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Protocol ID: 2019-0348

Study Title: A Pilot Study of FDA Approved Optiflow™ THRIVE versus Standard Non-Rebreathers in Patients with Potential High Risk of Airway Obstruction during Total Intravenous Anesthesia (TIVA) Procedures

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Sponsor: The University of Texas MD Anderson Cancer Center

Funded By: Fisher & Paykel Healthcare

SUMMARY TABLE

Title	A Pilot Study of FDA Approved Optiflow™ THRIVE versus Standard Non-Rebreathers in Patients with Potential High Risk of Airway Obstruction during Total Intravenous Anesthesia Procedures
Project Office	Division of Anesthesiology, Critical care and Pain Management; FC13.2036
Study Size (# of patients)	A proposed sample size of eligible 120 patients (60 patients randomized equally between two groups)
Study Design	This is a prospective randomized trial. All the eligible subjects will be randomly assigned to one of two groups: the Optiflow THRIVE group or the standard non-rebreather group.
Primary Objective	To investigate the performance of Optiflow™ THRIVE relative to Standard Non-Rebreathers in patients with high risk of difficult airway management undergoing total intravenous anesthesia (TIVA) procedures.
Secondary Objective(s)	To describe the episodes of hypoxia (defined by $SpO_2 \leq 92\%$) and the episodes of airway support which include: jaw thrust, chin lift or insertion of an airway supporting device, such as oral/nasal airway or supra airway device in order to recover the level of oxygenation above 92% associated with Optiflow™ THRIVE.
Inclusion Criteria	A patient who meets all the following criteria may be included in the study: 1. 18 years of age and older and signed consent for the study 2. Presents with a $SpO_2 \geq 95\%$ while breathing room air 3. Requires TIVA but not tracheal intubation during the proposed procedure – PLUS, any of the following: Body mass index (BMI) ≥ 32 kg/m^2; neck circumference ≥ 43 cm in a male and 41 cm in a female patient; has been diagnosed with moderate to severe obstructive sleep apnea (OSA) by a sleeping study with/without using a continuous airway pressure (CPAP) device; or, full course head and neck radiotherapy ≤ 6 months (The peak onset time of acute facial and airway edema)
Exclusion Criteria	A patient who meets any of the following will be excluded from the study: 1. Has a significant pulmonary disease requiring supplemental oxygen in daily life (severe pulmonary fibrosis, severe COPD, etc.) 2. Has significant cardiac disease (including history of myocardial infarction (MI) with concurrent evidence of ischemic myocardial damage at the event, cardiomyopathy with impaired left ventricular ejection fraction to less than 50% or uncompensated congestive heart failure (CHF) 3. Cannot tolerate TIVA or having a proposed procedure without TIVA 4. Requires endotracheal intubation 5. American Society of Anesthesiologists (ASA) classification 5 6. Non-English speaking 7. Requires an emergency procedure
Outcome(s)/Endpoint(s)	The primary endpoint is the total length of desaturation episodes (ToLDE) time (in minutes) during a fixed 60-minute observation window during TIVA in patients with high risk of difficult airway management. Desaturation episodes are characterized by the occurrence of hypoxia (defined by $SpO_2 \leq 92\%$).
Study Procedures	
Pretreatment Evaluation	Routine preoperative interview and physical evaluation. No special evaluation required.
On-Study Visits	Onsite data collection in all the study patients including: 1. FDA approved Intervention group: patients receiving Optiflow™ THRIVE 2. Standard of Care group: patients receiving non-rebreather mask Each patient will be followed for 60 minutes (from induction until 60 minutes thereafter).
Follow-up Visits	Per standard post-anesthesia care unit (PACU) discharge protocol
End of Study Visit	Per standard PACU discharge protocol

Brief Analysis Plan	For Primary Objective: A total of 120 eligible patients will be randomized in a 1:1 fashion using CORe. Blocking will be utilized to maintain exactly 60 patients per study group. The sample size is used to compensate for cases aborted post-randomization due to interventional radiology procedure changes interfering with the original treatment plan. This strategy will ensure at least 50 patients are randomized and evaluable per study arm. All patient data will be summarized using descriptive statistics. For each study group, the ToLDE time will be summarized using the mean, standard deviation, median, and range. Interval estimation of the difference between study groups in mean ToLDE time will be computed with a 95%CI. With at least 50 patients per group, the precision conferred on the bounds of a two-sided a 95% CI extends 0.39 units on each side of the observed mean assuming a common standard deviation of 1.0 per group (nQuery Advisor v7.0). Descriptive statistics will be used to summarize continuous outcomes, and histograms and scatter plots will be used to explore the distributional characteristics and bivariate relationships, respectively. Transformations to the data will be applied if appropriate. Interval estimates will be computed for continuous variables, such as the mean number of hypoxemia (defined by $SpO_2 \leq 92\%$) episodes within the pre-specified time period, for each study group (at least n = 50) independently using a 2-sided 95%. Exploratory analyses between study groups will be conducted using t-tests (Wilcoxon rank-sum tests) for continuous covariates and chi-square tests (Fisher's exact tests) for categorical variables. Linear regression will be used to estimate the mean ToDLE time difference while adjusting for select covariates of interest.

1. **OBJECTIVES**

Primary: To investigate the performance of Optiflow™ THRIVE relative to Standard Non-Rebreathers in patients with high risk of difficult airway management undergoing total intravenous anesthesia (TIVA), for the planning of future clinical studies.

Secondary: To describe the episodes of hypoxia (defined by $SpO_2 \leq 92\%$) and the episodes of airway support which include: jaw thrust, chin lift or insertion of an airway supporting device, such as oral/nasal airway or supra airway device in order to recover the level of oxygenation above 92% associated with Optiflow™ THRIVE.

2. **BACKGROUND**

Total intravenous anesthesia (TIVA), a general anesthesia technique typically achieved by continuous infusion of propofol with/without adjuvant agents, is commonly used for the diagnostic or brief therapeutic procedures to improve the patient's satisfaction.[1; 2] During TIVA, partial or total airway obstruction resulting in transient oxygen desaturation are the common issues requiring airway support with various maneuvers or use of an artificial device to recover adequate oxygenation.[2; 3] In addition, episodic centrally mediated apnea occurs due to changing in dosing and infusion rate of propofol administration; positive pressure ventilation with facemask may be needed at times.[4] However, when the airway obstruction occurs in a patient with a potential difficult airway such as obstructive sleep apnea (OSA), mass or edema in airway, decreasing or ceasing the oxygen flow delivered to the lungs due to obstruction of flow path quickly results in oxygen desaturation.[4-6] Managing the airway and re-establishing the oxygen flow to the lungs to maintain the adequate oxygen level in these patients imposes significant challenges to anesthesia providers; prolonged hypoxemia may occur and impose significant adverse influences to the outcomes.[7]

Delivering up to 70 L/min. humidified oxygen flow rate, Optiflow™ THRIVE (Fisher & Paykel Healthcare, Auckland, New Zealand), is proven to provide prolonged duration of apneic oxygenation and quickly restoring the oxygenation saturation to the patient's baseline level when the airway is under control.[8] Due to its high flow rate, the device offers multiple supports to the airway. First, it creates an oxygen-rich environment in the entire airway and reduces the ratio of dead space to tidal volume and therefore, increasing alveolar ventilation.[9] Secondly, it creates a dynamic positive airway pressure to promote slow and deep breathing achieved by decreasing airway resistance during inspiration and prolonging the expiratory phase by a low level of continuous positive airway pressure (CPAP).[10] In addition, it delivers humidified oxygen and improves mucocillary clearance in the airway; therefore, preventing airway mucosa dry-out for a prolonged

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application.[11] Thus, Optiflow™ provides ideal airway support during TIVA administration. Although the Optiflow™ has been studied in patients with normal airways, its use in patients with a high risk of airway obstruction during TIVA remains unclear.

TIVA is commonly used in the procedures in interventional radiology and gastrointestinal (GI) endoscopy procedures. At MDACC, challenging airways are often seen in these areas. Obesity, cancer airways, s/p head and neck radiotherapy, etc. increase the risk of difficult airway management; lengthy procedures increase the duration of airway management and the positions for procedures may prevent anesthesia providers to access the airways. Therefore, the patients undergoing these procedures with TIVA present unique chance to investigate the clinical feasibility of improving the airway safety by using Optiflow THRIVE to manage the case in high airway risk patients.

This study will assist with establishing the hypothesis that can be objectively assessed if an airway managed with Optiflow™ THRIVE will reduce the risk of intraoperative hypoxia in patients undergoing interventional radiology and GI procedures requiring total intravenous anesthesia (TIVA) by providing knowledge of study endpoints that reflect clinically viable differences. Moreover, we can better understand if Optiflow™ THRIVE assists with the need to provide manual rescue airway techniques (to maintain airway patency) while also decreasing the duration and episodes of hypoxia in patients undergoing the procedures requiring TIVA.

3. STUDY DESIGN DESCRIPTION

This is a prospective randomized controlled study. Patients will be randomized in a 1:1 fashion to one of two study groups, the treatment group or control group. The patients in the treatment group will receive oxygen via Optiflow™ THRIVE; while the patients in the control group will receive 100% oxygen via a non-rebreather facemask. CORe will be used to conduct the randomization, as well as random block sizes; recommending to CORe that block sizes of 2, 4, 6, and 8 are allowable. Blocking will be utilized to maintain exactly 50 patients per study group. Patient randomization will occur after a patient has been deemed eligible and consented to participate. The data below listed will be collected during the procedure and statistically compared between the two groups at the end of the study.

4. DISCUSSION OF SUBJECT POPULATION

4.1 Subject Characteristics

a) **Total number of subjects:** Due to lack of existing data to support a power analysis, the estimated number of study subjects is currently 120 eligible patients with 60 in each group. Due largely to the variation of caseload daily in IR, the average caseload for the study is expected no more than 2 cases/day. With the safety profiles in the previous reports mentioned above, the failure rate or the subject withdraw from the study is estimated no more than 1%.

All included cases will be scheduled elective procedures. Although we expect the rate of patient withdrawal to be low, we will not replace missing slots in the randomization list with the next eligible patient. Those patients will be considered randomized, but unevaluable. If needed, a protocol amendment will take place to increase the total number of randomized patients, only if this turns out to be an issue.

b) **Study subjects:** Optiflow™ is a standard airway device used routinely and internationally, for high flow nasal oxygen (HFNO) delivery. Multiple studies have demonstrated that Optiflow™ is superior to the existing comparable devices in terms of both oxygenation and CO_2 clearance. In addition, its safety profile in maintaining a patent airway is also superior to comparable devices during deep

sedation or general anesthesia (GA) without tracheal intubation. Standard anesthetic care will be provided to all patients with the exception of whether the patients receive HFNO or oxygen via non-rebreather face mask. Thus far, the literature has not demonstrated use in the pediatric population; patients < 18 years of age will not be included in this trial.

2. **Inclusion and Exclusion Criteria**

a) **Inclusion Criteria**: An individual that meets all of the following will be eligible/considered for the study:

1) 18 years of age and older and signed consent for the study.
2) Patients with an $SpO_2 \geq 95\%$ while breathing room air
3) Patients requiring TIVA, but not tracheal intubation during the proposed procedure - PLUS, any of the following criteria:
   - Body mass index (BMI) ≥ 32 kg/m^2
   - Or, neck circumference ≥ 43 cm in a male and 41 cm in a female
   - Or, has been diagnosed with moderate to severe obstructive sleep apnea (OSA) with/without using a CPAP device
   - Or, full course head and neck radiotherapy ≤ 6 months (The peak onset time of acute facial and airway edema)

b) **Exclusion Criteria**: An individual that meets any of the following will not be eligible/considered for the study:

1) Significant pulmonary disease requiring supplemental oxygen in daily life (severe pulmonary fibrosis, severe chronic obstructive pulmonary disease, etc.)
2) Significant cardiac disease (including history of MI with concurrent evidence of ischemic myocardial damage at the event, cardiomyopathy with impaired left ventricular ejection fraction to less than 50% or uncompensated congestive heart failure)
3) TIVA is contraindicate or having a proposed procedure without TIVA
4) Endotracheal intubation is required
5) ASA Physical Status classification 5
6) Patients who are non-English speaking
7) Emergency procedures

5. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

5.1 Method of Subject Identification and Recruitment

All study investigators, including the Principal Investigator (PI), Co-Investigators (Co-I) and/or collaborators of the study, are eligible for the identification of study candidates. The IR procedure daily schedule will be used for patient selection. Once eligibility of a study candidate has been identified, the study coordinator will be informed to start the patient interview and obtain written informed consent.

5.2 Consent Process

The study coordinator will be responsible for the study candidate interview and consenting. Informed written consent will be obtained either electronically or by paper. All signed study consents will be stored in locked file storage or a MDACC encrypted/passcode secured electronic device for any electronic scanned document.

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The study device is a standard airway tool that has been used in clinical routine practice for over a period of 10 years with no significant risk or complication for its clinical applications reported in the literature; In fact, its excellent safety profile may be of benefit, especially to those who have obstructive airway disease. In this study, standard application of 100% oxygen administration via non-breather facemask will be compared to administration of HFNO via Optiflow™. A structured informed consent for the study with information mentioned above will be discussed with study candidate and signed by this individual.

5.3 Cost to the Subject

The device application is used via routine anesthesia service for given scheduled procedure. There is no additional cost to the study subjects.

4. Payment for Participation

Not applicable.

5.5 Return of Individual Research Results

Not applicable.

6. SAMPLE SIZE JUSTIFICATION AND DATA ANALYSIS

6.1 Sample Size Justification

The primary endpoint is the total length of desaturation episodes (ToLDE) time (in minutes) during a fixed 60-minute observation window during TIVA in patients with high risk of difficult airway management undergoing interventional radiology or GI procedures. Desaturation episodes are characterized by the occurrence of hypoxia (defined by $SpO_2 \leq 92\%$).

A total of 120 eligible patients will be randomized in a 1:1 fashion using CORe. Blocking will be utilized to maintain exactly 60 patients per study group. The sample size is used to compensate for cases aborted post-randomization due to interventional radiology procedure changes interfering with the original treatment plan. This strategy will ensure that at least 50 patients are randomized and evaluable per study group.

For each study group, the ToLDE time will be summarized using the mean, standard deviation, median, and range. Interval estimation of the difference between study groups in mean ToLDE time will be computed with a 95% CI.

With at least 50 patients per group, the precision conferred on the bounds of a two-sided a 95% CI extends 0.39 units on each side of the observed mean assuming a common standard deviation of 1.0 per group (nQuery Advisor v7.0).

6.2 Planned Statistical Analysis

Descriptive statistics will be used to summarize continuous outcomes, and histograms and scatter plots will be used to explore the distributional characteristics and bivariate relationships, respectively. Transformations to the data will be applied if appropriate. Interval estimates will be computed for continuous variables, such as the mean number of hypoxemia (defined by $SpO_2 \leq 92\%$) episodes within the pre-specified time period, for each study group (at least n = 50) independently using a 2-sided 95% CI. Exploratory analyses between study groups will be conducted using t-tests (Wilcoxon rank-sum tests) for continuous covariates and chi-square tests (Fisher's exact tests) for categorical variables. Linear regression will be used to estimate the mean ToDLE time difference while adjusting for select covariates of interest.

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7. METHODS AND STUDY PROCEDURES

Patients will be randomized into 1 of the 2 arms of the study, the intervention group and control group, by the use of randomizing software (CORe) to indicate which study group the patient has been assigned to. The patients in intervention group will be given 100% oxygen via Optiflow THRIVE with a flow rate of 50 L/minute for a period of 3 minutes prior to anesthetic induction and 70 L/minute thereafter anesthetic induction until the end of procedure; and the patients in control group will receive 100 % oxygen at the flow rate of 8 L/minute via a non-rebreather mask for 3 minutes prior to anesthetic induction and maintain the same flow rate until the end of procedure. The type of anesthesia for both groups will be total intravenous anesthesia (TIVA) without a tracheal intubation or super laryngeal airway support. The anesthesia for both groups will be induced with propofol boluses or continuous infusion. The dose of boluses or the infusion rate will be the decision of anesthesiologist. However, midazolam or fentanyl is generally avoided during the study to avoid the synergetic effects in respiratory depression. The quality of anesthesia (the depth and amnesia effect of anesthesia) is monitored by a BIS device with reading between 40-60, as satisfactory. The study coordinator will be responsible to follow the study procedures, to ensure the validity and integrity of the study protocol. The study coordinator will also be responsible for data collection when the 60-minute assessment window for monitoring begins. All data collection will take place prior to, and during, the patient's scheduled IR procedure. The 60-minute assessment window will begin after induction (initial Propofol administration; bolus), once induction has been recorded in the patient's electronic medical record via online time stamping in EPIC, and will conclude 60-minutes after (the recorded time of induction). Total length of desaturation episode(s) (ToLDE) will be recorded by utilizing a stop-watch/clock. All other collected data will be recorded via observation and patient monitoring during the procedure. The following data will be collected during the procedure and statistically compared between two study groups after completion of data collection (see **Appendix A.**):

1. Patient's demographic information
2. Patients underline diagnosis and ASA Physical Status
3. Procedure data, name, duration and position
4. Episodes and percentage duration of oxygen desaturation defined by $SpO_2 \leq 92\%$ over the entire procedure
5. Episodes of manual airway support, including jaw thrust, or insertion of an artificial airway device
6. Episodes and duration of BIS number ≥ 61 during the entire procedure
7. Episodes of patient movement during the procedure
8. The total dose of propofol used during the entire procedure
9. Patient satisfaction after the procedure by post PACU discharge evaluation (see **Appendix B.**)

Preoperative care: No active intervention is planned on this phase of care. All procedures will be provided according to routine clinical care and clinical judgment.

Intraoperative care: Total intravenous anesthesia (TIVA) will be delivered using an intravenous infusion of propofol according to anesthesiologist clinical judgment. Intraoperative hemodynamic and temperature will be monitored and maintained according to routine clinical care. A BIS monitor measures the depth of anesthesia with reading between 40-60, as satisfactory.

Postoperative care: All patients will be monitored in PACU according to routine clinical care. If deemed necessary by the attending anesthesiologist, patients will be transferred to the intensive care unit.

8. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the

study at any time without prejudice. Should a patient withdraw from the study, the study data collection will be terminated. The standard clinical pathway in destroying the confidential patients' health information will be used to handle the collected data.

Subjects may be withdrawn from the study for the following reasons (but not limited to):

1. Subject non-compliance with study procedures
2. Unacceptable adverse events (safety or tolerability)
3. Voluntarily withdraw (at any time, for any reason)
4. Physician discretion

9. SAFETY AND REPORTABLE EVENTS

For study purposes, adverse events will be categorized at the investigative site into 2 groups: Relatable (Expected) Adverse Events (Grade 1-3) or Serious Adverse Events (Grade 4-5). Therefore, any AEs that are not relatable to the devices, themselves, will not be collected for study purposes. However, all non-relatable AEs will be recorded on the anesthesia record. The PI will determine if the event is related to the device or its deployment, or not related to the device or its deployment will assess the causal relationship of each adverse event.

9.1 Adverse Events Definitions

An adverse event (AE) is any undesirable clinical event occurring to the subject during a clinical study, whether or not it is considered related to the investigational product. This includes a change in a subject's condition or laboratory results, which has or could have a deleterious effect on the subject's health or well-being. An Adverse Event that is related to the investigational device may be referred to as an Adverse Device Effect (ADE). If any of the above-mentioned events occurs, the study will be terminated and case will report according to the standard clinical pathway.

An adverse event does not include:

- Medical or surgical procedures; the condition that leads to the procedure is not an adverse event
- Pre-existing disease, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions)
- Expected post-operative course

Unanticipated Adverse Device Effect (UADE): Any device related adverse event, the nature or severity of which is not consistent with or listed in the applicable product information (e.g., instructions for use, subject informed consent document, subject information brochure [if applicable], promotional literature) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

A serious adverse event (SAE) is defined as any adverse medical experience that results in any of the following outcomes:

- Death;
- Is life threating;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;

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- Requires medical/surgical intervention to prevent permanent impairment or damage

9.2 Reporting of Adverse Events

All adverse events, whether observed by the PI or study coordinator, elicited from or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience, the date of occurrence, the date of resolution, the duration and type of experience, the severity, the relationship to investigational product (i.e., drug or device), contributing factors, and any action taken with respect to the study drug/device.

Investigators and research coordinators will be instructed that all AE and corresponding relevant information should be recorded on the Adverse Event Form. In addition, the clinical site will be responsible for notifying the Sponsor within 24 hours of any UADE. All relevant information regarding an UADE should be recorded on the Adverse Event Form and reported to Sponsor via Fax within 24 hours of the event. In addition to the event form, copies of adverse device effect related source documents should be forwarded to the Sponsor.

The Principal Investigator is responsible for reporting AEs to the IRB of record in accordance with IRB procedures. The Sponsor is responsible for informing the appropriate regulatory authorities and other Investigators of any UADEs that have occurred.

The device used in the study is standard anesthesia equipment; further, the study is no more than a data collection process via routine anesthesia care, no modification from routine practice added to a study subject. Therefore, other than general precaution and potential risks from corresponding anesthesia care, the study itself does not have added risk to a study subject other than data collection. No additional risk justification needed for the study.

9.3 Responsibilities for Reporting Serious Adverse Events

The PI will record all serious adverse experiences that occur during the study period in the appropriate source documents and/or AE log as applicable.

9.4 Compliance

It is expected that all involved study personnel (Investigators, study coordinators, ancillary site personnel, and study subjects) will be compliant with the study protocol. Should it be determined that the site is non-compliant, reasonable efforts will be made to secure compliance. These efforts/actions shall be documented in writing and maintained within the study administration file at the Sponsor's location.

Should the site continue to remain non-compliant, the study Sponsor may restrict device availability and/or notify the governing IRB. Should efforts to bring the site into compliance fail, the site may be suspended from study participation until the noncompliance is resolved. Federal regulations require the Sponsor to report non-compliance with the study protocol to the appropriate regulatory authorities. Therefore, in the event of an Investigator or site suspension, the governing IRB and other appropriate regulatory authorities shall be notified.

9.5 Protocol Deviations

Protocol Deviations (PDs) will be documented on a Protocol Deviation Case Report Form. PDs are reportable to the institution's governing IRB and regulatory agencies during the annual reporting process, unless otherwise directed by the individual governing IRB requirements or as the specific circumstance dictates.

Every attempt shall be made to adhere to the study protocol. However, should an Investigator be required to deviate from the protocol to protect the life or physical well-being of a study subject in an emergent circumstance, such notice shall be given to the study Sponsor as soon as possible, but no more than 5 working days from the date the event occurred. With the exception of an emergent circumstance, prior approval from Sponsor and the appropriate regulatory authorities is required for any change in, or deviation from, the study protocol as such changes may affect the soundness of the investigation or the rights, safety, and welfare of study subjects.

9.6.Investigator Reports and Responsibilities

Investigators are responsible for ensuring the investigation is conducted in accordance with the study protocol and applicable Federal regulations (21 CFR, Part 812, Subpart E). Investigators are also responsible for:

- Obtaining IRB approval for study conduct and re-approval as applicable (if more than one Investigator is participating in the study at a site, the Principal Investigator shall be responsible for the IRB approval and re-approvals)
- Obtaining informed consent of study subjects prior to enrollment into the clinical study
- Protecting the subject rights, safety, and welfare
- Maintenance of subject records and confidentiality
- Record retention as defined in Federal regulations 21 CFR, Part 812.140 (a), (d), and (e)
- Management of investigation and study related activities according to the Clinical Investigator Agreement and the Study Research Agreement
- Submission of site-specific study closure report to governing IRB within 3 months of notification from study Sponsor (if more than one Investigator is conducting the study, the Primary Investigator is responsible for submission of the study closure report)
- Return of any unused investigational product to the study Sponsor upon request or at the conclusion of the clinical study

In addition:

- An Investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation
- If an Investigator uses a device without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs
- An Investigator shall, upon request by a reviewing IRB or regulatory agency official, provide accurate, complete, and current information about any aspect of the investigation

9.7.Sponsor Reports and Responsibilities

The study Sponsor is responsible for ensuring the study is conducted in accordance with the study protocol and applicable federal regulations (21 CFR, Part 812, Subpart C). Further, the study Sponsor is responsible for the following:

- Selecting qualified Investigators and providing Investigators with appropriate information for study conduct
- Ensuring review and approval process for governing IRB is obtained
- Training all clinical investigators in the study on how to properly use the Optiflow™ THRIVE
- Appropriate monitoring of the clinical study
- Prompt notification to the appropriate regulatory and all Investigators of UADE
- Record maintenance and retention per Federal regulations (21 CFR, Part 812.140 (b), (d), and (e)

- Submission of final study closure report that details cumulative study experience to the appropriate regulatory authorities, governing IRBs, and Investigators within 6 months of completing the clinical investigation, in addition to fulfilling annual reporting requirements

In addition:

- A Sponsor who conducts an evaluation of an UADE shall report the results of such evaluation to all reviewing IRBs and participating Investigators within 10 working days after the Sponsor first receives notice of the effect. Thereafter, the Sponsor shall submit such additional reports concerning the effect as an IRB request.
- A Sponsor shall notify all reviewing IRBs and participating Investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.
- At regular intervals, and at least yearly, a Sponsor shall submit progress reports to all reviewing IRBs. In the case of a significant risk device, a Sponsor shall also submit progress reports to the regulatory authority.
- A Sponsor shall notify all reviewing IRBs of any request that an Investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.
- In the case of a significant risk device, the Sponsor shall notify the IRB within 30 working days of the completion or termination of the investigation and shall submit a final report to all reviewing IRBs and participating Investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the Sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.
- A Sponsor shall submit to the IRB a copy of any report by an Investigator of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.
- If an IRB determines that a device is a significant risk device, and the Sponsor had proposed that the IRB consider the device not to be a significant risk device, the Sponsor shall submit to the appropriate regulatory agency a report of the IRB's determination within 5 working days after the Sponsor first learns of the IRB's determination.
- A Sponsor shall, upon request by a reviewing IRB, provide accurate, complete, and current information about any aspect of the investigation.

9.8. Study Termination

The Sponsor may terminate the study at any time. If terminated, the Sponsor will promptly notify the Investigator to cease enrollment of subjects. The study will also be terminated when the objectives have been fully met and all of the designated data collected.

10. RISK/BENEFIT ASSESSMENT

10.1 Potential Risks

In general, subjects will be a part of a study that may potentially affect how anesthetic providers practice and manage difficult airway patients. The potential risks are the same as routine anesthesia care when related to oxygen therapy/administration. No added risk to study subjects other general precaution or risks related anesthesia care.

10.2 Protection Against Risks (Risk Minimization)

The data collection will be terminated if an identifiable adverse event happens. The event will be handled and reported according the standard clinical pathway.

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10.3 Potential Benefits to Subjects

Improved oxygen delivery, administration, and oxygenation (potentially). The data collected during the study may improve the airway safety profile for future procedures. As a specific benefit, the high-flow oxygen delivery may provide stenting of the airway during the procedure and therefore supply additional airway support.

10.4 Alternatives to Participation

A standard anesthesia care will be delivered to the study subjects; however, no data collection during the procedure.

11. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources.[12] In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (May 2014) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335.

Those having access to the data include the study PI and research team personnel. Users are authenticated against MDACC's Active Directory system. External collaborators are given access to the database once approved by the PI, with their access expiring in 6 months but renewable in 6 months increments at the request of the PI. The application is accessed through Secure Socket Layer (SSL). All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number.

Following publication study data will be archived in REDCap. Since study data may be useful for future research studies performed under separate IRB approved protocols, study data will be archived indefinitely in REDCap. Since REDCap is a secure electronic database with controlled access, and because patient identifiers may be needed to link study data to data from other sources under future IRB approved protocols, patient's identifying information will be retained in the archived database.

11.1 Training of Clinical Site Personnel

The training of clinical site personnel will be the responsibility of the Sponsor. To ensure uniform data collection and protocol compliance, personnel from Sponsor will review the investigational plan, techniques for the identification of eligible subjects, instructions on data collection, methods for soliciting data from alternate sources, and schedules for follow-up, as necessary, with the research coordinator.

11.2 Data Reporting

All data will be recorded on the site's standard source documentation. The Investigator or designee is responsible for transferring the information to the appropriate Case Report Forms (CRFs) supplied by the Sponsor. The Investigator is responsible for ensuring the forms are accurately completed at the time

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of, or as soon as possible after, the subject procedure or the availability of test results. The Investigator is required to sign the CRF on the appropriate page(s) to verify that he/she has reviewed the recorded data.

11.3 Data Review

The Sponsor will review all CRFs for completeness and clarity upon receipt. Missing or unclear data will be requested as necessary throughout the study. The Sponsor will request further documentation such as physician procedure notes when UADEs and/or malfunctions are observed and reported.

The Sponsor will provide clinical monitoring, including comparison of CRFs to source documentation for accuracy and appropriateness, review of/for adverse events, prompt evaluation of UADE, and site compliance. To this end, the Principal Investigator will permit inspection of the study files and subject CRFs by Sponsor representatives and/or responsible government agencies.

Prior to trial initiation the study site will be trained on the clinical protocol, accepted clinical practices and Federal regulations pertaining to clinical research. The study site will receive interim monitoring, as needed, and a final visit prior to study closure.

11.4 Institutional Review Board (IRB)

Prior to participating in this investigation, the site will be required to obtain approval from its governing IRB. The Principal Investigator is responsible for obtaining and maintaining IRB approval to participate in this investigation. Prior to subject enrollment, a signed copy of the IRB approval letter addressed to the Investigator certifying study approval must be submitted to the Sponsor. The IRB for this study is the local IRB at the University of Texas MD Anderson Cancer Center in Houston, TX (IRB00000308, IRB00003763, IRB00004604 or IRB00008445).

The Investigator will report to the Sponsor immediately if, for any reason, the approval to conduct the investigation is withdrawn. This report will include a complete description of the reason(s) for which approval was withdrawn.

11.5 Subject Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Patient data will be entered into a password protected electronic spreadsheet and online database (i.e. REDCap). Only the investigators, who have been invited to participate in the study and who are registered with the IRB, as well as have documented completion of all IRB and HIPAA regulations will have access to the file and password. No identifiable data will be collected. Electronic records will be stored for five years after study conclusion on the agreed upon investigator's laptop computer, after which time they will be deleted. If there is a breach in confidentiality or violation of IRB and HIPAA regulations, the IRB will be notified in a timely manner (within 7 days) and appropriate actions taken thereafter.

No personal identity information including name, MRN will be collected from study subjects instead, a random sequential number labeled envelope will be assigned to each of the study subjects. Each envelope has a unique code linked to the study subject identifier. The study PI will be responsible to destroy the code after study.

The study data will be stored in a secured/locked place (for hard copy) or encrypted/passcode protected electronic device (for electronic data). All the data will be de-identified after the study for future databank to use.

Sponsor will consider all information and data sent to Sponsor concerning a subject or their participation in this investigation as confidential. Only authorized Sponsor personnel will have access to these confidential files and have the right to inspect and copy all of the records pertinent to this study for data verification. This may include medical information gathered prior to the onset of the study. All data used in the analysis and reporting of this investigation will be conducted without identifiable reference to specific subject name. The site will maintain a list matching each subject's name with the study identification.

Data collected and stored by Sponsor will be free of identifying information such as subject name and medical record numbers. Any photos taken during the study will make every effort not to include subject faces or other identifying marks such as scars or tattoos.

In order to ensure compliance with the Health Insurance Portability and Accountability Act (HIPAA), all subjects enrolled in the study will be required to provide authorization to disclose Protected Health Information (PHI). This authorization will be included in the informed consent document as required by the IRB. In all study reports and in any resulting publications, their initials and/or study identification number will not refer to subjects.

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APPENDICES

Appendix A. – Case report forms (CRFs); data collection forms
Appendix B. – PACU discharge patient satisfaction evaluation