GIDE – Glucose Time-In-Range Development Evaluation

(GIDE Study)

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EXECUTIVE SUMMARY

Sponsor Name:	This is an Investigator Initiated Study being funded by OptiScan Biomedical Corporation.
Objectives:	Assessment of glucose Time-in-Range (TIR) post implementation of the OptiScanner 5000 bedside glucose monitoring system (OptiScan Biomedical) in a Surgical ICU patient population. Assessment of the time it takes the patient to achieve in range glucose values (using participant's clinical care defined glucose target range) while connected to the OptiScanner.
Clinical Hypothesis:	Preventing glucose variability has been shown to be strongly associated with increased survival in non-diabetic critically ill adults (6-8). In clinical practice, it is very challenging to maintain critically ill patients' glucose values within a "target range" as the methods currently available to accomplish this are burdensome on the clinical care team and can be quite costly. The primary endpoint of this study is to assess the level of TIR obtained in a surgical ICU patient population after implementing the OptiScanner 5000 glucose monitoring systems.
Name of Investigational Device(s):	OptiScanner 5000 Glucose Monitoring System FDA Cleared on October 16, 2017 (K162042). The device will be used without Clinical Laboratory Improvement Amendments (CLIA) oversight for this study.
Design:	Single center, non-randomized, study evaluating the proportion of patients maintaining in range glucose values (using participants' clinical care defined glucose target range) and the time it takes for patients to achieve in range glucose values in a Surgical ICU population after implementing the OptiScanner 5000 Glucose Monitoring system

<table>
<tr><td>Planned Enrollment:</td><td>Enrollment into this trial will be in two phases. Phase One of the study will consist of study staff working with the clinical care team to operationalize the logistics involved with implementing the use of the OptiScanner. In addition, phase one subjects will provide the opportunity for the PI to observe the OptiScanner utility as a complement to the current glucose management of the patient. The continuous glucose monitoring provided by the OptiScanner may introduce additional glucose measurement information that would not have been known if it occurred between the routine clinical care glucose measurements and the clinical care team will be advised to confirm any OptiScanner glucose value (using routine clinical care methods) before making any modifications to patients' clinical care based on the OptiScanner glucose result. A research team member will be at the patient's bedside during his/her entire study participation to ensure that the clinical care team does not use the OptiScanner results independently to direct patient care and to observe how the additional glucose information is or is not used. A minimum of 50 patients will be enrolled in phase one.

<u>Phase Two will commence after the data from phase one has been evaluated. The protocol will be updated with Phase Two procedures after the completion of the analysis of phase one results.</u>

Study Completion:
The study will be completed after enrolling 50 phase one evaluable subjects. An evaluable subject is defined as a subject with a minimum of 48 hours of OptiScanner monitoring.</td></tr>
<tr><td>Duration of Participation:</td><td>Minimum of 48 hours of monitoring with the OptiScanner System

Maximum of 72 hours of monitoring with the OptiScanner System</td></tr>
<tr><td>Primary Endpoint:</td><td>Time-in-range (TIR), post-OptiScanner system implementation:

<table><tr><td>Target TIR</td><td></td><td>Primary Endpoint</td></tr><tr><td>According to participants' clinical care defined target glucose range</td><td></td><td>Evaluation of TIR</td></tr></table></td></tr>
<tr><td>Secondary Endpoint</td><td>Assessment of the time it takes the patient to achieve in range glucose values while connected to the OptiScanner.</td></tr>
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Safety Endpoints:	The proportion of subjects that experience one or more Device Related Serious Adverse Events (DRSAEs). Incidence of hypo/hyperglycemia

1.0 Introduction

1.1 Background and Rationale

Hyperglycemia [1-4], hypoglycemia [1,5] and glycemic variability [6-8] are independently associated with morbidity and mortality of critically ill patients. Blood glucose control with insulin has the potential to decrease morbidity and mortality of intensive care unit (ICU) patients. Blood glucose control with insulin, however, is associated with an increased risk of hypoglycemia and may not decrease glycemic variability. In addition, blood glucose control with insulin utilizing manual systems for glucose measurement is blood-consuming and time-consuming, since frequent blood draws for glucose measurements are necessary in order to achieve blood glucose control.

Severe hypoglycemia (blood glucose level < 40 mg/dl) is a feared complication of blood glucose control with insulin. Undoubtedly, with the implementation of blood glucose control with insulin the incidence of hypoglycemia increases [9-15]. Several reports showed a significant association between hypoglycemia and patient outcomes [1,5,8,16]. Recently, an association has even been suggested between moderate hypoglycemia (blood glucose level between 40–69 mg/dL) and patient outcomes. Incidences of moderate hypoglycemia are more prevalent than severe hypoglycemia. The risk of developing (severe or moderate) hypoglycemia hampers, at least in part, broad implementation of blood glucose control with insulin, in particular when aiming at normal blood glucose levels, such as 80 – 150 mg/dl [17,18].

Recent studies showed significant associations between glycemic variability and patient outcomes [6-8,19,20]. Krinsley, et al, demonstrated that a TIR of 70 to 140 mg/dl > 80% was strongly associated with survival in critically ill patients without diabetes, independent of ICU LOS or severity of illness [21].

Implementation strategies of blood glucose control have mostly been accomplished with manually operated portable whole blood glucose meters, which suffer from a variety of error sources that can put intensively managed patients at risk for insulin

over– and/or under–dosing [23]. Furthermore, all manually operated whole blood glucose monitoring measurement devices lack trending, though immediate feedback and predictability of the effects of insulin infusions are highly needed when infusing insulin in critically ill patients [24]. In addition, each blood glucose measurement not using a finger stick requires a substantial volume of blood and is time–consuming [25].

Automated, frequent, plasma-based glucose monitoring with the OptiScanner 5000 glucose monitoring system has the potential to improve a patient's glucose TIR by improving all 3 domains of glycemic control: reducing hyperglycemia while at the same time preventing hypoglycemia and reducing glycemic variability. Second, it could reduce the workloads associated with the high number of blood samples to be obtained and analyzed [22,26-29].

1.2 Device Description

The OptiScanner® 5000 Glucose Monitoring System from OptiScan Biomedical Corporation is an automated, bedside glucose monitoring system designed to quantitatively measure the concentration of venous blood glucose. When attached to a patient, the OptiScanner® 5000 Glucose Monitoring System automatically draws a 3 mL blood sample, retains a micro-sample of blood for analysis (0.17 mL), and returns the remaining portion of the blood to the patient. The OptiScanner® 5000 Glucose Monitoring System analyzes the retained portion of the blood sample and then displays a glucose value. The OptiScanner® 5000 Glucose Monitoring System provides trending glucose information, which allows for decision-making based on a trend rather than any single glucose value.

The OptiScanner automatically performs the following functions as part of its monitoring cycle:

- Draws blood from the patient.
- From the blood withdrawn, retains a micro-sample (0.17 mL) blood sample for glucose measurement.
- Returns the unused blood to the patient along with a small (2.5 mL) amount of saline solution.
- Spins the blood sample, separating plasma from red blood cells.
- Measures optical signals from the plasma sample using a mid-infrared spectrometer.
- Adjusts for interfering substances, referencing a proprietary measurement algorithm.
- Calculates the latest blood glucose value, displays it on-screen, and updates the trending graph with patient's real-time glucose information.

The OptiScanner disposable cartridge is the sterile container within which the blood sample is prepared and analyzed. The Cartridge is for single patient use only. A new sterile Cartridge must be used for each new patient. In normal usage, the Cartridge will last for up to three days (72 hours) of monitoring.

The connection between the OptiScanner and the patient is accomplished through a vascular access device. Vascular access devices for OptiScanner connection include Central Venous Catheters (CVC) and Multi-lumen Access Catheters (MAC). The OptiScanner patient connector design employs a standard universal luer connector and can be successfully used with these devices. The type of device selected and its placement on the subject shall be determined by the user. Placement of the vascular access device is performed in accordance with the vascular access devices instructions for use but must be connected to the venous side. The OptiScanner must be connected to the most proximal port of the CVC or MAC.

The OptiScanner is composed of three main components (see Figure 1 and 2):

- OptiScanner Instrument with integrated pump, spectrometer, and user interface
- OptiScanner Transport Cart with a single IV pole or double IV poles (Cart)
- OptiScanner Disposable Cartridge (Cartridge)

Figure 1: Instrument mounted on the transport cart (up to two poles may be assembled)

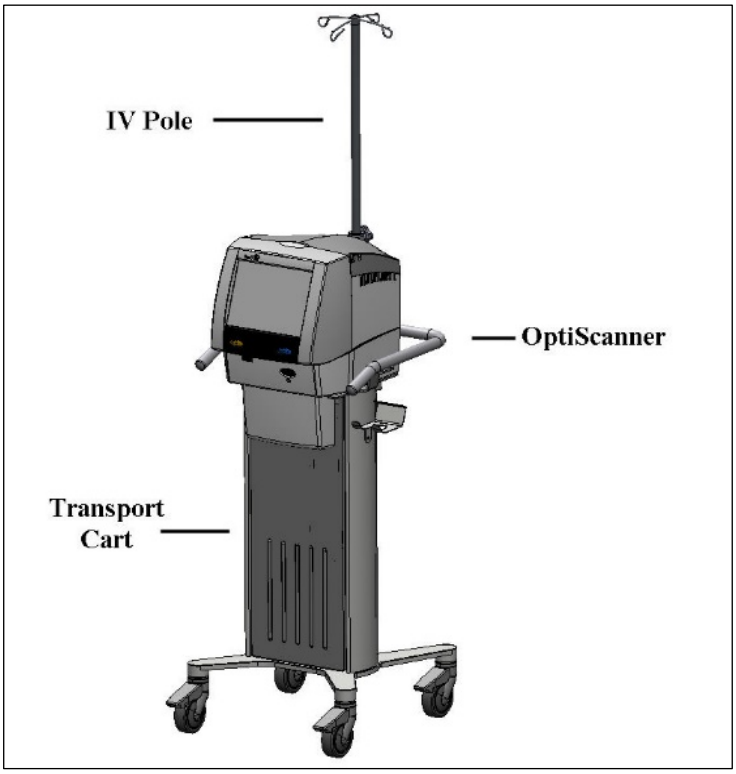
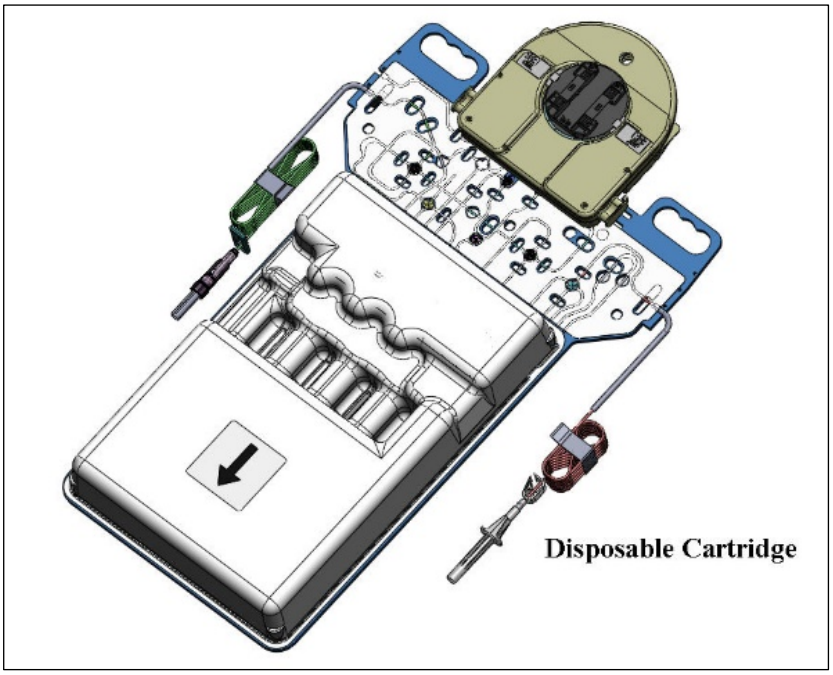


Figure 2: Disposable device



1.3 Indications For Use

The OptiScanner® 5000 Glucose Monitoring System is an automated, bedside glucose monitoring device indicated for detecting trends and tracking patterns in persons (age 18 and older) in the surgical intensive care unit. The system collects a venous whole blood sample via connection to a central venous catheter, centrifuges the sample, and measures the plasma glucose concentration. It is not intended for the screening or diagnosis of diabetes mellitus but is indicated for use in determining dysglycemia. The OptiScanner® 5000 Glucose Monitoring System is for in vitro diagnostic use.

1.4 Regulatory Status

The OptiScanner 5000 Glucose Monitoring System was FDA-Cleared for commercialization in the USA on October 16, 2017 (K162042) however this device is not currently commercially available in the US.

1.5 Risks and Benefits

There have been no serious adverse events related to the OptiScanner in any of the clinical studies performed to date.

Risk management in accordance with EN 14971, was completed on the study device. The conclusion is that the OptiScanner has an acceptable safety profile.

Because the OptiScanner system delivers automated, every 15 minutes glucose results and trends, it has the potential to improve a patient's glucose TIR by providing earlier identification of abnormal glucose values that would otherwise remain unknown until the clinical care scheduled glucose value was obtained (which typically are collected every 1 to 4 hours, depending on the condition of the patient). Therefore, the OptiScanner has the potential to improve all 3 domains of glycemic control: reducing hyperglycemia while at the same time preventing hypoglycemia and reducing glycemic variability. In the future, the OptiScanner may also reduce the workload associated with the high number of blood samples to be obtained and analyzed [22, 26-29].

2.0 Study Objectives

The primary objective of this study is to observe the Time-in-Range for patients whose glycemic control is being monitored with the OptiScanner system. A secondary objective is assessment of the time it takes the patient to achieve in range glucose values while connected to the OptiScanner. The study will evaluate patients requiring frequent glucose monitoring in a Surgical ICU.

3.0 Selection and Withdrawal of Subjects

3.1 Screening and Study Enrollment

The study population includes surgical critical care patients who require blood glucose monitoring.

Subjects must have a vascular access device [i.e., Central Venous Catheters (CVC), Multi-lumen Access Catheters (MAC) either in place or to be placed with an expected usage of at least 48 hours.

Subjects that meet all of the eligibility criteria and are deemed suitable by the Investigator will be invited to participate in the study.

Each potential study subject, or their legally authorized representative, must provide written Informed Consent using the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form before undergoing any study-related procedures.

A subject is considered enrolled in the study once the informed consent has been signed and all eligibility criteria have been verified, and the OptiScanner system has begun monitoring.

3.2 Inclusion Criteria

All subjects are required to meet the following inclusion criteria in order to be considered eligible for participation in this study:

1. Signed informed consent by the participant or his/her legally authorized representative;
2. At least 18 years old;
3. Admitted to a Surgical ICU or planned admission to a Surgical ICU at time of screening
4. Expected SICU stay of at least 48 hours at the time of enrollment
5. A vascular access device available for connection to the OptiScanner is either already in-place, or is planned to be placed with an expected usage of at least 48 hours.

3.3 Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following exclusion criteria:

1. Positive HcG (serum or urine) in women of childbearing potential (age < 60) who are not known to be surgically sterile and those that are obviously pregnant.
2. Patients undergoing peritoneal dialysis within the past week.
3. Patients actively receiving intravenous immunoglobulin therapy.
4. Patients receiving intravenous administration of high dose ascorbate (IVC) for the treatment of patients with cancer.
5. Patients following the administration of a D-Xylose absorption test < 12 hours

6. Patients being treated with Sodium Thiosulfate.
7. Patients being receiving IV glycerol.
8. Patients receiving substances containing maltose, or substances that can be metabolized into maltose. These substances include Extranneal, Gamimune N, HepaGam B, Octagam, Vaccinia Immune Globulin, and WinRho SDF Liquid.
9. Hct <15% within 24 hours of screening visit.

3.4 Withdrawal of Subjects

Subjects may voluntarily withdraw from the study at any time for any reason if they wish to do so, without any consequences. The PI may withdraw a subject from the study at his discretion due to safety or any other concerns (i.e. deliberate non-compliance).

4.0 Study Design

4.1 Study Design Description

This is a Single-center, non-randomized, study evaluating the TIR in a Surgical ICU population after implementing the OptiScanner system.

4.2 Insulin administration during the Study:

4.2.1 Phase One

4.2.1.1 During Phase One of the trial, the hospital's current standard of care for glucose management will be followed. Currently glucose values are measured using point of care glucose meters and/or by collecting a blood sample and sending it to the hospital laboratory. Patients' glucose values are currently monitored depending on their clinical condition with the frequency of glucose measurement typically occurring every one to four hours. Patients enrolled in this study will still be monitored in this same manner, depending on their clinical condition (using point of care meters and/or blood collection for the lab). The additional continuous monitoring provided by the OptiScanner may introduce additional glucose measurements. The clinical care team will be advised to confirm any OptiScanner glucose value (using routine clinical care methods) before making any modifications to the patient's clinical care based on the OptiScanner result (i.e. increase, decrease, stop insulin drip, etc.). The glucose results from the OptiScanner will not be recorded in the medical record. A research team member will be at the bedside during the patients' connection to the OptiScanner to ensure that the clinical team does not use the OptiScanner results to direct patient care and to observe the overall clinical care glucose management of the patient. Representatives from the sponsor may be present at the participant's

bedside to provide the research team technical support and assistance. The sponsor representatives will not have access to the protected health information for the participant.

4.2.2 Phase Two

Following the 1st phase of the trial, data on time-in-range and patient glucose management activities and responsiveness to insulin adjustments will be assessed by the PI, a statistician, OptiScan and potentially, ICU nursing and physician leadership. Phase II Study procedures will be developed based on the results.

4.3 Study Endpoints and Other Assessments

4.3.1 Primary Endpoint

The primary endpoint is an evaluation of the Glucose Time-in-range (TIR).

4.3.2 Secondary Endpoint

Assessment of the time it takes the patient to achieve in range glucose values while connected to the OptiScanner.

Target TIR		Primary Endpoint
According to participants' clinical care defined target glucose range		Evaluation of TIR

4.3.2 Additional Data Collected

The following data will be collected during the OptiScanner evaluation:

- Demographic Data
- Date of admission
- Primary and secondary diagnosis
- History of thromboembolic events and clotting disorders
- Medications administered during ICU stay
- Insulin administration: timing, dosage, route and protocol used
- Insulin adjustment: reason for the adjustment, OS glucose value prior to insulin adjustment and standard of care confirmatory glucose value obtained if adjustment was related to an abnormal OS glucose value, timing of insulin adjustment, dosage, and route
- Dextrose administration/IV: timing, and dosage
- Dextrose adjustment: reason for the adjustment, OS glucose value prior to insulin adjustment and standard of care confirmatory glucose

value obtained if adjustment was related to an abnormal OS glucose value, timing of dextrose adjustment, dosage, and route
- TPN and other nutrition
- TPN and other nutrition adjustment
- Number of Hypoglycemic events (defined as glucose < 70 mg/dL)
- Number of Hyperglycemic events (defined as glucose > 200 mg/dL)
- Ventilator days, ICU LOS, and HLOS
- Infection outcome data
- Procedures including imaging, dialysis, and transfusions
- Date and time of OS connection/disconnect
- Contrast administration
- Discharge disposition (i.e. home, rehab, nursing home, death, etc.)
- Device related AE's and SAE's

Additional data not typically collected in the patient's medical records:

- Types and frequency of alarms (both dysglycemia and others) downloaded from the OptiScanner after the case
- The frequency of CVC maintenance incidents requiring disconnection from the OptiScanner system
- Comparator measurements (at the start, at approximately 24-hour intervals, and when prompted by the OptiScanner (i.e. cartridge change) Patients will have a study blood draw after OptiScanner connection, at approximately 24-hour intervals, and when prompted by the OptiScanner (i.e. cartridge change). The sample may be point of care or sent to the laboratory for analysis.
- History of CVC line (occlusions, other clotting disorders, age, etc)
- Clinical care team action/inaction details related to all glucose values (both OptiScanner and standard of care values).

4.3.3 Safety Endpoint

The proportion of subjects that experience one or more Device Related Serious Adverse Events (DRSAEs). Incidence of hypo/hyperglycemia.

4.4 Sample Size

A minimum of 50 subjects will be enrolled in the study. The study will be divided into 2 phases: Phase One and Phase Two.

4.4.1 Phase One:

Phase One of the study will consist of study staff working with the clinical care team to operationalize the logistics involved with implementing the OptiScanner. In addition, phase one subjects will provide the opportunity for the PI to observe the OptiScanner

utility as a complement to the current glucose management of the patient. The continuous glucose monitoring provided by the OptiScanner may introduce additional glucose measurement information that would not have been known if it occurred between the routine clinical care glucose measurements and the clinical care team will be advised to confirm any OptiScanner glucose value (using routine clinical care methods) before making any modifications to patients' clinical care based on the OptiScanner glucose result. A research team member will be at the patient's bedside during his/her entire study participation to ensure that the clinical care team does not use the OptiScanner results independently to direct patient care and to observe how the additional glucose information is or is not used. A minimum of 50 patients will be enrolled in phase one.

4.4.2 Phase Two:

Following the 1st phase of the trial, data on time-in-range and patient glucose management activities and responsiveness to insulin adjustments will be assessed by the PI, a statistician, OptiScan and potentially, ICU nursing and physician leadership. Phase II Study procedures will be developed based on the results.

4.5 Duration of Subject Participation

Overall study enrollment is estimated to take approximately 12 months. Subjects enrolled in the study will participate for at least 48 hours and up to 72 hours. There are no follow-up visits or evaluation.

Participation in the study will be complete when either the subject is discharged from the SICU or hospital, or after 72 hours, whichever comes first.

4.6 Study Termination

The Principal Investigator, Grant Bochicchio, MD, MPH, FACS, may discontinue the study at any stage.

5.0 Assessment of Time-in-Range (TIR)

TIR is calculated as the number of points in range divided by the total number of measurements presented. When the smart alarm is active, readings during that period are excluded from the calculation.

6.0 Assessment of Safety

The rate of Device-Related Serious Adverse Events (DRSAEs). The relationship of the event to the study device and whether the event is considered serious will be determined by the Investigator.

7.0 Statistics

For Phase One of this study, no formal statistics will be performed as this phase is strictly observational. Results of Phase One will be used to inform the power analysis for the 2nd phase of the study.

8.0 Data Management

The Investigator is responsible for the development of appropriate case report forms. The Investigator will be responsible for the accurate and timely collection of data during the study. Quality assurance procedures will be established to ensure that complete, accurate and timely data are collected, that protocol requirements are followed, and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. The Investigator and site CRC will maintain all source documents as required by the protocol, supporting medical records, and signed Informed Consent Forms. All glucose data will be stored within the OptiScanner and will be downloaded for data analysis purposes and the electronic files will be submitted to the Investigator. The OptiScanner calculates percent in range.

9.0 Investigator Responsibilities

The Investigator is responsible for ensuring that this study is conducted according to this protocol and that a signed approved Informed Consent Form is obtained from each patient prior to their inclusion in this study. The Investigator will also ensure that all staff assisting with this study have the appropriate qualifications and are fully instructed on the study procedures and respect patient confidentiality, as specified in the Health Insurance Portability and Accountability Act (HIPAA) requirements.

The Investigator is responsible for ensuring that the conduct of this study conforms to with his or her IRB/EC requirements and provides all necessary communication with the IRB/EC including, but not limited to, annual study reports and required AE notifications.
The Investigator and study staff should make every possible effort to ensure that complete data is obtained for each study patient.

10.0 Ethics

10.1 Study Conduct

The study will be performed in accordance with the relevant parts of the U.S. Code of Federal Regulations (including 21 CFR parts 50, 54, 56 and 812), ICH Guidelines for Good

Clinical Practices, the European Standard ISO 14155, the Declaration of Helsinki, and any regional and/or national regulations.

10.2 Ethics Review

Before any subject can be enrolled in this study, the IRB or EC for the specific institution must review and approve this protocol.

10.3 Informed Consent

Informed consent will be required

11.0 Data Handling and Record Keeping

The Investigator must maintain detailed source documents on all subjects who are enrolled in the study. Source documents include medical records, hospital charts, clinic charts, Investigator study files, as well as the results of diagnostic tests (e.g., medication records, laboratory tests, hemodynamic studies).

The following minimum information should be entered into the subject's study and/or medical record:

- The date of enrollment and study ID
- The study protocol name and number
- Documented eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The duration of study participation
- Evidence that required evaluations were completed
- Use of any concurrent medications during study enrollment, and where infused
- Transfusions or Dialysis
- Documentation of specific device used
- Occurrence and status of any adverse events that in the Investigator's opinion are related to the OptiScanner
- All OptiScanner alarms
- The date the subject exited the study and a notation as to whether the subject completed the study or was discontinued, including the reason for discontinuation
- The insulin, dextrose, and nutrition administration delivery

12.0 Training and Case Support

12.1 Investigational Site Training

To ensure appropriate and reliable use of the OptiScanner system, OptiScan Biomedical (manufacturer) will provide didactic and hands-on training for all designated users. OptiScan Biomedical will outline an installation and continuous education program that is adequate for the hospital's SICU predefined users.

All device training will be documented in a training log that will be maintained in the site regulatory binder.

12.2 Clinical Case Technical Support

OptiScan Biomedical will assign a cross-functional team with clinical expertise to conduct training and support the SICU's clinical staff with any device related technical questions during all cases conducted in this study.

13.0 Adverse Events and Serious Adverse Events

It is anticipated that subjects in this study will experience a large number of adverse events associated with their underlying condition, which have no relationship to the study device. Therefore, for this study, Investigator will record only Adverse Events (AEs) that, in the Investigator's opinion, are possible, probably or definitely related to the study device. All such events must be recorded in the patient study and/or medical record. A description of the event, including the start date, resolution date, action taken, and the outcome should be recorded, along with the Investigator's assessment of the relationship between the event and the OptiScanner device.

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