PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Influence of videolaryngoscopy using McGrath Mac™ on the need for a helper to perform intubation during general anaesthesia: A multicentre randomised Video - No-Video trial
AUTHORS	Belze, Olivier; Coppere, Zoé; Ouattara, Jonathan; Thion, Laurie-Anne; Paqueron, Xavier; Devys, Jean-Michel; Ma, Sabrina; Kennel, Titouan; Fischler, Marc; Le Guen, Morgan

VERSION 1 – REVIEW

REVIEWER	Komasawa, Nobuyasu Osaka Medical College, Department of Anesthesiology
REVIEW RETURNED	18-Mar-2021

GENERAL COMMENTS	Thank you for giving me chance to read this interesting manuscript. The theme is very important and I sincerely appreciate their effort. I only have two suggestions to improve your work. 1, Please describe the definition 'assist' more clearly. Maybe this is the first study for assistance. 2, Please describe the comparison with other videolarygnscopes more clearly. Maybe, the MaCGRATH form strongly contribute to the result.

REVIEWER	Noppens, Ruediger Western University, Dept. of Anesthesia & Perioperative Medicine
REVIEW RETURNED	23-Mar-2021

GENERAL COMMENTS	Congratulations on this excellent trial.

REVIEWER	Kriege, Marc Johannes Gutenberg Univ Mainz, Anaesthesiology
REVIEW RETURNED	28-Mar-2021

GENERAL COMMENTS	Thank you for submitting your manuscript to BMJ Open and give me the opportunity to review this manuscript. The incidence on the need for help to perform videolaryngoscopy in elective surgery patients in the operating room is very important and relevant for future Guidelines and Recommendations in airway management. General comments: 1. The study includes anaesthesiologists and nurse anesthetists in the operating room. The participating physicians and nurses were experienced in orotracheal intubation. The means? Please

	describe the experience in airway management and address why the experience at least ten intubation with the McGrath Mac were sufficient for this study (reference?). Furthermore, were the intubation attempts performed through both or only by anaesthesiologists? 2. Your main outcome was the need for help. In my opinion that's a subjective outcome parameter by the discretion of the individual performing intubation and to perform atraumatic intubation. Do you characterize this point as the need for help by reduced glottis visualization or more than one laryngoscopic attempt? 3. The intubation sequence was recorded and reviewed by both anaesthesiologists. But they were not blinded, because the reviewer could detect if video or non video intubation were used. In the video group the physician look on the screen and performed a indirect visualization of the glottic, on the other group with a inactivated screen the physician must performed a direct visualization on the glottic and archive an alignment of the oro-pharyngeal-laryngeal axis. In my opinion that's a bias of the study and the evaluator was not blinded. Please address this point. 4. Do you limited the intubation attempts (e.g., time limit, Removement or replacement of the laryngoscope)? In which cases occurs a change of the operator? 5. Why includes centre 3 only 18 patents? Your primary sample size/ plan was to include 300 patients. Why you haven't recruited the excluded patients to reach the planned number of patients?

REVIEWER	Alshami, Ali Imam Abdulrahman Bin Faisal University
REVIEW RETURNED	06-May-2021

GENERAL COMMENTS	Statistical methods and analysis The authors adequately reported the statistical methods used. However, the authors need to name the continuous and categorical data. In addition, it is highly recommended to mention a statement about intention-to-treat analysis ("… analysis is done as if each subject received the treatment or control condition as planned"). 1) Outcomes (Item 6a) The authors measured more than 10 outcomes. This may increase the risk of type I error. Further details about the primary outcome measure are needed. a) what the primary outcome is (usually the one used in the sample size calculation), The primary outcome was the need for help in performing tracheal intubation (i.e., the proportion of orotracheal intubations where assistance is necessary upon request of the operator). b) how it was measured (if relevant; e.g. which score used), The method of how to measure the primary outcome (need for assistance) was not clear. c) at what time point, Not clear for most outcome measures. d) what the analysis metric was (e.g. change from baseline, final value)?

	Not clear for most outcome measures, especially where they are presented in Table 2. The unit of measurement is missing for most variables. 2) Sample size (Item 7a) Is there a clear description of how the sample size was determined, including a) the estimated outcomes in each group; 131 patients in each group. b) the α (type I) error level; 5% c) the statistical power (or the β (type II) error level); 80% d) for continuous outcomes, the standard deviation of the measurements? The primary outcome was the need for help in performing tracheal intubation (i.e., the proportion of orotracheal intubations where assistance is necessary upon request of the operator). However, the authors used the values of Intubation Difficulty Scale from a previous study to calculate the sample size. 3) Sequence generation (Item 8a) Method used to generate random allocation sequence. Does the description make it clear if the “assigned intervention is determined by a chance process and cannot be predicted”? Not clear. 4) Allocation concealment (Item 9) Is it clear how the care provider enrolling participants was made ignorant of the next assignment in the sequence (different from blinding)? Possible methods can rely on centralised or “third-party” assignment (i.e., use of a central telephone randomisation system, automated assignment system, sealed containers). The authors used a software used to allocate the patients to their group. 5) Blinding (Item 11a) a) healthcare providers, The two anaesthesiologists, who analysed the videos, were blinded to the study group b) patients, Not blinded. c) outcome assessors are blinded to the intervention? Not blinded. 6) Outcomes and estimation (Item 17a/b) Is the estimated effect size and its precision (such as standard deviation or 95% confidence intervals) for each treatment arm reported? When the primary outcome is binary, both the relative effect (risk ratio, relative risk) or odds ratio) and the absolute effect (risk difference) should be reported with confidence intervals. Descriptive data, 95% CI, p-values for the primary and secondary outcome measures for each group are presented in Table 2. 7) Harms (Items 19) Is the number of affected persons in each group, the severity grade (if relevant) and the absolute risk (e.g. frequency of incidence) reported? Are the number of serious, life threatening

	events and deaths reported? If no adverse event occurred this should be clearly stated. The reported that “no other adverse event occurred.” 8) Registration (Item 23) Is the registry and the registration number reported? If the trial was not registered, it should be explained why. Clinicaltrials.gov identifier: NCT02926144. I recommend adding whether the trial was registered retrospectively or prospectively. 9) Protocol (Item 24) Is it stated where the trial protocol can be assessed (e.g. published, supplementary file, repository, directly from author, confidential and therefore not available)? The authors reported in the CONSORT form, but not in the manuscript, that the trial protocol can be accessed on request. The authors reported in the manuscript that “dataset is available from the Dryad repository (DOI: 10.5061/dryad.280gb5mp6).” 10) Funding (Item 25) Are (1) the funding sources, and (2) the role of the funder(s) described? “This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.”

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comment 1. Please describe the definition 'assist' more clearly. Maybe this is the first study for assistance.
Response to Comment 1. This point is important. Our wish was twofold:
- to carry out a study under real-life conditions. These conditions vary from country to country and from institution to institution, with either a single person (anaesthetist or nurse anaesthetist) or a doctor and nurse anaesthetist pair. We have clearly defined that our study was done under our usual operating conditions. To be clearer, we have added the word "our" to the first sentence (Page 6/56, line 46): ”This randomised multicentre study done in our real-life conditions …”
- to assess if technological progress has practical consequences in the management of patients without a predicted difficult intubation. Therefore, we had the possibility to conduct a study using a usual primary objective such as intubation time or number of attempts. But gaining a few seconds is of little interest and the number of attempts is rarely different from 1 in this population. It seemed more interesting to see how the introduction of videolaryngoscopy in this population, the most usual one of course, can modify the work ergonomics of the anaesthesia team.
The reviewer raises the question of how to define the need for assistance. Our sentence (“Asking for help from the other member of the anaesthetic team was at the discretion of the individual performing intubation if they deemed it necessary to perform an atraumatic intubation”) seemed clear enough to us. In fact, the request for assistance is made when the person intubating considers that intubation is likely to be traumatic for the teeth and difficult because the vision of the glottis is not considered satisfactory. We have added the notion of ease to the request for assistance (Page 9/56, line 37): “Asking for help from the other member of the anaesthetic team was at the discretion of the individual performing intubation if they deemed it necessary to perform an easy and atraumatic intubation”. In addition, we have added this question to the limits of the study (Page 17/56, line 52): "Another major

point is that we used the need for assistance from a member of the anaesthetic team as the primary outcome. This choice is not usual, but it seemed to us more interesting than the time to successful tracheal intubation or the number of attempts, outcomes that have little interest in a population without risk of difficult intubation. On the other hand, we felt it was important to evaluate the possible benefit of a new technology on the ergonomics of the work of anaesthesiologists. However, one of the limitations of our primary outcome is its personal nature and we could have been more specific in the need for assistance and possibly create a score combining for example force exerted and POGO."

Comment 2. Please describe the comparison with other videolaryngoscopes more clearly. Maybe, the MaCGRATH form strongly contribute to the result.
Response to Comment 2. We agree with this comment and the initial text mentioned: “We chose this device since it requires limited training because of its similarity to the Macintosh laryngoscope with, especially, a similar blade.” Further on in the text we wrote: “Consequently, our results cannot be generalised to other videolaryngoscopes which differ by the shape of the blade, and the existence or not of a channel.” This sentence has been modified to respond to the Reviewer's comment (Page 17/56, Line 26): “Consequently, our results could be valid for other videolaryngoscopes having a blade-shape like the Macintosh laryngoscope (C-MAC or APA for example), but not acutely angled videolaryngoscopes (McGrath and GlideScope for example) or with an integrated channel videolaryngoscope (KingVision, AWS-S200, and Airtraq).”

Reviewer: 2
No comment.

Reviewer: 3
General comments:
General comment 1. The study includes anaesthesiologists and nurse anesthetists in the operating room. The participating physicians and nurses were experienced in orotracheal intubation. The means? Please describe the experience in airway management and address why the experience at least ten intubation with the McGrath Mac were sufficient for this study (reference?). Furthermore, were the intubation attempts performed through both or only by anaesthesiologists?
Response to General comment 1. Our text was awkward because all anaesthesiologists and nurse anaesthetists are experienced in orotracheal intubation !!! We wanted to say that there were no novices. We have modified the text to be clearer. As written in the text, laryngoscopy was performed by the anaesthesiologist or the nurse anaesthetist; we have changed the term “laryngoscopy” to “intubation” to avoid confusion. Lastly, the Learning curve is steep especially if practitioners are staff anaesthetists or nurse anaesthetists (Savoldelli et al. Learning curves of the Glidescope, the McGrath and the Airtraq laryngoscopes: a manikin study." Eur J Anaesthesiol 26(7): 554-558).
The following changes have been made:
- Page 8/56, line 43: “Patients received care during the induction and intubation periods from an anaesthesiologist and a nurse anaesthetist as is usual in the hospitals where the protocol took place. All anaesthesiologists and nurse anaesthetists had performed at least ten intubations with the McGrath Mac Videolaryngoscope. This experience seems sufficient since the learning curve is steep especially among this population12 especially since the professionals received specific training pertaining to the study procedures prior to the beginning of the trial including the fact that they must rely on the video screen in the Video group and use the direct view in the No-Video group.”
- Page 9/56, line 19: “Intubation was performed by the anaesthesiologist or the nurse anaesthetist using the device allocated at random when bispectral index was under 60 and when there was no muscle response to the train of four stimulation.”

General comment 3. The intubation sequence was recorded and reviewed by both anaesthesiologists. But they were not blinded, because the reviewer could detect if video or non video intubation were used. In the video group the physician look on the screen and performed a indirect

visualization of the glottic, on the other group with a inactivated screen the physician must performed a direct visualization on the glottic and archive an alignment of the oro-pharyngeal-laryngeal axis. In my opinion that's a bias of the study and the evaluator was not blinded. Please address this point.
Response to General comment 3. It is written in the text (Data collection section): “all cases were video recorded by a person not involved in the study which followed a mandatory script. This person, placed at the feet of the patient, was unable to see whether the screen of the videolaryngoscope was activated.”. Consequently, it is difficult to know whether the person intubating is looking at the screen or not. However, it is indeed possible that the judgement of the persons who was watching the video was flawed because they saw or thought they saw whether the video function was on or off. This point is added in the limits of the study (Page 18/56, line 8): “We sought to have this primary outcome assessed blind to the randomisation arm. As noted, the person recording the video sequence was positioned at the foot of the patient, making it impossible to see if there was an opaque cover on the videolaryngoscope screen. It is possible, however, that the persons who was watching the video could see, or thought they could see, if the video function was being used.”

General comment 4. Do you limited the intubation attempts (e.g., time limit, Removement or replacement of the laryngoscope)? In which cases occurs a change of the operator?
Response to General comment 4. The protocol did not limit number of intubation attempts, nor time to intubate or number of alternative techniques. This is now included in the revised version (Page 9/56, line 55): “Number of intubation attempts, time to intubate or number of alternative techniques were not limited by the protocol.”
We have recorded the number of “participants” and not the change of the first operator. We chose this because we assumed that the participants had almost identical skills.

General comment 5. Why includes centre 3 only 18 patients? Your primary sample size/ plan was to include 300 patients. Why you haven't recruited the excluded patients to reach the planned number of patients?
Response to General comment 5. First, centre 3 gave its approval to participate in the study but, in fact, their anaesthesiologists used mostly laryngeal masks. This explains the low number of included patients. As the randomisation scheme was balanced 1:1 and stratified by centre, our methodologist considered this to be acceptable.
Secondly, our protocol did not plan the replacement of missing patients since we took a margin of 38 patients as stated in the initial text: “Presuming that the video function would decrease this proportion to 12.5 %, with type 1 error set at 5 % and power set at 80 %, 131 patients were needed in each group (i.e., 262 patients in total). We planned to recruit 300 patients to mitigate an attrition of the sample or the absence of values.”

Reviewer: 4
General comment on Statistical methods and analysis: The authors adequately reported the statistical methods used. However, the authors need to name the continuous and categorical data. In addition, it is highly recommended to mention a statement about intention-to-treat analysis (“... analysis is done as if each subject received the treatment or control condition as planned”).
Response to General comment on Statistical methods and analysis: It seems to us that the answer to the first part of this comment would make the text more cumbersome. Therefore, we propose to add a supplementary file with the classification of the intubation variables (continuous or categorical) and the timeline of their measurements:
- Page 10/56, Line 46: “Timeline of measurement of each variable is summarised in a Supplementary Table.”
- Page 12/56, Line 20: “The types of all variables, categorical or continuous, are summarised in a Supplementary Table.”

On the other hand, we have modified the text to respond to the second part of this comment (Page 12/56, Line 8): “Statistical analysis was conducted using the principle of the intention-to-treat analysis.”

1) Comment on Outcomes (Item 6a):
The authors measured more than 10 outcomes. This may increase the risk of type I error. Further details about the primary outcome measure are needed.
a) what the primary outcome is (usually the one used in the sample size calculation), The primary outcome was the need for help in performing tracheal intubation (i.e., the proportion of orotracheal intubations where assistance is necessary upon request of the operator).
b) how it was measured (if relevant; e.g. which score used),
The method of how to measure the primary outcome (need for assistance) was not clear.
c) at what time point,
Not clear for most outcome measures.
d) what the analysis metric was (e.g. change from baseline, final value)?
Not clear for most outcome measures, especially where they are presented in Table 2.
The unit of measurement is missing for most variables.
Response to Comment on Outcomes (Item 6a):
Firstly, we agree with the Reviewer’s comment on the risk of type I error due to multiple comparisons, but we think that this concerns only the calculation of the p values for the Intubation Difficulty Scale (which is now p=0.05) and for its parameters since the other comparisons are independent. Consequently:
- we have modified the Statistical analysis section (Page 12/56, Line 23): “Bonferroni correction was used to correct p values of the comparison between groups of the Intubation Difficulty Scale and of its parameters.”
- we have modified the p values for the main outcome in the Abstract and in the results section (Page 13/56, Line 19): “Requirement for assistance was not decreased in the Video group (36.1% [95% CI 27.9-44.9] versus 45.5% [95%CI 36.5-54.7] in the No-Video group, p=0.74 after Bonferroni correction; Odds Ratio: 0.7 [0.4-1.1] and Absolute Risk: 0.10 [-0.03-0.22]. Requirement for assistance was similar between groups when considering each centre separately (p=0.99).”
- since recommendations for authors mention that “we recommend your article does not exceed 4000 words, with up to five figures and tables. This is flexible but exceeding this will impact upon the paper’s ‘readability’”, we have taken the opportunity to separate Table 2 into two Tables: Table 2 which reports the Intubation variables and a new Table 3, which reports the parameters used to calculate the Intubation Difficulty Scale (with P values calculated after Bonferroni correction). We believe that this presentation of the results will make them easier to read by also addressing the Reviewer's Note. The numbers of Tables 3 and 4 (initial version) have been changed in the revised version.
a) the primary outcome was adequately reported in the initial version.
b) the method of how to measure the primary outcome (need for assistance) has been better defined in the revised version (Page 10/56, line 54): “The primary outcome, the proportion of orotracheal intubations where assistance was necessary upon request of the operator, is obtained from the video of the intubation sequence.”
c) it seems to us that the answer to this part of the comment will make the text more cumbersome. Therefore, we propose to add a supplementary line with the classification of the intubation variables (continuous or categorical) and the timeline of their measure. We could introduce this data in the text if the Editor wishes.
In addition, we have deleted the last sentence of the chapter “Data collection” to avoid duplication.
d) Table 1 refers to patient characteristics (title not changed in the revised version), Table 2 refers to intubation variables (title changed in the revised version: “Intubation variables (final values)”, Table 3 refers to Bispectral index, heart rate and arterial pressure measurements (title changed in the revised version: “Bispectral index, heart rate and arterial pressure measurements (change from baseline and

from preintubation period)", Table 4 to Intra- and postoperative complications (title not changed in the revised version). When necessary, units of measurement have been added in the revised version as requested.
In fact, as we have a new Table 3 (Parameters of the Intubation Difficulty Scale) to allow separation of the Intubation Difficulty Scale parameters from other variables describing intubation (making the use of the Bonferrroni correction easier to understand for the reader), the former Table 3 becomes Table 4, former Table 4 (Bispectral index, heart rate and arterial pressure measurements) becomes Table 5, and the former Table 5 (Intra- and postoperative complications) becomes Table 6. Table numbering has been changed in the revised version.

2) Comment on Sample size (Item 7a):
Is there a clear description of how the sample size was determined, including
a) the estimated outcomes in each group;
131 patients in each group.
b) the α (type I) error level;
5%
c) the statistical power (or the β (type II) error level);
80%
d) for continuous outcomes, the standard deviation of the measurements?
The primary outcome was the need for help in performing tracheal intubation (i.e., the proportion of orotracheal intubations where assistance is necessary upon request of the operator). However, the authors used the values of Intubation Difficulty Scale from a previous study to calculate the sample size.
Response to Comment on Sample size (Item 7a): The point is well taken. However, the text mentions the frequency of the use of an external laryngeal pressure as reported by Adnet et al. in their 2011 paper. This manoeuvre, the first and most frequent action performed when intubation appears difficult, requires the need for assistance. However, to be in line with the Reviewer's comment, we have modified the sentence to avoid any confusion (Page 11/56, Line 41): "The number of patients to be included took into consideration the frequency with which external laryngeal pressure is used. Adnet et al. published in 2001 a survey of tracheal intubation difficulty among 1171 surgical patients and found that the Intubation Difficulty Scale was > 0 in 522 cases (45%) and that external laryngeal pressure, requiring an assistant to help, was used in 271 of these cases (23% of all patients).20 Based on this data, the expected rate for the assistance of another person for intubation was 25 % for patients in the No-Video group. Presuming that the video function would decrease this proportion to 12.5 %, with type 1 error set at 5 % and power set at 80 %, 131 patients were needed in each group (i.e., 262 patients total). We planned to recruit 300 patients to mitigate an attrition of the sample or the absence of values."

3) Comment on Sequence generation (Item 8a): Method used to generate random allocation sequence. Does the description make it clear if the "assigned intervention is determined by a chance process and cannot be predicted"? Not clear.
Response to Comment on Sequence generation (Item 8a): We disagree with this comment for three reasons:
- The sequence generation item was: "Centralised randomisation using fixed-size blocks had been performed by an independent biostatistician not involved in the trial. The randomisation scheme was balanced 1:1 and stratified by centre."
- Randomisation was performed just before anaesthesia: "Once in the operating room, inclusion criteria were confirmed by the anaesthesiologist in charge and randomisation was managed online."
- Several people participated in the study in each centre.
These three elements make it impossible to predict assigned intervention.

4) Comment on Allocation concealment (Item 9):

Is it clear how the care provider enrolling participants was made ignorant of the next assignment in the sequence (different from blinding)? Possible methods can rely on centralised or "third-party" assignment (i.e., use of a central telephone randomisation system, automated assignment system, sealed containers). The authors used a software used to allocate the patients to their group.
Response to Comment on Allocation concealment (Item 9): Our text was correct regarding this item.

5) Comment on Blinding (Item 11a):
a) healthcare providers,
The two anaesthesiologists, who analysed the videos, were blinded to the study group
b) patients,
Not blinded.
c) outcome assessors are blinded to the intervention?
Not blinded.
Response to Comment on Blinding (Item 11a): We disagree with this comment as:
- patients are blinded since the intervention occurred when they were asleep.
- outcome assessors were blinded to the intervention since all cases were video recorded by a person not involved in the study which followed a mandatory script. This person, placed at the feet of the patient, was unable to see whether the screen of the videolaryngoscope was activated. Consequently, the outcomes assessors, who reviewed the video, could not see if the person intubating was looking at the screen or not. Reviewer 3 questioned the blindness of their reading. It is indeed possible that the reviewers' judgement was flawed because they saw or thought they saw whether the video function was on or off. This point is added in the limits of the study (Page 18/56, line 8): "We sought to have this primary outcome assessed blind to the randomisation arm. As noted, the person recording the video sequence was positioned at the foot of the patient, making it impossible to see if there was an opaque cover on the videolaryngoscope screen. It is possible, however, that the persons who was watching the video could see, or thought they could see, if the video function was being used."

6) Comment on Outcomes and estimation (Item 17a/b): Is the estimated effect size and its precision (such as standard deviation or 95% confidence intervals) for each treatment arm reported? When the primary outcome is binary, both the relative effect (risk ratio, relative risk) or odds ratio) and the absolute effect (risk difference) should be reported with confidence intervals. Descriptive data, 95% CI, p-values for the primary and secondary outcome measures for each group are presented in Table 2.
Response to Outcomes and estimation (Item 17a/b):
We have added the absolute effect (risk difference) in the revised text (Page 13/56, line 19):
"Requirement for assistance was not decreased in the Video group (36.1% [95% CI 27.9-44.9] versus 45.5% [95%CI 36.5-54.7] in the No-Video group, p=0.74 after Bonferroni correction; Odds Ratio: 0.7 [0.4-1.1] and Absolute Risk: 0.10 [-0.03-0.22]."
7) Comment on Harms (Items 19): Is the number of affected persons in each group, the severity grade (if relevant) and the absolute risk (e.g. frequency of incidence) reported? Are the number of serious, life threatening events and deaths reported? If no adverse event occurred this should be clearly stated. The reported that "no other adverse event occurred."
Response to Comment on Harms (Items 19): We have modified the Abstract and the last sentence of the Results section (Page 14/56, line 8): "No serious adverse event occurred".

8) Comment on Registration (Item 23): Is the registry and the registration number reported? If the trial was not registered, it should be explained why. Clinicaltrials.gov identifier: NCT02926144. I recommend adding whether the trial was registered retrospectively or prospectively.
Response to Comment on Registration (Item 23): The protocol has been registered with the competent authorities under the N° ID-RCP 2013-A01307-38 and on the Clinicaltrials.gov before inclusion of the first patient. The revised text is as follows (Page 7/56 and line 19): "The complete protocol, registered with the competent authorities under the N° ID-RCP 2013-A01307-38, can be

obtained on request." On the other hand, the original text mentioned that the first inclusion was performed after registration on the Clinicaltrials.gov web site: "After approval by the Ethics Committee … and by the French Regulatory Office, and after registration on the web site ClinicalTrials.gov (NCT02926144, first Posted on October 6, 2016), patients were enrolled in the study after they gave their written informed consent including videorecording and blurring of patients' faces if necessary."

9) Comment on Protocol (Item 24): Is it stated where the trial protocol can be assessed (e.g., published, supplementary file, repository, directly from author, confidential and therefore not available)?
The authors reported in the CONSORT form, but not in the manuscript, that the trial protocol can be accessed on request. The authors reported in the manuscript that "dataset is available from the Dryad repository (DOI: 10.5061/dryad.280gb5mp6)."
Response to Comment on Protocol (Item 24): The text has been revised to respond to this item (Page 7/56, line 19): "The complete protocol, registered with the competent authorities under the N° ID-RCP 2013-A01307-38, can be obtained on request from the corresponding author."

10) Comment on Funding (Item 25): Are (1) the funding sources, and (2) the role of the funder(s) described?
"This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors."
Response to Comment on Funding (Item 25): Our text was correct regarding this item.

VERSION 2 – REVIEW

REVIEWER	Kriege, Marc Johannes Gutenberg Univ Mainz, Anaesthesiology
REVIEW RETURNED	26-Jun-2021

GENERAL COMMENTS	The reviewer thanks the authors for their responds