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Clinical Trial Protocol

Study Title: Bougie use in Emergency Airway Management (BEAM)

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Phase: IV

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
DSMB	Data safety and monitoring board
ED	Emergency Department
ETT	Endotracheal tube
GEB	Gum-elastic bougie
HCMC	Hennepin County Medical Center
IRB	Institutional review board
ITT	Intention-to-treat
LAR	Legally-authorized representative
SAE	Serious Adverse Event

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1 INTRODUCTION

Rapid and definitive airway management is an essential skill for all emergency physicians. Orotracheal intubation is the most common means to obtain a definitive airway, and is classically performed using an endotracheal tube with an intubating sylet inserted into the tube for rigidity. The tube and stylet are passed under direct vision. Using these methods, the majority of patients in the emergency department can be successfully intubated, and therefore successfully oxygenated and ventilated.

The concept of first-pass success, that is, passing the endotracheal tube successfully on the first intubation attempt, is paramount in emergency airway management. It has been shown that for every attempt after the first, complications increase dramatically.[1] While emergency medicine has been improving airway management and first pass success over the past several years, a large cross-sectional sample demonstrated that first pass success remains approximately 85%.[2] First pass success is likely lower in the hands of less experienced operators, such as emergency medicine residents in training. Therefore, there is substantial room for improvement. A simple adjunct to endotracheal intubation, the gum elastic bougie (GEB), may increase first pass success and decrease rates of intubation-associated hypoxemia.

The GEB is a 60 or 70-centimeter stylet with an approximately 30-degree angle at its tip. When used during an intubation attempt, the GEB is passed between the vocal cords; then the endotracheal tube is passed over the GEB into the trachea. The GEB essentially serves as a flexible guide into the trachea.

It can enable successful intubation in difficult airways due to its flexible material, allowing the intubating provider to be able to direct its tip anteriorly through the vocal cords. Proper placement of the GEB can be performed by direct visualization, video assisted visualization, and also both the feeling of “clicks” as the GEB passes over tracheal rings and a “hard stop” when the GEB comes into contact with a mainstem bronchus at the level of the carina.[3,4]

1.1 Previous published literature

The first report of adjunctive GEB use in difficult endotracheal intubation was in 1949, described by Macintosh.[5] Although it did not receive much attention in the literature for many years thereafter, the late 1980’s and early 1990’s saw multiple case reports and case series describing the effectiveness of the GEB in these clinical scenarios. [3,6-8] As the GEB became more popular, several larger series were published supporting its use. One series of 2000 anesthesiology incident reports of difficult intubations concluded that the most successful airway adjunct was the

GEB.[9] Another retrospective trial found a 99% success rate when using the GEB during 301 difficult intubations over an 8-year period.[10]

Several prospective studies have also been published describing the use of the GEB in difficult airways. One prospective trial found that 199 out of 200 attempts at placing the GEB in the trachea were successful.[11] In this study, the providers elected to use the GEB due to a poor laryngeal view or failed attempts at conventional sylet intubation. Another prospective observational cross-over study described the use of the GEB in cadaveric airways.[12] The cadavers were manipulated to have either a Cormack-Lehane Grade 1 or Grade 3 view, and emergency medicine residents intubated them with either a stylet or a GEB. The authors found a trend toward increased success in the GEB group in the Grade 3 view cadavers but this result did not achieve statistical significance.

The first randomized study to assess the efficacy of the GEB was conducted in 1993.[13] This study simulated cervical spine injuries to create a difficult airway. The patients in this study had manual in-line stabilization maintained during intubation, which significantly decreased the view of the larynx. Patients were randomized to direct visualization versus intubation using a GEB. The authors found that all patients who had failed intubation in the direct visualization group were successfully intubated within 45 seconds using the GEB. Another randomized trial describing GEB use was published in 1996.[14] The authors of this study randomized patients to a GEB versus a standard stylet during direct laryngoscopy. The authors created difficult intubation scenario by simulating a Cormack-Lehane Grade 3 view with laryngoscope placement. Each group had two attempts at intubation with their randomized equipment before they could cross over. They found that the GEB group was successful 96% of the time while the stylet group was successful 66% of the time after the first two attempts, demonstrating compelling evidence for the use of the GEB in difficult airways.

Certain types of difficult airways may be more amenable to GEB-facilitated intubation. One scenario that has been well described is the difficult trauma airway, particularly those with facial and neck trauma.[13,15,16] The trauma airway provides a unique set of complications to airway control including active hemorrhage, distorted anatomy, and cervical immobility due to cervical collar use. Another scenario in which the use GEB is commonly described is in the setting of pre-hospital difficult airways.[17-20] Based on its observed success, one group reported that the GEB became part of a pre-hospital institutional algorithm for difficult airway management.[17]

Most of the evidence describing the use of the GEB has stemmed from the anesthesiology literature, with relatively little reference to its use in the emergency departments. Few studies describe emergency providers utilizing the GEB on airway task-trainers,[21] manikins,[22,23] and cadavers,[12] but all are limited by artificial airway simulations.

There are two observational trials in humans published in 2011 by the same group of authors.[24,25] These trials report data on the use of the GEB as a rescue device after failed intubation. The success rates described in these trials were 20 out of 26 (76.9%) and 70 out of 88 (79.6%) attempts, respectively. These success rates are lower that what is typically cited, but the authors identified limitations including the fact that the participants in their study were residents using the GEB for the first time, suggesting the need for education on its use prior to utilization in the emergency department.

1.2 Rationale for further investigation

Based on this review of the literature, there is evidence supporting GEB use as an adjunct for difficult airways. However, because it is not always possible to anticipate a difficult airway, or even semi-difficult airway, before an intubation attempt begins, the bougie may improve the overall success of routine intubations as well, especially for patients with any difficult airway characteristics.

However, while the GEB has significant face validity in its ability to improve intubation success, a large multi-center study demonstrated that only 3.5% of first attempts use the GEB.[2] This speaks to the possibility that increasing the use of the GEB, a simple, low-cost intervention, may improve first pass success and decrease intubation-associated complications.

The practice in the Emergency Department at Hennepin County Medical Center (HCMC), however, varies from nationwide practice in that the GEB is available for every first intubation attempt. Based on the treating physicians preference, the GEB may or may not be used on the first attempt. Thus, it is standard of care at HCMC to use *and* not use the GEB on the first attempt. We have experienced faculty members, many of whom are airway experts, who feel strongly on both sides, with some stating that it should be used uniformly, and others saying that it should be reserved for intubations that are not successful on the first attempt. Thus, there is a clinical equipoise on whether to use or not use a GEB on the first attempt.

To our knowledge there are no randomized control trials studying first pass success and peri-intubation hypoxemia with and without the use of a GEB. This proposed research study will attempt to answer the question of whether the use of the GEB is superior to non-use of the GEB in emergency department airway management.

1.3 Known risks of the interventions

While the procedure of endotracheal intubation has many inherent risks, there are no significant differences in risk between orotracheal intubation with and without a bougie.

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1.3.1 Known risks of orotracheal intubation without a bougie

Risks of orotracheal intubation without a bougie include: inability to pass the ETT and stylet past the hypopharnx through the vocal cords, and inability to slide the endotracheal tube over the stylet. There are rare case reports of breakage of the metal tip of the stylet. Patients intubated with an endotracheal tube without a bougie are at risk for airway perforation, oropharyngeal trauma, laryngeal trauma, tracheobronchial trauma, and esophageal intubation.

1.3.2 Known risks of orotracheal intubation with a bougie

Risks of orotracheal intubation with a bougie includes: inability to pass the GEB past the hypopharynx through the vocal cords, and inability to pass the endotracheal tube over the bougie [25]. There are rare mechanical complications that have been reported with the GEB, including breakage of the GEB tip,[26] and fracture of the material.[27] Major medical complications of GEB use are rare.. The reported complications of GEB use include hemopneumothorax [28], pharyngeal wall perforation,[29] traumatic bleeding within the airway,[30,31] and tracheal injury.[32] Several of these case reports describe patients with post-surgical and complex airway anatomy, and GEB use as the sole inciting mechanism for the trauma is debatable..

1.4 Proposed Study Population

Adult patients undergoing orotracheal intubation in the ED with a Macintosh blade (using either video or direct laryngoscopy) for any indication will be randomized to use of the GEB during the first intubation attempt. All other care will be at the discretion of the treating emergency physician.

2 STUDY OBJECTIVES

2.1 Primary outcome

The primary outcome of this study will be first pass success.

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First pass success is defined as placement of the endotracheal tube (ETT) into the trachea on the first attempt. An attempt begins when the laryngoscope enters the mouth, and ends if either of the following occur:

1. the laryngoscope leaves the mouth, regardless of whether an attempt was made to pass the endotracheal tube or bougie.
2. if the operator cannot intubate the trachea with the first tube device (ETT or bougie), and switches to any other tube device, even if the laryngoscope blade remains in the mouth.

A patient will be considered to achieve the primary outcome if they are intubated successfully on the first attempt.

Tracheal position of the ETT is confirmed immediately using a standard protocol involving multiple modalities (physical exam, capnography, and chest x-ray, among others).

2.2 Secondary outcomes

1) First pass success without hypoxemia. Hypoxemia is defined as a pulse oximetry value (SpO2) less than 90% at any point during intubation, or a drop of more than 10% from baseline if starting below 90%. The outcome of hypoxemia will be recorded beginning when the first attempt begins and ending one minute after inflation of the ETT cuff.

   A patient will be considered to achieve this outcome if 1) they are intubated successfully on the first attempt, *and* 2) do not experience hypoxemia on the first attempt.

2) Time to intubation (first attempt only). Time to intubation will be defined as the time elapsed between the beginning of the intubation attempt to inflation of the ETT cuff when the tube is in the trachea.

3) Esophageal intubation: defined as passage of the ETT into the esophagus, with subsequent ventilation, and then removal. Clinically, esophageal intubation is identified by the absence of end-tidal carbon dioxide, abnormal physical exam, and hypoxia. This does not count passage of the ETT into the esophagus during the attempt if the ETT is removed during the attempt.

4) Hypoxemia, as defined above.

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3 MEASUREMENT OF STUDY OUTCOMES

3.1 Measurement of primary outcome

A trained research assistant will be present in the room for all study subjects. This trained assistant will observe the intubation and record the number of attempts. The intubating physician will also be asked the number of attempts at the end of the case. In cases where there is a discrepancy between the research assistant and the intubating physician, the video for the stabilization case will be reviewed to determine the actual number of attempts.

3.2 Measurement of secondary outcomes

For secondary outcome 1): First pass success will be measured as described above. For hypoxemia, a research assistant will record the SpO2 at the beginning of the attempt and every 20 seconds thereafter, until 1 minute after inflation of the ETT cuff. The lowest SpO2 will also be recorded, even if this does not fall at a 20-second interval.

For secondary outcome 2): The research assistant will have a stopwatch and record the time to intubation, as defined in 2.2.

For secondary outcome 3): The intubating physician will fill out a data collection sheet after the intubation. This form will include whether there was an esophageal intubation, as defined in 2.2.

For secondary outcome 4):. Hypoxemia will be measured, as described above in secondary outcome 1).

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4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This Phase IV study is designed as a randomized, unblinded, two-arm study that will be conducted at a single center. The primary aim is to determine if first pass success differs by more than 9% (absolute difference) in patients who use a GEB during the first intubation attempt compared to those that do not.

4.1.1 Study Population and Randomization

Adult patients undergoing orotracheal intubation in the ED with a Macintosh blade (using either video or direct laryngoscopy) for any indication will be enrolled into the study.

If the patient meets all of the eligibility criteria, he/she will be enrolled and randomized at a 1:1 ratio to undergo intubation with or without a GEB for the first attempt. The randomization will be permuted-block with random block sizes of 2, 4, 6, 8, and 10. The randomization will be stratified into two groups: 1) those with any of the following: cervical collar, obesity (gestalt), and apparent facial or neck trauma; and 2) those with none of those characteristics. A trained research coordinator who will not be performing any data collection or chart review during the study will generate the treatment assignments.

The study allocations will be sealed in sequentially numbered opaque envelopes and stored in the critical care area. When an eligible patient is enrolled, the next sequential envelope will be opened to reveal the treatment assignment. Skipping a study number is not allowed.

4.1.2 Study Treatment and Blinding

The study will be unblinded because it is not possible to blind physicians to this study, and no sham intervention is possible.

4.2 Assessments

4.2.1 Outcome Assessments

Described in section 3

4.2.2 Safety Assessments

Any adverse events related to the use or non-use of the GEB should be observed immediately in the ED during the intubation process. If either device fails to

intubate the patient, a second attempt will be performed. The second attempt can proceed with any device or strategy that the intubating physician feels is best for the patient. Direct trauma to the mouth, upper airway, and airway are possible in both groups. Full assessment of the mouth, upper airway, and airway is not possible without exposing the patient to further harm from repeated laryngoscopy and bronchoscopy. Therefore, to assess any direct trauma, the intubating physician will be asked if there was any direct trauma to the mouth, upper airway, or airway, and if there was any excessive bleeding during or after intubation while in the ED.

4.3 Study Duration

A patient's participation in this trial will begin at enrollment, and end 1-minute after successful intubation. No further data will be collected from the patient or electronic medical record.

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5 STUDY POPULATION SELECTION

5.1 Study Population

Adult patients undergoing orotracheal intubation in the ED with a Macintosh blade (using either video or direct laryngoscopy) for any indication will be enrolled into the study. To be eligible for enrollment, the patient must meet all of the inclusion criteria and none of the exclusion criteria.

The subgroup of patients with any of the following difficult airway characteristics will be the primary analysis population, though all enrolled patients will be included in a secondary analysis. Difficult airway characteristics include: cervical immobility, obesity, large tongue, short neck, small mandible, facial or neck trauma, airway edema, blood in the airway, or vomit in the airway.

5.2 Inclusion Criteria

Patients must meet all of the following criteria to be eligible to participate in the study:

1. The patient must be undergoing orotracheal intubation in the ED with a Macintosh blade (using either video or direct laryngoscopy)
2. The patient must be presumed to be 18 years of age or older at the time of enrollment.

5.3 Exclusion Criteria

Patients who meet any of the following criteria are not eligible to participate in this study:

1. Known anatomic distortion of the upper airway or perilaryngeal structures.
2. Prisoner or under arrest
3. Known or suspected to be pregnant, based on the opinion of the treating physician.

5.4 Subject Withdrawal Criteria

As the study duration is very short, there will not be time for subject withdrawal.

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6 STUDY CONSENT

This investigation will be conducted under 45 CFR 46.116 Waiver of Informed Consent, as both devices are standard of care.

45 CFR 46.116 (d) is copied below:

> (d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
>
> (1) The research involves no more than minimal risk to the subjects;
>
> (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
>
> (3) The research could not practicably be carried out without the waiver or alteration; and
>
> (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
>
> (e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.
>
> (f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

6.1 Research involves no more than minimal risk to the subjects

The use or non-use of the GEB both are the current standard of care in the Emergency Department. The decision whether to use a GEB depends on the intubating physician's preferences and biases. The resident physicians (who perform approximately 98% of the endotracheal intubations) receive extensive training in intubating with and without a GEB, and routinely perform endotracheal intubation with and without a GEB.

Though patients requiring intubation are critically ill by definition, and have significant risk of morbidity and mortality throughout the hospital stay, this risk is imparted by the underlying illness or injury, and should not be altered more than

minimally by the use or non-use of a GEB for intubation. Because both methods are acceptable as standard of care for the first intubation attempt, there is currently no reason to think that one has any higher risk than the other; that is, there is minimal added risk to the patient beyond the risk caused by their severe illness or injury.

6.2 The waiver or alteration will not adversely affect the rights and welfare of the subjects

There is no reason this waiver of consent could adversely affect the rights nor welfare of the subjects. All subjects will receive the highest level of care provided by the HCMC Emergency Physicians. All other care is at the discretion of the treating physicians.

6.3 The research could not practicably be carried out without the waiver or alteration

Patients who require emergent endotracheal intubation in the ED are critically ill by definition. Many are obtunded or comatose; others are dyspneic and unable to talk; still others have myriad severe illnesses that preclude an involved discussion regarding the study along with its risks and benefits. For these reasons, it is not practical to obtain informed consent for this investigation for the vast majority of critically ill patients.

A patient who requires emergent endotracheal intubation has a pressing need for medical intervention that cannot be delayed for any reason. Orotracheal intubation must be completed on an emergent basis, and cannot wait for the consent of a legally authorized representative (LAR), unless the LAR is at the bedside of the patient.

Patients who are critically ill often become critically ill unexpectedly. There are a multitude of acute illnesses that occur without warning: major trauma, head trauma, stroke, spontaneous intracranial hemorrhage, sepsis, drug overdose, acute coronary syndrome, and many others. There is no reasonable method to prospectively identify individual patients likely to become eligible for participation in this clinical trial.

If only critically ill patients who *were* able to provide informed consent were included in this study, the results would not be generalizable to critically ill who could not provide informed consent, as this is a more ill cohort.

Previous randomized trials examining emergency intubation have been completed under a waiver of informed consent.[33,34]

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6.3.1 Patient objection

Because this trial involves no more than minimal risk to the patient, and because endotracheal intubation must be completed emergently, the patient will not be approached for consent. In the unlikely event the patient is able to have a reasoned conversation prior to intubation, the patient will be asked if he/she would like to decline being in a research study. If the patient declines, he/she will not be enrolled.

6.3.2 LAR or Family member objection

If a LAR or family member is at the bedside prior to endotracheal intubation, they will be asked if they object to the patient being enrolled in an emergency airway investigation. If they object, the patient will not be enrolled

6.4 Notification after enrollment

As the soonest feasible opportunity after study enrollment, the patient or the patient's LAR will be notified of the study enrollment. Details of the investigation will be provided on an information sheet with the contact information of the investigators and research office.

Because the study will have been completed 1 minute after successful intubation, it will not be possible to withdraw from the study.

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7 STUDY PROCEDURES

Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated times of the study as detailed.

7.1 Study Entrance Criteria

At baseline, each patient will be reviewed for eligibility against the study entrance criteria. Patients who do not meet the study entrance criteria will not be allowed to participate in the study. Patient eligibility according to the study inclusion and exclusion criteria will be confirmed at baseline.

7.2 Enrollment

If the patient is eligible for enrollment and neither the patient nor a LAR or family member object to enrollment, the patient will be enrolled into the study. Upon enrollment, the study allocation will be revealed and disclosed to the treating physicians.

7.3 Baseline and ED Data Collection

Baseline vital signs will be collected immediately after randomization. If time permits, the intubating physician will be asked to determine which, if any, difficult airway characteristics the patient has. This data will be recorded on a structured data collection form. Attempts at endotracheal intubation will be collected in real time. Further baseline information, and information regarding difficult airway characteristics (if not already gathered), will be obtained after the patient has left the critical care area. All data gathered is listed in Appendix 1.

7.4 Adverse Event Assessments

Any adverse events (AE) related to the use or non-use of the GEB should be observed immediately in the ED during the intubation process. If either device fails to intubate the patient, a second attempt will be performed. The second attempt can proceed with any device or strategy that the intubating physician feels is best for the patient. Direct trauma to the mouth, upper airway, and airway are possible in both groups. Full assessment of the mouth, upper airway, and airway is not possible without exposing the patient to further harm from repeated laryngoscopy and bronchoscopy. Therefore, to assess any direct trauma, the intubating physician will be asked if there was any direct trauma to the mouth, upper airway, or airway, and if there was any excessive bleeding during or after intubation while in the ED.

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7.4.1 Adverse Event Monitoring and Period of Observation

AEs will be monitored continuously while the patient is in the ED, during which any AE related to the study would be evident..

7.4.2 Reporting Serious Adverse Events

The local IRB will be notified of any related severe and unexpected, life-threatening, or fatal SAE as soon as possible, generally within 24 hours depending on the day of week. The data safety and monitoring board will also be notified as soon as possible.

7.5 Safety-Related Stopping Rules

An independent data safety and monitoring board (DSMB) will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study.

On an ongoing basis, the DSMB will review SAEs that are judge to be at least possibly related to the study. The DSMB will be notified immediately of the SAE and requested to make an assessment within five working days. Based on the DSMB's assessment of the event, as well as evaluation of the overall accumulating safety data from the trial, the DSMB will make a recommendation as to whether the study should be halted if there is a safety concern or should continue as planned.

See section 8.7.2 for possible stopping after the planned interim analysis.

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8 PLANNED STATISTICAL METHODS

8.1 General Considerations

All statistical analyses will be performed with STATA Version 12.1 (StataCorp. 2011. College Station, TX).

Unless otherwise specified, summary tabulations will be presented by treatment group. For categorical variables, the number and percentage of patients within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles with associated two-sided 95% CI, as well as percentage of censored observations.

Formal statistical hypothesis testing will be performed on the primary and key secondary outcomes, with all tests conducted at the 2-sided, 0.05 level of significance.

8.2 Sample size calculation

Assuming a first pass success rate in the GEB group of 95%, to detect an absolute difference of 9% (86% without use of GEB) with 80% power between groups, 374 patients (187 per group) with a difficult airway characteristic will need to be enrolled. Approximately 1,500 patients are intubated annually in our Emergency Department. Because of logistic considerations, we predict that only 1,000 patients will be able to be enrolled, 30-40% of whom will have a difficult airway characteristic. Therefore, we plan to enroll for 1 calendar year, or until we enroll 1,000 patients, whichever occurs first. If we have not enrolled 374 patients with a difficult airway characteristic at that time, we will discuss with the IRB about extending the timeframe of the investigation.

This sample size calculation was performed in STATA version 12.1 with the following command: sampsi 0.95 0.86, p(0.8).

8.3 Method of Assigning Study Patients to Treatment Groups

See section 4.1.1.

8.4 Population Description

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8.4.1 Analysis Populations

The intent-to-treat (ITT) population will be the primary outcome analysis population. This group will include all patients who are endotracheally intubated after randomization, excluding those intubated with a device other than a Macintosh Blade, because this group could not possibly use a bougie or endotracheal tube. Patients who have no intubation attempt performed will not be a part of the ITT population and will be considered screening failures. This will sometimes occur because emergent endotracheal intubation is planned, but the patient's condition sometimes rapidly improves, obviating the need for intubation. Because this is a patient group that is vastly different than patients who are intubated, and because they received no airway procedure, they will not be included in the ITT analysis.

The primary outcome will be analyzed for the subset of patients in the ITT population who have any difficult airway characteristic. This will be the main outcome of the investigation. The data from all enrolled patients will also be presented in the final analysis, as it is plausible that the GEB improves first pass success significantly in even routine intubations.

8.4.2 Treatment Compliance

It is anticipated there will no patient compliance issues. The actual device used for the first intubation attempt will be recorded, and the number of times this deviates from protocol will be recorded. The IRB will be notified of all protocol deviations.

8.5 Outcome Analysis

The chi square test will be used to compare the primary outcome between the two treatment groups, with the primary analysis including only those with any difficult airway characteristic, and a secondary analysis of all enrolled patients.

Secondary outcomes with categorical and continuous variables will be analyzed as the appropriate confidence interval of the difference between the two groups, again stratified by the presence of any difficult airway characteristic.

Other data will be presented descriptively.

8.6 Statistical/Analytic Issues

8.6.1 Handling of Missing Data

For the primary outcome, if both the research assistant data collection form and the treating physician post-intubation collection form are missing, the stabilization case

video will be reviewed to determine if first pass success without hypoxemia was achieved. If the video is not available, the patient will be excluded from the analysis.

Secondary outcomes: if data for these outcomes is missing, the stabilization case video will be reviewed to ascertain the true value(s). If the video is missing, the patient will be excluded from analysis of the relevant outcomes.

8.6.2 Interim Analysis and Data Monitoring

An interim analysis will be performed after 500 patients are enrolled. The data will be analyzed for the primary outcome only.

The trial will be stopped early only for futility. After the data from the first 500 patients is analyzed, a sensitivity analysis will be performed. An analysis will be performed with a sample size of 1000 patients (equal allocation in both arms) with the following assumptions:

- First pass success rate with non-use the GEB remains the same in the second half of the trial
- First pass success rate with use of the GEB is 15% higher (absolute difference, up to a success rate of 100%) than observed in the first half of the study

If no difference is found in first pass success with this analysis, then the trial will be stopped early for futility.

As detailed in section 9.2, an independent DSMB will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study. Any additional analyses for DSMB review may be scheduled at the discretion of the DSMB.

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9 ADMINISTRATIVE CONSIDERATIONS

9.1 Institutional Review Board Approval

The study will not be initiated until written IRB approval has been obtained for this investigation.

9.2 Data monitoring committee

An independent DSMB will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study. The DSMB will include Michelle Biros, MD. ***

On an ongoing basis, the DSMB will review SAEs that are judged to be at least possibly related to study drug. The DSMB may also be asked to review on an ongoing basis other SAEs of concern. The DSMB will be notified immediately of the SAE and requested to make an assessment within five working days. Based on the DSMB's assessment of the event, as well as evaluation of the overall accumulating safety data from the trial, the DSMB will make a recommendation as to whether the study should be halted if there is a safety concern or should continue as planned.

9.3 Protocol Violations/Deviations

The investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB and the appropriate regulatory authorities have given approval. Changes to the protocol will require written IRB approval opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB.

Any departures from the protocol will be fully documented as a protocol deviation. Protocol deviations will be required to be submitted to the IRB.

9.4 Premature Closure of the Study

If the investigator, DSMB, or regulatory authorities discover conditions arising during the study that indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated.

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