

Ochsner Clinic Foundation

Ochsner Health System

**TOTAL INTRAVENOUS VERSUS INHALED ANESTHESIA IN ENDOSCOPIC SINUS SURGERY FOR
ADVANCED PARANASAL DISEASE**

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List of Abbreviations

CRS- Chronic Rhinosinusitis

IA- Inhaled Anesthesia

PONV- Postoperative nausea and vomiting

TIVA- Total Intravenous Anesthesia

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Study Summary

Title	Total Intravenous versus Inhaled Anesthesia in Endoscopic Sinus Surgery for Advanced Paranasal Disease
Short Title	TIVA in high-risk endoscopic sinus surgery
Protocol Number	Pro00011453
Phase	
Methodology	Randomized controlled trial
Study Duration	18 months
Study Center(s)	Ochsner Clinic Foundation
Objectives	Evaluate the role of TIVA for maintenance of anesthesia during endoscopic sinus surgery. Outcome measures of operative visual field, change in sinus related quality-of-life, surgical time, complications and postoperative nausea and vomiting will be collected with subgroup analysis of patients with advanced paranasal sinus disease.
Number of Subjects	110
Diagnosis and Main Inclusion Criteria	Chronic rhinosinusitis. English speaking patients undergoing endoscopic sinus surgery for treatment of inflammatory paranasal sinus disease.
Study Product, Dose, Route, Regimen	Propofol, 100-200 mcg/kg/min IV for maintenance of anesthesia with goal mean arterial pressure of 70-80 mmHg
Duration of administration	Limited to maintenance of anesthesia during endoscopic sinus surgery
Reference therapy	Inhaled anesthesia

Statistical Methodology	All parametric data is tested for normal distribution and characterized by mean +/- standard deviation. Differences between the visual field and change in quality-of-life measure for the two treatment groups are evaluated using a <i>t</i> -test. The association between the treatment groups and surgical procedure is tested using the chi-square test. The association between the treatment groups and pathological groups is tested using Fisher's exact test.
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1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 *Background*

Successful endoscopic sinus surgery (ESS) is largely dependent on identification of anatomic landmarks within a visually limited surgical field. Tight structural spaces, inflammatory tissues and intraoperative bleeding combine to decrease surgical exposure, with resultant increases in operative time, total blood loss and intraoperative complications. Maneuvers to improve the endoscopic visual field include reverse Trendelenburg positioning, nasal decongestion and infiltration of the lateral nasal wall with vasoactive epinephrine, and are currently accepted as standard of care¹. Utilization of total intravenous anesthesia (TIVA) has been proposed as an additional method to improve visualization during ESS, largely due to its physiologic decrease in cardiac output without the peripheral smooth muscle relaxation and resultant vasodilation associated with inhaled anesthetics (IA)². Propofol, when utilized for maintenance of anesthesia, is associated with decreased blood loss in several orthopedic and obstetric procedures³⁻⁵. However, despite this physiologic basis for improved intraoperative visualization with TIVA, conclusive evidence remains elusive⁶⁻¹⁰. While two recently published meta-analyses cite suggestive evidence for improved visual fields in ESS with TIVA, definitive recommendations could not be made due to limitations in the constituent studies^{11, 12}. The objective of this study is therefore to evaluate the effects of TIVA versus IA on intraoperative visual field in ESS.

This application seeks to improve clinical practice paradigms by evaluating the use of TIVA for maintenance of anesthesia in ESS for advanced paranasal sinus disease. Despite several previous studies evaluating the effect of TIVA on endoscopic visual field in ESS, limited study sizes and heterogeneous outcome measures prevent definitive recommendations. Additionally, the role of TIVA has not been reported among a subset of patients with advanced paranasal sinus disease. This study seeks to address these concerns, and will utilize the validated Wormald Visual Scale¹³ as a standardized outcome measure with the sensitivity to detect changes in visual field not recognized by other means (Boezaart Grading Scale, total blood loss).

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Investigational Agent
Propofol (Diprivan)

1.2 Preclinical Data

Since its introduction in the 1970s, propofol has become the most widely used IV hypnotic in clinical use today. Building on work on the sedative properties of phenol derivatives in mice, propofol was developed in the United Kingdom by Imperial Chemical Industries as ICI 35868. The current formulation was launched in 1986¹⁴.

1.3 Clinical Data to Date

Propofol is used for induction and maintenance of anesthesia and for sedation in and outside the operating room. Its mechanism of action is likely the enhancement of γ -aminobutyric acid (GABA)-induced chloride currents. Propofol causes a dose-dependent decrease in arterial blood pressure through a decrease in cardiac output and systemic vascular resistance and produces moderate respiratory depression. A unique action of propofol is its antiemetic effect, even at concentrations less than those producing sedation¹⁴.

1.4 Dose Rationale and Risk/Benefits

Propofol is suitable for the induction and maintenance of anesthesia.

The IV induction dose is 1 to 2.5 mg/kg.

Maintenance dose is 50-150 μ g/kg/min IV combined with N₂O or an opiate. The infusion rate is titrated to individual requirements and the surgical stimulus¹⁴.

Induction of anesthesia with propofol is often associated with pain on injection, apnea, hypotension, and, rarely, thrombophlebitis of the vein into which propofol is injected¹⁴.

2 Study Objectives

The objective of this study is to evaluate the effects of TIVA versus IA on intraoperative visual field in ESS for the treatment of advanced paranasal sinus disease.

SPECIFIC AIMS

1. Determine the effect of total intravenous versus inhaled anesthesia on intraoperative visual field in endoscopic sinus surgery for advanced paranasal sinus disease

This study seeks to evaluate the effect of total intravenous anesthesia (TIVA) on the intraoperative visual field during endoscopic sinus surgery (ESS). Subgroup analysis of patients with allergic fungal sinusitis, pan-sinus opacification and nasal polyposis will further evaluate the role of TIVA in advanced sinus disease.

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2. Evaluate clinical outcomes associated with choice of total intravenous versus inhaled anesthesia in endoscopic sinus surgery

Clinical outcomes among patients receiving TIVA versus IA will be made with assessment of change in quality of life scores, pharmacologic effects (postoperative nausea and vomiting, recovery time) and surgical complications.

3. Evaluate relative costs associated with total intravenous versus inhaled anesthesia in endoscopic sinus surgery

Comparative cost analysis will be included to evaluate potential barriers to implementation of total intravenous anesthesia in endoscopic sinus surgery.

3 Study Design

3.1 General Design

Double blind, randomized controlled trial of total intravenous versus inhaled anesthetic for maintenance of anesthesia during endoscopic sinus surgery.

3.2 Primary Study Endpoints

110 patients will be enrolled for study participation. Validated measure of intraoperative visual field will be utilized for primary outcome measure.

3.3 Secondary Study Endpoints

Secondary outcome measures include change in sinus-related quality-of-life, intraoperative bleeding, surgical time, post anesthesia care unit recovery time, postoperative nausea and vomiting (PONV), complications and response duration.

3.4 Primary Safety Endpoints

Safety endpoints include adverse surgical (intraoperative orbital/dural injury and postoperative hemorrhage/cerebrospinal fluid leak) and pharmacologic (severe PONV) events.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Inclusion criteria include English-speaking patients undergoing endoscopic sinus surgery for the treatment of inflammatory paranasal sinus disease, including subgroups of patients with allergic fungal sinusitis, chronic rhinosinusitis with nasal polyposis, chronic rhinosinusitis with eosinophilia and rhinosinusitis with pan-sinus opacification.

4.2 Exclusion Criteria

Exclusion criteria includes noninflammatory sinonasal disease, disease extending through the skull base or orbital wall, patients <18 years old, American Society of Anesthesiologists Preoperative Health Status >II, known non-pharmacologic coagulopathy (platelet < 50000/mL, INR>1.2), preoperative anticoagulants within 7 days of surgery and allergy to one of the study medications.

4.3 Subject Recruitment and Screening

Patients will be screened for study inclusion by the principal investigator (EDM) during their preoperative visit in the Department of Otolaryngology. Those meeting inclusion criteria will be introduced to the study at this time. A full description of the research purpose, personnel, procedures, risks and benefits will be presented, and a copy of the study consent documentation will be provided for home review.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Study personnel will remain available to participants at all times during the study period, and may be reached via the hospital operator. Withdraw notification can be given at any time, and will be immediately reported to the clinical coordinator for documentation.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Completion of study participation will have no bearing on clinical follow-up. Withdrawn subjects will complete follow-up as clinically indicated, without further data collection.

5 Study Drug

5.1 Description

Propofol (Diprivan)

5.2 Treatment Regimen

Anesthesia Protocol

Preoperative medications may be given according to routine clinical care, which may include Midazolam 1-2 mg IV prior to being taken to the operating room. Standard ASA monitors will be placed. Induction of general anesthesia will follow the normal standard of care. Induction of anesthesia for both groups will include: Propofol 2 mg/kg, Lidocaine 0.5-1 mg/kg, Fentanyl 1-2 mcg/kg, with muscle relaxation with either Succinylcholine 1-2 mg/kg or Cisatracurium 0.15-0.2 mg/kg for intubation. Maintenance of anesthesia will consist of Cisatracurium 0.03- 0.04 mg/kg and the appropriate anesthetic per protocol described below.

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Patients in the inhaled anesthesia group will receive Sevoflurane in an end expiratory concentration of 1.4% to 3% corresponding to near minimum alveolar concentration (MAC) of ~0.5-1.5%. The carrier gas flow for both groups will consist of a combination of oxygen and air to a total flow rate of 2 l/m to maintain oxygenation per standard of care. Patients in the TIVA group will receive an infusion of Propofol in a dose of 100-200 mcg/kg/min for maintenance. IA group will adjust the Sevoflurane concentration and TIVA group will adjust the Propofol and Remifentanil dosing with the goal of maintaining mean arterial pressure 70 -80 mmHg.

Both groups will be allowed to utilize Phenylephrine, Ephedrine, Labetalol or Esmolol as needed to maintain target blood pressure. Patients will be reversed with Neostigmine and Glycopyrrolate at the conclusion of the case. Post-operative pain relief will include either Morphine or Dilaudid per standard of care. No Acetaminophen may be given for either group for pain control.

Surgical Protocol

All patients are placed in 30 degree Reverse Trendelenberg positioning. 10 minutes prior to start of surgery, patients are pretreated with 4% cocaine-soaked nasal pledgets and local injection of 1% xylocaine with 1:100,000 epinephrine into the submucosa at the anterior attachment of the middle turbinate and crista ethmoidalis. Topical thrombin and epinephrine soaked pledgets will be available for intraoperative maintenance of hemostasis. Endoscopic sinus surgery will be completed following the modified Messerklinger technique, with utilization of endoscopic surgical equipment for video documentation of the surgical field. Recording equipment includes the Storz 4mm 0° rigid endoscope (Karl Storz, Tuttlingen, Germany) connected to a high definition camera and Olympus Evis Extra II light source. The video is recorded in MPEG2 digital format and transferred to the password protected study database. Visual field is recorded following the standardized method reported by Wormald et al., with the protocol as follows:

Prior to completion of surgery, old blood is suctioned from the nasal cavity with care not to traumatize mucosal surfaces and reinitiate bleeding. The surgical field is then recorded in a systematic fashion, with observation of four intranasal structures. Moving from anterior/superior to posterior/inferior, the frontal recess, ethmoidal cavity (endoscope positioned just anterior to the middle meatus), sphenoidal recess, and postnasal space are serially recorded for ten seconds each.

Following completion of surgery total blood loss will be calculated by the nursing circulator, with subtraction of the volume of intraoperative irrigation from the total volume contained in all suction canisters and saturated towels. The patient will be transferred to post-operative recovery and released home upon meeting established criteria. Patients will undergo routine postoperative follow-up, with evaluation at 1, 2, 4 weeks and as needed. A new SNOT-22 questionnaire will be completed as part of the postoperative week 2 and 4 visit.

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5.3 Method for Assigning Subjects to Treatment Groups

On the day of surgery, eligible participants will be admitted to the Day of Surgery Department, where a member of the Anesthesia team will review study information and confirm informed consent. A randomly assigned, sealed envelope will then be opened to assign participants to either the TIVA, or IA cohort. At no time will the patient or surgeon be made aware of the patient's cohort.

5.4 Preparation and Administration of Study Drug

Staff in the department of Anesthesia will administer perioperative medications in accordance with surgical standard of care.

5.5 Subject Compliance Monitoring

N/A as study intervention limited to perioperative maintenance of anesthesia.

5.6 Prior and Concomitant Therapy

Medications for induction, maintenance of anesthesia, reversal and postoperative recovery will be given as described in the “Anesthesia Protocol” (section 5.2).

5.7 Packaging

Packaging of study medication will be concealed from surgeons and study participants.

5.8 Blinding of Study Drug

At no time will the patient or surgeon be made aware of the patient's cohort. During the procedure the surgeon is blinded to the type of anesthesia by placement of a high drape at the head of the operative table. Study reviewers will be blinded to treatment arm without cohort assignment at time of review for determination of visual field score.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.9.2 Storage

The study medication will be stored in the hospital pharmacy and distributed to Anesthesia personnel in accordance with surgical standard of care.

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5.9.3 Dispensing of Study Drug

Staff anesthesiologists will dispense study drug in the perioperative setting. Drug administration will be recorded and maintained in the surgical record.

6 Study Procedures

Participants make no clinic/hospital visits for purposes of study completion as all patient interaction limited to visits and surveys completed as part of routine clinical care.

6.1 Visit 1

Clinic presentation: A 22-item Sinonasal Outcome Test (SNOT-22) survey is completed per routine clinical care. Patients considering endoscopic sinus surgery for treatment of inflammatory paranasal sinus disease are initially screened for study participation. The principal investigator (EDM) presents the research purpose, personnel, procedures, risks and benefits of the study, and provides a written copy of the study consent for home review.

6.2 Visit 2

Preoperative visit: Study consent reviewed with an investigator and signed at this time. Enrolled patients will be assigned a randomly generated unique study identification number. The patient's demographic information will then be entered into the password-protected study database (Excel, Microsoft, Redwood, WA), which will be maintained on a HIPAA compliant server with access restricted to identified study computer maintained in the department of Otolaryngology.

6.3 Visit 3

Day of Surgery: Study consent reviewed and treatment group assigned. Intervention limited to perioperative maintenance of anesthesia with recording of deidentified endonasal endoscopic video for independent analysis of surgical visual field.

6.4 Visit 4

Routine 1-week postoperative follow-up.

6.5 Visit 5

Routine follow-up 4 weeks after date of surgery with completion of SNOT-22 survey.

6.6 Visit 5

Routine follow-up 12 weeks after date of surgery with completion of SNOT-22 survey.

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7 Statistical Plan

7.1 Sample Size Determination

Sample size determination was calculated using the OpenEpi Sample Size Tool (Available: <http://www.openepi.com/SampleSize/SSCohort.htm>). The Wormald visual field has not been used to evaluate the effect of TIVA versus IA on endoscopic visual field, so previous reports using the Boezzart scale were used to estimate the mean size difference¹². This calculation provided a n=52 per cohort, or sample size of 104. Sample size increased to 110 to allow for patient dropout.

7.2 Subject Population(s) for Analysis

Subgroup analysis will be completed of patients deemed “high risk” for endoscopic sinus surgery. This includes patients with diagnoses of allergic fungal sinusitis, CRS with nasal polyposis, CRS with eosinophilia and advanced paranasal sinus disease (LM>12). The analysis plan has been reviewed by an in-house statistician.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity

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- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following surgery.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

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8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.2.1 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB within 10 working days. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator's binder.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments,

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copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The Investigator will ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities, and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices. The protocol will be registered on clinicaltrials.gov in accordance with regulation.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal

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prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment A for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

There is no financial sponsor for the study at this time.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Ochsner investigators will follow the institutional conflict of interest policy.

12.3 Subject Stipends or Payments

No incentives are associated with study participation.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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15 Attachments

- A. Subject informed consent form
- B. HIPAA authorization
- C. Table 1. Collected Data
- D. Study Monitoring Plan

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