Linking Investigations in Trauma and Emergency Services

Task Order 0005

Prehospital Airway Control Trial (PACT)
PROTOCOL

VERSION 7
2/13/2023

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PROTOCOL SYNOPSIS

Protocol Title:	LITES Task Order 0005 Prehospital Airway Control Trial (TO-5 PACT)
Protocol Number:	STUDY20110369
NCT Number:	NCT 04100564
Version # and Date:	Version 7 dated 2/13/2023
Investigational Devices:	i-gel, King, LMA (Supreme and Unique)
Trial Sites:	• University of Pittsburgh, University of Pittsburgh Medical Center, PI Jason Sperry, Co-PI Frank Guyette • Additional sites: Please see Appendix I
IDE Sponsor:	Jason L Sperry, MD, MPH
Study Aims:	**AIM#1:** To compare the effect of a standard strategy of airway management vs. a strategy of first attempt with supraglottic airway (SGA) upon 24- hour survival after traumatic injury. **AIM#2:** To compare the effect of a standard strategy of airway management vs. a strategy of first attempt with supraglottic airway (SGA) upon hospital survival after traumatic injury. **AIM#3:** To compare the effect of a standard strategy of airway management vs. a strategy of first attempt with supraglottic airway (SGA) upon major adverse events after traumatic injury.
Study Design:	Open label, multi-center, stepped wedge randomized trial comparing a standard airway management strategy and a strategy of initial use of SGA for airway management of prehospital trauma patients
Planned Sample Size:	2,009
Planned Study Time:	5 year study with 4 years of enrollment
Major Inclusion Criteria:	1. Traumatic injury requiring advanced airway management 2. Transporting (or intended transport) to an enrolling LITES Trauma Center
Major Exclusion Criteria:	1. Less than 15 years of age 2. Pregnancy 3. Prisoner 4. Initial advanced airway attempted by non-PACT provider 5. Cardiac Arrest without return of spontaneous circulation (ROSC) at the time of the intervention 6. Caustic substance ingestion 7. Airway burns 8. Objection to study voiced by subject or family member at the scene
Primary Endpoint:	24-hour survival

1. OBJECTIVE, SPECIFIC AIMS, BACKGROUND, AND SIGNIFICANCE

1.1 OBJECTIVE

Compare standard strategies of advanced airway management to a strategy of initial supraglottic airways in trauma patients within the prehospital setting.

1.2 SPECIFIC AIMS

Airway, Breathing, and Circulation (ABC) support is the prevailing strategy for the management of trauma. Current trauma resuscitation guidelines rank airway management among the highest clinical priorities[1]. The standard approach to prehospital advanced airway management is endotracheal intubation (ETI). However, ETI is difficult and error-prone[2,3]. Delays in airway management have been associated with increased morbidity and mortality. The use of ETI in trauma cases is controversial, and ETI is associated with increased mortality in traumatic brain injuries (TBI)[4,5]. Intubation requires a high burden of training and most Emergency Medical Services (EMS) personnel have limited ETI skill and experience[6,7].

Alternatives to standard advanced airway management include supraglottic airways (SGA) such as the laryngeal tube, i-gel, and laryngeal mask airway. Compared with standard management, SGAs are simpler to insert, an easier skill to learn, and can provide adequate ventilation[8-10]. However, the comparative effectiveness of prehospital SGA and standard management in trauma patients is unknown.

LITES Task Order 0005 aims to compare different strategies of trauma airway management in the prehospital setting with the following aims:

AIM #1: To compare the effect of a standard strategy of airway management vs. a strategy of first attempt with supraglottic airway (SGA) on 24-hour survival after traumatic injury.

Hypothesis #1: The null hypothesis is that 24-hour survival is similar between standard strategy and initial SGA strategy.

AIM #2: To compare the effect of a standard strategy of airway management vs. a strategy of first attempt with supraglottic airway (SGA) on hospital survival after traumatic injury.

Hypothesis #2: The null hypothesis is that hospital survival is similar between standard strategy and initial SGA strategy.

AIM #3: To compare the effect of a standard strategy of airway management vs. a strategy of first attempt with supraglottic airway (SGA) on major adverse events.

Hypothesis #3: The null hypothesis is that the incidence of major adverse events is similar between standard strategy and initial SGA strategy.

1.3 BACKGROUND and SIGNIFICANCE

Prehospital trauma airway management is a low frequency, high consequence event

for both military and civilian providers. Airway management failures account for 8 to 15% of combat deaths deemed to be potentially preventable[11-13]. Prehospital airway management consists of some combination of basic airway maneuvers and bag valve mask (BVM) ventilation to temporize the patient, followed by advanced management with either ETI, SGA, or a surgical airway (SA) procedure. While ETI is the gold standard in prehospital airway management, its safety and efficacy have been questioned, particularly following trauma and traumatic brain injury[5]. However, other investigators have demonstrated associations between survival and ETI in trauma patients, resulting in equipoise based on the existing literature[11].

In both civilian and military prehospital environments, the acquisition and maintenance of the skills necessary for airway management are exceptionally difficult. Previous studies on ETI have indicated that prehospital providers require 10 or more intubations to obtain proficiency and approximately 5 to 12 intubations per year to maintain proficiency[7]. Yet, the average prehospital provider performs fewer than two interventions per year[6]. Lairet et al. describe ETI as the most frequently missed lifesaving intervention, accounting for 53% of missed interventions in combat[12]. The reasons for ETI failure are complex and include patient, provider, and environmental factors[13].

The current alternative used in military airway management is surgical airway procedures. While these account for only 1.8% of military prehospital airway procedures, they account for 12% of missed lifesaving interventions. While the success of the procedure is as high as 82%, SA is also a rare procedure for which training and experience are limited[12].

SGAs have been shown to require less time and less practice to achieve proficiency to place[8,9]. Although older devices performed poorly in military use, newer devices may have several advantages over standard management strategies, including ETI. The devices in the newer generation have simplified insertion procedures, lack balloons, do not require syringes for inflation, and have ports that allow for venting and decompression of the stomach.

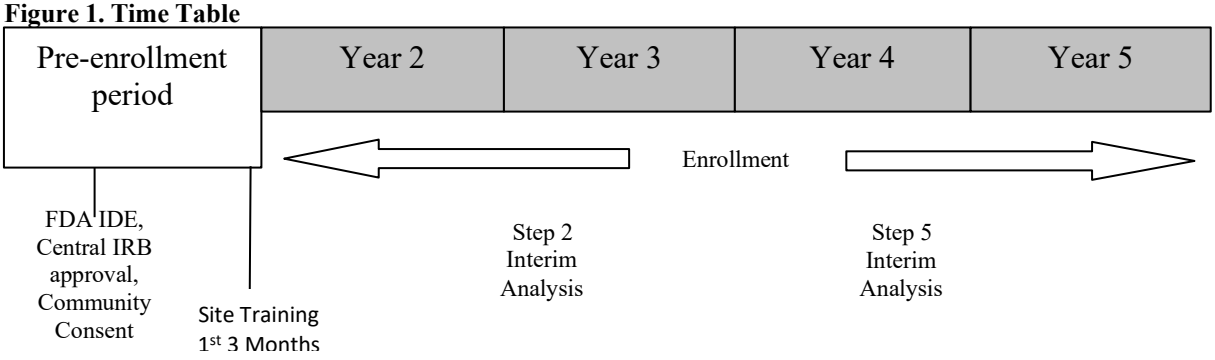
In addition to their speed and ease of use, SGAs can be placed blindly without the need for the additional equipment required for a laryngoscopy. In tactical situations, blind insertion techniques may limit tactical exposure and improve light discipline[14]. SGAs have been associated with shorter prehospital scene times, which may translate into reduced risk for the provider and decreased patient mortality. Use of SGAs may also be a less perishable skill than the use of ETI, allowing for better retention and faster pre-deployment training.

2. RESEARCH DESIGN AND METHODS

2.1 CLASSIFICATION AND METHODOLOGICAL DESIGNS

We propose the LITES Task Order 0005 Prehospital Airway Control in Trauma (PACT) trial, a 5-year (4-year enrollment), open label, multi-center, stepped wedge randomized trial comparing standard airway management strategy and a strategy of initial use of SGA for the airway management of prehospital trauma patients (Figure 1). The trial will be carried out at sites within the LITES Network. The LITES Network is an operational trauma center consortium with the expertise, track record, and confirmed capabilities to conduct prospective, multicenter, injury care and outcomes research relevant to the U.S. Department of Defense.

Figure 1. Time Table



2.1.1 Randomization

PACT will employ a stepped wedge design (Figure 2) in which all participating EMS agencies transition from the control arm, standard airway management strategy, to the intervention arm, initial SGA strategy, with some agencies applying the intervention before others[15]. Once an agency has stepped to the initial SGA arm, they will remain assigned to this arm for the remainder of the study. Blinding is not possible with this intervention. This trial design allows us to perform a pragmatic trial for an intervention strategy that has agency level variation as a result of differences in provider makeup (EMT/paramedic, dual paramedic, paramedic/nurse), transport mode (air/ground), the availability of rapid sequence intubation (RSI), the use of adjuncts (oropharyngeal and nasopharyngeal airways, tracheal introducers, video laryngoscopy), and training.

The trial will be conducted over approximately 48 months with 17 prehospital agencies crossing from standard care arm to intervention arm in one of seven periods. 287 subjects will be enrolled in each enrollment period, before stepping to the next enrollment period. This will continue until 1,722 subjects are enrolled, when all prehospital agencies will be exposed to the intervention arm.

Figure 2. Schematic illustration of the PACT stepped wedge randomized trial with six steps.

Approx. time	Year 1		Year 2		Year 3		Year 4
Enrollment period → Step number ↓	287 subjects	574 subjects	861 subjects	1,148 subjects	1,435 subjects	1,722 subjects	2,009 subjects
1							
2							
3							
4							
5							
6							

	Standard care (control arm)
	Initial SGA (intervention arm)

2.2 BRIEF DESCRIPTION OF STUDY DESIGN

Standard Care Arm: Airway management in the standard care arm of this pragmatic trial will be dictated by local protocols. We will accrue data on all participants who met all the inclusion criteria and none of the exclusion criteria regardless of which airway management strategy is utilized.

Initial SGA Arm: EMS agencies randomized to the intervention arm will follow a strategy of initial advanced airway management with an SGA. Airway management of eligible subjects will be initiated at any time between EMS initial contact and the transfer of care to the receiving trauma center. Only the initial advanced prehospital airway management strategy is dictated by the study protocol; all other interventions, including preparation and subsequent attempts at advanced airway management, will be dictated by local protocols.

In the event that a prehospital provider is unable to complete preparations, such as bag valve mask ventilation, and place an advanced airway, the subject will be retained and analyzed according to the intended arm assignment.

In both arms, study data will be abstracted from EMS records, including indications for airway management, vital signs, use of adjuncts, pharmacological treatment, and timing of interventions and will be entered into an electronic data management system.

2.3 COORDINATION OF STUDY

2.3.1 Clinical Coordinating Center (CCC)

Clinical Coordination specific to the PACT trial will be performed by LITES Network Coordinating Center and its dedicated research team at the University of Pittsburgh. The CCC's responsibilities include all regulatory requirements, provider and coordinator training, and clinical monitoring.

2.3.2 Data Coordinating Center (DCC)

Data Coordination specific to the PACT trial will be performed by the Epidemiology Data Center (EDC), led by Dr. Wisniewski at the Graduate School of Public Health at the University of Pittsburgh. The DCC will design data collection forms, build and maintain an electronic data management system, provide training and technical assistance for site-based data entry personnel, develop and implement quality control mechanisms (including in-person and remote monitoring), and produce reports. The DCC will also plan, coordinate, and carry out all statistical analyses and make the datasets available for public use after the trial is over.

2.3.3 Training and Participating Site Coordination

The CCC is responsible for all research coordinator training and prehospital provider training. Research coordinators, prehospital providers, and associated staff will be trained during the months prior to the trial start date on the scientific basis for the trial, specific inclusion and exclusion criteria, data collection and processing, prehospital procedures, and standard operating procedures (SOPs). Training verification and retraining will occur if new staff members are hired at individual participating sites. Trial enrollment will be tracked monthly using the web-based data platform. Screening, enrollment, and data completeness and accuracy will be assessed via a site visit (in-person or remotely) initially after the first three subjects are enrolled. Subsequent monitoring visits will then occur at least twice annually.

During the site initiation visit and the visit prior to the site switching strategies, we will review the participating EMS agencies' airway protocols. Specifically, we will reinforce the assessment and treatment of inadequate ventilation using an advanced airway. We will review recognition and treatment of incorrect placement of the device, dislodgements, air leak and possible laryngospasm. We will review strategies for management of patients who have vomited at any time during the prehospital period including suctioning and gastric decompression following the placement of the advanced airway. We will address sedative and analgesic medication administration to facilitate advanced airways in accordance with the EMS agencies' local protocols. All EMS agencies will review absolute and relative contraindications to advanced airway placement including but not limited to caustic ingestion, inability to open the mouth, and gagging on insertion of the device.

2.4 STUDY DEVICES

2.4.1 Study Device Dispensing

As part of the pragmatic design of the study, prehospital services will continue to utilize the specific airway management devices that are already in use and in supply at their respective agencies. Although the SGAs used on enrolled subjects during the interventional arm will be considered investigational devices, they will not be provided by the study.

2.4.2 Device Selection

The study will focus on airway management strategies using second generation SGAs as our intervention. Second generation SGAs have fewer fail points than the previous devices. Additionally, prehospital providers have a higher first pass success rate and novice users generally find the devices easier to place, decreasing the amount of training required and lessening the burden of skill maintenance. SGAs employ a rapid, blind technique for placement that requires less equipment then endotracheal intubation. SGAs also provide a less invasive airway management strategy which may allow the provider to focus on other time dependent tasks.

To emphasize the comparison of the airway management strategy rather than the individual device, EMS agencies will continue to use the device they currently have in service. As a pragmatic trial we will not ask them to change devices or training regimens. We plan *a priori* subgroup analyses to examine differences in SGA type used within the intervention strategy.

2.4.3 Device Accountability

SGAs used in enrolled subjects will be tracked per FDA requirement. As these devices are already in use by the prehospital services per their standard care protocols and will not be provided to the agencies by the study, we will only be tracking the individual devices that are used in enrolled subjects in the investigational arm. Tracking of these study devices will be consistent with record-keeping and other responsibilities as required under 21 CFR 812.

2.4.4 Rescue Strategy

Only the initial attempt at advanced airway management is dictated by study protocol. All subsequent attempts at management will be at the provider's discretion and will be based on local protocol.

2.5 STUDY ENDPOINTS

Primary Outcome: The primary outcome for the trial is 24-hour survival.

Secondary Outcomes: Secondary outcomes include survival to hospital discharge, expected clinical events (including incorrect placement of the airway, inadequate ventilation, airway trauma, or concern for aspiration as defined as documented vomiting and/or need for suctioning), airway management performance (including initial pass success, overall success, and use of rescue technique), ICU length of stay, ventilator days, and expected adverse events including airway trauma, pneumothorax, incidence of acute respiratory distress syndrome (ARDS) and incidence of ventilator associated pneumonia (VAP).

Primary Outcome Definition:

24-hour Mortality: A binary variable defined as death within 24 hours

Secondary Outcome Definitions:

Secondary outcomes will be assessed from arrival at the trauma center through day 30 or discharge, whichever is first.

In-Hospital Mortality: A binary variable defined as death recorded any time after hospital arrival.

Airway Management Performance: The elements of airway management performance include airway misplacement (including endotracheal tube misplacement), initial pass success (the successful placement of device on the first attempt past the teeth confirmed by EtCO2), sequence of airway insertion, airway insertion success and time, number of airway insertion attempts, inadequate ventilation, and any instances of airway conversion (change of airway in the first 24 hours).

Acute Respiratory Distress Syndrome (ARDS): The Berlin definition for mild ARDS (PaO2/FIO2 ≤ 300 mm Hg plus timing, imaging, and origin criteria) will be utilized as a threshold value to determine the incidence of ARDS within 24 hours of presentation. We will further stratify patients into mild, moderate (PaO2/FIO2 ≤ 200 mm Hg), or severe (PaO2/FIO2 ≤ 100 mm Hg) ARDS.[16]

ICU length of stay (LOS): Defined as the number of days spent admitted to the Intensive Care Unit. ICU LOS will be recorded to the first decimal place.

Ventilator Days: Defined as number of days on a mechanical ventilator. Ventilator days will be recorded to the first decimal place.

Ventilator Associated Pneumonia: A binary variable defined as VAP in the first 24 hours as evident by a new infiltrate on chest image and ≥1 of the following: temp >38 or less than 36 degrees C, WBCs >12,000, purulent secretions from the airways and or reduction in gas exchange (PaO2/FIO2 ≤ 300 mm Hg). (Michetti Trauma 2012)

Other Adverse Events: Binary variables defined as the onset of one of the following adverse events in the first 24 hours after enrollment: oropharyngeal trauma, hypopharyngeal trauma, pneumothorax, aspiration pneumonitis, ARDS, and VAP.

2.6 STATISTICAL ANALYSIS

2.6.1 Statistical Analysis Plan

The analyses will describe the baseline demographic and clinical characteristics of the overall

population first by randomization unit (agency or combination of agencies), and then stratified by airway management strategy (standard management compared to initial SGA). A separate analysis for each step will be performed. For discrete variables, proportions will be generated and a chi-square test will be used to test for differences between the proportions. For continuous characteristics, means (medians) and standard deviations (interquartile ranges) will be calculated and t-tests (Wilcoxon) will be used to compare the means (distributions) among those with standard airway management vs. those managed by initial SGA. Variables that are imbalanced will be included as a covariate in multivariable models when assessing the association between strategy and outcomes.

We will calculate the difference in outcomes divided by the estimated "robust" standard error based on the Huber-White sandwich estimator in order to account for within-randomization unit correlation and variability, which might depart from the classical assumptions. To quantify the treatment effect, we will calculate the 95% confidence interval for the difference in event rates. We will perform the analysis on an intention-to-treat (primary analysis) and treatment-received (secondary analysis) bases.

Hypothesis #1: For the primary outcome, an indicator of death within 24 hours will be generated for each participant. A generalized linear mixed model (i.e. logistic regression model) will be used to assess the independent impact of initial SGAs on 24-hour survival, with a random effect of randomization unit a fixed effect for each step, and fixed effects of airway management (standard vs. initial SGA) and the potential confounding effects of baseline characteristics. The estimated intra-randomization unit correlation and time effect from this model will be reported to help design future randomized trials and to describe the potential confounding effects of calendar time. For time-to-event data, a mixed effects Cox-proportional hazards regression model will be used to assess the independent impact of airway management strategy on time to death, with randomization unit as a random effect and step, airway management strategy, and the potential confounding effects of baseline characteristics not balanced through random assignment as fixed effects.

Hypothesis #2: The same analytic approach that was carried out for hypothesis #1 will be implemented, but the outcome of interest will be survival to hospital discharge.

Hypothesis #3: The analytic approach for the secondary outcomes will vary based on the type of outcomes. For binary outcomes (e.g., 24-hour and in hospital mortality, ventilator associated pneumonia, and post-traumatic ARDS), the same analytic approach that was carried out for Hypothesis #1 will be implemented. For continuous outcomes (e.g., hypotension or hypoxia dose) a generalized linear mixed model (i.e., linear model) will be used to assess the independent effect of airway management strategy on outcome, with a random effect of randomization unit, a fixed effect for each step, and fixed effects of airway management strategy (standard airway versus initial SGA) and the potential confounding effects of baseline characteristics.

Subgroup Analysis: The general approach to assessing the homogeneity of a treatment effect across subgroups will be to include an interaction term between the use of airway management strategy (standard versus initial SGA) and the characteristics defining the subgroup in the regression model. A statistically significant interaction term would indicate that the null hypothesis of a homogenous effect can be rejected, indicating a differential effect from airway management strategy across the subgroups. For example, when examining the homogeneity of the effect of airway management strategy on the primary outcome among those with and without a TBI, the logistic model will be modified to include a main effect for TBI and the two-

way interaction between airway management strategy and TBI.

2.6.2 Sample Size Determination

This stepped wedge randomized control trial will use 24-hour mortality as its primary outcome to power the trial. This sample size was calculated using the formula presented by Hemming and Taljaard and takes into account the design feature that airway management strategy will be switched from standard care to initial SGA sequentially by 17 prehospital agencies over 7 time periods (6 steps).[17] The intra-randomization unit correlation coefficient (ICC) for the primary outcome was assumed to be 0.025 based on preliminary data from Pittsburgh's prehospital agencies. To detect a decrease from 16.7% to 9.7% (a difference of 7%), with 80% power at 5% significance level, a sample size of 1,904 will be required. To account for 5% dropout, we will need to enroll 118 participants from each of the 17 prehospital agencies over the seven enrollment periods (17 participants per agency per period). Therefore, the total required sample size is 2,006, however, to enroll equal numbers of patients in each enrollment period, we will enroll 2,009 patients.

2.6.3 Predefined Subgroups

Predefined subset analyses will be performed on: 1) participants with drug assisted advanced airway management, 2) participants treated by air medical services as compared to ground services, 3) services with video laryngoscopy, 4) participants with significant traumatic brain injury (Head Acute Injury Score (AIS) > 2) versus those without significant brain injury (Head AIS $\leq$ 2), 5) participants enrolled from the scene of injury versus those enrolled from a referral hospital, 6) participants who suffered blunt injury as compared to those who suffered penetrating injury, 7) participants with high versus low field to ED transport times (median split subgroups), 8) participants with BLS airway management prior to arrival the of the PACT participating agency, and 9) participants that were in arrest at the time of enrollment that achieved return of spontaneous circulation (ROSC).

We recognize that the trial is not appropriately powered for these subgroup comparisons; therefore, the results and conclusions formulated from these subgroup analyses will be considered exploratory in nature and will not be used as a basis for treatment recommendations.

2.6.4 Enrollment of Ineligible Patients

It is anticipated that there will be a small proportion of patients who are deemed eligible by a participating EMS agency and treated with the intent to enroll but are later determined to have been ineligible. In this circumstance, an intent to treat principle will be followed, dictating that their data be analyzed according to the intended arm of treatment. Subgroup analyses based on eligibility criteria will be performed if the number of ineligible patients is large.

2.6.5 Non-Adherence

In some circumstances, subjects may receive standard care instead of an initial SGA when on the treatment arm. In keeping with the intention-to-treat analytic design, these participants will be analyzed according to the intended arm of treatment.

2.6.6 Interim Analyses

Prior to initiation, and in concert with the DSMB, the final monitoring plan will be developed to serve as a guide to the DSMB's decision-making process concerning early stopping of the trial. In making the decision to recommend termination of the trial, the DSMB will be guided by information on safety outcomes by treatment group.

Two interim safety analyses will be conducted, one at the completion of the second step (third period) and one at the completion of the fourth step (fifth period, out of seven periods). The frequency of the composite safety outcome (mortality, failure to place an advanced airway on first attempt, failure to

ventilate) in the two groups will be summarized. The null hypothesis that there is no difference in the proportion of the rate of the composite safety outcome between the two groups will be tested using a generalized linear mixed model. Group sequential methods, such as a Lan and Demets approach with an O'Brien and Fleming spending function will be used to ensure that the overall type I error rate of 0.05 is maintained across the three tests (two interim and one final), with the majority of the type I error reserved for the final test. Based on the expected recruitment of 287 participants per period (2,009/7 periods), we expect a sample size of 861 for the first interim analysis (information fraction of 43%) and 1,435 for the second interim analysis (information fraction of 71%). For the first interim analysis the upper/lower boundaries will be +/- 3.22 with a nominal alpha level of 0.001. The second interim analysis will have upper/lower boundaries of +/- 2.42 with a nominal alpha level of 0.015. The final analysis will have upper/lower boundaries of +/- 2.00 with a nominal alpha level of 0.045.

Further—and in relation to the interim safety analyses—safety data by group will be provided periodically to the DSMB. Safety data serious adverse events include frequency, a description of each event, and the date of each event.

2.6.7 Handling Missing Data

The general strategy for missing data will concentrate on a tactical approach rather than only on an analytical one. The goal is to prevent missing data as much as possible because there is no analytical methodology that can recover the robustness and unbiased character of estimates derived from a complete case scenario. We expect very little missing data due to the nature of the trial design and related preparation and efforts to realize a well-conducted clinical trial. Because the intervention spans a short time and takes place mostly during the prehospital phase, we do not expect a considerable dropout during the treatment phase. Because we expect about 5% dropout, we have inflated the sample size by 5% to reduce the related effect on power adequacy.

For interim and final analyses, we will use multiple imputation for the final value for participants whose 24-hour mortality cannot be determined. For sensitivity analyses, we will report the data with and without multiple imputation. We will also report an analysis consistent with that used in other trauma studies, which count those with missing data as 'alive' and 'dead' using the overall mortality rate for the trial at 24 hours. Missing data will be documented along with the related causes, continuously monitored, and mitigated accordingly. The electronic data management system prevents study personnel from skipping questions and requires an appropriate missing data code.We will assume that data are not missing at random. A likelihood-based analysis, including regression, multiple imputations, and random-effects regression models could be implemented in this regard. Missing outcomes can be predicted from individuals' observed data using models based on observed individuals. The final analyses will explicitly state the assumptions underlying the treatment of missing outcomes and explain the use of compressive data descriptions and sensitivity analysis. Sensitivity analysis will allow us to explore the robustness of conclusions compared to alternative plausible assumptions. We will follow the CONSORT statement in reporting the number of randomization units with missing outcome data by treatment arm.[18] All methods used in treating missing data will be adequately reported.[22]

2.6.8 Data Management

Data Sources: Data will be collected prospectively while care progresses and abstracted later from patient records. Abstraction will include a review of the ground and air medical patient care report(s), emergency department records, and hospital records, both electronic and on paper.

Data Entry: The DCC will create an electronic data management system that will include a password protected SSL website for data entry by participating sites with built in dynamic features such as data encryption, user authentication, range and data type checks, real time reports, data corrections tracking, and the capability to save and reload incomplete forms. The DCC will also draft a comprehensive data management manual that includes detailed instructions and provide training and technical assistance. Subjects will be identified by a study ID only. Sites will be required to store hard copy source documentation separately in a secured, locked cabinet.

Database Management: A two-tiered database structure will be created. A front-end database will serve the needs of web entry at the sites, using a database management system well suited to handling updates from multiple interactive users. The data from this database will be transferred on a regular schedule to a data repository that can be used by statistical software packages. These data sets will be the basis of data queries and monitoring reports. Various versions of this database will be kept as needed, such as for quarterly performance reports. Access to data will be limited to those who need access to perform their tasks. The database management system can manage large quantities of data, merge data from multiple databases as required, handle complex and possibly changing relationships, and produce analysis datasets that can be imported into a variety of statistical analysis packages. Data will be backed up at regular intervals, with full transaction log files in use, and copies of the data will be stored offsite with a secure service. Servers will be migrated to a new host in the event of a hardware failure. All servers are behind an enterprise firewall and access must be granted through the firewall even within the University network.

2.6.9 Data Elements

Prehospital Elements: To include (but not be limited to) scene time, vital signs, times and description of prehospital interventions, procedure type(s), device type(s), airway adjuncts used, rapid sequence intubation, associated medications and dosages used, number of procedure attempts, reason for failed attempt(s), progression to surgical airway, time to successful airway management, time to advanced airway, procedure complications, time and dose of any medications administered (for induction, post intubation sedation, and resuscitation), transport time, vital signs during transport, times and description of interventions provided during transport, and mode(s) of transport (e.g. ground, air). Also includes provider level data—including level of training—and system level data, including staffing, service volume, frequency of airway management, and ambulance location (rural/urban).

In-Hospital Elements: To include (but not be limited to) relevant vital signs, relevant laboratory studies (including arterial blood gases), and interventions (especially time to extubation and/or reintubation as applicable). Ventilator associated pneumonia, post- traumatic acute respiratory distress syndrome (ARDS), and patient disposition will also be collected.

Outcome Elements: To include (but not be limited to) 24-hour survival, hospital length of stay, length of stay in ICU, ventilator days, and in-hospital survival through day 30.

Exploratory Analyses: To include (but not be limited to) associations that may represent the underlying mechanisms associated with airway management's effect on 24-hour survival. When the necessary data are available, we will examine time to definitive airway, exposure to hypoxia,

superoxia, hypotension, hypocarbia and hypercarbia. Exposure will be examined as a categorical value and as a continuous variable calculated as a function of depth (calculated from a given normal value) times duration. The value of this expression will be regressed to look for an association with mortality.

2.7 QUALITY CONTROL, ASSURANCE, AND CONFIDENTIALITY

2.7.1 Protocol Compliance

The participating site investigators will not intentionally deviate from the protocol for any reason without prior written approval from the IRB, except in when the safety of the research participant is at risk. In that event, the site investigator will notify the IDE Sponsor and the reviewing IRB immediately, if possible, and request approval of the protocol deviation. If prospective IDE Sponsor and IRB approval is not possible, the site investigator will notify the IDE Sponsor and reviewing IRB promptly following the respective protocol deviation. The site investigator will inform the reviewing IRB of all protocol deviations and unanticipated events involving risks to the research subjects and others and will obtain prospective IRB approval for all proposed protocol changes. Persistent or serious noncompliance may result in termination of the site's participation in the clinical trial.

2.7.2 Protocol Deviations **and unexpected problems:**

Successful implementation of the trial will depend on the protocol being carried out as intended. Sites will be expected to closely monitor activities at the level of the patient, EMS agency and site, report protocol deviations promptly using the electronic data management system, and take necessary actions (including retraining), as appropriate, to bring about a resolution and/or prevent a recurrence. The CCC and DCC, meanwhile, will be tracking activities at the trial level. Serious deviations will be discussed with the other investigators, the DOD, and the FDA to see if the protocol needs to be amended or recruitment put on hold.

2.7.3 Privacy and Confidentiality:

The site investigators and members of their research teams will make a reasonable effort to ensure the confidentiality of research subjects. Subjects' names and other identifiable information will be kept in a secure, locked, limited access area separate from the electronic data management system.

2.7.4 Investigator Responsibilities

The site investigators will agree to implement the IRB approved protocol and to conduct the trial in accordance with 21 CFR Part 812, Subpart E, and the ICH GCP Guidelines (E6, Section 5), as well as with all applicable national, state and local laws. The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH / Good Clinical Practice, and with applicable regulatory requirements.

3. HUMAN SUBJECTS

TO 0005 PACT will be conducted under the federal provisions governing Exception from the Requirement for Informed Consent for Emergency Research (21 CFR 50.24), including community consultation, public notification, and the notification of participants or their legally authorized representative as soon as feasible after enrollment. Notification may be through oral and/or written communication and will include the opportunity to opt out from ongoing participation.

Community consultation as determined by the IRB will be undertaken prior to final IRB approval. Because the population eligible for enrollment includes all citizens in the trial regions, it will not be possible

to target any particular small group. Feedback from the community regarding any concerns they may have about potential enrollment will be obtained by research personnel. Public notification and community consultation, as directed by the IRB, may include the use of electronic surveys, ads in local media outlets and on public transportation, and/or consultation with community leaders. Due to their ongoing participation in numerous multicenter research studies involving emergency research, the institutions participating in PACT have significant experience with community consultation and notification practices.

3.1 SUBJECT POPULATION

TO 0005 PACT will include prehospital patients who are experiencing traumatic injury, require advanced airway management, and are receiving care from participating EMS agencies. The trial will include only EMS agencies with personnel capable of performing advanced airway management including ETI and SGA placement.

3.2 INCLUSION CRITERIA

1. Traumatic injury requiring advanced airway management. Indicators of the need for advanced airway management include: a) GCS < 8, b) SpO2 < 90 despite supplemental oxygen, c) ETCO2 > 60 despite supplemental ventilation, or d) provider discretion.
2. Transport (or intended transport) to an enrolling LITES Trauma Center

3.3 EXCLUSION CRITERIA

1. <15 years of age
2. Pregnancy
3. Prisoner
4. Initial advanced airway attempted by a non-PACT provider
5. Cardiac arrest without ROSC at time of intervention
6. Caustic substance ingestion
7. Airway burns
8. Objection to study voiced by subject or family member at the scene

Inclusion and exclusion criteria will be assessed based on information available at the time of enrollment, defined as the time on scene by the Enrolling EMS Agency. Although all reasonable efforts will be made by the emergency medical crew to either directly witness or obtain documentation of eligibility criteria, due to the nature of the emergency prehospital setting, there may be occasions where the emergency medical crew must rely on verbal report of eligibility criteria from referring hospital or emergency crew. In these instances, if, after subsequent review of outside hospital and/or ground crew documentation, it is determined that the subject did not meet eligibility criteria, the subject will remain enrolled in the study based on the intention-to-treat principle but the incident will be reported as a protocol deviation and the patient will be excluded from the per protocol group for the purpose of analysis.

All patients are prospectively enrolled. The interventions, including standard care, are completed prior to arrival at the hospital. Any patient not identified as an enrollment at the time of treatment will be a missed enrollment. After the interventions are applied, the medical director, who is ultimately responsible for enrollment, will confirm the patient met all inclusions and none of the exclusion criteria. A grace period of three business days is allowed for clarification of an enrollment for those instances where incomplete or conflicting information is provided. If this occurs, documentation in the form of email communication or an addendum to the chart by the crew member will be used to clarify the intent of enrollment by the EMS clinician.

If a verbal report must be used in lieu of physical documentation or directly witnessing eligibility criteria, documentation of the verbal report will serve as the source documentation for determining eligibility. Verbal reports will be documented outlining the source as well as the details.

4. IRB APPROVAL AND FDA AMENDMENTS

A central IRB at the University of Pittsburgh will be utilized for the regulatory needs of this trial. All current LITES Network sites have IRBs that have experience and engagement with central IRB procedures.

The Investigator will obtain from the University of Pittsburgh Institutional Review Board (IRB) prospective approval of the clinical protocol and corresponding informed consent form(s) as well as modifications to the clinical protocol and corresponding informed consent forms.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event that the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IDE application, or in the event of the Investigator's decision to modify the previously accepted clinical protocol, the Sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IDE describing any change to the protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

5. ENROLLMENT AND INFORMED CONSENT PROCEDURES

5.1 ENROLLMENT METHODS:

Potentially eligible patients will be identified prospectively by air medical and ground transport personnel trained on and familiar with the inclusion and exclusion criteria. The intervention will take place in the prehospital environment, performed by personnel trained in prehospital trauma airway management. Those who meet all inclusion and no exclusion criteria will be assigned to standard care or initial SGA based on the randomization arm currently active for that EMS agency. EMS personnel will notify site personnel of enrollments. Once notified, site personnel will review inclusions and exclusion criteria to verify eligibility and report protocol deviations.

There will be some instances where, despite the original intentions of the EMS provider, enrolled subjects will ultimately be transported to non-participating hospitals. In these instances, we will retain these subjects as enrolled and will notify them of their enrollment into the trial, but we will not anticipate receiving any data from their in-hospital encounter. 24-hour mortality may be obtained by searching public records for vital status or by other sIRB approved means.

5.2 2 INFORMED CONSENT PROCEDURES

All guidelines and requirements for notification for exception of consent for emergency research will

be followed. Patients with major trauma who require advanced airway management during or directly preceding emergency medical transport are experiencing an immediate life-threatening condition, with the patient commonly intubated, unconscious, or not responsive. In this emergent situation, it will not be possible to contact legal representatives at the time of study enrollment. Research coordinators will make every effort to contact legal representatives as soon as feasible after admission to the hospital to notify them that the subject was enrolled in a randomized trial and to attempt to obtain consent for ongoing data collection. Such notification will be in person whenever possible. Summary of these efforts will be documented. If the subject becomes competent during the study period, then he/she will be approached by research personnel for notification of enrollment and a similar provision of an opportunity to opt out from ongoing data collection.

The investigators will utilize social workers, law enforcement personnel, or any other available means to try to locate the patient's legally authorized representative. If that search is unsuccessful, a notification letter will be sent to the subject's authorized representative explaining the study and providing contact information for answering questions. The letter will be sent via a traceable method, such as registered mail or by UPS, and documentation of the addressee and date of mailing will be kept.

If the subject expires prior to being notified or obtaining consent, a letter of notification of enrollment will be sent to the subject's representative via a trackable method. This letter will contain important details describing the study, as well as provide contact information for the study team and/or the IRB to allow the family to ask questions or express concerns with the study.

If the subject recovers quickly or unexpectedly and is discharged from the hospital prior to the study team notifying and obtaining consent, a notification will be mailed to the subject via a trackable method.

6. DATA AND SAFETY MONITORING

6.1 DATA SAFETY MONITORING BOARD

A Data and Safety Monitoring Board (DSMB) will be appointed to review TO 005 PACT and to provide recommendations about trial continuation to the IDE Sponsor. After initial approval and at periodic intervals (to be determined by the committee) during the trial, the DSMB responsibilities are to:

a. Review the research protocol, informed consent documents, and plans for data and safety monitoring.
b. Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, subject enrollment and retention, subject risk versus benefit, adverse events, unanticipated problems, performance of the trial sites, and other factors that can affect the trial outcome.
c. Consider relevant external information, such as scientific or therapeutic developments that may have an impact on the safety of the subjects or the ethics of the trial.
d. Review clinical center performance, make recommendations, and assist in the resolution of problems reported by the IDE Sponsor or site investigators.
e. Protect the safety of the trial subjects.
f. Report on the safety and progress of the trial.
g. Make recommendations to the IDE Sponsor and, if required, to the FDA concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the intervention.
h. Monitor the confidentiality of the trial data and the results of site monitoring
i. Assist the IDE Sponsor by commenting on any problems with conduct of the trial, enrollment, sample size, and/or data collection.

The DSMB will include experts in emergency medicine, surgery (trauma / critical medicine), bioethics, and biostatistics. DSMB members must be independent of the investigators and have no financial, scientific, or other conflict of interest with the trial. Written documentation attesting to the absence of conflict of interest will be required.

The University of Pittsburgh Office of Clinical Research, Health Sciences will provide logistical management and support for the DSMB. A safety officer (chairperson) will be identified at the first meeting. This person will be the contact person for serious adverse event reporting. Procedures for this will be discussed at the first meeting.
The first DSMB meeting will take place before trial initiation to discuss the protocol, approve the commencement of the trial, and establish guidelines to monitor the trial. The frequency of further meetings will be determined during the first meeting. An emergency meeting of the DSMB will be called at any time by the chairperson should questions of subject safety arise.

6.2 DATA SAFETY MONITORING PLAN

Monitoring of safety and data quality in the proposed study will be the responsibility of all personnel on the project, with primary responsibility and supervision by the Investigator. The Institutional Review Board will approve the Statement of Informed Consent for the study and provide institutional oversight of data and safety issues. The study protocol will be approved prior to enrolling any participants. Moreover, the study will be reviewed at a minimum of annual basis (or more frequently as deemed necessary) by the IRB committee. Regarding monitoring of data quality and protected health information, all required personnel proposed for this project will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing source documents containing patient identifiers in locked cabinets within locked offices or locked data rooms, using study IDs rather than subject identifiers in the electronic data management system, and aggregating data across subjects. The key linking subject names and study identification numbers will be kept separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers. Oversight of all aspects of data management will occur with the DCC.

6.2.1 Parameters to be Monitored

The following parameters will be monitored by the DSMB throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data.

- An evaluation of the progress of the research study, including subject enrollment and retention as well as an assessment of the timeliness and quality of the data.
- A review of collected data (including adverse events, unanticipated problems, and subject withdrawals) to determine whether there is a change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated.
- A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

6.2.2 Frequency of Monitoring

The Investigator, sub-investigators, and the research staff will meet regularly to re-evaluate study goals, subject recruitment, data coding and retention, documentation and identification of adverse events, complaints and confidentiality of subjects. There will be an evaluation of the progress of the research study, including assessments of data quality, time lines, participant recruitment, accrual, and retention. The Investigator will also review the outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study

participation and whether the study should continue as originally designed or should it be re-evaluated and changed.

6.3 REPORTABLE ADVERSE EVENTS

An adverse event (AE) refers to any untoward medical occurrence caused by, or associated with, the study or study device(s). All potential AEs will be documented by the sites using the electronic data management system. All reported adverse events will be reviewed in consideration of the treatment arm and further classified by a) Severity (serious or non-serious); and b) Expected or Unexpected. For serious, unexpected adverse events felt to be possibly associated with the research intervention, the Coordinating Center will notify the reviewing IRB, FDA, DSMB, and Department of Defense in accordance with requisite reporting time frames.

Some adverse events are commonly observed in patients following traumatic injury and may or may not be attributable to the airway management. Examples of these include Fat Embolism Syndrome, cardiac arrest, myocardial infarction, sepsis, cerebral bleeding, stroke, Deep Vein Thrombosis (DVT), pulmonary embolus, rhabdomyolysis, abdominal compartment syndrome, upper gastrointestinal bleeds, HITT, extremity compartment syndrome, seizures, surgical interventions, complications due to specific injuries as well as other major medical or surgical complications are commonly observed in these patients.

Some of these events may be recorded as noted in the medical record however, none of the expected events will be reported as adverse events.

6.3.1 Adverse Events Reporting Timeline

A table summarizing reporting timelines is provided below:

Organization	Fatal/Life Threatening Reportable Adverse Event	Non-fatal, non-life threatening Reportable Adverse Event	Expected Adverse Events	Unanticipated Problem (not involving risk)	Unanticipated Problem (involving risk)
IRB	24 hours	10 working days	No requirement	No requirement	10 working days
FDA	7 calendar days	15 calendar days	No requirement	No requirement	14 days*
Dept of Defense	7 calendar days	No requirement	No requirement	No requirement	14 days*
DSMB	24 hours	7 calendar days	No reporting	At next meeting (every 6 months)	14 days*

*Reporting occurs only after an IRB determination of UPIRTSO has been received

6.4 RISKS MANAGEMENT PROCEDURES

6.4.1 Protection Against Risks of Data Collection

The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected. All

demographic and clinical information about the subject will be stored in an electronic password protected electronic data management system under the supervision of the DCC for this protocol. All staff involved in this study will be properly credentialed and instructed in the areas of testing, confidentiality, and safety.

The Investigator will retain the data for the entire period of this study and will retain the specified records and may continue to use and disclose subjects' de-identified information for the purpose of this study for a minimum of seven years after final reporting or publication of the study. If the subject is a minor, records will be retained until his/her age of majority (18 years) and then for seven years, at minimum. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

6.5.2 Protection Against Potential Risks of Experimental Intervention

The investigational devices utilized for this trial are those which are already in use by the prehospital providers. All providers have been trained in the proper use of the devices and demonstrate competency in accordance with their local protocols and regulations.

7. COSTS

There are no additional costs associated with the research study for the subject, subject's insurance, or enrolling provider. Enrolling providers are managing the subject's airway as part of necessary clinical care and are utilizing the devices already in supply just as they would normally.

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Appendix I – Study Sites

*All of the Oregon EMS agencies share training, standard protocols, and clinical competencies. Furthermore, they participate in mutual aid of trauma patients (more than one agency responding to and caring for a single patient). We will step all Oregon EMS agencies at the same time to ensure that patients enrolled in Oregon will have care that is consistent with a single randomization unit.

Site	EMS Agency	Participating Trauma Center(s)
Tulane University	New Orleans EMS	University Medical Center
University of Pittsburgh	City of Pittsburgh EMS	UPMC Presbyterian, UPMC Mercy, Allegheny General Hospital
University of Pittsburgh	STAT MedEvac	UPMC Presbyterian, UPMC Mercy, UPMC Altoona, UPMC Hamot, UPMC Susquehanna, Allegheny General Hospital
University of Pittsburgh	EmergyCare	UPMC Hamot
University of Pittsburgh	Susquehanna Regional EMS	UPMC Susquehanna
Vanderbilt University	Nashville Fire	Vanderbilt University Medical Center
Emory University	Grady EMS	Grady Medical Center
University of Louisville	Louisville Metro EMS	University of Louisville Hospital
University of Louisville	St. Matthews EMS	University of Louisville Hospital
Washington University at St. Louis	Air Evac Lifeteam	Barnes-Jewish Hospital
Washington University at St. Louis	St. Louis Fire	Barnes-Jewish Hospital
East Carolina University	Vidant EastCare	Vidant Medical Center
East Carolina University	Pitt County EMS	Vidant Medical Center
East Carolina University	Wilson County EMS	Vidant Medical Center
East Carolina University	Lenoir County EMS	Vidant Medical Center
Oregon Health & Sciences University	American Medical Response*	Oregon Health & Sciences University Hospital
Oregon Health & Sciences University	Metro West Ambulance*	Oregon Health & Sciences University Hospital
Oregon Health & Sciences University	Hillsboro Fire*	Oregon Health & Sciences University Hospital
Oregon Health & Sciences University	Molalla Fire*	Oregon Health & Sciences University Hospital
Oregon Health & Sciences University	Canby Fire*	Oregon Health & Sciences University Hospital
Oregon Health & Sciences University	Tualatin Valley Fire & Rescue*	Oregon Health & Sciences University Hospital
Oregon Health & Sciences University	Clackamas Fire District 1*	Oregon Health & Sciences University Hospital
Oregon Health & Sciences University	Lake Oswego EMS*	Oregon Health & Sciences University Hospital
Cook County/Chicago	Chicago Fire Department	John H. Stroger Jr. Hospital of Cook County
University of Chicago	Chicago Fire Department	UChicago Medicine
Northwestern University	Chicago Fire Department	Northwestern Memorial Hospital
Mount Sinai	Chicago Fire Department	Mount Sinai Hospital

Appendix II – PACT EFIC PLAN

PACT EFIC Plan

Prehospital Airway Control Trial (PACT)
Open label, multi-center, stepped wedge cluster randomized trial comparing standard airway management strategy and strategy of initial use of SGA for airway management of prehospital trauma patients.

Lead Investigators: Jason L. Sperry, MD, MPH
Frank Guyette, MD, MPH

Supported by: Department of Defense

ClinicalTrials.gov ID: TBD

CONTENTS

INTRODUCTION

The goal of this document is to describe the implementation of the protections associated with 21 CFR 50.24, Exception from Informed Consent (EFIC) Requirements for Emergency Research in the PACT clinical trial. Implementation of this plan is the first phase of conducting the proposed trial. The findings acquired from planned activities will be presented to the Single IRB (sIRB) to help the sIRB assess community attitudes related to the study.

Research involving the acute care of patients with traumatic injury requiring advanced airway management presents ethical challenges. Respecting participants and their autonomy through the informed consent process is a cornerstone of ethical research, but patients with traumatic injuries that require airway support are unable to participate in an informed consent process. When available, a legally authorized representative (LAR) may act as a surrogate decision maker for an incapacitated patient. The LAR can decide if the patient will participate in the research study, even though the wishes of the patient may not be known. However, for many patients with traumatic injuries, no LAR is readily available during the patient's resuscitation and emergency care. Excluding patients without capacity or an available LAR from trauma research does not necessarily defend patient autonomy since the patient's actual wishes are unknown. In fact, when they can be asked, patients and their representatives choose to participate more often than not. Excluding patients without capacity, however, limits the ability to ever scientifically improve care, and makes enrollment in the emergency setting impracticable. Therefore, this study will enroll participants for whom an LAR is unavailable with EFIC.

OVERVIEW

All patients meeting eligibility criteria for PACT will generally be obtunded or comatose and unable to give informed consent to participate. Participants will be enrolled in this trial with exception from informed consent (EFIC) for emergency research under the conditions established at 21CFR50.24.

Upon hospital arrival of an eligible subject, study teams will diligently attempt to determine the patient's identity and the availability of an LAR. Attempts will be made to notify an LAR at the earliest opportunity, and consent to continue in the study will be sought.

<u>Enrollment with EFIC</u>

Upon hospital arrival of an enrolled subject, study teams will diligently try to determine the patient's identity and the availability of an LAR. Both routine hospital and study team resources/processes should contribute to these efforts. The steps undertaken to identify the patient and find the LAR should be documented in the subject record on an informed consent/contact log. Once the LAR is available and as soon as it is feasible, the LAR will be informed of the subject's enrollment in the study. Details of the study, the potential risks, and potential benefits of participating in the study will be explained to the LAR. After discussing the study with the LAR, the LAR will be given the option of allowing the subject to continue study participation, or to withdraw from further participation the study. The LAR will be informed that the decision to continue participation in the study may be withdrawn at any time throughout the course of the study. If the LAR wants to continue the subject's participation, the LAR will sign the informed consent form.

The informed consent/contact log is used to document the continuing efforts to locate an LAR, the notification of the LAR, the consent process, and the decision of the LAR. This log will include the types of attempts made, the number and times of those attempts, and the outcome of each attempt. If the subject regains decision-making capacity, the patient will be notified of the study and will be asked if he or she wants to continue the study. If no LAR is found and the subject never regains decision-making capacity, the subject will remain enrolled under EFIC. For subjects who expire prior to identification of an LAR, consent is not obtained. If an LAR is eventually located, they should be notified of the subject's participation. In the rare case where an LAR cannot be found and the subject remains incapable of consent at 30 days post admission, attempts to find an LAR will be discontinued, but documentation of the LAR search process until that time, and the subject's decisional capacity, will be documented.

<u>Withdrawal from Participation</u>

An LAR may withdraw the subject from further participation at any time and for any reason. If the subject regains consciousness and decision-making capacity, subjects may also withdraw from further participation. Whenever possible, the reason for wishing to withdraw should be determined. Consistent with OHRP and FDA guidance, participant data collected prior to withdrawal from the study is maintained in the study database, but no additional participant data will be collected from the participant or their medical record following withdrawal from the study.

REGULATORY CRITERIA FOR USE OF EFIC

FDA regulations identify the specific circumstances in which EFIC is appropriate. PACT fulfills these requirements for emergency research. In the following section, the components of the regulation are reproduced (in italics), along with an explanation of how PACT will comply with each requirement.

Traumatic injury requiring advanced airway management is life-threatening and available treatments are unsatisfactory or unproven.

> *21 CFR 50.24(a)(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.*

Prehospital trauma airway management is a low frequency, high consequence event for both military and civilian providers. Airway management failures account for 8-15% of trauma deaths deemed to be potentially preventable. Prehospital airway management consists of some combination of basic airway maneuvers and bag valve mask (BVM) ventilation to temporize the patient followed by advanced management with either an endotracheal tube (ET), supraglottic airway (SGA), or a surgical airway. While ET intubation is the gold standard in prehospital airway management, its safety and efficacy have been questioned, particularly following trauma and traumatic brain injury. However, other investigators have demonstrated associations with survival and ET intubation of trauma patients, resulting in equipoise based on existing literature.

In both civilian and military prehospital environments, acquisition and maintenance of the skills necessary for airway management is exceptionally difficult. Previous studies have indicated that prehospital providers require ten or more intubations to obtain proficiency at endotracheal intubation and approximately between 5-12 per year to maintain proficiency. Yet the average prehospital provider performs <2 interventions per year. Lairet et al. describe ET intubation as the most frequently missed life-saving intervention, accounting for 53% of missed interventions in combat. The reasons for ET intubation failure are complex and include patient, provider, and environmental factors.

The current alternative used in military airway management is surgical airway (SA). While these account for only 1.8% of military prehospital airways, they account for 12% of missed procedures. While the success of the procedure is as high as 82%, it is also a rare procedure for which training and experience are limited.

SGAs have been shown to require less time and less practice to achieve proficiency to place. Although older devices performed poorly in military use, newer devices may have several advantages over ET. The newer generation of devices have simplified insertion procedures, lack balloons, do not require syringes for inflation, and have ports that allow venting and decompression of the stomach. In preliminary studies, the I-gel has demonstrated superior first pass success when compared to other SGAs.

In addition to their speed and ease of use, they can be placed blindly without the need for the additional equipment necessary for laryngoscopy. In tactical situations, blind insertion techniques may limit

tactical exposure and improve light discipline. SGAs have been associated with shorter prehospital scene times which may translate into risk reduction for the provider and decreased patient mortality. Use of the I-gel may also be a less perishable skill than ET, allowing for better retention and faster pre-deployment training.

Obtaining prospective informed consent is not feasible.

> *21 CFR 50.24(a)(2) Obtaining informed consent is not feasible because: (i) the subjects will not be able to give their informed consent as a result of their medical condition; (ii) the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.*

Potential subjects with traumatic injuries requiring advanced airway management are unconscious and unable to provide informed consent due to their medical condition. For patients who require ventilatory support, airway management must be initiated rapidly. There is no therapeutic window available during which an informed consent discussion could take place either with the subject or, in the exceedingly rare event that one is present at the scene, an LAR.

In previous EFIC trauma trials conducted at the Clinical Coordinating Center (CCC), the consent for continued participation after EFIC enrollment and retention rates were very high. Since traumatic injury is generally accidental and unpredictable, there is no reasonable way to prospectively identify the individuals who will become eligible for participation in the research.

Participation holds prospect of direct benefit to subjects

> *21 CFR 50.24(a)(3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) subjects are facing a life-threatening situation that necessitates intervention; (ii) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.*

Subjects enrolled in this study are in a life-threatening situation by nature of requiring an airway intervention following their trauma. Several preclinical studies have been completed on the topic and two recent RCTs have been completed in a prehospital cardiac arrest population demonstrating no difference between the interventions (Airways 2) or superiority of the intervention (PART). The risks associated with this study are reasonable as both of these methods are standard care for prehospital airway management in trauma. Participation in this study offers the potential for direct benefit to the patient through an intervention that offers the possibility of reduced mortality associated with airway management in trauma. This study could also result in reduced exposure to adverse events such as delayed airway management, hypoxia and hypotension. In addition, all providers participating in this study will have reinforced training with respect to trauma airway management and mitigation of associated complications all of which may provide direct benefit to the patient.

The trial cannot be practicably carried out without exception from informed consent

> *21 CFR 50.24(a)(4) The clinical investigation could not practicably be carried out without the waiver.*

This research could not be carried out without EFIC because airway management needs to begin rapidly. Since trauma patients in need of airway support are unable to consent for themselves and there is rarely a LAR available, all subjects will be enrolled under EFIC. In airway management, time to sufficient ventilation is critical. Inability to obtain informed consent in the absence of EFIC can limit the ability to discover better treatments for this critical and life-threatening condition.

Need for rapid airway management precludes consent from an LAR

> *21 CFR 50.24 (a)(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.*

The nonexistent therapeutic window described above, the inability of patients requiring airway support to communicate, and the lack of an LAR available to provide surrogate consent in almost all subjects precludes the possibility of obtaining informed consent for eligible patients in PACT. Attempts to contact LAR for notification and consent to continue participation will be tracked and summarized at continuing reviews if requested.

REGULATORY PROTECTIONS FOR IMPLEMENTING EFIC

The regulations for EFIC research mandate additional requirements for the implementation of this kind of clinical trial. Each of these additional protections and components of the regulation are reproduced (in italics) here, followed by an explanation of how the PACT trial will comply with the requirement. Further details about implementation will follow in a subsequent section.

Provision of an informed consent document

> *21 CFR 50.24(a)(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.*

A written informed consent document for this study will be reviewed and approved by the sIRB. Subjects enrolled in PACT, or their LAR, are approached for consent at the earliest possible opportunity after arrival to the trauma center. The study team will be notified of the arrival of all enrolled subjects. The study team notifies the subject or LAR/family about the subject's enrollment, provides information about the study, the subject's rights, and the responsibilities of the investigators. The study team answers any questions about the study and further participation. A written informed consent document is used to reinforce the information provided in the consent discussion, and to document the decision to continue in the study or to not participate any further. A copy of this form is provided to the subject.

Community Consultation

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: (i) consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn*

The community will be consulted prior to the initiation of research. The community will be asked to give their opinions about the research and the need for EFIC in order to complete this trial. A detailed menu of acceptable options for community consultation is included later in this plan. The site will choose from this menu and perform sufficient consultations to ensure the sIRB that community consultation has been satisfactorily completed at each site. Reporting of community consultation results will be standardized across the PACT sites.

Public Disclosure

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: ….(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results*

Public disclosure is the primary element in making certain that PACT is conducted in an entirely transparent manner. Methods of announcing information about the trial, and the development of advertising and other materials about the trial, will take place both locally and nationally. Public disclosure will be initiated prior to approval of the trial, may continue during enrollment, and will conclude with dissemination of study results after the trial is completed. A menu and discussion of many public disclosure methods and procedures is included later in this plan. The sIRB will approve the types and forms of public disclosure. Reporting of public disclosure efforts will be standardized. Summaries of public disclosure will be reported to the sIRB and made publicly available.

Data Monitoring Committee

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: ….(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation;*

A Data and Safety Monitoring Board (DSMB) will be appointed to review PACT and to provide recommendations about trial continuation to the IDE Sponsor. After initial approval and at periodic intervals (to be determined by the committee) during the trial, the DSMB responsibilities are to:

a. Review the research protocol, informed consent documents, and plans for data and safety monitoring.
b. Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual, and retention, participant risk versus benefit, adverse events, unanticipated problems, performance of the trial sites, and other factors that can affect the trial outcome.
c. Consider relevant external information, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial.
d. e. Protect the safety of the trial participants.
f. Report on the safety and progress of the trial.
g. Make recommendations to the IDE Sponsor and, if required, to the FDA concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the intervention.
h. Monitor the confidentiality of the trial data and the results of site monitoring.
i. Assist the IDE Sponsor by commenting on any problems with conduct of the trial, enrollment, sample size, and/or data collection.

Contacting Other Family

> *21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: …. (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.*

EFIC enrollment will not proceed if an LAR or any other surrogate present at the scene remotely declines participation on behalf of the potential subject. However, we anticipate that it will be exceedingly rare that any LAR or surrogate will be available at the scene to voice any concern. As previously noted, there is no available therapeutic window during which it would be possible to conduct an informed consent discussion with any party, including a non-legally authorized representative.

Post Enrollment Notification and Consent to Continue

> *21 CFR 50.24(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.*

Subjects enrolled in PACT, or their LAR, are informed of the subject's inclusion in the clinical investigation at the earliest possible opportunity as detailed above. Attempts to notify the subject or an LAR are repeated until successful or until all reasonable efforts and avenues to identify an appropriate LAR are exhausted. All notification attempts are logged and recorded in the subject's research file. Reports of these attempts will be available for inclusion in annual reports to the sIRB if requested.

Record Keeping

> *21 CFR 50.24(c) Like other IRB records, records of the determinations above must be kept for a minimum of three years after the completion of the clinical investigation. Again, like other IRB records, these are subject to inspection and copying by FDA.*

Records documenting the enrollment of participants using EFIC, procedures for notification of enrollment, and informed consent forms will be kept for a minimum of seven years after completion of the clinical investigation.

IDE Requirement

> *21 CFR 50.24(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug*

> *application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Secs. 312.30 or 812.35 of this chapter.*

This trial has been reviewed by FDA, including intent to enroll with EFIC, and the Agency has reviewed and provided approval for an IDE for the trial (IDE#G190002).

Communication of IRB Determination

> *21 CFR 50.24(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.*

PACT will be reviewed and approved by an sIRB. If the sIRB does not approve the trial, no subjects will be enrolled at any site, and all stakeholders will be informed. Because of an sIRB, there will be no opportunity for discordant IRB findings, and no other reporting of disapprovals.

COMMUNITY CONSULTATION PRINCIPLES

Implementation of community consultation (CC) in this trial is based on the applicable regulatory language, applicable FDA guidance documents (from March 2011, updated April 2013), and the investigators' own empirical ethics research and experience in developing best network practices.

Goals

The regulatory intent and specific goals of community consultation are not explicit in the regulations and have been the subject of academic disagreement. As described in the FDA guidance, the goals of community consultation include:

- To **show respect for persons** by informing the community about the study in advance;
- To inform community members about the trial in advance and provide a means for **affected communities to provide meaningful input to the IRB** before its decision to approve, require modifications to, or disapprove the study;
- To show respect for the community by allowing **representatives of the community** to identify potential community-level concerns and effects of the research; and
- To show respect for subjects' autonomy. Respect may be shown by including in community consultation activities **individuals who may have, or be at risk for, the condition under study** (and thereby obtain input from a group that is expected to be similar to the eventual study subjects).

This EFIC plan incorporates and interprets these goals into the following specific actionable elements.

To **show respect for persons**, we suggest CC events that include going out into the community to talk to people where they already gather, rather than simply asking them to come to us at events that we originate. Showing respect also may involve CC events that specifically engage the investigators responsible for the research with the members of the community, rather than only allowing consultations that can be outsourced or delegated.

To create effective opportunities for the **affected communities to provide meaningful input to the IRB**, we train for and promote event formats that ensure that study teams listen as much as they talk. Simply giving a presentation about the trial and then asking if there are any questions is not effective CC. Deliberately brief descriptions of the trial, preferably with few or no slides, are followed by probing the community members for what additional information is important to them, and by soliciting the values and experiences of the community members that are most relevant to the research. Community members are experts about themselves. How their own narratives intersect with the proposed research and the way in which it will be carried out (under EFIC) is the most useful input the community can provide to the IRB.

To show respect for the community, CC activities explicitly reach out both to individuals in the community without specific roles, and to **representatives of the community**. Representative of the community may be religious leaders, community organizers, patient or disease advocates, local political leaders, or others best equipped to identify group-level concerns.

Demonstrating respect for the autonomy of a group of **individuals who may have, or be at risk for, the condition under study** is particularly challenging in this population because traumatic injuries can happen to anyone. We meet this goal by asking sites to describe the breadth and depth of the communities they serve, and then asking that they complete CC activities that reflect a sufficient portion of that spectrum.

It is also important to explicitly reinforce the FDA guidance by stating the goal of CC is **not** intended to represent community consent. Consent to participate in research is meaningful only as an individual decision; community support of the research does not reflect consent for all members of the entire community. Community consultation is therefore not intended to be a form of unbiased voting, deliberative democracy, or other purely quantitative activity, but rather an opportunity for open discussion and commentary. The IRB makes the final determination on study approval based on information obtained from the community consultation.

Definition of Community

For the purposes of EFIC, the definition of community includes “the community in which research will take place” and the “community from which subjects will be drawn.” In other words, the community includes the geographical area from which patients will be drawn and the group of patients with, or at risk for, the disease of interest. Communities have many subgroups that can be defined by innumerable characteristics such as race, ethnicity, religion, age, gender, wealth, education, employment, neighborhood and other factors. Community consultation should consider the heterogeneity of the community and seek diverse input. It is understood, however, that it is impracticable to reach every possible subgroup, but each site will complete activities that reflect a sufficient portion of the spectrum of their relevant communities.

Content

The content of community consultation will inform the community participants that informed consent will not be obtained prior to enrollment in the trial. Informational materials developed for PACT community consultation activities are included in the appendix of this plan and are subject to sIRB approval. Additional materials developed later will be submitted to the sIRB for approval before being used in any CC/PD activities. Specifically, the content of all CC activities will:

- Tell the community about the most relevant aspects of the trial including its potential risks and potential benefits, and the lack of any therapeutic window
- Hear the perspective of the community on the proposed research, elicit values and experiences

Types of Events

Based on our interpretation of the regulations and their proposed ethical basis, we have prepared a menu of the types of events and activities that PACT sites may use to meet their requirements for CC. Sites will prepare a site plan that lists all the events and activities that they will use to engage the community. Each site plan will:

- Provide opportunities for broad community discussion

- Ensure that representatives from relevant communities participate in the consultation process
- Include more than one type of event or activity to provide for effective community consultation
- Consider multiple factors including, but not limited to, the size of the communities, the languages spoken within those communities, the heterogeneity of the population

COMMUNITY CONSULTATION MENU

A (Optional)	B (Required)
A presentation and discussion by an investigator visiting a meeting of an existing group (visits to existing meetings)	Web-based survey (provided by coordinating center)
Focus group (moderated small group session)	In-person solicited survey e.g. waiting room (template provided by coordinating center)
In-person individual interviews or meetings	
A booth or table at community events involving interactive discussions (not just surveys)	
Meetings convened by the investigators inviting the targeted audience (preferably with RSVP)	
Social media messaging	

Required mix is at least 4 total CC events or activities. Among these 4 events or activities must be those provided in column B and at least 2 events or activities must be of a type in column A. The 2 events of a type in column A may be of the same type, for example, they could both be focus groups or visits to existing groups. Events should include participants representing a sufficient breadth of the diversity of the geographic community primarily served by the enrolling sites' institution. There is no expectation that all of the subgroups of a community can be engaged.

<u>Visits to existing meetings or existing groups</u>
In this method of community consultation, members of the study team, sometimes accompanied by representatives of their participating institutional research leadership, ask to present the study and lead a discussion about the study at a regularly scheduled meeting of a relevant community group. Sometimes, the existing group may hold a special meeting for this purpose, but the study team still goes to the group (rather than asking members of the group to come to the study team).

Existing groups that might be consulted using this method may include, but are not limited to: trauma-related support or interest groups, civic groups, neighborhood groups, service organizations, athletic groups (inclusive of athletes, coaches, and trainers at any level of competition from high school to professional), parent-teacher associations, faith-based organizations, political or governmental bodies, business groups, social clubs, retiree groups, and college fraternities or others. Examples of governmental bodies include law enforcement and fire and EMS department groups, city councils, and community boards. This approach may also include study team visits to senior centers or rehabilitation facilities. Participation in an existing meeting shows respect for community by bringing the information to the community, reduces inconvenience to the community, and exposes the study to a diverse audience. Community members may be more comfortable expressing their opinions in a known setting. Investigators may have to travel, attend multiple meetings, and conform to the community group's schedule. Using this method can encourage more involvement by co-investigators and other members of the study team, which can be advantageous.

Prior to and during the visit, the study team must clearly communicate that being allowed to attend the meeting

does not imply any implicit approval or endorsement by the group being visited.

Best Practices:

- An investigator or study team member should be present to take and answer questions from the community.
- Presentation should be brief (i.e., 10 to 15 minutes).
- If a presentation is longer than 15 minutes, it should be interactive throughout the presentation.
- The presenter should be knowledgeable about the study and comfortable with the group.
- Allow ample time for community discussion (at least 15-30 minutes).
- Often best to ask for 30 minutes on an existing meeting agenda to allow 10 minutes to present, 15 minutes for discussion, and 5 minutes to hand-out and get back evaluation surveys. Insufficient time for solicitation of feedback greatly reduces the utility of this method.
- Probe for discussion using open-end questions. Ask participants about their experiences and what they care about.
- Ensure that the discussion includes feedback from the participants on EFIC.
- Light refreshments may be sponsored, direct monetary incentives are uncommon.
- An anonymous survey for group participants to indicate their thoughts, feelings, and opinions about the EFIC regulations and the study is typically collected at the end of the event.

Focus groups

In this approach, a trained facilitator interviews and moderates a discussion in several small groups (generally about 8 to 12 participants). This method can be conducted with or without an investigator present, but the former is favored. Unlike focus groups designed for other research purposes, these focus groups are performed as community consultations. They are an opportunity for investigators to directly listen to community members, and to show their respect by listening humbly. An investigator may often start the session by briefly presenting information about the trial or may elect to allow the facilitator to proceed and listen and be available to clarify issues and answer questions. The facilitator runs the discussion using an explicit guide prepared by or reviewed beforehand by the investigative team. The facilitator elicits the group's views, questions, concerns and comments about the study. The interaction is generally audio-taped (and possibly videotaped) for review by the investigative team and the facilitator to allow subsequent analysis and reporting of the session. Focus groups could solicit feedback from any relevant focus of the community, including: the general public, individuals affiliated with particular organizations or subgroups, or specific patient populations.

Recruitment methods for focus group participants will depend on the targeted population. Participants may be recruited by mail or telephone, at random from volunteer banks or public data sets, or from special populations (such as patients with prior traumatic injury or their families, advocacy group representatives or other vested interest groups).

Compared to other methods of community consultation, focus groups may allow for more in-depth discussion of the study because of their small size. They also allow for interaction not only between the facilitator and participant but between participants. For these reasons, focus groups offer a rich set of information and have often been found by investigators and IRB members to be a high-quality source of information.

Best Practices:

- The meeting should be at an accessible location and time for the population included.
- The session should generally be run by a trained facilitator; sometimes it is helpful if it is someone who is also demographically concordant with the focus group participants (experience, race, ethnicity, or gender).
- Sessions should be small, generally including 8 -12 participants.
- Focus groups generally run 1 to 2 hours in length.
- Refreshments should be provided.
- Participants are generally paid for participation in focus group sessions in an amount and form appropriate to the participant population.

- An anonymous written survey for group participants to indicate their thoughts, feelings, and opinions about the study and the focus group session should be conducted at the end of the event.

Convened (invited) meeting

Sometimes called a “Town Hall Meeting”, this type of CC uses the same structure and best practices as visits to regularly scheduled meeting but invites a target audience to a meeting convened by the study team. The potential advantage of this method is that multiple groups of attendees can be invited to the meeting and have a chance to interact with each other and the investigator. Because the meetings are typically open to the public, there is the potential to involve everyone. The disadvantage with this method is that organizing such a meeting and attaining adequate attendance can be burdensome and difficult. To be successful, however, an intensive effort to diligently invite several potential attendees and secure their commitment to participate is needed. Merely advertising a public meeting and seeing who shows up leads to events with very few community members. Such low attendance events have been commonly held in prior EFIC trials but are not acceptable for PACT. The use of invited meetings, therefore, is discouraged unless the site has a track record of successfully using this method in the past.

Community events - interactive or survey

In this type of event, the study team and investigator typically set up a booth or table at an existing community event and interact with individuals one at a time as they browse or stop by the booth. Events of this kind have occurred at State Fairs, Fire and Emergency Services Open Houses, Farmers Markets, Art Festivals, Music Concerts, Health Fairs, Ice Cream Socials, Disease-related Fundraising Events, Tailgates and other Sporting Events. This kind of event often allows exposure to a large number of community members. Depending on the kind of event, it may allow investigators to reach a focused or very diverse group and a large number of participants. Because conversations are typically one on one, this method often allows more intimate and revealing opportunities for the investigator and members of the public to interact. The disadvantage of this approach is that most of the contacts are very brief, usually limiting the opportunity to exchange information. Also, the time commitment from the study team to staff the booth for the duration of the event may be significant, making this potentially inefficient. This type of event can be conducted in a way that is more interactive, in which an investigator or other study team member primarily engages participants in conversations, often concluding with having the participant fill out a survey either through an interview or by completing a written tool. The event can also be conducted in a way that is primarily driven by just giving out written information about the study and asking participants to fill out a written survey. In this case, the booth can be staffed without an investigator present, which can be more efficient for the study team.

Best Practices:

- Booths should have good signage that attracts passers-by.
- Have small treats or “swag” to attract participants and thank them for taking time to talk to you.
- Have enough staff at the booth to engage with anyone who wants to talk.
- Have enough clipboards and pens to make certain no one has to wait to complete written feedback.
- It is often effective to make this kind of event a fun social team-building exercise for the study team.

Telephone (random digit dialing) survey

Large telephone surveys can provide the most statistically representative description of community responses to questions about the study and EFIC. This approach also has the potential to access the views of members of the community that are unlikely to attend other types of community consultation activities. Interviewers should be trained by the study team about PACT. Telephone surveyors are trained to read information verbatim provided to them by the study team about the study and EFIC. They then ask close-ended questions and solicit open-ended comments and questions. This information is then summarized and reported back to the investigators and the sIRB. It is important that the survey and accompanying guide used by the interviewers should be carefully written and tested by the study team. Vendors can potentially perform large online surveys that are akin to these large random digit dialing surveys.

There are several limitations to this method. Telephone surveys can be intrusive and unwelcomed. Also,

because they are delegated rather than conducted directly by the investigators, they do not allow investigators to demonstrate the same level of interpersonal respect for persons or communities as other methods. Questions are typically narrow and closed ended in this approach. Professional surveyors are also not generally equipped to answer clarifying questions about the trial or EFIC. To achieve a reasonable sample size, telephone surveys have to be short. The presentation of EFIC and PACT is therefore necessarily very limited, so responses may not be as well informed or may be less reflective than responses solicited in more interactive methods. The extent to which this method produces systematically different responses is unknown.

Simple solicited surveys like those performed online, in waiting rooms, or at booths

Simple individual surveys, whether performed on-line or in person, can also be used to solicit community questions and views. This method can be used to reach large numbers and a wide variety of respondents. Online surveys can be linked to social media platforms or can be easily solicited by email. Respondents can also be recruited to complete surveys distributed in-person in relevant clinical settings like emergency department or clinic waiting rooms. These simple survey methods can potentially provide more background information and are much less expensive. Internet and paper surveys also allow respondents to see visual aids and diagrams not possible with telephone surveys. Waiting room surveys may allow focus on populations with particular health care or traumatic injury experience. Online and waiting room surveys otherwise have the same limitations as telephone surveys. Careful writing and testing of surveys remains critically important. If surveys are distributed in person, surveyors need to be well trained in the study protocol and in the EFIC regulations.

Best Practices:

Whenever possible, these surveys should be conducted by members of the study team, and/or delegated surveyors with medical knowledge and training in the protocol and EFIC. Medical students and residents can sometimes be recruited as surrogates for the investigative team.

Other social media

Social media offers a low cost, potentially far reaching, and potentially interactive method to exchange information with members of a community. Recent data suggest that the penetrance of social media is very high with 80% of adults in the US accessing Facebook, Youtube, Instagram, Pinterest, Snapchat, LInkedin, Twitter, or WhatsApp daily (while only 29% read print newspapers daily). Social media may also allow messages to be directed to selected subgroups and demographics. Also, different platforms are favored by different demographics. Social media is a medium that blurs the line between one-way communication (as used in public disclosure) and dialog (as used in community consultation). The former type of use is probably more common, but truly interactive social media communications are also possible. If chosen as a CC activity, the content of the presentation, the methods to allow interaction, and gaps in the available population should be clearly described.

REPORTING COMMUNITY CONSULTATION RESULTS

All community consultation activities must be reported to the CCC. Study site personnel will send their aggregate data of their community consultation activities, by event. Data required includes: information about the participants, the presentation, participant questions and comments, and responses to closed- and open-ended survey questions. The results will be further collated to produce individual site or trial-level reports.

PUBLIC DISCLOSURE PRINCIPLES

Public disclosure (PD) is defined in guidances as the “dissemination of information about the research sufficient to allow a reasonable assumption that communities are aware of the plans for the investigation, its risks and expected benefits and the fact that the study will be conducted”. It also includes “dissemination of information after the investigation is completed so that communities and scientific researchers are aware of the study’s results.”

Goals

The regulatory intent and specific goals of PD are not explicit in the regulations and have been the subject of

academic disagreement. This plan is based on the presumption that the primary goal of public disclosure is transparency.

Transparency is achieved when information about the study is broadly and publicly disseminated through multiple channels. We note that transparency has a protective effect because investigators will not propose anything that they would not be willing to announce and defend openly.

Adequacy of public disclosure and transparency is best measured like advertising, by the size of the potential audience of the disclosure, rather than by knowledge or recollection of the audience. In fact, the more benign and acceptable the content of a public disclosure is, the less likely it will be internalized and recalled.

Content

The content of PD materials will vary with the media used. Advertisements (whether signs, print media, broadcast, or electronic) may have limited space. These disclosures may convey short messages and how the audience can obtain more detail. Follow up examples may include ways to talk to the study team, or a link to the study website. Short messages should at a minimum emphasize:

- That a research study of patients with traumatic injury that require airway support is being conducted locally.
- That the study will enroll patients with injuries that prevent them from participating in informed consent.
- Who to contact or where to find additional information.

Other forms of disclosure, such as press releases, websites, or brochures for example, allow for greater detail and should, depending on available space, also include:

- Information about airway management and how it is performed
- The purpose of the research
- Who will be included in the study
- A description of the two treatment strategies being compared
- A balanced description of the potential clinical and research risks and benefits
- Synopsis of the research protocol and study design
- Participating sites/institutions
- Description of the attempts to contact a LAR

After the clinical trial is completed, further public disclosure should include:

- The findings of the trial
- Impact of what was learned on patient care
- Where to find resources for further information
- Gratitude and thanks to the study subjects, their families, and their communities.

PUBLIC DISCLOSURE MENU - PRE-TRIAL

A (Optional)	B (Required)
Paid online advertisements (banner, block, or video ads purchased from Google, Facebook, Youtube, etc.)	National or local study website (provided by the coordinating center)
Social media/internet postings (Youtube, Facebook, Twitter, etc.)	Press release (template provided by CC)
Mailings (including email circulars/bursts and direct paper mailings)	
Booth/Table Community event	

Outdoor advertising (placards, bus ads, billboards, etc.)	
Television and radio ads (broadcast advertising)	
Newspaper advertisement (and similar print advertising)	
News stories, interviews (print, radio, or TV)	
Newsletters (articles or informational ads, print or electronic)	
Brochures, flyers, handouts, bulletin boards	
Radio or TV PSA (public service announcements)	

Several different channels of PD should be used. This will increase the depth and breadth of market penetration. The required mix is at least 4 total PD activities, including at least 2 of a type in column A, and both types in column B. Distribution of activities should be cognizant of the anticipated audiences and should include audiences representing a sufficient breadth of the diversity of both the geographic community primarily served by the enrollment site, and the community either at-risk for, or familiar with, traumatic injury. There is no expectation that all potential audiences will be reached. It is expected that PD efforts will represent a good faith effort to provide transparency across the relevant communities.

Networking

Electronic platforms can provide a passive or interactive approach to disseminating information that has benefits and challenges. Measurement of the audience reached by these methods may be elusive. Access may be limited to those segments of the population with regular computer access, although internet access through cell phones is rapidly becoming common in all parts of society. Despite these minor concerns, electronic social media and other e-platforms are inexpensive to develop, are wide-reaching and can be relatively democratic, and can even permit continuous and anonymous input from the public. Hospitals and community-based organizations often host and curate websites, social media accounts (Facebook, Twitter, etc) and listservs, that can be efficiently leveraged to disseminate a message broadly.

Paid advertising

Purchased advertising in broadcast and print media ensures dissemination of accurate materials to a wide audience. Advertisement of the study may occur on a major news radio station serving the area surrounding the study hospitals. A 30 to 60 second sound bite should include a general description of the study, the website address, and contact information where more information can be provided if desired. Printed materials, including advertisements for publication in newspapers and magazines, brochures, and flyers, will be provided by the CCC. Advertisements should be placed in both English language and foreign language newspapers as appropriate to the local community. Printed advertisements should provide a general description of the study, the national and/or local website address, as well as site contact information.

Conventional informational outlets

Press releases leading to newspaper and periodical articles are an effective form of public dissemination. Investigator appearances on local news, radio or television call-in talk shows can accomplish both public disclosure and community consultation. In addition to traditional news outlets, it is often possible to obtain coverage in local health focused newsletters, in direct mail advertisements and educational materials sent out by health care organizations and in newsletters of traumatic injury advocacy and support groups. A video on the proposed study will be available for use in public service announcements and for dissemination to media outlets. Local community access cable stations may be accessible to investigators. Cable access channels may offer appearances on shows presenting issues of local interest or may offer to broadcast prepared materials.

Brochures and flyers may be disseminated in locations including:

- Medical sites (e.g., emergency department waiting rooms, medical clinics, dentist offices, etc.)
- Health fairs (community, employer, school, etc.)
- Support groups and other existing community groups
- Schools, universities,
- Churches and other religious affiliates
- Grocery & laundry-mat bulletin boards
- Through large employers (i.e., hospitals, universities, etc.)

Local flyers and brochures distributed should reference the study website as an additional resource for patients, families, and healthcare providers to get information as well as ask questions about PACT.

PUBLIC DISCLOSURE ACTIVITIES - POST-TRIAL

Post-trial public disclosure activities may include any of the methods used pre-trial, especially press releases because results of trials can be especially newsworthy. Post-trial public disclosure also includes a number of more specific additional methods. Post-trial disclosure includes publication of the trial results in a major scientific journal and presentation of the results at scientific meetings. Through these publications and presentations, it usually possible to leverage the existing public relations machinery of the journals and the meeting to amplify the message through broader media outlets as well.

REPORTING PUBLIC DISCLOSURE ACTIVITIES

All public disclosure activities must be reported to the CCC. Study site personnel will provide data on each activity including: name and type of activity, size of anticipated audience, and characteristics of the intended audience, and timing and duration when relevant. Activity data will be further collated to produce individual site or trial-level reports.

CONTACTING A LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

The definition and hierarchy of LAR is determined by local state regulations.

When more than one LAR are present, the LAR highest in the local hierarchy should give consent. However, unless otherwise stated in local or state regulations, any LAR may consent if others are not promptly available.

EFIC does not obviate the need to seek patient or LAR consent to continue participation after EFIC enrollment. Potential subjects are also not enrolled under EFIC if any family objects to enrollment at the scene, even if they are not an LAR. Subjects enrolled in PACT, or their LAR or family, are informed of the subject's inclusion in the clinical investigation at the earliest feasible opportunity. The subject (or LAR or family) is approached, and an informed consent process initiated, as soon as possible.

LAR identification and tracking will typically be a shared responsibility between the onsite social workers (or equivalent) and the study team. The site team should review the local protocol for an LAR search and assure that it is sufficient (multiple methods for locating LAR and multiple attempts), and if not, recommend additional steps be put in place.

Once available after an EFIC enrollment, an LAR will be informed of the patient's enrollment into the study and of the study details and potential risks and potential benefits of study participation. At that time, the LAR will be given the option to continue participation in the study, or to cease participation then or at any time throughout the course of the study. If the LAR wants to continue participation, an informed consent process is performed and an informed consent form signed by the LAR will be obtained. If an established LAR has given consent for the participant to continue, other family members' objections to inclusion will not result in the participant's removal from the study. If the participant regains decision making capacity, the participant will be asked to consent to or decline continued participation in the study. If the participant wishes to continue, the participant will sign an informed consent form.

The study team will document efforts to find the LAR. This will include contact person (Subject, LAR, Other), number of attempts, date and time and outcome of attempts. The tracking process should continue until

consent or withdrawal is obtained or notification of enrollment is provided. The tracking process is complete once one of the following has occurred:

- **the LAR or subject has provided consent,**
- **the LAR or subject has withdrawn,**
- **the subject has expired and LAR has been notified of study inclusion,**
- **a period of at least 30 days has passed without subject regaining capacity and all attempts to identify an LAR have failed.**

For participants who expire prior to identifying an LAR or before LAR consent is obtained, consent should not be pursued further. However, once an LAR is located, they should be informed of the subject's participation. The study team should document the notification conversation. If it is not possible to have this notification conversation with the LAR or family of a deceased subject in the hospital, a "family notification letter for a deceased subject'' should be used to notify the LAR or other family. A copy of the family notification letter (with return receipt) should be kept with the study documents.

In the rare case where no LAR consent is obtained, the LAR is never available, and the participant remains incapable of consent at six months, documentation of the attempt process and condition of the participant will be recorded.