A Multi-center Evaluation of the NEMO™ Gauge to Aid in Correct Positioning of the Endotracheal Tube after Intubation of Critically Ill Patients

STUDY PROTOCOL

Revision 1

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Background and Significance:

Endotracheal tube (ETT) malposition is associated with high incidence of adverse outcomes such as severe atelectasis, pneumothorax, refractory hypoxemia, and even death[1]. The rate of ETT malposition among experienced clinicians in the literature is reported to be between 9 and 16%[2-5].

In the setting of emergent intervention that determines life altering outcomes, physicians often rely on point of care devices and modalities to guide their management plans. Currently, chest radiographs are utilized to assess for ETT position after intubation[6]. The median cost of a chest radiograph typically ranges between $100 and $500[7]. The average time between the request for a chest radiograph and visual evaluation of the study by a radiologist or experienced clinician is rarely less than one hour. Novel and cost-effective technology is needed to rapidly aid in confirming ETT position immediately after a critically ill patient is intubated.

Device Overview:

The NEMO™ Gauge (Ciel Medical, San Carlos, CA) is an ETT positioning *bougie* that has color-coded depth markers to help the user determine and confirm the position and depth of the tip of the ETT. The NEMO™ Gauge is commercially available in the USA and falls under the FDA regulation Section 868.5790 Tracheal tube stylet, and Classification Product Code BSR (Figure 1).

[A] Deployment Cap
[B] Handle
[C] Measurement Marking
[D] Catheter Shaft
[E] Expandable Tip
[F] Positioning Clip

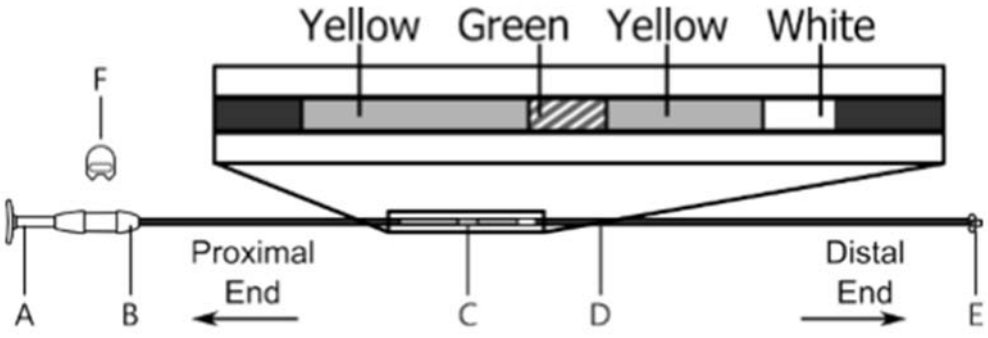


Figure 1: Overview of the NEMO™ Gauge

When the deployment cap (A) is engaged, the expandable tip (E) is advanced out of the catheter providing a bumper to engage with the carina in the patient's airway.

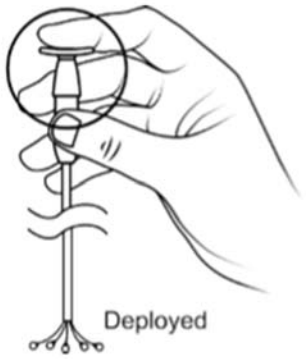
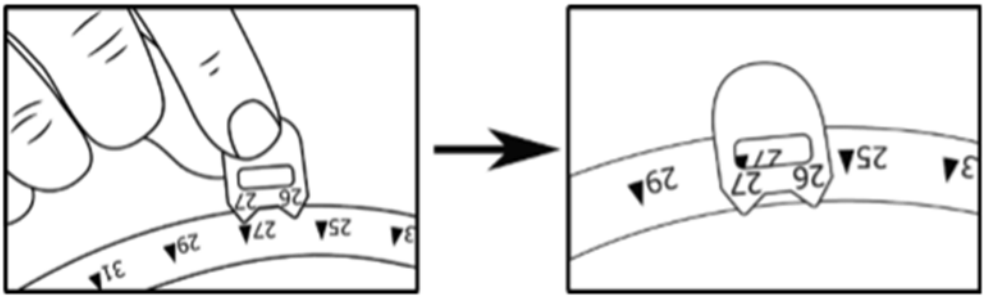


Figure 2: Deployed expandable tip

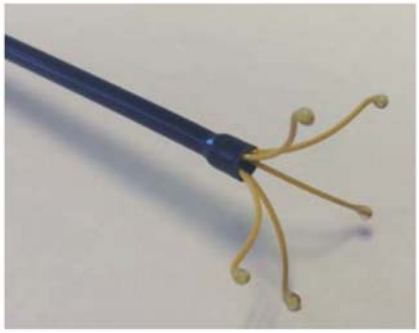
The expandable tip of the NEMO^{TM} Gauge is made of formed spring wires that are covered with a Pebax sleeve (Figure 2). Pebax is the trade name for a Nylon plastic commonly used in medical devices. The ends of the expandable tip are rounded to present a smooth, round surface on contact with the trachea wall.

The manafacturer's instructions for use include:

1. The user removes the positioning clip from the device handle and aligns it on the ETT between the marked distances:

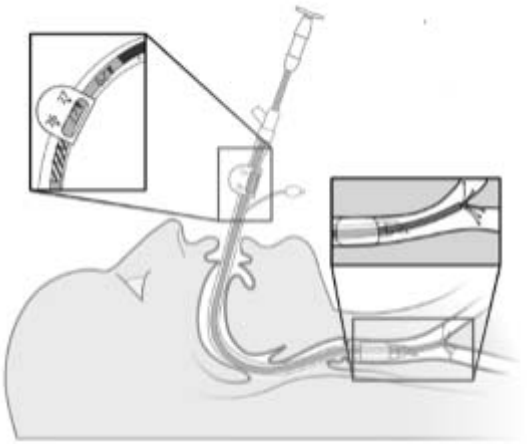


2. The user inserts the NEMO^{TM} Gauge into the ETT until the WHITE measurement marker on the NEMO^{TM} Gauge is visible in the positioning clip window. This indicates that the distal end of the NEMO^{TM} Gauge is aligned with the tip of the ETT.
3. The user expands the distal tip by advancing the deployment cap and continues to advance the NEMO^{TM} Gauge until resistance is felt, and the expandable tip has reached the carina.

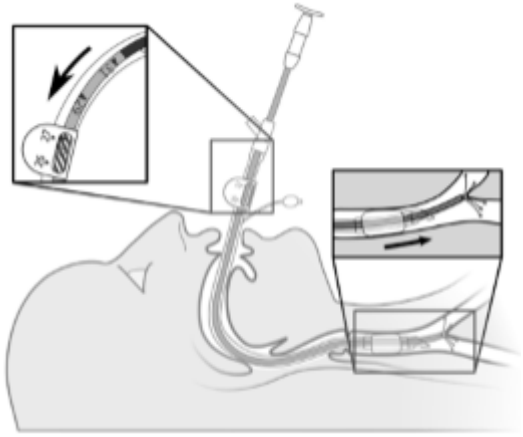


4. Once resistance is felt, the user refers to the color of the measurement marker on the NEMO™ Gauge that is present in the positioning clip window. If the window is completely filled by the GREEN measurement marker, the ETT is safely positioned and the NEMO™ Gauge may be removed.
5. If the YELLOW measurement marker on the NEMO™ Gauge is present in the positioning clip window, the ETT position should be adjusted until the GREEN marker is present as shown in the figure below:

ETT position too high



Adjustment of ETT tube to proper location



Green marking represented by white and dark grey diagonal stripes

Previous Device Testing:

Prior testing of the device by the manufacturer has focused on two main areas:

- Evaluating efficacy of the device in human cadavers
- Evaluating safety of the device in bench models and live porcine models.

Efficacy

Cadaver testing during development of the NEMO™ Gauge has been completed on seven adult cadaver specimens, four male and three female cadavers. All cadaver specimens were fresh (i.e. not embalmed) and were provided by the Stanford University Anatomy Department. At no point during development was any visible damage observed on the tracheal wall or carina of these cadavers.

During a June 2014 cadaver lab, eight Stanford Hospital respiratory therapists were asked to evaluate the feasibility and ease of use of the NEMO™ Gauge. All therapists were provided with a brief in-service training on the use of the device and then asked to confirm ETT position in a cadaveric model. The results were as follows:

- All eight were successful in placing the ETT 2-5 cm above the carina (confirmed by rigid bronchoscopy).
- Of the participants that completed a survey following use (5/8 participants), all of them stated that the tactile feedback during use of the device was adequate and/or that it was clear when they reached the carina.
- On a scale of 1-5, all survey respondents rated the ease of use of the device as a "2 - easy". (1-very easy, 2-easy, 3-neutral, 4-somewhat difficult, 5-difficult).

Testing in human cadavers has shown the device to be effective at confirming the ETT location as 2-5 cm above the carina.

Safety

The NEMO™ Gauge has been used in a live porcine model to evaluate the risk for mucosal damage during use of the device. A 66-kg pig was intubated with a size 8 ETT. Due to the long length of the porcine airway, the NEMO™ Gauge was not used to position the ETT 2-5 cm above the carina (as expected in humans), but the device was advanced approximately 10 cm through the airway until it engaged with the carina (Figure 3).

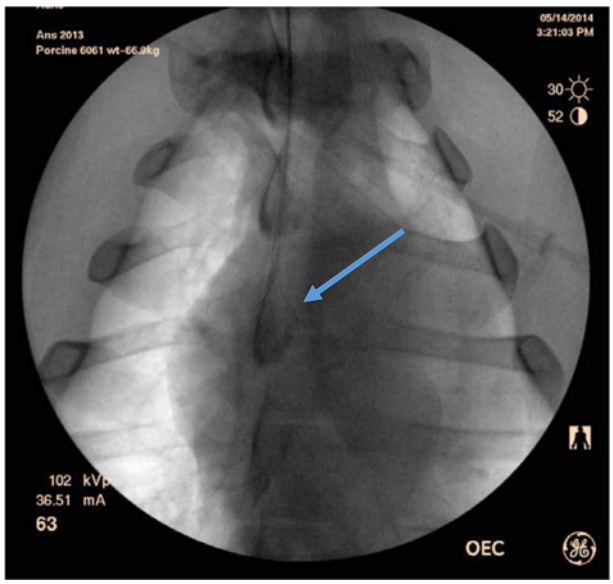


Figure 3: Chest x-ray taken of the porcine model showing the NEMO™ Gauge (blue arrow) expanded within the porcine airway.

Images were taken before and after use of the NEMO^{TM} Gauge device with a fiberoptic bronchoscope to evaluate mucosal damage (Figure 4 and 5). There was no visible bleeding seen with bronchoscopy.

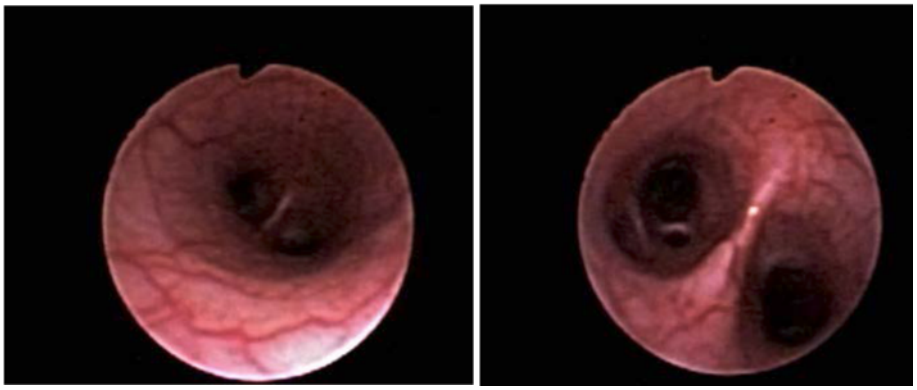


Figure 4: Bronchoscopy images taken before use of the NEMO^{TM} Gauge.

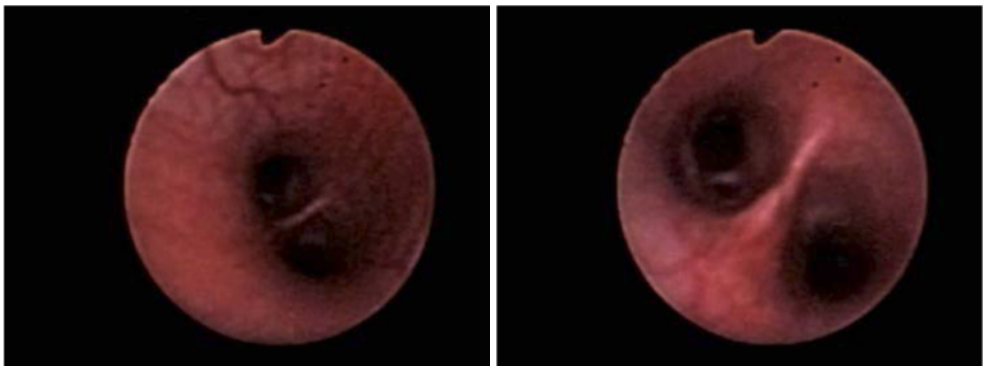


Figure 5: Bronchoscopy images taken after repeated (4x) use of the NEMO^{TM} Gauge.

A second, bench model was used to characterize the forces exerted on the tracheal wall by the NEMO^{TM} Gauge during use. The device was inserted into an acrylic 18 mm tracheal model and a 1 mm thick, 1 cm wide, and 6 cm long pressure sensor (TactArray Pressure Sensor, PPS, Los Angeles, CA) was placed on the tracheal internal surface. The maximum pressure exerted by the device was acquired using dedicated software (PPS Camelon TVR Software, PPS, Los Angeles, CA). The average maximum pressure recorded during advancement of the NEMO^{TM} Gauge was 0.54 psi (0.82 psi max). The average maximum pressure recorded during adjustment of the ETT depth in the simulated trachea was 1.78 psi (2.80psi max). Thus, the

forces exerted during advancement of the NEMO™ Gauge are significantly less than the forces exerted during routine adjustment of the ETT.

The above testing suggests that the NEMO™ Gauge is safe for human use. An IRB approved trial is currently underway at a U.S. academic medical center (per Ciel Medical, the manufacturer). This prospective trial studies the use of the NEMO™ Gauge in up to 50 intubated patients undergoing bronchoscopy. Main outcomes include confirmation of accurate measurement of the ETT tip-to-carina distance using the NEMO™ Gauge compared to bronchoscopy measurement, and assessment of mucosal damage during the use of the NEMO™ Gauge. In this study, a bronchoscopy was performed after the use of the NEMO™ Gauge. An interim analysis of 17 patients showed 94% accurate measurement using NEMO™ Gauge (2-5cm from the carina). In one patient (6%) the ETT tip was determined to be inside the 2-5 cm range using the NEMO™ Gauge but was actually at 5.5cm. Eight (8) patients displayed signs of mild mucosal irritation and nine (9) patients showed no irritation after use of the device. No adverse events have been reported to date (ongoing study, unpublished results provided by Ciel Medical).

Specific Aims:

The aim of this study is to investigate the NEMO™ Gauge's ability to accurately and safely determine ETT position, and if needed, guide repositioning of the ETT into the correct position, compared with standard chest radiography.

Inclusion Criteria:

1. Adult patients ≥ 18 years of age admitted to the intensive care unit (ICU)
2. Patients who have been intubated or at high risk of being intubated, requiring confirmation of ETT position after intubation as determined by the clinical team
3. Endotracheal tube size 7.0 mm to 8.5 mm in diameter

Exclusion Criteria:

1. Patients with active hemoptysis
2. Patients with known tracheal or bronchial masses prior to endotracheal intubation
3. Patients with known tracheal or bronchial abnormalities requiring surgical repair

4. Patients with ongoing hypoxemia (defined as $SaO_2 < 85\%$) after endotracheal intubation
5. Any individual involuntarily confined or detained in a penal institution

Study Procedure:

Study physicians will be trained on the use of the NEMO™ Gauge device by viewing a video tutorial, reading the manufacture instructions provided with the device, and performing an ETT position confirmation with the NEMO™ Gauge on a trachea simulation model (mannequin).

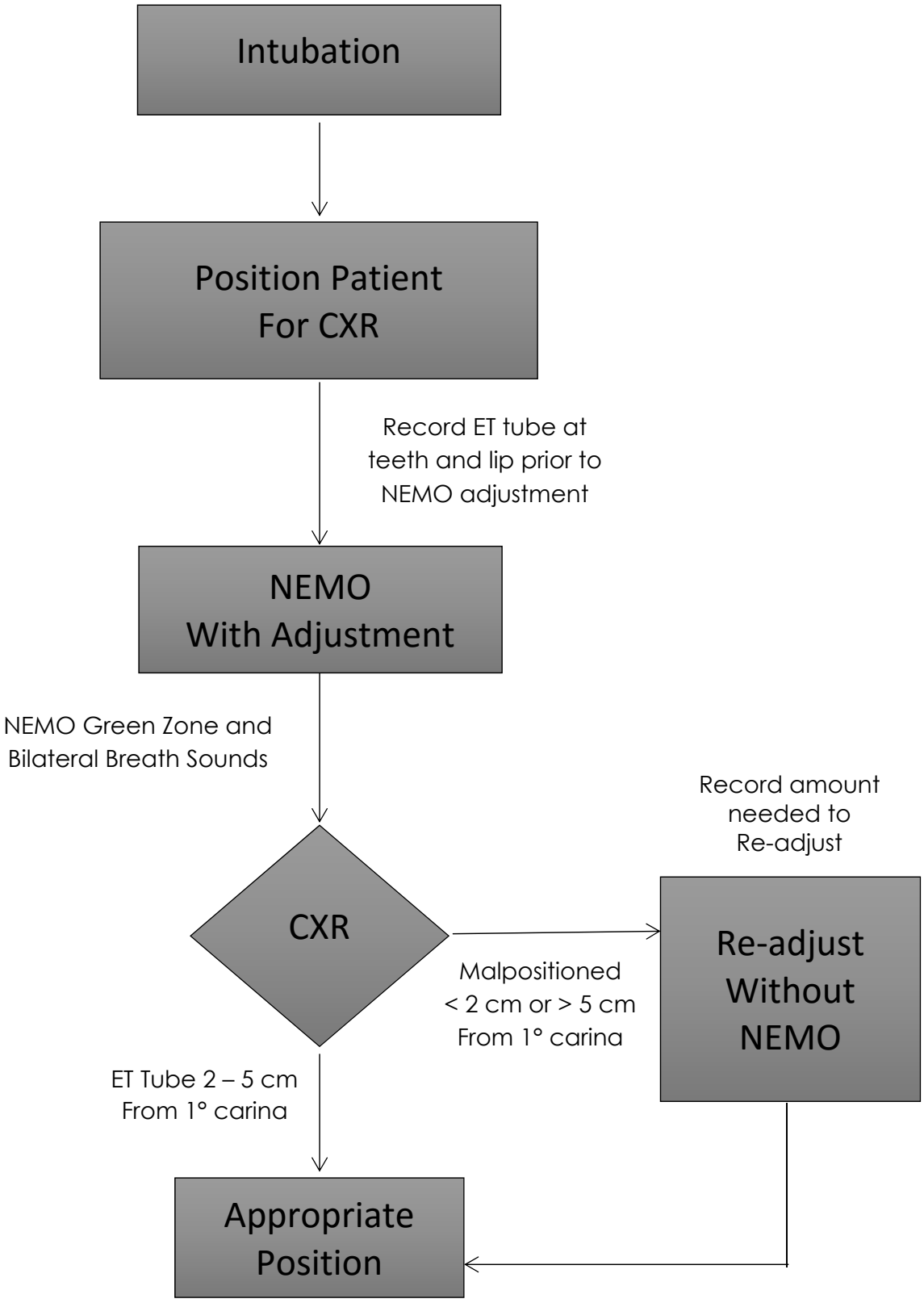
Patients who are intubated and meet enrollment criteria will be selected for the study procedure (Figure 6). After intubation, the patient will be positioned for the chest radiograph by standard practice. Prior to obtaining the chest radiograph, the NEMO™ Gauge will be used to determine proper tube positioning and should it be necessary the ET tube will be repositioned as per the NEMO™ Gauge's manufacture instructions. Additionally, the operator will auscultate the patient's lung for bilateral breath sounds.

Immediately after use of the NEMO™ Gauge and confirmation of bilateral breath sounds, a chest radiograph will be completed. The distance from the tip of the ET tube to the carina will be measured on the radiograph and will be recorded. Based on current clinical practice [8-9], the ET tube will be considered a malposition if it is located less than 2 cm from the main carina, more than 5 cm from the main carina, in the right main stem bronchus, or in the left main stem bronchus.

If the ET tube is considered in a malposition as determined by the chest radiograph, it will be re-adjusted as per standard practice, now without the NEMO™ Gauge. The distance that the ET tube is adjusted will be recorded.

Demographics, diagnostic data, ventilator settings, and ongoing treatments will be recorded. The reason for intubation, ETT size, ETT position, and ETT adjustments will also be recorded. Any complication as a result of the intubation, ETT positioning, and/or NEMO™ Gauge will be recorded.

Figure 6: An outline of the Study Procedure



Primary Outcome:

The percentage of correct ETT position as confirmed by chest radiographs after using the NEMO™ Gauge.

Sample Size / Number of Subjects:

Based on our literature review, correct ETT position after intubation are observed in approximately 91% of patients when verified by standard chest radiograph (the null hypothesis). We hypothesize that use of the NEMO™ Gauge to detect ETT position and make necessary adjustments will result in 98% correct ETT position.

Using a one-sided binomial test, a sample size of 68 patients will detect an increase in ETT correct position of 7% with the use of the NEMO™ Gauge, having a power of 0.84 and a significance level of 0.0492.

Statistical Analysis:

Simple descriptive analysis will be performed, including the percentage of correct ETT position and any complication after the use of the NEMO™ Gauge. See also Interim Analysis below.

Study Duration:

The duration of study enrollment will be 6 months with expected enrollment of approximately 1 patient per week at each participating intitution (1 patient x 3 sites x 4 weeks x 6 months ~ 72 patients). We plan to terminate the study after 68 evaluable patients with complete data are enrolled, per the above sample size calculation. Enrollment is planned to start on June 1st, 2016. An interim analysis will be performed at one-half enrollment.

Data Collection:

The investigators at each respective site will collect all data on a standardized case report form. See next paragraph for a listing of the specific data to be collected. All study records, including those which could provide identification, will be kept in a locked file cabinet in a locked office. All electronic records will be kept on a password protected network drive at the

respective sites. Only non-personally identifiable information will be shared with Loma Linda University for data analysis purposes.

Data share agreement between a study site and Loma Linda University must be completed before any data is transferred from the site to Loma Linda University Medical Center (LLUMC). Each study site will submit subject case report forms to the study lead investigator (SLI) for entry into a common database stored at LLUMC. The database is stored on a password protected computer network drive, accessible in the SLI's locked office and research laboratory at LLUMC. Data are de-identified with no PHI.

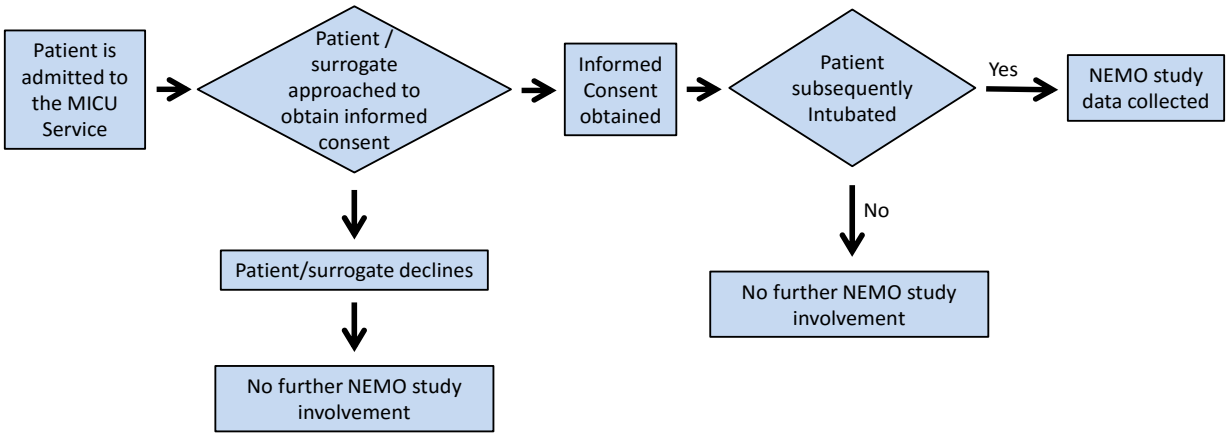
Data Collected:

The following data variables will be collected for every subject: Date of enrollment (consent), name of individual obtaining consent, date of use of the NEMO™ device, name of physician investigator who used the device, patient identifiers, age, height, weight, medical comorbidities, presence/absence of bilateral breath sounds following intubation, endotracheal tube (ETT) size and positioning measurements, record of ETT position changes after use of NEMO™ Gauge, duration of time for the use of the NEMO™ Gauge, time of ordering chest radiograph (CXR), time CXR performed, CXR findings and recording of distance from distal ETT to the main carina, documentation of any additional re-position of the ETT, complications (if any) with intubation and/or use of the NEMO™ Gauge, investigator assessment of whether any complications were related to use of the NEMO™ Gauge.

Human Subjects/Consent:

The enrollment criteria for this study consist of patients requiring or at high risk for requiring intubation and placement on invasive mechanical ventilation. These patients may have altered sensorium and may not be able to provide written informed consent at the time of meeting study enrollment criteria. In such case informed consent may be obtained from a legal authorized representative (LAR).

Patients admitted to the ICU service (irrespective of physical location in the hospital) or their LAR will be presented information about this study and given an opportunity to participate after all their questions have been answered. No study procedures will occur prior to their written informed consent. The consent process is as follows in the figure:



Since it is impossible to know in advance which patients will require intubation and mechanical ventilation in the ICU, we will obtain prospective written informed consent shortly after ICU admission in all patients who may or may not yet require intubation. Not all ICU admitted patients will require intubation during their ICU stay. Thus, we anticipate that only a portion of consented patients may ultimately have study procedures performed on them.

Potential Risks:

Endotracheal intubation is associated with a significant number of adverse events, some of which are serious. These events related to intubation are relatively common and have been studied extensively. Our study is NOT examining the intubation itself, but rather the correct adjustment (if any) of the endotracheal tube AFTER intubation has already occurred. With this in mind, one of the study investigators, not directly involved in the patient care or study procedures will make a determination whether or not events surrounding the intubation are related to intubation vs. to the NEMO^{TM} Gauge.

Nearly all intubated patients undergo suctioning of airway secretions right after intubation and on a regular, as needed basis, multiple times each day for as long as they remain intubated. Suction catheters frequently cause irritation and occasionally bleeding from the tracheal mucosa. The risks associated with the use of the NEMO^{TM} Gauge are approximately similar to the risks associated with routine endotracheal suctioning.

There are always unforeseen risks beyond those of routine endotracheal suctioning; however, we believe the incremental risks from use of this device are minimal. This is based on the pre-clinical device testing (described above) that has occurred as well as to the clinical experience with the device since it has been on the market. The major potential risk associated with this device is the possibility of minor tracheal damage from contact with the tracheal wall. There is a theoretical possibility that the forces exerted on the tracheal wall may cause local mucosal damage during use. The manufacturer has conducted technical performance testing in both live porcine models and bench models to show similar exertion forces as other commercially available products, with favorable results. However, if signs of tissue damage are apparent during use, the NEMO^{TM} Gauge will be removed and the investigators will evaluate the severity of the adverse event and, as needed, will initiate immediate corrective measures. The investigators will determine if any adverse event is attributed to the NEMO^{TM} device. Any serious and/or unexpected adverse device events will be reported to the IRB at the respective site and appropriate federal agencies per their requirements (see Data Safety Monitoring below).

Plan for Communication among IRB:

Any serious adverse events (SAE) associated with this trial will be reported to the local institution IRB immediately in accordance with local reporting regulations. Other non-serious adverse events will be recorded in the local study records and reported to the IRB at the time of continuing review.

Data safety monitoring:

We will follow the FDA guidance, "Medical Device Reporting for User Facilities": (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095266.pdf).

Table 1 - Summary of MDR Reporting Requirements

REPORTER	REPORT WHAT?	TO WHOM?	WHEN?
User Facility	Deaths	FDA and Manufacturer	Within 10 work days
	Serious injuries*	Manufacturer FDA only if manufacturer unknown	Within 10 work days
	Semiannual report of deaths and serious injuries	FDA	January 1 and July 1

*Serious injuries – an injury or illness that is 1) life threatening; 2) results in permanent impairment of a body function or permanent damage to a body structure; or 3) necessitates medical or surgical intervention to preclude permanent damage or impairment.

All deaths and serious injuries at a study site that are determined to be caused by or contributed by the NEMO^{TM} Gauge shall be reported by the site PI, following the site's institutional process for medical device reporting to the FDA; i.e. the same process used for any FDA-approved medical device. The timeline for reporting should follow the FDA requirements as in Table 1 above.

In addition to the required FDA reporting, the site PI will also submit the report (FDA Form 3500A) to the study lead investigator (SLI) within 72 hours of the event. The SLI will then notify all study sites and the IRB at Loma Linda University of such event.

If the site PI did not voluntarily report the event to MedWatch, the SLI will report such event to MedWatch: https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home. Such voluntary reporting to MedWatch will potentially be beneficial to society regarding the risk of the NEMO gauge device.

The SLI will also report other deaths or serious injuries to the FDA, MedWatch, and the IRB at Loma Linda University that have not been reported by the individual sites.

Interim Analysis:

A Data Safety Monitoring Board (DSMB) will be organized to provide oversight of the study. The DSMB will consist of two (2) independent intensivists and one (1) biomedical ethicist

unrelated to the study. Dr. Gerald Winslow, PhD, Vice-President for Mission and Culture at Loma Linda University, will be invited as our ethicist on the DSMB.

The SLI will organize a mid-study interim analysis at one-half enrollment (34 out of total 68 subjects). Data will be analyzed by the study team (including the SLI, site PI's, and statistician). Results of the analysis will include the percentage of correct endotracheal tube position and any adverse events (including serious injuries and deaths) from the use of the NEMO^{TM} Gauge.

The results of the mid-study analysis will be submitted to the DSMB for review. Depending on the number and severity of adverse events, the SLI and DSMB will determine whether enrollment at all study sites should cease.

The SLI will also perform an event related interim analysis throughout the study period if a death or serious injury is determined to be caused by or contributed by the NEMO gauge. The event will be reported to the IRB at Loma Linda University. In such situation, the SLI and DSMB will determine whether enrollment at all study sites should cease until a complete review of the event is completed.

References:

[1] Hagberg C, Georgi R, Krier C. Complications of managing the airway. Best Pract Res Clin Anaesthesiol. 2005;19:641-59.

[2] Salem MR. Verification of endotracheal tube position. Anesthesiol Clin North America. 2001;19:813-39.

[3] Brunel W, Coleman DL, Schwartz DE, Peper E, Cohen NH. Assessment of routine chest roentgenograms and the physical examination to confirm endotracheal tube position. Chest. 1989;96:1043-5.

[4] Lotano R, Gerber D, Aseron C, Santarelli R, Pratter M. Utility of postintubation chest radiographs in the intensive care unit. Crit Care. 2000;4:50-3.

[5] Brunel W, Coleman DL, Schwartz DE, Peper E, Cohen NH. Assessment of routine chest roentgenograms and the physical examination to confirm endotracheal tube position. Chest. 1989;96:1043-5.

[6] Schwartz DE, Lieberman JA, Cohen NH. Women are at greater risk than men for malpositioning of the endotracheal tube after emergent intubation. Crit Care Med. 1994;22:1127-31.

[7] Chen SI, Dharmarajan K, Kim N, et al. Procedure intensity and the cost of care. Circ Cardiovasc Qual Outcomes. 2012;5:308-13.

[8] Goodman LR, Conrardy PA, Laing F, Singer MM. Radiographic evaluation of endotracheal tube position. AJR Am J Roentgenol. 1976;127:433-4.

[9] Conrardy PA, Goodman LR, Lainge F, Singer MM. Alteration of endotracheal tube position. Flexion and extension of the neck. Crit Care Med. 1976;4:8-12.