PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	BOugie or stylet in patients UnderGoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan for a randomized clinical trial
AUTHORS	Driver, Brian; Semler, Matthew; Self, Wesley; Ginde, Adit; Gandotra, Sheetal; Trent, Stacy; Smith, Lane; Gaillard, John; Page, David; Whitson, Micah; Vonderhaar, Derek; Joffe, AM; West, Jason; Hughes, Christopher; Landsperger, Janna; Howell, Michelle; Russell, Derek; Gulati, Swati; Bentov, Itay; Mitchell, Steven; Latimer, Andrew; Doerschug, Kevin; Koppurapu, Vikas; Gibbs, Kevin; Wang, Li; Lindsell, Christopher; Janz, David; Rice, Todd; Prekker, Matthew; Casey, Jonathan

VERSION 1 – REVIEW

REVIEWER	Daniel Fein Yeshiva University Albert Einstein College of Medicine, Medicine
REVIEW RETURNED	04-Jan-2021

GENERAL COMMENTS	For both the emergency medicine and critical care communities, the BEAM trial was practice changing, despite the fact that it was a single center study and done in an emergency room setting alone. The authors have put together an exciting protocol for a now much anticipated new study. The authors should be applauded for taking on this same clinical question from the BEAM trial and substantially broadening the population and institutions involved. Commensurate with the experience of the investigators, the study question is sound and the methods are well thought out. I look forward to the results of this investigative work.

REVIEWER	Annery Garcia-Marcinkiewicz Children's Hospital of Philadelphia Pediatrics Residency Program
REVIEW RETURNED	15-Jan-2021

GENERAL COMMENTS	The Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE) multicenter trial is a very interesting study aiming to address an important question- whether a bougie or stylet can improve first-attempt tracheal intubation success rate during emergent intubations in the ED or ICU setting. The authors are to be applauded for setting up this multicenter study, the results of which can significantly contribute to improving patient safety. As described by the authors, this is a pragmatic trial, which has several advantages. However, there are a few components of the study methods that can lead to significant confounding regarding whether it is truly the use of a bougie or stylet that improves first-attempt tracheal intubation success. I will mention these below and provide my suggestions:

	1. The planned laryngoscopy device. The authors mention that the planned laryngoscopy device will be a non-hyperangulated laryngoscope blade. It is great that the authors are standardizing the blade type (in this case non-hyperangulated) in order not to introduce the variability that can occur when both hyperangulated and non-hyperangulated blades are used. We know that hyperangulated blades require a different technique. However, as I understand from the methods described, the planned laryngoscopy device may be direct laryngoscopy or indirect laryngoscopy (use of a video-screen). This introduces significant variability and observed differences in first-attempt success might be due to whether direct laryngoscopy vs video-laryngoscopy is used and may have nothing to do with whether a bougie or stylet is used. There are several large clinical trials comparing direct versus video laryngoscopy for this very outcome (first-attempt success) and we know that a difference in first -attempt success rates exists between the two devices. One suggestion is to standardize the type of laryngoscopy not just to non-hyperangulated blades but to video laryngoscopy. This will help eliminate the possibility that it is the device itself (video vs. direct) that is leading to the improvement in first-attempt success. 2. Sedative used for induction. Need to provide more clarification here. Aside from patients who are unresponsive who might not receive any medications prior to the intubation, are all others to receive neuromuscular blocking drugs? If so, what kind? Will all receive rocuronium? Will some receive succinylcholine (shorter acting), will some not receive neuromuscular blocking drugs? Although the pragmatic approach has many advantages, if you truly want to answer the question of whether it is the bougie or stylet improving first-attempt success, you need to make sure that intubation conditions are as optimized as possible (and similar) in both groups. 3. Approach to pre-oxygenation at the discretion of the treating clinician. As above. Particularly is difference in hypoxemia is going to be compared in both groups as a secondary outcome, it will be important as much as possible to protocolize the duration of pre-oxygenation when ever possible (even if pre-oxygenation is delivered through different interfaces prior to the intubation (nasal cannula, face mask, etc.). 4. Patient position- Understandably, these are emergent intubations and there may not be sufficient time in some cases to optimize patient position, however, whenever possible this should be protocolized as well, as we know optimal patient position will improve intubation success rates. Overall, interesting study question, and generally good approach. I would recommend considering the above points to strengthen the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
For both the emergency medicine and critical care communities, the BEAM trial was practice changing, despite the fact that it was a single center study and done in an emergency room setting alone. The authors have put together an exciting protocol for a now much anticipated new study. The authors should be applauded for taking on this same clinical question from the BEAM trial and substantially broadening the population and institutions involved. Commensurate with the experience

of the investigators, the study question is sound and the methods are well thought out. I look forward to the results of this investigative work.

Thank you for these comments. We, too, look forward to leveraging the strengths of a pragmatic, multicenter trial to address the limitations of the BEAM trial and advance the field of emergency airway management.

Reviewer #2

1. The planned laryngoscopy device. The authors mention that the planned laryngoscopy device will be a non-hyperangulated laryngoscope blade. It is great that the authors are standardizing the blade type (in this case non-hyperangulated) in order not to introduce the variability that can occur when both hyperangulated and non-hyperangulated blades are used. We know that hyperangulated blades require a different technique. However, as I understand from the methods described, the planned laryngoscopy device may be direct laryngoscopy or indirect laryngoscopy (use of a video-screen). This introduces significant variability and observed differences in first-attempt success might be due to whether direct laryngoscopy vs video-laryngoscopy is used and may have nothing to do with whether a bougie or stylet is used. There are several large clinical trials comparing direct versus video laryngoscopy for this very outcome (first-attempt success) and we know that a difference in first -attempt success rates exists between the two devices. One suggestion is to standardize the type of laryngoscopy not just to non-hyperangulated blades but to video laryngoscopy. This will help eliminate the possibility that it is the device itself (video vs. direct) that is leading to the improvement in first-attempt success.

Thank you very much for this suggestion. We agree that there is substantial practice variation in the performance of endotracheal intubation, including laryngoscope availability, selection, and use. In this trial protocol, we intentionally take a pragmatic approach to our study question with the goal of maximizing the generalizability of trial results.

However, several steps are planned to mitigate confounding as it pertains to video versus direct laryngoscopy. First, we mandate that operators declare the device they plan to use for the first tracheal intubation attempt (direct laryngoscope vs video laryngoscope) before the randomization assignment is known. This is addressed in the Randomization and Treatment Allocation section (first paragraph, page 9). This ensures that the use of direct vs video laryngoscopy will not be different between the bougie and endotracheal tube with stylet groups, which otherwise could be a source of confounding, as the reviewer has noted. Second, we will collect the laryngoscope used on the first attempt and whether the operator used the video screen or intubated via direct line-of-sight. We will monitor these variables at regular intervals during patient enrollment to ensure that randomization distributes them evenly between groups and that the laryngoscope utilized on the first intubation attempt matches the device the operator had indicated before study randomization. Third, we will perform analysis of effect modification addressing the question of whether the choice between direct and video laryngoscope modified the effect of bougie vs endotracheal tube with stylet on the outcome of first-pass success (see Effect Modification section, paragraph 2, page 17).

By 1) capturing data on laryngoscope use, 2) ensuring that the distribution of devices is balanced between groups (and not influenced by group assignment), and 3) pre-specifying analyses that evaluate whether or not laryngoscope type modifies the effect of a bougie, we believe this study design represents the best and most robust design to evaluate the effect of a bougie across a broad range of centers.

2. Sedative used for induction. Need to provide more clarification here. Aside from patients who are unresponsive who might not receive any medications prior to the intubation, are all others to receive neuromuscular blocking drugs? If so, what kind? Will all receive rocuronium? Will some receive succinylcholine (shorter acting), will some not receive neuromuscular blocking drugs? Although the pragmatic approach has many advantages, if you truly want to answer the question of whether it is the bougie or stylet improving first-attempt success, you need to make sure that intubation conditions are as optimized as possible (and similar) in both groups.

Thank you for these comments. The reviewer is exactly right that ensuring similarity in baseline characteristics between study groups is important to trial rigor and this includes sedatives and neuromuscular blocking drugs used to optimize intubating conditions on the first attempt. Within our network, sedative and neuromuscular blocker choice is largely governed by institutional protocols – with operators performing intubation at a given site adhering to that site's structured protocol for selecting a sedative and a neuromuscular blocking agent. To account for this in the trial design, we stratify randomization by study site – so that use of a bougie is being compared to use of a stylet among patients at a study site using the same protocol. We describe stratification by site on the bottom of page 8. In prior trials conducted by our network >97% of patients have received etomidate and rocuronium for rapid sequence intubation.

3. Approach to pre-oxygenation at the discretion of the treating clinician. As above. Particularly is difference in hypoxemia is going to be compared in both groups as a secondary outcome, it will be important as much as possible to protocolize the duration of pre-oxygenation whenever possible (even if pre-oxygenation is delivered through different interfaces prior to the intubation (nasal cannula, face mask, etc.).

We appreciate this suggestion. Study site protocols specify the minimum duration of pre-oxygenation, with some variation expected as operators tailor pre-oxygenation to the patient's physiology and the urgency of the intubation procedure. Regarding device selection, the BOUGIE trial enrolls in both Emergency Departments and Intensive Care Units, and these varied settings are likely to use a range of preoxygenation devices based on the patient population, indication for intubation, and the devices available in their setting (non-invasive ventilation and high flow nasal cannula are not readily available in some Emergency Departments). As above, stratifying randomization by study site should address the reviewer's concern (that an imbalance in preoxygenation device could bias the results), and increase generalizability of the trial results.

4. Patient position- Understandably, these are emergent intubations and there may not be sufficient time in some cases to optimize patient position, however, whenever possible this should be protocolized as well, as we know optimal patient position will improve intubation success rates.

Thank you for this suggestion. Institutional protocols and best practices at our study sites include an assessment of head and neck positioning prior to beginning laryngoscopy. We acknowledge that certain circumstances in emergency airway management, including ED cervical in-line stabilization in suspected neck trauma, may compete with standard optimal positioning of the airway. The existence of institutional protocols and stratifying randomization by site should ensure balance between groups. Further, a bougie may be determined to be most useful in cases where optimal positioning cannot be obtained (cervical spine immobilization). We are collecting data on cervical immobilization and other anatomic challenges to successful tracheal intubation to evaluate whether if modifies the effect of the bougie. As above, we believe this design choice maximizes generalizability and provides the most robust answer to the trial question.

VERSION 2 – REVIEW

REVIEWER	Annery Garcia-Marcinkiewicz Children's Hospital of Philadelphia Pediatrics Residency Program
REVIEW RETURNED	29-Mar-2021

GENERAL COMMENTS	The authors have appropriately clarified and addressed prior suggested points in this revision. I look forward to the results of the BOUGIE Trial. Best wishes to all!