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| Title: | **The Videolaryngoscopy in Small Infants (VISI) Trial** |
| Short Title | VISI |
| Drug or Device Name(s): | Storz C-MAC Video Laryngoscope and Standard Direct Laryngoscope |
| eIRB Number | 17-014302 |
| Protocol Date: | February 28, 2018 Version 2.0 |
| Sponsor: | Anesthesia Patient Safety Foundation (APSF) |

Amendment 1 Date: May 3, 2018 Amendment 3 Date:

Amendment 2 Date: July 31, 2018 Amendment 4 Date:



**Study and Site Principal Investigator**
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## SITE INVESTIGATORS SIGNATURE PAGE

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|---|---|
| Protocol Title | **The Videolaryngoscopy in Small Infants (VISI) Trial** |
| Short Title | VISI |
| Lead Investigator | |
| Academic Affiliation | |
| Protocol Version | Version 2.0 |
| Version Date | July 31, 2018 |

I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Site Principal Investigator Name

Site Principal Investigator Signature

Date:

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## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
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| AE | Adverse event |
| APSF | Anesthesia Patient Safety Foundation |
| ASA | American Society of Anesthesiologists |
| CFR | Code of Federal Regulations |
| CHOP | The Children's Hospital of Philadelphia |
| CRNA | Certified Nurse Anesthetist |
| DL | Standard Direct Laryngoscopy |
| DSMB | Data Safety Monitoring Board |
| DUA | Data Use Agreement |
| EDC | Electronic Data Collection |
| FDA | Food and Drug Administration |
| HIPAA | Health Information Portability and Accountability Act |
| ICF | Informed consent form |
| MRN | Medical records number |
| OR | Operating room |
| PHI | Protected health information |
| REDCap | Research Electronic Data Capture |
| SAE | Serious Adverse Events |
| SAE | Serious adverse event |
| TI | Tracheal Intubation |
| VL | Video Laryngoscopy |
| EDC | Electronic Data Capture |

## ABSTRACT

Context:
Complications related to infant (< 1 year) airway management are under-appreciated because of few rigorous and targeted studies. We have recently shown that multiple tracheal intubation (TI) attempts are a key risk factor for intubation-related complications in small children[1]. Tracheal Intubation using Video laryngoscopy (VL) has become popular in anesthesiology practice because of several advantages over conventional direct laryngoscopy (DL). Studies show that VL improves the view of the airway compared to DL, requires fewer intubation attempts, but may take more time to intubate the trachea. Our multicenter quality improvement project of children with difficult intubations demonstrated that using VL instead of DL was associated with fewer TI attempts and fewer complications.

Objectives:

- Primary Objective
  To compare the tracheal intubation (TI) first attempt success rate using VL vs. DL in children < 12 months old.
- Secondary Objectives
  - Number of attempts for successful intubation
  - Frequency of failure to intubate with assigned device
  - Frequency of complications such as hypoxemia related to intubation with the two study devices

Study Design:
Prospective, randomized, multi-center parallel group trial

Setting/Participants:
This will be a multi-center study with a minimum of four participating centers. The target population will be children < 12 months age scheduled for elective surgery requiring general anesthesia with endotracheal intubation.

Study Interventions and Measures:
The study intervention will be a 1:1 randomization to perform tracheal intubation with the Storz C-Mac Video Videolaryngoscopy (VL) or the Standard Direct Laryngoscope (DL).

Main study outcome measures are as follows:

- The first intubation attempt success rate with each device
- The number of attempts for successful intubation with each device
- Complications associated with intubation

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **Study Title** | **The Videolaryngoscopy in Small Infants (VISI) Trial** |
| **Funder** | Anesthesia Patient Safety Foundation (APSF) |
| **Study Rationale** | Tracheal Intubation in normal infants maybe associated with complications related to multiple failed attempts. Using VL is associated with fewer failed attempts and complications in patients with difficult airways. No studies have compared the performance of VL to DL in small children with normal airways in the operating room. |
| **Study Objective(s)** | **Primary**<br>To compare the tracheal intubation (TI) first attempt success rate in children < 12 months as compared to DL vs DL<br>**Secondary**<br>• Number of attempts for successful intubation<br>• Frequency of failure to intubate with assigned device<br>• Frequency of complications such as hypoxemia related to intubation with the two study devices |
| **Test Article(s)** | Storz C-MAC Video Laryngoscope and Standard Direct Laryngoscope |
| **Study Design** | Prospective, randomized, multi-center controlled trial |
| **Subject Population key criteria for Inclusion and Exclusion:** | **Inclusion Criteria**<br>1) Males or females age 0 to <12 months.<br>2) Scheduled for non-cardiac surgery or procedure lasting longer than 30 minutes under general anesthesia where oral endotracheal intubation will be performed.<br>3) For clinician participants: anesthesia attending, or anesthesia fellow, or anesthesia resident who is willing provide baseline clinical experience information<br><br>For clinician participants:<br>1) Anesthesia attending, anesthesia fellows, or anesthesia resident<br><br>**Exclusion Criteria**<br>1) History of difficult intubation<br>2) History with abnormal airway<br>3) Predictive of difficult intubation upon physical examination |

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| | 4) Parents/guardians who, in the opinion of the investigator, may be unable to understand or give informed consent |
| **Number Of Subjects** | It is expected that approximately 650 subjects will be enrolled to produce 550 evaluable subjects. Single site enrollment will be capped at 250 subjects or 200 evaluable subjects.<br><br>It's expected approximately 500 anesthesia clinician participants will be enrolled. There is no maximal allowed participating clinicians at each site. |
| **Study Duration** | Each subject's participation will last up to 24 hours post intubation. We expect to complete the enrollment in about two years. |
| **Study Phases**<br>**Screening**<br>**Study Treatment**<br>**Follow-Up** | (1) Screening: identifying potential subjects and obtaining consent<br>(2) Intervention: randomization<br>(3) Follow-up: Chart review for intubation related adverse events up to 24 hrs Post-intubation<br><br>For clinician participants<br>(1) Screening: identifying anesthesia clinicians from the department list<br>(2) Consent: verbal consent will be obtained<br>(3) Clinical experience data will be collected<br>(4) |
| **Efficacy Evaluations** | The primary efficacy endpoint will be successful tracheal intubation |
| **Safety Evaluations** | Tracheal intubation by VL or DL are routine standard of care at each participating center. Other than randomization, there is no study intervention that will be introduced to the subjects. Subjects will be monitored per institutional standard practice. Any procedure related AEs will be treated per institutional standard practice. |
| **Statistical And Analytic Plan** | We will consider a 10% improvement in first attempt success rate for VL compared to DL to be indicative of a significant clinical effect. The statistical analysis of this change will be based on a logistic regression model where an odds ratio greater than 2.98 will be considered evidence of efficacy of VL compared to DL. The GEE method will be applied to adjust for clinician-level correlation of the outcome variable. There will be an interim analysis when 224 evaluable subjects are enrolled. The proportion of subjects that are successfully intubated at the first attempt will be compared for VL and DL using conditional logistic regression with alpha = 0.029 |

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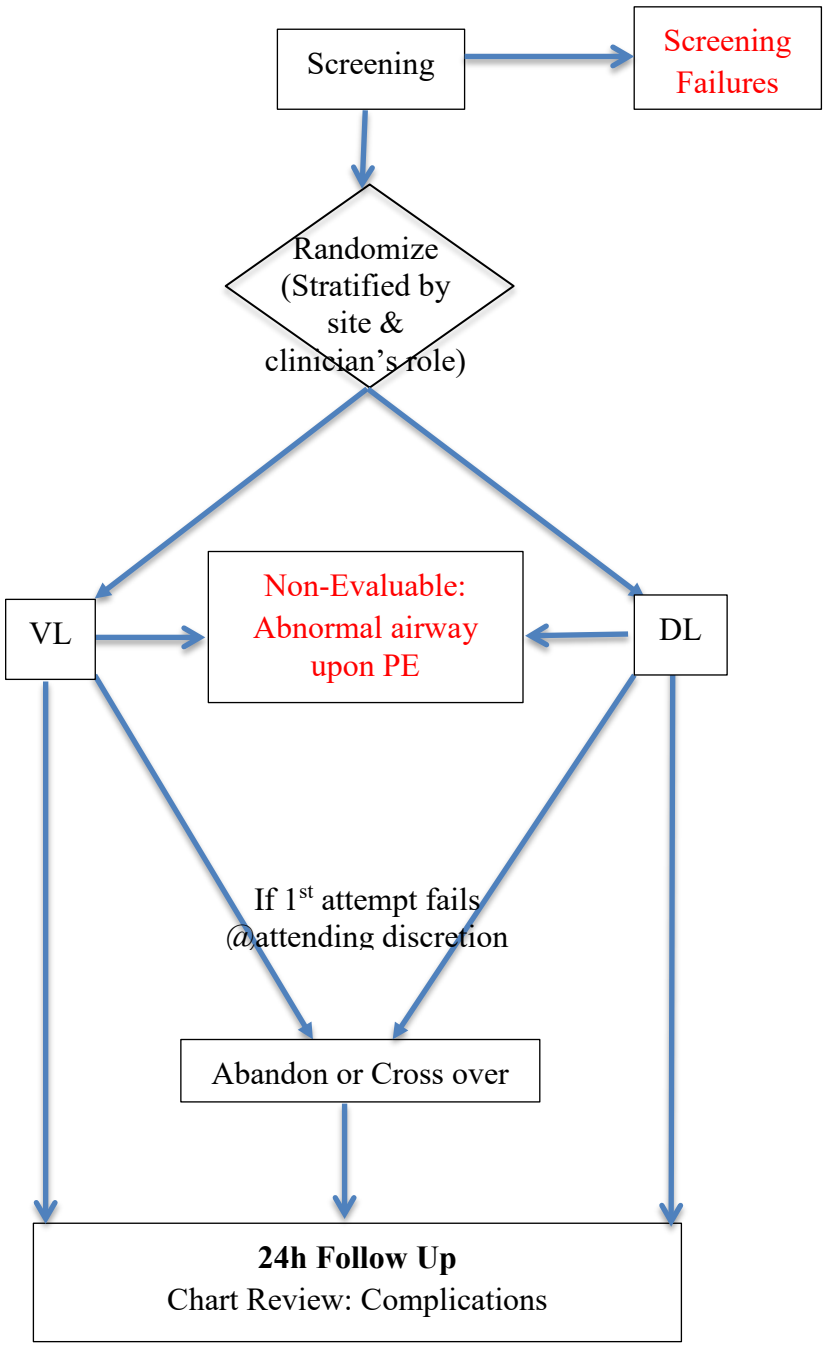
| | used for significance. This more stringent criteria for significance (0.029 instead of 0.05) is Pocock's method of correction for maintaining overall study significance level at 0.05 when there is one interim analysis the overall estimate. |
| **DATA AND SAFETY MONITORING PLAN** | Each participating site PI will be responsible for oversight of the study safety. We expect no more than standard clinical risks associated with intubation. There is no DSMB for this study. |

**FIGURE 1: STUDY DIAGRAM**



# 1 BACKGROUND INFORMATION AND RATIONALE

## 1.1 Introduction

Our preliminary work and others have shown that complications in airway management are related to the persistent use of direct laryngoscopy and multiple tracheal intubation attempts. Our previous multicenter study showed that 20% of children experienced a complication and children who weighed less than 10kg had 2x the complication rate OR(95% CI) 2.09(1.51-2.88) $p < 0.0001$. In both our difficult airway and normal airway populations more than 2 attempts increased the complication rate 1.5x and 1.4x respectively. This proposal seeks to reduce complications by reducing the number of attempts. Multiple tracheal intubation attempts often occur because, in many teaching centers, trainees make the first attempt and after a variable number of failures, the supervising anesthesiologist steps in to repeat the technique. The supervising anesthesiologist often repeats direct laryngoscopy because they are unable to assess the view obtained by the trainee using standard direct laryngoscopy. Our finding of increased complications has transformed our thinking about repeated intubation attempts. Each attempt is a potentially high-risk event and represents an opportunity for hypoxemia, esophageal intubation, laryngospasm, bronchospasm, cardiac arrest, airway trauma and other adverse outcomes. It has become evident to us that multiple tracheal intubation attempts are a key modifiable risk factor to reduce tracheal intubation associated complications in children. Videolaryngoscopy allows the supervising clinician to share the view of the trainee and guide them more effectively. Experienced laryngoscopists also benefit from videolaryngoscopy because they obtain a magnified and improved view. Videolaryngoscopy may narrow the success rate gap between trainees and experienced laryngoscopists. We hypothesize that VL as the first attempted device will reduce the number of tracheal intubation attempts and tracheal intubation related complications, specifically intubation associated hypoxemia.

## 1.2 Name and Description Intervention

Tracheal intubation per clinical standard practice by using the randomized intubation device which are both institution approved devices used routinely.

## 1.3 Relevant Literature and Data

Sun and colleagues performed a meta-analysis of randomized controlled trials comparing VL and DL in children and concluded that VL improved laryngeal visualization, but that this came at the expense of prolonged intubation time and increased intubation failures [1]. The investigators found no significant difference between first attempt success rates of DL and VL[2]. This meta-analysis had significant weaknesses because of marked heterogeneity in patient characteristics; the clinician's experience, the type of VLs used and varied definitions of outcomes. The authors included fourteen trials in this meta-analysis, but only two studies specified the same age range of patients. Age is an important factor when

determining the clinical efficacy of laryngoscopes since the pediatric airway is in transition from birth until about age 2.

Lingappan and colleagues attempted to compare DLs and VLs in neonates, but were unable to do so due to the lack of randomized controlled trials that specifically compared VL to DL in neonates[3].

Multiple attempts at tracheal intubation have been associated with severe complications in diverse clinical settings[4-7].

- Souza et al. found in a study of 147 children in the ICU that 14.3% required 5 or more attempts and that attempts were associated with more trauma, hypoxemia and bradycardia[8].
- Another study examined the impact of introducing non-angulated video laryngoscopy on advanced airway management success by critical care transport paramedics and nurses in the prehospital setting. After the introduction of videolaryngoscopy, first pass success rates increased from 75.4% to 94.9% (significant at CI 99%, chi square = 35.12, Fisher's exact test), combined first and second pass success rates increased from 89.2% to 97.4% (significant at CI 99%, chi square = 12.44, Fisher's exact test).
- We conducted a prospective multicenter study (PeDI Registry) examining our tracheal intubation practice in children with difficult airways and found that hypoxemia was common and hypoxemic cardiac arrest occurred in 1:80 patients. We associated multiple attempts >2 with more complications and every attempt was associated with more complications odds ratio 1.5 per attempt (95% CI 1.4-1.6; $p<0.0001$). In a large comparative retrospective analysis of VL to DL using the National Emergency Airway Registry for Children's ICU database, our team found that using videolaryngoscopy was independently associated with a lower occurrence of tracheal intubation adverse events (adjusted odds ratio, 0.57; 95% CI, 0.42-0.77; $p< 0.001$) but not severe tracheal intubation adverse events (adjusted odds ratio, 0.86 CI, 0.56-1.32; $p =0.49$) or fewer multiple attempts at tracheal intubation (adjusted odds ratio, 0.93; 95% CI, 0.71-1.22; $p= 0.59$). Videolaryngoscopy was associated with lower odds of bronchial intubation (OR, 0.40; 95% CI, 0.22-0.74; $p= 0.003$), esophageal intubation with immediate recognition (OR, 0.49; 95% CI, 0.34-0.69; $p < 0.001$) and dysrhythmia (OR, 0.49; 95% CI, 0.15-0.88; $p = 0.019$)[9]. Although in this study videolaryngoscopy did not reduce multiple attempts, we believe this result is not applicable to our proposed study for a few reasons. Firstly, there was heterogeneity in the type of videolaryngoscopy being used i.e. non-angulated and angulated videolaryngoscopy were used and the type was not noted on all the data collection forms. Angulated videolaryngoscopes have been shown to prolong intubation time and are associated with more difficulty with inserting the breathing tube. Secondly, the population studied was primarily older children in ICU's, and

finally, there was a selection bias in the study, with videolaryngoscopy being disproportionately chosen for children with difficult airways.

- A recent Cochrane review of videolaryngoscopy vs direct laryngoscopy for tracheal intubation in children (excluding neonates) further highlights the urgent need for high quality prospective randomized studies. In that review the authors had difficulty reaching conclusions because of "very low quality evidence due to imprecision, inconsistency and study limitations"[10].
- We performed a retrospective cohort analysis (data pending publication) using our electronic medical records to rigorously analyze our experience with infants with normal airways presenting for elective surgery between January 24, 2015 and August 1, 2016. Of the 7125 cases performed on children younger than 12 months old, we included those managed with direct laryngoscopy without comorbidities presenting for elective surgery. We analyzed the final dataset of 1343 cases and found that 15.6% of cases required more than 1 attempt. We used our electronic medical record data logs to determine episodes of severe hypoxemia (sp02 <90% for more than 1 minute) occurring around the time of intubation (from anesthesia start to anesthesia ready). We found that the number of laryngoscopy attempts was significantly associated with hypoxemic events (Univariate - Poisson: RR 1.4257 (95% CI 1.2576 - 1.6164) p <.0001 , Negative Binomial: RR 1.4421 (95% CI 1.2289 - 1.6922) p <.0001, GEE: RR 1.4421 (95% CI 1.2596 - 1.6510)) p <.0001), (Multivariate - Poisson: RR 1.3256 (95% CI 1.1363 - 1.5463) p= 0.0003, Negative Binomial: RR 1.3707 (95% CI 1.1327 - 1.6585) p= 0.0012 , GEE: RR 1.3707 (95% CI 1.1302 - 1.6623) p=0.0014)). Our analysis showed that the (371 of 1134) 32.7% of children with one attempt experienced severe hypoxemia while (101 of 210) 48.1% of those with multiple attempts experienced severe hypoxemia. These results are likely an over estimation of the true incidence of severe hypoxemia since there was no way for us to exclude low oxygen saturation readings related to tourniquets applied during intravenous access. Nevertheless, the differences between the two conditions (multiple vs. single attempt) are likely accurate since it is unlikely there was a disproportionate application of tourniquets in one group versus the other.

Taken together these preliminary data and prior studies demonstrate the significance of the problem and the feasibility and validity of our intervention to reduce complications. A prospective randomized trial is the only way to eliminate these issues.

### 1.4 Compliance Statement

This study will be conducted in full accordance all applicable Federal and state laws and regulations including 45 CFR 46, and the HIPAA Privacy Rule. Any episode of noncompliance will be documented and reported.

The investigators will perform the study in accordance with this protocol, will comply with applicable institutional research policies, and will report unexpected problems in accordance with institutional IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective is to determine if VL increases the first TI success rate in children < 12 months as compared to DL

## 2.2 Secondary Objectives

- Number of attempts for successful intubation
- Frequency of failure to intubate with assigned device
- Frequency of complications such as hypoxemia related to intubation with the two study devices

# 3 INVESTIGATIONAL PLAN

## 3.1 General Schema of Study Design

This study is a prospective, randomized, multi-centered controlled trial.

### 3.1.1 Screening Phase

Potential subjects will be identified from patients scheduled for elective surgery or procedure per protocol inclusion and exclusion criteria. Parental/guardian permission (informed consent) will be obtained prior to any study related procedures being performed.

Potential clinician participants will be identified from departmental anesthesia clinician lists including attending anesthesiologists, anesthesia fellows, and anesthesia residents.

### 3.1.2 Study Intervention Phase

#### 3.1.2.1 Randomization:

The only research procedure is randomization to TI device as VL or DL for the first intubation attempt.

#### 3.1.2.2 Intubation:

Tracheal intubation using VL or DL are clinical standards of care devices at all participating centers.

#### *3.1.2.3 Follow-up (Up to 24 hours after intubation)*

Chart review to collect information regarding any intubation related AEs.

## 3.2 Allocation to Treatment Groups and Blinding

CHOP will be the Data Coordinate Center (DCC). The DCC will generate the randomization sequence by statisticians. The randomization sequence will be maintained in study EDC, a CHOP REDCap registry, by study manager at DCC.

Randomization will be stratified by site and clinician's role at each site with random block sizes of 2, 4 or 6 to ensure equal numbers of VL and DL subjects within each site and type of clinician, and, to avoid predictability of the device. Randomization is only for the first intubation attempt. Any subsequent attempts will be at the supervising clinician's discretion either with the randomized device or an alternate device

Blinding of study device and study staff is not feasible in this study. However, the statisticians will be blinded at the time of data analysis.

## 3.3 Study Duration, Enrollment and Number of Sites

### 3.3.1 Duration of Study Participation

The study duration per subject will be up to 24 hour post-intubation.
The study duration for clinician participants could be up to the study enrollment duration.

### 3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at 4-10 centers in the United States, United Kingdom and Australia. It is expected that approximately 650 subjects will be enrolled to produce 550 evaluable subjects. Single site enrollment will be capped at 250 subjects or 200 evaluable subjects.

It's expected approximately 500 qualified anesthesia clinician participants will be enrolled. The number of qualified anesthesia clinicians varies across the sites. We estimate about 20-200 per site. There is no maximal allowed participating anesthesia clinicians at each site.

## 3.4 Study Population

### 3.4.1 Inclusion Criteria

1) Males or females age 0 to <12 months.
2) Scheduled for non-cardiac surgery or procedure lasting longer than 30 minutes under general anesthesia where oral endotracheal intubation will be performed by an anesthesiology clinician.
3) Parental/guardian permission (informed consent).

For clinician participants:

1) Anesthesia attending, anesthesia fellows, or anesthesia resident

### 3.4.2 Exclusion Criteria

1) History of difficult intubation
2) History with abnormal airway
3) Predictive of difficult intubation upon physical examination
4) Parents/guardians who, in the opinion of the investigator, may be unable to understand or give informed consent

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

# 4 STUDY PROCEDURES

## 4.1 Screening Visit

Eligible subject's parent(s) or guardian(s) will be approached by investigator and/or study staff prior to surgery. Parent(s) or guardian(s) will be provided a written informed consent before any study specific procedures are performed. Following activities will be conducted at this visit:

- Medical Record Review
- Informed Consent
- Data collection

## 4.2 Study Procedure

### 4.2.1 Clinician qualification:

Since the study procedure is standard clinical care at all centers, anyone who is licensed to perform the tracheal intubation at the participating center is allowed to conduct the intubation on the subjects. These clinicians include attending anesthesiologists, anesthesia fellows, or anesthesia residents.

All clinicians who are caring for a VISI trial patient will be consented. In clinical emergency situations, the attending anesthesiologist may request subsequent intubation attempts assistance from another attending anesthesiologists who may not be consented. This will not be considered as protocol violation nor deviation. We will request consent from these clinicians after the intubation. If they decline consent, none of their study information will be collected. No study procedure will be performed till consent is obtained.

### 4.2.2 Randomization:

To ensure balance in treatment assignment, a permuted-block randomization approach will be applied. The block size will be varying (among 2, 4, 6) to avoid the predictability of device assignment. To further balance device assignment against potential predictors on the outcome, we'll stratify the randomization by study site (5-10 sites) and clinician's experience (anesthesia attending, anesthesia fellow & anesthesia resident). There will be 15-30 (Site number*3) strata in total. Separate randomization schedule will be generated for each stratum.

Randomization will be conducted through the study REDCap EDC after the consent is obtained. The subject is required to be registered in REDCap via a computer or mobile device per institutional policy prior to randomization. To avoid protocol deviation, only eligible subjects and study allowed anesthesia clinicians are able to be randomized in REDCap by a designated site study staff. Then the clinician will be notified of the randomized device.

### 4.2.3 Intubation:

Anesthesia induction will be left to the discretion of the attending anesthesiologist per institution standard practice. However, it's strongly recommended that all subjects should receive a neuromuscular blocking drug and confirmed train of four ≤ 1 twitch at the adductor pollicis muscle prior to attempting intubation. It's strongly recommended that the use of a malleable stylet for all intubations and use usual cuffed tracheal tubes per institutional standard of care. It's strongly recommend to follow below guidelines:

- ID 3.0mm cuffed (birth to < 1 month; >3kg body weight);
- ID 3.5mm cuffed (1 month to < 8 months);
- ID 4.0mm cuffed (8 to 12 months).

If the first attempt at tracheal intubation attempt fails, the device used for subsequent attempts will be at the discretion of the attending anesthesiologist.

A member of the research staff is required to observe the intubation and record the study information.

### 4.2.4 Follow-Up (Post intubation chart review)

Subject records will be reviewed up to 24 hours after intubation or upon discharge from PACU for intubation related AEs

**The following data elements will be collected**:

- Demographics including MRN, name, gender, weight, and elements of dates including date of birth et al
- Birth history including post menstrual age et al
- Medical history and surgical history including diagnosis and any other intubation history et al
- Physical exam including ASA physical status and airway abnormality et al
- Surgical information including procedure date, type of surgical procedure, surgery length et al.
- Anesthesia records including number of TI attempts, oxygen saturation, TI device used, clinician's names, medications, and associated complications et al
- Subject records will be reviewed up to 24 hours after intubation for any intubation related AEs

## 4.3 Subject Completion/Withdrawal

The subject may be discontinued from the study procedure at the discretion of the Investigator due to AEs or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded and reported to institutional IRB.

Clinician participates maybe withdraw from participating in the study at the first intubation attempt. If this occurs, their names will removed from the eligible clinicians list in REDCap.

### 4.3.1 Early Termination Study Visit

If a subject withdraws from the study, then their data which has already been collected will remain in the study. If they withdraw after being intubated, the 24 hour post intubation review of records will be done to assure no AE has occurred as a result of the intubation for safety monitoring. However, if subject withdraws prior to being intubated, no further data will be collected and no study procedure will be performed.

# 5 STUDY EVALUATIONS AND MEASUREMENTS

## 5.1 Screening and Monitoring Evaluations and Measurements

### 5.1.1 Medical Records Review

- Demographics including MRN, name, and elements of dates including date of birth at el
- Birth history including post menstrual age and congenital birth defect et al
- Medical history and surgical history including diagnosis and any previous intubation history et al

- Chart review to collect clinical information up to 24-hour post intubation or upon discharge from PACU
- ASA physical status
- Airway assessment
- Surgical information including procedure date, type of surgical procedure, surgery length et al.
- Anesthesia records including vital signs, oxygen saturation, medications, and notes
- Post intubation assessment including complications associated with intubation

#### 5.1.2 Clinician's Records

- Clinician's clinical role and years of professional experiences
- Experiences of study device intubation on infant

#### 5.1.3 Intubation

- Clinicians' name who perform the intubation
- Number of attempts
- Intubation devices
- Intubation associated complications

### 5.2 Safety Evaluation

Subject safety will be monitored and treated by per institutional standard clinical of care since the study procedure is institutional standard practice. Any adverse event related to intubation will be recorded on the study Case Report Form (CRF).

## 6 INVESTIGATOR STATISTICAL CONSIDERATIONS

### 6.1 Primary Endpoint

The primary aim is to determine the proportion of tracheal intubation success on first attempt of VL compared to DL. The primary endpoint is the successful tracheal intubation at first attempt. The first-attempt success of intubation will be coded as a dichotomous variable (success=1, nonsuccess=0). As a comparative effectiveness study, the treatment procedure will be randomly assigned to participants after consent is obtained in a two-arm, parallel design. If warranted, we will use a logistic regression model in the mixed model framework to allow for the inclusion of multi-level effects for individuals nested within sites and site-specific effects such as staffing, caseload, experience of staff, etc. In this analysis, we can address systematic effects that possibly lead to different success rates between sites, and/or clinicians, without compromising the integrity of the randomization procedure. Although the main interest is in successful intubation, secondary aims can also be investigated through the logistic regression mixed models approach.

### 6.2 Secondary Endpoint

The secondary endpoint is successful tracheal intubation.

## 6.3 Statistical Methods

### 6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). To test the difference of demographic variables between treatment groups, student's t-test or Wilcoxon test will be used for continuous variables, while Chi-square test, or Fisher's exact test will be used for categorical variables. Comparisons of demographic characteristics between the sites will be accomplished by reporting effect size measurements (i.e., Cohen's d, phi-coefficient, odds ratios) between each site as a descriptive analysis of differences at baseline.

### 6.3.2 Statistical Analysis

The study is powered for the primary outcome: successful tracheal intubation on first attempt. Assuming that a 10% increase in successful tracheal intubation (i.e., intubation on first attempt) is clinically meaningful, and that a reasonable rate for baseline success is (84%) (Based on our single center data) an overall sample size of 540 randomly assigned to VL or DL, will provide approximately 80 % power at the nominal two sided 5% level of significance. This calculation accounts for approximately 10% withdrawal, dropout, missing data and other data quality issues. We assume the success rate will be similar across sites. The statistical package SAS's module: PROC SEQDESIGN, was used for the sample size determination. The order of assignment of intubation method (VL vs. DL) for patients intubated by the same clinician will be done using blocked randomization with block sizes of 2, 4 or 6. The primary analysis will be based on intention-to-treat approach and include all the randomized subjects. Logistic regression will be used to compare first-attempt success proportion of tracheal intubation between DL and VL. To adjust for clinician-level clustering of outcome variable, we will apply generalized estimating equations (GEE) method to the logistic regression model to get the marginal odds ratio for first-attempt success comparing VL and DL. . We will include the patient characteristics: ASA status, thyromental distance and weight (less than 10kg, & more than 10kg) as covariates in the logistic regression model. Since there will be an interim analysis the p-value is considered significant if it is less than 0.029 to maintain the overall significance level of the study (Type I error rate) at 0.05[14] Also, it may be that VL offers greater advantage for those with less experience such as residents as compared to attending physicians or fellows. To assess if there is this effect modification we will include class of clinicians with intervention (DL vs VL) as an interaction term in the logistic regression. In addition, we will analyze the number (not dichotomizing) of intubation attempts using a generalized linear model with the negative binomial distribution. Difference in complications, such as lowest oxygen saturation during tracheal, between treatment groups will be analyzed in multivariate linear models or generalized linear models as appropriate. General linear models and GEE

approach will be used for these models to adjust for site-level and clinician-level clustering of outcome variables.

### 6.3.3 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all randomized subjects.

The primary efficacy endpoint will be a successful tracheal intubation following the procedure. We will consider a 10% improvement between VL compared to DL to be indicative of a significant clinical effect. The statistical analysis of this change will be based on a logistic regression model where an odds ratio greater than 2.98 will be considered evidence of efficacy of VL compared to DL. Marginal odds ratios with 95% confidence intervals will be reported for the sample overall, as well as each site, if appropriate.

## 6.4 Sample Size and Power

The primary objective of the trial is to determine whether VL will increase the success rate on first tracheal intubation in children < 12 months as compared to DL. The null hypothesis is that first-attempt success rate will not be different between VL and DL for children < 12 month. The alternative hypothesis is that the first-attempt success rate will be different between VL and DL for children < 12 month. The mathematical formula are:

$H_0$: $p_{VL} = p_{DL}$

$H_1$: $p_{VL} \neq p_{DL}$

An interim analysis will be done, and Pocock's method will be used to adjust for this 2-stage sequential analysis. According to CHOP's recordings, first tracheal intubation success proportion was 84% for DL, and we expect a difference in the success proportion of 10% to be clinically meaningful. Using SAS PROC SEQDESIGN procedure, a sample size of 167 per treatment group (334 in total) will provide approximately 80% power at the nominal two sided 5% level of significance. To adjust for 10% extra protocol deviation, the sample size adds up to 186 per treatment group (372 in total).

We're also aware that the outcome variable will be clustering on each physician since different physician perform differently in tracheal intubation. The following inflation factor formula will be used to adjust for this clustering:
$DE=1+(m-1)*\rho$ [13]
Where DE stands for design effect, m stands for the average clustering size, and $\rho$ stands for intra-cluster correlation coefficient (ICC). Since there is no reported ICC of the tracheal intubation success rate among clinicians, we assume it to be 0.05, which means 5% of the variance in success rate is explained by the variation between clinicians. We also assume that every clinician will intubate 10 patients on average in the current study. Thus, the

inflation factor is 1.45. Thus, the sample size is inflated to 270 per treatment group (540 in total).

### 6.5 Interim Analysis

There will be an interim analysis after 224 evaluable subjects are enrolled. The proportion of subjects that are successfully intubated at the first attempt will be compared for VL and DL using logistic regression with alpha = 0.029 for significance. This more stringent criteria for significance (0.029 instead of 0.05) is Pocock's method of correction for maintaining overall study significance level at .05 when there is one interim analysis. We will include ASA status, thyromental distance and weight less than 10kg as covariates in the logistic regression. The probability of stopping at the interim analysis (mid-point) is 46.4%, if the true improvement in intubation first attempt success rate is 10.0% (i.e. 84% true first attempt success rate for DL vs. 94% true success rate for VL). However, if the true improvement in first attempt intubation success rate is 12.0% (i.e. 84% vs 96% for DL and VL respectively), then the probability of stopping early increases to 83.0%.

## 7 STUDY DEVICE

### 7.1 Description

Both Storz C-Mac Video Laryngoscope (VL) and Standard Direct Laryngoscope (DL) are FDA approved and used clinically for study population at all participating center.

Standard Direct Laryngoscope

Storz C-Mac blade

The Storz C-Mac blade is a standard direct style blade with a CMOS camera embedded at the distal tip. The image from the camera is transmitted to a foldable display on the handle of the device. The imaging display is viewable by nearby other clinicians.
The standard direct blade is a rigid style, visualization occurs by direct line of sight.

## 8 SAFETY MANAGEMENT

### 8.1 Clinical Adverse Events

Clinical adverse events (AEs) related to intubation will be monitored throughout the study.

## 8.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with institutional IRB SOP. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

## 8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs related to the study intervention/intubation will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

# 9 STUDY ADMINISTRATION

## 9.1 Treatment Assignment Methods

### 9.1.1 Randomization

The randomization schedule will be generated by statistician and randomized by using REDCap randomization feature. To avoid protocol violation, the randomization option in REDCap is only available to consented subjects when consented and anesthesia clinicians are scheduled to perform the intubation. Randomization schedule will be maintained by study manager at DCC in REDCap. The randomization will be stratified by site and clinicians role to ensure an equal number of study DL or VL participants at each center. REDCap will keep a permanent and unchangeable randomization records.

### 9.1.2 Blinding

Blinding of the PI and clinician is not feasible in this study. The statisticians will be blinded at the time of generating the randomization schedule and remain blinded at the time of analysis.

## 9.2 Data Collection and Management

DCC will be housed at CHOP. CHOP could also be IRB of record for other US based participating sites. CHOP REDCap will be utilized as Electronic Data Capture (EDC).

Minimal identifiable information might be printed on paper for study eligibility clarification, study data collection, and data validation. Any un-needed paper data which has identifiable information could be shredded as soon as possible per institutional policy.

Study electronic records will be stored in institutional approved secured network drives or websites or databases, which are fully tracked with user credentials and only authorized research personnel have the access. Paper records will be secured in a locked office where only authorized research personnel have access.

### 9.3 Data Transfer

Study data including identifiers (MRN and names) and dates will be entered in the study EDC. Scanned ICF could be uploaded to study EDC for monitoring. Full dataset could be exported from the EDC and saved in the DCC secured network for study monitoring and auditing, and data management. Only the site study staff and DCC would have access to site identifiers. Coded Limited dataset (including dates) could be shared with the statistician for data analysis and participating centers.

### 9.4 Retention

When the study is completed, all study paper records might be scanned and then destroyed to store along with other electronic study records for retention. These will be stored and backed up in an institutional approved secured network drive, website or database. Only authorized study personnel will have access. All study materials, including PHI and the master list, though not the information linking subject PHI with study data, will be retained for 10 years after the subjects turn 18 years old. Then the master link code will be permanent deleted.

### 9.5 Confidentiality

All data and records generated during this study will be kept confidential in accordance with each site's Institutional policies and HIPAA on subject privacy. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Safeguards to maintain subject confidentiality are described under Data Collection and Management.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (participating centers) of the data and the recipient researchers (CHOP) before sharing a limited dataset (PHI limited to dates).

HIPAA does not apply to clinician participants.

# 10 REGULATORY AND ETHICAL CONSIDERATIONS

## 10.1 Data and Safety Monitoring Plan

The participating center's principal investigator will oversee the safety of the data and that of the research subjects. During the study period, each subject will be monitored for any adverse events or safety concerns. Contacts will be provided to all enrolled subject's parents/legal guardians with any concern. Study principal investigator will oversee overall safety of data.

### 10.1.1 Risk Assessment

Both devices are approved and used in accordance with their labeling, both approaches are currently used as part of routine clinical care at the institution; experienced clinicians will oversee the procedure and the protocol allows for cross-overs. The main risk of the study is due to randomization (to an intubation approach the subjects may not have undergone if their clinician had made the decision). Additionally VL may take longer however this has been shown to be clinically insignificant in all studies. The risks are no greater than minimal.

### 10.1.2 Potential Benefits of Trial Participation

This study might benefit some participants by faster intubation. They may have fewer intubation attempts thereby reducing intubation related risks.

**Risk-Benefit Assessment**

The risks of this study are no different than those associated with current practice for airway management in children undergoing general anesthesia for elective surgery. There are potential benefits to the greater population of children in that we will have knowledge about the efficacy of VL vs DL.

## 10.2 Recruitment Strategy

The PI at each participating center will provide an in-service to surgical and anesthesia team and related care providers. Potential subjects will be identified from the scheduled surgical list. A Study team member will review medical records to identify eligible subjects and will only approach permissible subjects.

Subjects will be approached by a study team member in a private setting. The study will be explained to the parent(s)/legal guardian(s) at an appropriate time when available to give consent.

Clinician participants will be identified from the departmental clinician list. The site PI could initiate an email to all qualified clinicians. It will be reiterated that the confirmation that their decision to participate, or not, or their performance on the study will not impact

their performance evaluations or employment. They will have ample time to consider participating.

### 10.3 Informed Consent/Assent and HIPAA Authorization

Parent(s)/legal guardian(s) will be approached by study members prior to the surgery in a private setting. The primary aim, risks, benefits and study procedures for the study will be explained and the parent(s)/legal guardian(s) will have the ample time and opportunity to ask questions. Investigator will be available to answer any additional questions the parent(s)/legal guardian(s). It will be reiterated that the decision to participate or decline to participate in the study will have no bearing on their medical care.
A combined consent-authorization document will be used. Only one signature from parent or legal guardian will be required for this study.

For clinician participants, the primary aim and their obligations and requirements will be explained in the initial site PI's email. Consent could be obtained via email, text message, phone calls, or in-person. For clinician who requested to assist subsequent intubation attempts on a VISI patient during the clinical emergency situation, study staff will approach to obtain the consent after the intubation has occurred. Consenting process will have to be documented electronically in study EDC and paper record will be optional or per institutional policy.

### 10.4 Payment to Subjects/Family

None

## 11 PUBLICATION

The results of this study will be published in a high impact journal, our target journal is the Lancet.

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