PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of endotracheal tube plus STYLET versus endotracheal tube alone on successful first-attempt tracheal intubation among critically ill patients: The multicenter randomised STYLETO study protocol
AUTHORS	Jaber, S.; ROLLE, Amélie; Jung, Boris; Chanques, Gerald; Bertet, Helena; Galeazzi, David; Chauveton, Claire; MOLINARI, Nicolas; DE JONG, Audrey

VERSION 1 – REVIEW

REVIEWER	Brian Driver MD Hennepin County Medical Center, Minneapolis, MN, USA
REVIEW RETURNED	27-Jan-2020

GENERAL COMMENTS	The authors have submitted a study protocol for an ongoing multi-center trial of ICU patients in France, comparing first attempt intubation success between use of an endotracheal tube plus stylet to an endotracheal tube alone. The study question is sound and the protocol is well-written. I note that the trial began in October, which limits the ability to recommend any substantive changes to the trial. I have the following comments: INTRODUCTION The introduction might want to frame the existing evidence comparing styletted tubes compared to unstyeltted tubes, citing the primary literature to provide some evidence of what we already know about this study question. Reference 12 is a great guideline, but I think the readers would appreciate primary literature. The stylet allows the intubator to pre-shape the tube, which may be helpful. The stylet also provides additional rigidity to the tube which may aid in tube passage, which may be worth noting in the introduction. Page 7, first paragraph: Citing reference 10, it is said that "...has assessed the effect of adding a stylet in case of difficult intubation in prehospital setting." The study (ref 10) examined the bougie in the Emergency Department, which is slightly different than an endotracheal tube with stylet in the prehospital setting. OUTCOMES Page 8-9, Main secondary outcome: I appreciate the investigation into complications associated with use of either intervention. However, the composite outcome does seem too broad, including too many potential complications.

	-While a delay in intubation might lead to severe hypoxemia, any correlation between either of the study arms with cardiovascular collapse, cardiac arrest not due to hypoxemia, and death during intubation not due to hypoxemia seems more tenuous. -The moderate complications of arrhythmia requiring intervention and agitation likewise seem to have an unclear association with study interventions. It would be helpful if difficult intubation and pulmonary aspiration were defined. -If at all possible, I suggest removing those variables that are not clearly tied to the intervention and instead present them as exploratory outcomes. INTERVENTIONS With respect, I believe a great limitation of this study is the sole use of direct laryngoscopy without use of video laryngoscopy. As mentioned in the Discussion (page 21), this was decided to avoid confounding (presumably, because video laryngoscopy results in higher first pass success). I understand that the trial is already ongoing and this is not likely to be changed, but it will be a significant limitation to the study since the results will be difficult to generalize to video laryngoscopy, which is becoming the dominant method of intubation in the emergency department and intensive care unit. Page 10, second paragraph through the end of the page: It's hard for me to tell if this list of interventions is mandated by the study, or just recommended for study participants. Can you clarify? SAMPLE SIZE An explanation for why 10% was chosen as the clinically significant difference in first pass success between groups would be helpful. I understand that there is no established clinically important difference that has been established in the literature. That said, it would be nice to hear the rationale for selecting 10% in this case. DISCUSSION Page 20: As mentioned above, the stylet adds rigidity to the tube (along with the ability to pre-shape the tube), which may be another reason success would be higher. The sentence beginning at the end of page 20 and going to page 21: "If combined use….its use could become standard practice worldwide." With respect, I think this may be too broad of a conclusion. I think a reasonable conclusion might be something like "If this trial demonstrates superiority of the endotracheal tube with stylet, intubation without a stylet might decrease significantly worldwide." I think this conclusion is more straightforward since a single-center study demonstrated higher first attempt success with a bougie compared to a styletted endotracheal tube, and a multi-center study is ongoing that may demonstrate superiority of the bougie over the endotracheal tube with stylet in a variety of settings (or may not). Page 21: "We chose not to allow videolaryngoscopy for the first attempt of intubation…" As mentioned briefly above, it seems that the confounding mentioned here refers to the fact that video laryngoscopy often results in higher first attempt success, which is desirable for patients. Video laryngoscopy is becoming the dominant intubation method in the ICU and the emergency

	department in many parts of the wordl, and I worry that strict use of direct laryngoscopy will limit the generalizability of these results. I understand the trial is ongoing now and this will not be able to be changed, but a more robust discussion of why the study was limited to DL would be worthwhile.

REVIEWER	Jann Foster Western Sydney University Australia
REVIEW RETURNED	03-Feb-2020

GENERAL COMMENTS	I appreciate the opportunity to review the protocol submitted by Samir Jaber and colleagues where they outline their study comparing stylet to endotracheal alone. The lack of research on this topic was surprising, and this is an important and clinically relevant study. This is a pragmatic trial examining the question whether the use of a stylet would increase successful first-attempt tracheal intubation among critically ill patients. The background, methods, proposed analysis and discussion are well-written and appropriate. All ethical considerations are addressed. The authors are experienced researchers in the area of endotracheal intubation, and have a track record performing high-quality trials. I await the results of the study with interest.

REVIEWER	Todd Rice Vanderbilt University Medical Center United States of America
REVIEW RETURNED	06-Feb-2020

GENERAL COMMENTS	This is a study protocol manuscript for the STYLETO study protocol investigating the effect of adding a stylet to endotracheal tubes during emergenct tracheal intubation in critically ill patients. My comments are as follows: 1) Inclusion/Exclusion criteria - given the descriptions in the rest of the manuscript that patients must be intubated with direct laryngoscopy (and in fact a Macintosh direct laryngoscopy blade), shouldn't this be included in the inclusion/exclusion criteria? Like exclusion criterion is patient planned to be intubated with videolaryngoscopy or Miller (straight) direct laryngoscopy blade? 2) Page 8 - Primary Outcome paragraph - some discussion/description of why successful first attempt endotracheal intubation has been chosen as the primary outcome would be beneficial. There is a brief discussion in the discussion section, but it really simply states this has been used in previous studies of tracheal intubation. However, are there other reasons? Do the authors think this is what stylet is most likely to affect? Is time to successful intubation important or just overall success rate? 3) Page 8 - Primary Outcome paragraph- how is first pass success defined in patients who do not have end-tidal exhaled carbon dioxide (like if the patient suffers a cardiac arrest during the intubation - since intubations in patients already experiencing a cardiac arrest are excluded)? 4) It is interesting that potential complications of the stylet, are not included in the main secondary composite outcome of incidence of complications related to tracheal intubation in the hour following intubation. While I understand these might also reflect safety endpoints, I would think they would be counted as complication of tracheal intubation.

	5) Exploratory Outcomes - how will new infiltrate, pneumothorax, or pneumomediastinum on chest imaging be determined? Will these be based on a radiologist read, adjudication by investigators, etc? 6) Given the recent publication demonstrating reduction in hypoxemia when bag-mask ventilation is delivered between induction and laryngoscopy, will this be part of the routine intubation procedures? It is not described as part of the intubation procedure on page 10 of the submission. 7) Page 12 - nature and number of operators and their training is listed as being recorded during the four hours before intubation. Shouldn't this be recorded immediately after intubation so if rescue operators are needed the data will reflect who actually performed the procedure? 8) Delay between the time where the intubation is decided and its realization is listed as a data point for collection. How will the time intubation is decided be determined? 9) Page 15 - in the pre-specified subgroups to evaluate for effect modification, neuromuscular blocking agent is listed - with one of the options being none. Is this possible in this trial given the intubation protocol that is outlined in detail on page 10? 10) Page 20, 7th-9th line of the third paragraph - this sentence is very awkward and difficult to understand. 11) In the concluding paragraph, the qualifier that this trial will only give the effect of adding stylet to endotracheal tube for tracheal intubation in critically ill patients intubated using a MacIntosh direct laryngoscopy blade. It will not directly inform on the effect if videolaryngoscopy or non-MacIntosh direct blade is utilized. 12) Figure 2 - should the complications that might be directly related to the Stylet use (i.e. mucosal bleeding, laryngeal, tracheal, mediastinal, oesophageal injury, etc) be reflected in the figure?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
The authors have submitted a study protocol for an ongoing multi-center trial of ICU patients in France, comparing first attempt intubation success between use of an endotracheal tube plus stylet to an endotracheal tube alone. The study question is sound and the protocol is well-written. I note that the trial began in October, which limits the ability to recommend any substantive changes to the trial.

I have the following comments:

We thank the reviewer for its careful reading and its valuable comments.

Question 1. INTRODUCTION
The introduction might want to frame the existing evidence comparing styletted tubes compared to unstyeltted tubes, citing the primary literature to provide some evidence of what we already know about this study question. Reference 12 is a great guideline, but I think the readers would appreciate

primary literature. The stylet allows the intubator to pre-shape the tube, which may be helpful. The stylet also provides additional rigidity to the tube which may aid in tube passage, which may be worth noting in the introduction.
Page 7, first paragraph: Citing reference 10, it is said that "...has assessed the effect of adding a stylet in case of difficult intubation in prehospital setting." The study (ref 10) examined the bougie in the Emergency Department, which is slightly different than an endotracheal tube with stylet in the prehospital setting.

Response 1. We agree with the reviewer's comment. We pointed out the potential advantages of using a stylet as suggested by the reviewer, corrected the misleading sentence about reference 10 and searched for primary literature regarding the operating room setting. However, no randomized controlled trial about stylet use was found, only case reports or use of a stylet with special devices.

Following the reviewer's recommendations, we modified the introduction accordingly as follows (Page 4): "The stylet is a rigid but malleable introducer which fits inside the endotracheal tube and allows for manipulation of the tube shape; usually into a hockey stick shape, to facilitate passage of the tube through the laryngeal inlet. The stylet also provides additional rigidity to the tube which may aid in tube passage. The stylet can help to increase success of intubation in operating rooms, although the available literature is poor.
However, some complications from intubating stylets have been reported including mucosal bleeding, perforation of the trachea or oesophagus, and sore throat. In 2018, one study has ~~assessed the effect of adding a stylet in case of difficult intubation in prehospital setting~~ compared the use of a bougie to the use of the endotracheal tube plus stylet in the emergency department. However, in ICU, the systematic use of a stylet is still debated and recent recommendations do not recommend to use or not to use such devices for first-attempt intubation."

Question 2. OUTCOMES
Page 8-9, Main secondary outcome: I appreciate the investigation into complications associated with use of either intervention. However, the composite outcome does seem too broad, including too many potential complications.
-While a delay in intubation might lead to severe hypoxemia, any correlation between either of the study arms with cardiovascular collapse, cardiac arrest not due to hypoxemia, and death during intubation not due to hypoxemia seems more tenuous.
-The moderate complications of arrhythmia requiring intervention and agitation likewise seem to have an unclear association with study interventions. It would be helpful if difficult intubation and pulmonary aspiration were defined.
-If at all possible, I suggest removing those variables that are not clearly tied to the intervention and instead present them as exploratory outcomes.

Response 2. We understand the reviewer's concerns regarding the main secondary outcome. However, it is a well recognized outcome in all the studies performed by our group, and we decided to keep it as it as a secondary outcome to be consistent with previous randomized controlled trials (De Jong et al., ICM 2016;Baillard et al, BJA 2018, Baillard et al., AJRCCM 2006) and observational studies (Jaber et al., ICM 2010, Jaber et al, CCM 2006, De Jong et al, AJRCCM 2013).

The protocol was accepted by our ethics committee and the study is now ongoing with inclusion of patients started. We regret that we cannot modify anymore this main secondary outcome. However, a separate analysis of the components of this secondary outcome is planned (Page 7, exploratory outcomes paragraph).

Question 3. INTERVENTIONS
With respect, I believe a great limitation of this study is the sole use of direct laryngoscopy without use of video laryngoscopy. As mentioned in the Discussion (page 21), this was decided to avoid confounding (presumably, because video laryngoscopy results in higher first pass success). I understand that the trial is already ongoing and this is not likely to be changed, but it will be a significant limitation to the study since the results will be difficult to generalize to video laryngoscopy, which is becoming the dominant method of intubation in the emergency department and intensive care unit.

Response 3. We understand the reviewer's comment and had the same concerns regarding this limitation of the study. However, we have recent data in France (data just published, Martin et al., Ann Intensive Care 2020), showing the results of an online nationwide survey in 180 French ICUs: "The OTI method used for the first attempt in patients with a difficult or unremarkable airway was Macintosh laryngoscopy alone in 150/180 (83.3%) ICUs; a stylet or bougie with Macintosh laryngoscopy in 16 (8.9%) and 6 (3.3%) ICUs, respectively; a videolaryngoscope in 6 (3.3%) ICUs; and a videolaryngoscope with a stylet in 2 (1.1%) ICUs."

Therefore, only 3% of ICUs in France do use a videolaryngoscope for first-intubation attempt. We added this important justification in the discussion section as follows (Page 19): "We chose not to allow videolaryngoscopy for the first-attempt of intubation, to avoid confounding factors regarding the association between stylet use and first-attempt success. Besides, according to recent data showing the results of an online nationwide survey in 180 French ICUs, the videolaryngoscopy was used for the first attempt in only 8 (4%) ICUs. Therefore, the external validity of our study will be higher focusing on Macintosh direct laryngoscopy for first-attempt success. "

Question 4. Page 10, second paragraph through the end of the page: It's hard for me to tell if this list of interventions is mandated by the study, or just recommended for study participants. Can you clarify?

Response 4. We totally agree with the reviewer. The Montpellier Intubation protocol is a suggestion for physician, however as it is a pragmatic study it is not mandatory. The sentence was modified as follows (Page 8): "The Montpellier intubation protocol will be strongly advised to be followed for each procedure."

Question 5. SAMPLE SIZE
An explanation for why 10% was chosen as the clinically significant difference in first pass success between groups would be helpful. I understand that there is no established clinically important difference that has been established in the literature. That said, it would be nice to hear the rationale for selecting 10% in this case.

Response 5. We agree with the reviewer, an explanation for the choice of this threshold of 10% is needed. We wanted to show a clinical important difference between the two methods used and considered that 10% will be a significant improvement. Moreover, it was very close to the difference of 9% taken by Driver and colleagues or the difference of 15% taken into account by Lascarrou and colleagues. This was added in the methods section as follows (Page 9): "The primary outcome is the first-attempt success during intubation procedure. For this study, 2 × 485 patients are needed to detect a 10% difference in the first-attempt success rate during intubation procedure (from 70% without stylet to 80% with stylet, difference judged clinically important), at a two-sided α level of 0.05 and a statistical power of 95%."

Question 6. DISCUSSION
Page 20: As mentioned above, the stylet adds rigidity to the tube (along with the ability to pre-shape the tube), which may be another reason success would be higher.

Response 6. We agree with the reviewer's comment and modified the discussion as suggested (Page 18): "Use of a stylet allows to pre-shape the endotracheal tube, adds rigidity to the endotracheal tube and could help to improve the ability to catheterize the trachea."

Question 7. The sentence beginning at the end of page 20 and going to page 21: "If combined use….its use could become standard practice worldwide." With respect, I think this may be too broad of a conclusion. I think a reasonable conclusion might be something like "If this trial demonstrates superiority of the endotracheal tube with stylet, intubation without a stylet might decrease significantly worldwide." I think this conclusion is more straightforward since a single-center study demonstrated higher first attempt success with a bougie compared to a styletted endotracheal tube, and a multi-center study is ongoing that may demonstrate superiority of the bougie over the endotracheal tube with stylet in a variety of settings (or may not).

Response 7. We entirely agree with the reviewer's comment and deleted the misleading sentence. The discussion was modified as follows (Page 19): "~~If combined use of endotracheal tube plus stylet facilitates tracheal intubation of ICU patients compared to endotracheal tube alone, its use could become standard practice worldwide.~~ If this trial demonstrates superiority of the endotracheal tube with stylet, intubation without a stylet might decrease significantly worldwide."

Question 8. Page 21: "We chose not to allow videolaryngoscopy for the first attempt of intubation…" As mentioned briefly above, it seems that the confounding mentioned here refers to the fact that video laryngoscopy often results in higher first attempt success, which is desirable for patients. Video laryngoscopy is becoming the dominant intubation method in the ICU and the emergency department in many parts of the wordl, and I worry that strict use of direct laryngoscopy will limit the generalizability of these results. I understand the trial is ongoing now and this will not be able to be changed, but a more robust discussion of why the study was limited to DL would be worthwhile.

Response 8. We understand the reviewer's concerns and modified the discussion as follows (Page 19): "We chose not to allow videolaryngoscopy for the first-attempt of intubation, to avoid confounding factors regarding the association between stylet use and first-attempt success. Besides, according to recent data showing the results of an online nationwide survey in 180 French ICUs, the videolaryngoscopy was used for the first attempt in only 8 (4%) ICUs. Therefore, the external validity of our study will be higher focusing on Macintosh direct laryngoscopy for first-attempt success."

Reviewer: 2
I appreciate the opportunity to review the protocol submitted by Samir Jaber and colleagues where they outline their study comparing stylet to endotracheal alone. The lack of research on this topic was surprising, and this is an important and clinically relevant study. This is a pragmatic trial examining the question whether the use of a stylet would increase successful first-attempt tracheal intubation among critically ill patients.
The background, methods, proposed analysis and discussion are well-written and appropriate. All ethical considerations are addressed. The authors are experienced researchers in the area of endotracheal intubation, and have a track record performing high-quality trials. I await the results of the study with interest.

We really thank the reviewer for these positive comments.

Reviewer: 3
Question 1. This is a study protocol manuscript for the STYLETO study protocol investigating the effect of adding a stylet to endotracheal tubes during emergenct tracheal intubation in critically ill patients. My comments are as follows:
1) Inclusion/Exclusion criteria - given the descriptions in the rest of the manuscript that patients must be intubated with direct laryngoscopy (and in fact a Macintosh direct laryngoscopy blade), shouldn't this be included in the inclusion/exclusion criteria? Like exclusion criterion is patient planned to be intubated with videolaryngoscopy or Miller (straight) direct laryngoscopy blade?

Response 1. We understand the reviewer's comment. However, the intubation with a Macintosh laryngoscope is part of the procedure used in the protocol, after having taken into account the inclusion and exclusion criteria. To our knowledge, there is no formal indication of using a videolaryngoscope for intubation a priori in critically ill patients.

Question 2. Page 8 - Primary Outcome paragraph - some discussion/description of why successful first attempt endotracheal intubation has been chosen as the primary outcome would be beneficial. There is a brief discussion in the discussion section, but it really simply states this has been used in previous studies of tracheal intubation. However, are there other reasons? Do the

authors think this is what stylet is most likely to affect? Is time to successful intubation important or just overall success rate?

Response 2. We understand the reviewer's comment and followed his suggestion as follows: The criterion "first-attempt intubation success" was chosen because directly related to the potential benefits of using a stylet and associated with complications related to intubation. The time to successful intubation is also important but was less likely to be affected by the use of a stylet. This is now pointed out in the discussion section as follows (Page 18-19): "The criterion "first-attempt intubation success" was chosen because directly related to the potential benefits of using a stylet and associated with complications related to intubation. In a large, multicenter database retrospective analysis of complications related to 1844 intubation in the ICU, we recently reported that first-attempt success was associated with fewer complications related to intubation than first-attempt failure. The time to successful intubation is also important but was less likely to be affected by the use of a stylet."

Question 3. Page 8 - Primary Outcome paragraph- how is first pass success defined in patients who do not have end-tidal exhaled carbon dioxide (like if the patient suffers a cardiac arrest during the intubation - since intubations in patients already experiencing a cardiac arrest are excluded)?

Response 3. We really thank the reviewer for this very interesting comment. In case of absence of end-tidal exhaled carbon dioxide (dysfunction or cardiac arrest during intubation), the first-attempt success was defined using pulmonary auscultation: Auscultation for bilateral breath sounds and absence of stomach inflation. This is now pointed out in the methods section as follows (Page 6-7): "Primary outcome variable is the proportion of patients with successful first-attempt endotracheal intubation, which is defined based on a normal-appearing waveform of the partial pressure of end-tidal exhaled carbon dioxide curve over 4 or more breathing cycles. In case of absence of end-tidal exhaled carbon dioxide (dysfunction or cardiac arrest during intubation), the first-attempt success was defined using pulmonary auscultation: Auscultation for bilateral breath sounds and absence of stomach inflation."

Question 4. It is interesting that potential complications of the stylet, are not included in the main secondary composite outcome of incidence of complications related to tracheal intubation in the hour following intubation. While I understand these might also reflect safety endpoints, I would think they would be counted as complication of tracheal intubation.

Response 4. We understand the reviewer's concerns, also raised by another reviewer. However, the main secondary outcome is a well recognized outcome in all the studies performed by our group, and we decided to keep it as it as a secondary outcome to be consistent with previous randomized controlled trials (De Jong et al., ICM 2016;Baillard et al, BJA 2018, Baillard et al., AJRCCM 2006) and observational studies (Jaber et al., ICM 2010, Jaber et al, CCM 2006, De Jong et al, AJRCCM 2013).

The protocol was accepted by our ethics committee and the study is now ongoing with inclusion of patients started. We regret that we cannot modify anymore this main secondary outcome. However, a full analysis of the complications of the stylet will be performed (safety analysis).

Question 5. Exploratory Outcomes - how will new infiltrate, pneumothorax, or pneumomediastinum on chest imaging be determined? Will these be based on a radiologist read, adjudication by investigators, etc?

Response 5. We thank the reviewer for raising this important point. New infiltrate, pneumothorax, or pneumomediastinum on chest imaging will be determined by the referent local ICU investigator. This is now pointed out in the methods section as follows (Page 8): “The other exploratory procedural and safety outcomes will be the incidence of lowest SpO2 less than 90% from induction to 2 minutes after intubation; change in SpO2 from SpO2 at induction to lowest SpO2; desaturation, defined as a change in SpO2 of more than 3% from induction to 2 minutes after intubation; Cormack-Lehane grade of glottic view; operator-assessed difficulty of intubation; need for additional airway equipment or a second operator; number of laryngoscopy attempts; lowest SpO2, highest FiO2, and highest PEEP from 0-1 hours and 1-6 hours after intubation; new infiltrate on chest imaging in the 48 hours after intubation; new pneumothorax on chest imaging in the 24 hours after intubation, new pneumomediastinum on chest imaging in the 24 hours after intubation. New infiltrate, pneumothorax, or pneumomediastinum on chest imaging will be determined by the referent local ICU investigator “

Question 6. Given the recent publication demonstrating reduction in hypoxemia when bag-mask ventilation is delivered between induction and laryngoscopy, will this be part of the routine intubation procedures? It is not described as part of the intubation procedure on page 10 of the submission.

Response 6. We thank the reviewer for this very interesting comment. The protocol advised was the Montpellier intubation protocol, that does not recommend bag-valve mask ventilation between induction and laryngoscopy, only in case of desaturation (Page 9): “During the procedure, after preoxygenation, the patient will be ventilated in case of desaturation to less than 90 %.” We think that more studies are needed to validate the systematic application of such a procedure. However, the protocol was only “ strongly advised”, and we modified this part as follows (Page 8): “The Montpellier intubation protocol will be strongly advised to be followed for each procedure.”

Question 7. Page 12 - nature and number of operators and their training is listed as being recorded during the four hours before intubation. Shouldn't this be recorded immediately after intubation so if rescue operators are needed the data will reflect who actually performed the procedure?

Response 7. We totally agree with the reviewer’s comment and moved the “nature and number of operators” to the part “after intubation” as follows (Page 11): “After the intubation procedure (until one hour after): arterial blood gases with calculated PaO2/FiO2 ratio if performed at 5-min and 30-min and ventilatory settings will be recorded. Moderate and severe complications occurring and nature,

number of operators, and their training, will be collected."

Question 8. Delay between the time where the intubation is decided and its realization is listed as a data point for collection. How will the time intubation is decided be determined?

Response 8. We thank the reviewer for this comment. The time where the intubation is decided is determined by the moment the physician choose to perform intubation procedure. It is a marker of the emergency of the procedure: real emergency (endotracheal intubation required without delay), relative emergency (endotracheal intubation required within one hour), deffered emergency (endotracheal intubation required in more than one hour), as defined for the first time in the paper from Jaber et al., CCM 2006. This is now pointed out in the methods section as follows (Page 11): "The following parameters will be recorded during the four hours before intubation: ~~nature and number of operators, and their training,~~ arterial pressure and lowest saturation, arterial blood gases with calculated arterial oxygen tension to FiO2 ratio (PaO2/FiO2) ratio if performed, delay between the time where the intubation is decided and its realization (defining real emergency (endotracheal intubation required without delay), relative emergency (endotracheal intubation required within one hour), deffered emergency (endotracheal intubation required in more than one hour)), presence of vasopressor drugs, prior noninvasive ventilation or high-flow nasal cannula oxygen use, existence of predictive criteria of difficult intubation evaluated by the MACOCHA score."

Question 9. Page 15 - in the pre-specified subgroups to evaluate for effect modification, neuromuscular blocking agent is listed - with one of the options being none. Is this possible in this trial given the intubation protocol that is outlined in detail on page 10?

Response 9. We thank again the reviewer for his careful reading. Yes, it is possible, because the protocol is "strongly advised", as pointed out now, and not mandatory. As it is a pragmatic study, we could not make the protocol mandatory for centers that would apply a different protocol. However, we wanted to guide the procedure as much as possible. We modified that in the methods section as follows (Page 8): "The Montpellier intubation protocol will be strongly advised to be followed for each procedure."

Question 10. Page 20, 7th-9th line of the third paragraph - this sentence is very awkward and difficult to understand.

Response 10. The awkward sentence was (Page 18): "The ability to succeed first-attempt intubation is of critical importance to prevent the development of subsequent complications, which can lead to intubation-related cardiac arrest." And was changed to "The first-attempt success is of paramount importance in preventing the development of subsequent complications including intubation-related cardiac arrest."

Question 11. In the concluding paragraph, the qualifier that this trial will only give the effect of adding stylet to endotracheal tube for tracheal intubation in critically ill patients intubated using a MacIntosh direct laryngoscopy blade. It will not directly inform on the effect if videolaryngoscopy or non-MacIntosh direct blade is utilized.

Response 11. We totally agree with the reviewer's comment and modified the conclusion as follows (Page 19): "In conclusion, the STYLETO trial is an investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that adding a stylet to the endotracheal tube in comparison to the endotracheal tube alone allows to increase first-attempt success and decrease intubation-related complications during the intubation procedure using a Macintosh direct laryngoscopy blade of ICU patients requiring mechanical ventilation."

Question 12. Figure 2 - should the complications that might be directly related to the Stylet use (i.e. mucosal bleeding, laryngeal, tracheal, mediastinal, oesophageal injury, etc) be reflected in the figure?

Response 12. We thank again the reviewer for his very careful reading and modified the figure including the complications that might be directly related to the Stylet use.

VERSION 2 – REVIEW

REVIEWER	Brian Driver Hennepin County Medical Center, Minneapolis, MN, USA
REVIEW RETURNED	13-Apr-2020

GENERAL COMMENTS	The authors have submitted this protocol as a revision of the previously submitted protocol. This multi-center randomized trial will compare first attempt success when a styletted tube is used versus a non-styletted tube. I have reviewed the revised protocol and they have addressed all of my prior comments. While I think that widespread use of video laryngoscopy is inevitable, it makes sense that they are studying direct laryngoscopy since this is how the majority of ICU intubations are performed in France. This will hurt generalizability outside of France, but will enable good generalization in the study country. When the final trial manuscript is published, it should be noted that the secondary outcomes include measures that may not correlate with first attempt success and hence may not be due to study interventions, including cardiovascular collapse, cardiac arrest not due to hypoxemia, and death during intubation, as well as the moderate complications of arrhythmia requiring intervention and agitation. Differences between groups for cardiovascular collapse and death during intubation would only be due to differences in first attempt success of great magnitude, seems unlikely.

	Thank you for the opportunity to review this trial protocol.