Becher
Dr. Matthias Lindner
Dr. Florian Roßkopf
Dr. Armin Sablewski
Dr. Christine Eimer
Dr. Phil Klose
Dr. Helene Selpien
Nina Schulz-Ruthenberg
Corinna Buchholz

If you decide to allow the patient you represent to participate in the study, we kindly ask for your signature on the consent form. A copy of the patient information and consent form provided to you is for your records.

We sincerely thank you for your cooperation.

„Automatic Adjustment of Oxygen Concentration by the Ventilator“

## Consent Form for Patients

Dr. [Name of Doctor] has provided me, [Patient's Name], with a detailed explanation about the nature, significance, and scope of this clinical study, as well as the procedures and implementation involved.

I have read and understood the written information for patients. I was given sufficient time and opportunity to ask questions. My questions have been answered thoroughly and to my satisfaction. I have been informed that if I have any further questions during the course of the study, I can contact the principal investigator, who will provide answers to the best of their knowledge and ability.

I consent to the collection of my medical and study data within the framework of this clinical study, both in paper form and on electronic storage devices, in pseudonymized form (without using my name). I understand that these data will be stored for 20 years and may be used for scientific publications. If necessary, the collected data may be shared in pseudonymized (encrypted) form with scientific collaborators of UKSH. I am aware that I can withdraw this consent at any time without giving a reason, and that no disadvantages will result from this. Upon withdrawal, all collected data will be deleted upon my request, unless complete anonymization has already been performed.

I, [First Name, Last Name], born on [Date of Birth], agree to participate in the above-mentioned study.

I have received the patient information and a copy of the consent form.

**Date and Signature of Patient**: _____

**Date and Signature of Doctor**: _____