PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Automated control of mechanical ventilation during general anesthesia – study protocol of a bicentric observational study (AVAS study)
AUTHORS	Schädler, Dirk; Miestinger, Georg; Becher, Tobias; Frerichs, Inéz; Weiler, Norbert; Hörmann, Christoph

VERSION 1 - REVIEW

REVIEWER	Thomas Muders, MD, DESA University Hospital Bonn, Germany
REVIEW RETURNED	15-Nov-2016

GENERAL COMMENTS	Dr. Schaedler and co-workers present the protocol of a planed observational study. The aim of the planed study is to investigate feasibility and safety while using “smart vent control”, a system for automated control of ventilator setting during general anaesthesia. The leading centre in Kiel provides all know how to successfully run the study. The provided protocol sounds reasonable. I just have some minor comments. - Exclusion criteria: o ARDS is listed twice. If ARDS per se is an exclusion criterion, it is not meaningful to mention it in the list of organ failure combinations. o Patients with known neuro-muscular diseases have to be excluded - Monitoring of arterial blood gases: there is no need routinely use an arterial line in ASA I and II patients during upper or lower limb surgery. Although, arterial blood gas analysis seems to be useful to test safety of the automated control system. Therefor, an arterial line should be declared as non-routine in ASA I an II patients and participants have to consent to this. As an alternative, SpO2 and etCO2 should be monitored. - In all patients receiving neuro-muscular blockade relaxometry (TOF, …) should be performed to monitor neuro-muscular recovery

REVIEWER	Andreas Reske Heinrich-Braun-Hospital, Zwickau, Germany and University Hospital Leipzig, University of Leipzig, Leipzig, Germany
REVIEW RETURNED	16-Nov-2016

GENERAL COMMENTS	The authors should be complimented on designing and planning a most interesting study in the field of computer-assisted improvement of anesthesia care. I read the study protocol with great interest and do agree, in general, with the planned study protocol. Based on my own experience with similar studies, however, I have several

	comments. Some of these comments appear crucial to me and I strongly recommend to the authors to consider appropriate changes to their protocol. I also suggest to have the protocol reviewed by an expert in the field of GCP-conform evaluations of medical technology, which have recently become quite complicated because of new legal regulations, not only in Germany/Europe. I added/inserted my comments directly into the .pdf as comments to highlighted text passages (see attached .pdf file). I decided to disclose my name, I am Andreas Reske, feel free to contact me, if I can be of any help in improving the protocol for this most interesting study. Thank you very much for allowing me to review your scientific work. The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 1 – AUTHOR RESPONSE

Comments reviewer 1
C1: Exclusion criteria: ARDS is listed twice. If ARDS per se is an exclusion criterion, it is not meaningful to mention it in the list of organ failure combinations.
R1: We agree and deleted ARDS in the list of organ failures (please see page 9).
C2: Exclusion criteria: Patients with known neuro-muscular diseases have to be excluded
R2: We agree and inserted known neuro-muscular diseases as additional exclusion criterion (please see page 9).
C3: Monitoring of arterial blood gases: there is no need routinely use an arterial line in ASA I and II patients during upper or lower limb surgery. Although, arterial blood gas analysis seems to be useful to test safety of the automated control system. Therefore, an arterial line should be declared as non-routine in ASA I and II patients and participants have to consent to this. As an alternative, SpO2 and etCO2 should be monitored.
R3: The management of an arterial blood gas analysis, the insertion of an arterial line aa well as the insertion of a gastric tube are at the discretion of the physician in charge and will not be influenced by the study protocol. To clarify this, we changed the word “routine” into “if clinically indicated” (please see page 11 and 12).
C4: In all patients receiving neuro-muscular blockade relaxometry (TOF, …) should be performed to monitor neuro-muscular recovery
R4: We agree and inserted TOF monitoring into the protocol (please see page 12).
Comments reviewer 2
C5 (page 2 line 34): General anesthesia alone, or combined with regional anesthesia techniques for postoperative pain management? If general anesthesia will be combined with regional anesthesia in some patients, this needs to be listed as a confounder (secondary outcome) because respiratory drive depends significantly on the pain level, which varies with regional +/- general anesthesia.
R5: We will not include patients receiving a combination of general and regional anesthesia. We therefore changed the first inclusion criterion. It reads now (please see page 2 and page 9):
• “Elective surgery of the upper limb, lower limb or peripheral vascular surgery in general anesthesia (without any additional regional anesthesia technique)”
C6 (page 2 line 36): In my opinion, the device chosen for securing the airway should be a secondary endpoint, too. This parameter may significantly influence your other endpoints.
R6: The choice of the artificial airway is at the discretion of the physician in charge. It will not be influenced by the study protocol or by the investigated study device. Therefore, we would prefer not to include the used artificial airway as the secondary endpoint. However, the used artificial airway will be documented (please see page 14, last paragraph) and this information will be available.
C7 (page 2 line 43): In line 16, you use "assisted ventilation". For the sake of clarity and straightforward definition of study outcomes, I recommend using consistent

nomenclature/terminology.
R7: We agree and use now the term “assisted ventilation” consistently. Please note that the term “augmented ventilation” is part of the Smart Ventilation Control user interface.
C8: (page 2, line 52): You mentioned etCO2 as secondary endpoint already 2 lines above. You list (too) many respiratory variables as separate secondary endpoints. Would it be possible to combine them to obtain a properly defined multiple outcome?
R8: We agree that many respiratory variables are planned to be analyzed as secondary endpoints. The reason why is that the investigated device is mainly a ventilation controller. Specifically, the endtidal partial pressure of CO2 will be analyzed in two different ways. Firstly, as a composite endpoint “proportion of time within the target zones for tidal volume and PetCO2 as individually set by the user for each patient” and, secondly, we plan to analyze the frequency distribution of the endtidal partial pressure of CO2.
C9: (page 2, line 52): Why did you choose only the "most extreme" complication in the early post-anesthesia period? What about desaturation below, for example, 90%? You could also record the saturation per se, or other indicators of atelectasis, and of course, requirement of supplemental oxygen or noninvasive ventilation or CPAP in the PACU.
R9: Oxygenation is not monitored and inspired fraction of oxygen as well as positive endexpiratory pressure are not controlled by the investigated system. However, we will record peripheral saturation of oxygen. We inserted the following sentence into the methods section (please see page 7 last paragraph):
“Inspired fraction of oxygen and positive endexpiratory pressure are not controlled automatically.”
The study period ends with the initiation of the patients’ transfer from the operation room to the recovery room. Therefore, we are not able to monitor complications occurring in the postanesthesia care unit.
C10 (page 3, line 3): The abstract has an "ethics" subheading, however, no information is provided in the abstract, that approval by an ethics committee was indeed already obtained.
R10: We agree and inserted the following sentence in the paragraph “Ethics and Dissemenination”(please see page first paragraph):
“The study was approved by the Ethics Committee of both participating study sites.”
C11: (page 3, line 8): You need to define "acceptable" here.
R11: We define “acceptable” in the revised text on page 16 in the last paragraph where it reads:
“In case that safety and efficacy are acceptable (i.e. the study was not stopped per the early termination rule) in this study, a randomized controlled trial comparing SVC with the usual practice may be warranted.”
C12: (page 4, line 4): I recommend to elaborate more on the introduction to the context of your interesting study (true background) and to move issues related to your methodology to the pertinent section of the paper.
R12: We moved the description of the system into the methods section and rewrote the whole introduction section.
C13 (page 4, line 7): I wouldn't say "commonly applied" here, "have been introduced" probably reflects reality better.
R13: We performed the changes as requested.
C14 (page 4, line 44): "can be customized"?
R14: We performed the changes as suggested.
C15 (page 5, line 5): How do you define "sufficient"? In clinical routine anesthesia, recurring spontaneous breathing activity is usually "very ineffective", i.e. low respiratory rates, small tidal volumes and elevated etCO2. Still, your system should switch to assisted ventilation. Can you please elaborate on this?
R15: Sufficient means that PetCO2 is classified as mild hypoventilation. In the manuscript it reads now (please see page 8, first paragraph):
“In case that “encourage spontaneous breathing” is activated SVC will automatically change the ventilator mode from controlled mechanical ventilation (pressure controlled ventilation, PCV) to

assisted ventilation (pressure support ventilation, PSV) if PetCO2 is classified as mild hypoventilation."
C16 (page 6, line 6): Please provide details regarding this screening procedure. Will all eligible patients be screened consecutively, by selected physicians or all physicians who happen to work in the office for preanesthesia visits?
R16: The study team (study nurses and study physicians) will screen consecutively for eligible patients the day before surgery. We changed the text in the section "Patient screening" as follows (please see page 8 last paragraph):
"The study team (study nurses and study physicians) will screen consecutively for eligible patients the day before surgery. Possible study candidates will be informed about the study in detail and asked to give consent for study participation.
C17 (page 6, line 19): "planned elective" is a pleonasm
R17: We agree and deleted "planned".
C18 (page 6, line 21): Please refer to my comment in the abstract, would be the combination of regional and general anesthesia techniques be an exclusion criterion?
R18: We will not include patients receiving a combination of general and regional anesthesia and changed the first inclusion criterion accordingly. Please see also R5.
C19 (page 6, line 36): What about respiratory diseases such as pneumonia, atelectasis, prior lung surgery, etc. and previous or ongoing drug abuse?
R19: We will include patients with pneumonia, atelectasis, or prior lung surgery as long as they do not meet ARDS criteria. Patients with previous or ongoing drug abuse will also be included because we do not expect any problems with the use of SVC in these patients.
C20 (page 6, line 50): It is hard to imagine a situation in which patients suffering from acute onset of organ failures would undergo elective surgery. I recommend to use "acute organ failures" as an exclusion criterion per se.
R20: We expect that this may happen sometimes, e.g. patients scheduled for an implantation of a hip prosthesis. The use of a general exclusion criterion "acute organ failures" without providing a list of possible organ failures and without using precise criteria would be inaccurate. We agree that our list of organ failures refers to acute organ failures and we inserted the word "acute" into the exclusion criterion 4 (please see page 9 line 14).
C21 (page 6, line 53): ARDS was listed already 4 lines further up
R21: As requested, we deleted ARDS 4 lines up (please see also R1)
C22 (page 7, line 11): See my comment above, obtaining proper written informed consent in this situation is impossible.
R22: We agree that patients with acute cerebral failure may not be able to give written informed consent for study participation. However, it may happen, that a patient gave already consent for study participation before the acute cerebral failure. As these patients may introduce study bias (e. g. expected transfer to the intensive care unit after surgery with ongoing mechanical ventilation) we would not like to delete this exclusion criterion.
C23 (page 7, line 32): These reasons, or at least typical reasons, should be pre-specified in the study protocol.
R23: It is the responsibility and the ethical duty of the study physician to override the ventilatory settings provided by SVC or even stop SVC for any safety reason. Should a list of possible reasons for overruling or stopping be defined in the study protocol, the individual decision of the study physician might be limited or influenced. Therefore, we decided not to provide such a list. We plan to categorize reasons for overriding or stopping SVC after the completion of the whole study. From our point of view this is an interesting ethical discussion and we included the following paragraph into the "Ethics and dissemination" section of the manuscript (please see page 16 last paragraph):
"Regarding the study design one may argue that a prespecified list for overruling or stopping the system may be provided to the study physicians. Such a list may prohibit inaccurate overriding or stopping of SVC. From our point of view, it is the responsibility and the ethical duty of the study physician to override the ventilatory settings provided by SVC or even stop SVC for any safety

reason. Should a list of possible reasons for overruling or stopping be defined in the study protocol, the individual decision of the study physician might be limited or influenced. Therefore, we decided not to provide such a list. We plan to categorize reasons for overriding or stopping SVC after the completion of the whole study."
C24 (page 8 line 5): assisted? I suggest using consistent terminology here.
R24: Please note that the term "augmented ventilation" is part of the SVC user interface. Therefore, we would prefer if we do not need to change it.
C25 (page 8, line 10): These opioids all differ in the way (and duration) they suppress spontaneous breathing activity. Wouldn't it be preferable to use only one substance for this study? I suggest to "standardize" the anesthetic regime by using a technique for monitoring the depth of anesthesia. You could, for example, predefine a desired range of BIS readings, acknowledging the limitations of this technology, of course.
R25: We agree that the use of a standardized anesthesia protocol using only specified drugs, BIS monitoring and detailed recommendations for drug dosing may positively influence the time period between anesthesia induction and the begin of spontaneous breathing activity. However, we are not able to use such a protocol due to the observational study design and we will not measure the above mentioned time period.
C26 (page 8, line 17): As I said above, I really think that the type of airway should be considered as an important confounder.
R26: The choice of the artificial airway is at the discretion of the physician in charge and it will not be influenced by the study protocol or by the investigated study device. Therefore, we prefer not to include the used artificial airway as the secondary endpoint.
C27 (page 8, line 30): Depending on the local practice, using a gastric tube in patients undergoing peripheral orthopedic or vascular surgery will be quite far from routine ... what is the reason for this requirement?
R27: The management of an arterial blood gas analysis, the insertion of an arterial line and the insertion of a gastric tube will not be influenced by the study protocol but according to the clinical routine. To clarify this, we changed the word "routine" into "as clinically indicated" (please see also R3). We agree that the use of a gastric tube in this specific group of patients is rare.
C28 (page 8, line 32): See previous comment. Some colleagues will have problems understanding why you consider an arterial blood gas (single puncture or catheter?) a routine intervention for uncomplicated orthopedic or vascular surgery. You should explain this to prevent others from inferring that this intervention is specific for your study. Make sure this was/is adequately addressed in your ethics application. This is a crucial point.
R28: Please see R27. We deleted the word "routine".
C29 (page 9, line 10): If you really intend to use a muscle relaxant, I consider neuromuscular monitoring ("relaxometry") obligatory, it should be recorded as secondary outcome.
R29: We agree and inserted the TOF monitoring into the protocol (please see R4).
C30 (page 9, line 10): I recommend using only one substance to reduce the number of confounders.
R30: Please see R25.
C31 (page 9, line 15): see your previous point, are you really using relaxants together with laryngeal masks?
R31: No, it is not planned to use muscle relaxants in combination with the use of a laryngeal mask. All drugs will only be used as clinically indicated (please see R25).
C32: (page 9, line 56): what action would the study protocol propose if the patients is not awake by coughing and "fighting" the tube? This is not an uncommon situation and should be addressed in the protocol.
R32: In this situation, we will wait until the patient is awake. We would prefer not to define specific recommendations for the management of the described clinical setting in the study protocol because of the observational study design.
C33 (page 10, line 21): This is impracticable, many patients require much longer periods to experience desaturation or CO2 accumulation during anesthesia ventilation. Why would this be an

AE?
R33: An apnea for longer than 90 seconds regardless whether it leads to hypoxia and/or hypercapnia should not happen during mechanical ventilation with SVC but may happen when the user deactivates SVC. The endpoints will only be analyzed during mechanical ventilation with activated SVC. We clarify this now in the section “End-point determination” where it reads now (please see page 14 line 19):
“The end-points of the study are evaluated using the recorded and protocolled data of the study team only during mechanical ventilation with activated SVC.”
C34 (page 10, line 23): how is "target" defined?
R34: We inserted the definition of the target as requested. It reads now (please see page 13 line 13):
• Hyperventilation defined as PetCO2 lower than 5 mm Hg of the lower target setting for SVC for longer than 5 minutes. The responsible anesthesiologist defines a target for the arterial partial pressure of carbon dioxide (PaCO2_target) before the induction of the general anesthesia and sets the corresponding end-tidal CO2 range in the automated ventilation system. 15 minutes after the beginning of the surgical procedure, an arterial blood gas analysis will be performed and PaCO2 will be measured.
C35 (page 10, line 43): Please refer to the comments I made re the secondary endpoints above (abstract).
R35: Please see R6, R7, R8 and R9
C36 (page 10, line 48): How is this target defined? Please specify.
R36: Please see R34.
C37 (page 11, line 50): Where will this data be stored? Will these data files include names or other information from which the patient could be identified? What about anonymization or use of pseudonyms?
R37: Data will be pseudonymized and then stored in a secured web space. We inserted this sentence in the section data recording (please see page 15 first paragraph).
C38 (page 11, line 52): How? Is the "routine" gastric tube you mention above equipped to measure esophageal pressure? If so, this should be explained in detail in the methods!
R38: Esophageal pressure measurement will only be performed if the insertion of a gastric tube is clinically indicated. Insertion of a gastric tube for decompression is part of routine clinical practice in endotracheally intubated patients. For this study, we will use a gastric tube that is additionally equipped with a balloon for measurement of esophageal pressure. We inserted a detailed description in the methods section. It reads now (please see page 10 third paragraph):
“Insertion of a tube for gastric decompression is part of our routine clinical practice in endotracheally intubated patients. For this study, we will use a gastric tube for decompression that is additionally equipped with an esophageal balloon for assessment of esophageal pressure (Nutrivent, Sidam, Mirandola, Italy).”
C39 (page 12, line 18): I have problems to understand your reasoning here. Please provide sufficient detail on how you calculated the sample size. I do not at all intend to be overcritical here, but the current description of the sample size calculation will description will in no way be accepted by reviewers of a future publication. You need to provide more detail, e.g. alpha and beta error, power, assumptions etc.
R39: To our best knowledge, a power calculation cannot be performed due to the study design (one study arm).
C40 (page 12, line 27): I hope you will not interpret my comments in an overly sensitive mindset, but everything you wrote in this paragraph should be moved to the introduction. Here, under the subheadings "ethics and dissemination", you are expected to discuss ethical issues related to your study. For example, you should discuss the justification of additional interventions performed solely for the purpose of the study, in your case I see arterial puncture/catheters and gastric tubes/esophageal pressure measurements. What benefit will enrolled patients have from participating in the study? What will be the "global" benefit for patient undergoing anesthesia.
Dissemination refers to the way you plan to publish and/or present your results to colleagues and

patients. You should comment on this.
Again, please take my comments as a help to prevent unpleasant experiences when trying to publish your results. I am indeed sharing my own experiences with you.
R40: We thank you very much for your very valuable comments. We will not perform any additional study-specific interventions (please see R3, R27, R28, R38). The possible benefits for the participating patients are described in the discussion section (please see page 16 first paragraph):
“Therefore, an automated system that supports assisted ventilation as early as possible may have beneficial effects like decreasing the frequency of pulmonary complications, the amount of anesthesia and vasoactive drugs and recovery time.”
We inserted the following details regarding the dissemination in a new last paragraph in the ethics and dissemination section (please see page 17 last paragraph):
“A three-step dissemination strategy is planned as follows: first, the study results will be presented at international anesthesia conferences; second, the study will be published in a peer-reviewed journal; third, a multicenter randomized controlled study will be designed.”
C41 (page 13, line 22): Please define criteria for "acceptable", this is crucial as you are evaluating an endpoint regarding its acceptability.
R41: Please see R11
C42 (page 20, line 17): induction of anesthesia
R42: Corrected.
C43 (page 20, line 34): when is esophageal pressure measurement performed?
R43: In patients with a gastric tube, esophageal pressure is recorded continuously until extubation. We modified the corresponding sentence in section “Data recording”. It reads now (please see page 15 line 6):
“In patients with a gastric tube, esophageal pressure swings will be recorded continuously (“fast data”) until extubation.”
C44 (page 21, line 51): All my comments above do apply also to the following text, please adapt the following text in line with the changes you decide to make to the text above.
R44: We performed all the changes in the manuscript and the study protocol as well.