halfpint

Bedside Reference Binder

1. Study Overview

Stress hyperglycemia, a state of abnormal metabolism with supra-normal blood glucose levels, is often seen in critically ill patients. Tight glycemic control (TGC) was originally shown to reduce morbidity and mortality in a landmark randomized clinical trial (RCT) of critically ill adult surgical patients but has come under intense scrutiny in the setting of conflicting results of recent adult trials. One pediatric RCT has been published that demonstrated survival benefit but was complicated by an unacceptably high rate of severe hypoglycemia. The Heart and Lung Failure – Pediatric Insulin Titration (HALF-PINT) trial is a multi-center, randomized clinical trial comparing two ranges of glucose control in critically ill hyperglycemic children with heart and/or lung failure. Both target ranges of glucose control fall within the range of "usual care" for critically ill children managed in pediatric intensive care units.

HALF-PINT is a multi-center randomized clinical trial that tests the efficacy of a tight glycemic control protocol to reduce mortality and ICU Length of Stay (LOS) in critically ill children. This nurse-driven protocol has been studied in over 800 children in the cardiac ICU and is safe and manageable in the critical care setting. Study teams at approximately 20 ICUs will enroll patients who meet inclusion criteria (see section 2). Upon developing hyperglycemia (BG ≥150 mg/dL), a consented patient will be randomized to either the TGC-1 group (target BG: 80-110 mg/dL) or the TGC-2 group (target BG: 150-180 mg/dL). Randomized subjects in both groups will be treated for high blood glucose from the time of consent to ICU discharge or Day 28, whichever occurs first. The duration of tight glycemic control depends upon the duration of hyperglycemia.

2. Patient Selection and Inclusion/Exclusion Criteria

Study-trained staff will recruit pediatric patients with cardiovascular and/or respiratory failure in participating ICUs according to the following criteria:

Inclusion Criteria:

(1) Cardiovascular failure (on intravenous vasopressors or inotropes, i.e., dopamine or dobutamine >5 mcg/kg/min, or any dose of epinephrine, norepinephrine, milrinone, or vasopressin if used to treat hypotension)
and/or
Respiratory failure (acute mechanical ventilation via endotracheal tube or tracheostomy anticipated for >24 hours).
(2) Age ≥2 weeks and corrected gestational age ≥42 weeks
(3) Age <18 years (has not yet had 18th birthday)

Exclusion Criteria:

(1) Expected to remain in ICU <24 hours
(2) Previously randomized in HALF-PINT
(3) Enrolled in a competing clinical trial
(4) Family/team have decided to limit or redirect from aggressive ICU technological support
(5) Chronic ventilator dependence prior to ICU admission (non-invasive ventilation and ventilation overnight or while sleeping via tracheostomy are acceptable)

(6) Type 1 or 2 diabetes
(7) Cardiac surgery within prior 2 months or during/planned for this hospitalization (cardiac procedures, such as cardiac catheterization, are acceptable)
(8) Diffuse skin disease such that placement of a subcutaneous glucose sensor would be difficult to secure
(9) Ward of the State
(10) Pregnancy

3. Study Devices

The study employs several devices to enhance safety and improve workflow. These devices are used consistently across study sites but may be new to your center. The risks and benefits of using the study devices are outlined in the study protocol and the devices have been approved by an Institutional Review Board (IRB) prior to use in subjects. Subjects and/or their legal guardians will give informed consent to allow use of these devices.

Continuous Glucose Monitor

The Continuous Glucose Monitor (CGM) consists of three components:

1. A glucose sensor (Enlite®) that is inserted subcutaneously and provides continuous measurement of glucose concentration. It is composed of a platinum-plated sensor encased in a permeable membrane that is inserted with minimal discomfort into the subcutaneous space of the patient and functions under battery power for up to six days. The Enlite is approved for clinical use in the European Union but is not FDA approved to be marketed for clinical use in the United States. It is an improved version of the sensor that is currently FDA approved and marketed for use in the United States (Sof-Sensor).
2. A transmitter (MiniLink®) that is attached to the sensor and wirelessly transmits an average sensor measurement every 5 minutes to a monitor. The MiniLink transmitter is FDA-approved and marketed for use in the United States.
3. A monitor (Paradigm Veo®) that receives and displays glucose measurement transmissions from the sensor and alarms when glucose measurements near the hypoglycemia range. The Paradigm Veo is approved for use in Europe but is not FDA approved to be marketed in the US. It is an improved version of the monitor that is currently FDA approved and marketed in the US (Guardian RT®).

The continuous glucose monitor is used in this trial to help safely achieve a target range of 80-110 mg/dL (TGC-1, 4.4-6.1 mmol/L) vs. a target range of 150-180 mg/dL (TGC-2, 8.3-10 mmol/L). It alarms if a glucose level falls below pre-set values. For the purposes of this trial the low glucose alarm limit is preset to 70 mg/dL. No high alarm is set because of the high rate of false positive alarms. Values are not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a meter blood glucose measurement may be required.

Hospital Glucose Meter

The NOVA StatStrip® Glucose Hospital Meter (Nova Biomedical Corp., Waltham, MA) is an FDA-approved blood glucose monitor system marketed for in vitro diagnostic use by health care professionals for Point-of-Care quantitative measurement of glucose in whole blood (arterial, venous, or capillary).

Blood Sampling System

The Venous Arterial blood Management Protection System, Jr. (VAMP Jr.®, Edwards Lifesciences, Irvine, CA) blood sampling system is used to reduce blood waste and the risk of iatrogenic anemia due to multiple blood glucose sampling during the study. VAMP Jr. is an FDA-approved device and has been used with great success in the SPECS trial, as well as in standard clinical care in the Children's Hospital Boston ICUs**.**

4. Procedures for Obtaining Study Samples

Blood samples will be withdrawn from pre-existing vascular access, such as arterial lines, central venous lines (CVLs), peripheral intravenous lines or peripherally inserted central catheters (PICCs) (please reference Line Placement Recommendations for VAMP Jr. Device document for limitations and assistance determining the most appropriate line for placement). BGs will be measured at the bedside using a hospital approved glucose meter (Nova StatStrip) and by each site's clinical laboratory. All other blood tests will be performed at each site's clinical laboratory or via unit-based blood gas analyzer. No new lines will be placed solely for the purposes of the study.

5. Recruitment Methods

All subjects will be cared for in the Pediatric ICU. All ICU admissions will be screened for potential eligibility in HALF-PINT at least once daily. Research Coordinators or the Site Director will be responsible for conducting these screenings. The attending physician or a delegate will be notified of any patient who meets eligibility criteria and will be asked for permission to approach the family for consent. Parents/guardians of eligible patients will be approached by a member of the study-trained staff who is not currently caring for the patient clinically and will explain the study and the essential elements of informed consent. Most patients will be intubated, mechanically ventilated and sedated so will be unable to provide assent while acutely ill. Patients will be asked to provide assent when they are cognitively capable. Clinical sites will be instructed to follow their local IRB recommendations regarding the age of assent.

More than 1,880 patients will be consented in order to study 1,880 (940 per group) who have blood glucose levels greater than 150 mg/dL.

6. Potential Risks

The primary risk of the study is hypoglycemia. The methodology of HALF-PINT centers on minimizing the risk of hypoglycemia by using CGM as an added alarm system and an insulin titration algorithm to give nurses explicit guidance about the frequency of BG checks and insulin infusion doses. This same infusion protocol resulted in a severe hypoglycemia rate of 3.2% in children randomly assigned to a BG target range of 80-110 mg/dL (unpublished data). This is the lowest severe hypoglycemia rate of any published prospective trial of TGC (adult or pediatric) and supports our methodology to limit this risk.

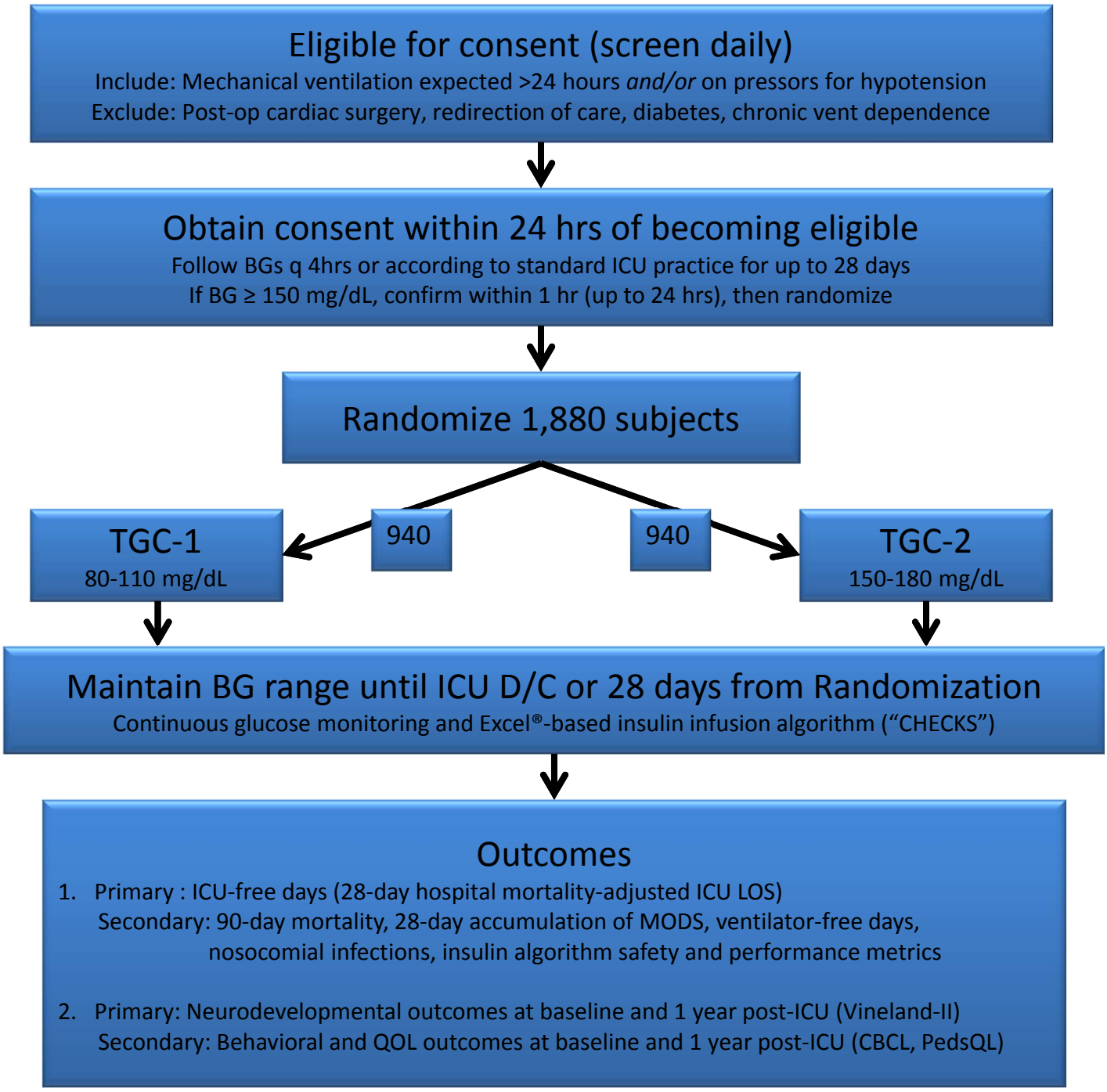
There is also a non-significant risk of hypokalemia with insulin therapy. Potassium is measured twice daily for study subjects on insulin. Hypokalemia is treated with parenteral or enteral administration of potassium per usual ICU practice. It should be noted that episodes of hypokalemia are relatively frequent in critically ill children, especially in children requiring the use of loop diuretics (e.g., furosemide, bumetanide). Potassium supplementation is a very frequent practice in the pediatric ICU.

There is no significant risk associated with the use of the CGM device. This device is composed of a platinum-plated sensor encased in a permeable membrane. The device measures glucose concentration in the interstitial fluid of the subcutaneous space every 10 seconds and reports an average of these measurements every 5 minutes. It is inserted with minimal discomfort, often into a sedated patient. There may be scant bleeding or bruising at the sensor insertion site with such devices, though no injuries, serious bleeding, or infections have been reported in the ongoing SPECS trial after >900 insertions in children less than 3 years of age.

7. Potential Benefits

Potential direct benefits of the intervention include shortened ICU and hospital lengths of stay, lower mortality rate, more ventilator-free days, and/or accumulation of fewer multiple organ dysfunctions with improved neurodevelopmental behavior. An indirect benefit to society is improved knowledge about the implementation and safety of tight glycemic control.

Half Pint Study Design



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Randomization Procedure Checklist

☐ **Subject has met randomization criteria. Patient had blood glucose result ≥ 150 mg/dL. This was repeated and confirmed to be ≥ 150mg/dL. Both results should be recorded on "Enrolled Subject Bedside Sheet".**

☐ **No change in subject eligibility status (e.g., still intubated/ventilated or on vasopressors/inotropes; no limitation of care/DNR, no new cardiac surgery, no withdrawal of consent, less than 28 days since consent was obtained).**

☐ **Patient currently has access available to infuse insulin.**

- ***If no, DO NOT randomize at this time*.**
- **If access becomes available within 24 hours of *initial* blood glucose measurement which was ≥ 150mg/dL, subject will be randomized when access is available.**
- **If access does not become available within 24 hours of initial measurement ≥ 150mg/dL, subject will be study discharged (not randomized during this ICU admission).**

☐ **Obtain Half-Pint cart.**

☐ **Plug in cart power cord. Ensure StatStrip dock and laptop cords are plugged into power strip.**

☐ **Open internet explorer on laptop. Open www.Halfpintstudy.org. Log on (upper right corner) with your generic site ID and password.**

☐ **Click on "Initialize Subject" under "Quick Links" and follow the prompts. You will need the subject-specific ID and password from the Enrolled Subject Bedside Sheet in the front of the Bedside Reference Binder.**

☐ **You will be prompted to ensure that insulin is ordered.**

INSULIN COMPATIBILITY CHART

The following drugs are known to be COMPATIBLE:

Amino acids (TPN)
Amiodarone
Ampicillin
Ampicillin-sulbactam
Aztreonam
Bumetanide
Cefazolin
Cefepime
Cefotetan
Ceftazidime
Clarithromycin
Esmolol
Gentamicin
Heparin
Hydrocortisone
Fat emulsion
Lidocaine
Magnesium Sulfate
Meperidine
Meropenem
Metoclopramide
Midazolam
Milrinone
Morphine
Nitroglycerin
Nitroprusside
Pantoprazole
Potassium Chloride
Propofol
Sodium Bicarbonate
Tobramycin
Vancomycin
Vasopressin

The following drugs are known to be INCOMPATIBLE:

Aminophylline
Cisatracurium (NI)
Chlorothiazide
Dexmedetomidine (NI)
Digoxin
Diltiazem
Dopamine
Dobutamine
Epinephrine (NI)
Labetolol
Lasix (NI)
Levofloxacin
Nafcillin
Nesiritide
Norepinephrine
Octreotide
Pancuronium (NI)
Phenobarbital
Ranitidine
Vecuronium (NI)

(NI) -No Information available

SENSOR SITE CARE

Check sensor site at least every 4 hours.

Cover with sensor overlay dressing; reinforce with a transparent dressing (e.g., Tegaderm).

If dressing requires changing, pull off with caution, starting at the transmitter end (small quarter sized gray portion).

When sensor is removed, SENSOR can be discarded. Unclick from transmitter/gray portion. To do this, push in tabs on either side and pull straight out. Do not twist or bend up and down.

The transmitter (small quarter sized gray portion) is re-attached if a new sensor is inserted, or is used for a new subject after appropriate cleaning by study staff.

***NOTE: DO NOT DISCARD THE TRANSMITTER**. Place TRANSMITTER (gray quarter sized portion) in bag with monitor. Transmitters are not disposable and are very expensive!!*

PARADIGM VEO CONTINUOUS GLUCOSE MONITOR:

INITIALIZATION and TURNING OFF

1. INTIAL SET-UP OF MONITOR

- Press **ACT**, scroll down to Sensor – press **ACT** again
- "Edit settings" press **ACT**
- "Sensor" press **ACT**
- Scroll down to "On" press **ACT**
- Press **ESC**
- Scroll up to "Link to Sensor" press **ACT**
- "New Sensor" press **ACT** then press **ACT** again
- Press **ESC** to go back to main graph screen (press 3 times)
- Monitor will either display "**WARM UP**" or:

<u>If monitor does NOT display "WARM UP"</u> (empty antenna is not displayed on the screen)

- Go back to "Sensor"," Sensor Start", "New Sensor". Press **ACT**, then **ACT** again.
- Screen should display "Sensor Ready 2 Hrs"
- Press **ACT** and check if empty glass appears
- Press **ESC** to go back to graph screen (press 3 times)

2. NEXT STEP- <u>'METER BG NOW'</u>- CALIBRATING THE MONITOR

After a sensor initiation, or "warm up" period of approximately two hours, the monitor will beep and display "**METER BG NOW**." You can now enter the glucometer value you obtained.

- Silence the alert (Press ESC, then ACT)
- Press **ACT**, scroll down to "Sensor", Press **ACT**
- "Calibrate" press ACT
- Use up and down arrow buttons to enter the BG. Press **ACT**
- Press **ESC** to go back to main graph screen (press 2 times)
- Monitor should display "METER BG"

It will take approximately 10-15 minutes for monitor to display this new BG value

3. REMOVING SENSOR: VERY IMPORTANT TO TURN OFF SENSOR VIA MONITOR

When removing a sensor prior to the 6 day expiration (i.e., the subject has been study discharged and will no longer require glucose monitoring), it is very important to "end" the sensor from the monitor prior to physically removing the sensor. From the home screen:

- Press **ACT**
- Scroll to "Sensor", Press **ACT**
- Go to "Turn off Sensor", Press **ACT**
- When prompted "Do you want to turn off sensor?" Press **ACT**

Note: BG Alarm Settings: LOW ALARM: 70 mg/dL; HIGH ALARM: OFF

PARADIGM VEO CONTINUOUS GLUCOSE MONITOR: *CALIBRATION*

1. Check a glucometer glucose just prior to calibrating the monitor
2. Press ACT
3. **Sensor** → press ACT
4. **Enter Meter BG** → press ACT
5. Use the up and down arrow buttons to adjust the BG value until it matches the glucometer glucose value
6. Press **ACT**
7. Press **ESC** (back arrow) until you return to the main screen (with graph display)
8. Check the monitor in 10-15 minutes for the **NEW** re-calibrated BG value to be displayed

NOTE: For optimal sensor performance, BGs for calibration should be entered when glucose is are stable. Check for rapid change arrows before checking the glucometer glucose, and wait 15 or more minutes if arrows are present on the monitor.

TO VERIFY WHEN LAST CALIBRATED

1. Press **ACT**
2. **Sensor** → Press **ACT**
3. Press down arrow to "**Sensor Update Hist**." Press ACT
   Note last calibration date/time

PARADIGM VEO CONTINUOUS GLUCOSE MONITOR: *COMMON ALARMS*

Remember to SCROLL DOWN using the down arrow to read the entire message on the screen.

"METER BG NOW"
Scroll down to read the entire message by using the down arrow on the side of the screen. Silence the alarm ("ESC" then "ACT").
This alarm means a new calibration is needed immediately. Calibrate the monitor now with a new blood glucose (BG) (glucometer) value.

"LOW GLUCOSE or LOW SG"
Scroll down to read the entire message by using the down arrow on the side of the screen. Silence the alarm ("ESC" then 'ACT").
Check a BG immediately and enter into the CHECKS algorithm. Utilize *Early Glucose Sensor Entry* as needed.

"LOW PREDICTED"
Scroll down to read the entire message by using the down arrow on the side of the screen. Silence the alarm ("ESC" then 'ACT").
This means sensor glucose may reach or go below the low limit of 70 within the next 15 minutes.
Check a BG immediately and enter into the CHECKS algorithm. Utilize *Early Glucose Sensor Entry* as needed.

"CAL ERROR"
Scroll down to read the entire message by using the down arrow on the side of the screen. Silence the alarm ("ESC" then 'ACT").
This means an error occurred when entering a new meter BG measurement to calibrate the system.
Some possible causes are:

- An incorrect blood glucose number was entered from the meter (glucometer) into the Paradigm Veo monitor. This causes the monitor to see a big difference between the sensor BG and the meter BG.
- A BG was entered when the glucose was rising or falling rapidly.
- The glucose sensor is no longer reading the sensor glucose (SG) correctly.

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If you receive a Cal Error, enter a new BG meter reading for calibration *if the glucose is stable*. Wait 15-30 minutes if the BG was entered at a time of rapid glucose change. If you receive a Cal Error on your second calibration, a CHANGE SENSOR alert will occur.

"CHANGE SENSOR"
Scroll down to read the entire message by using the down arrow on the side of the screen. Silence the alarm ("ESC" then "ACT").
This means the system has detected a sensor that isn't working correctly. If this resulted after 2 Cal Errors in a row, replace the sensor.

“SENSOR END”
Scroll down to read the entire message by using the down arrow on the side of the screen. Silence the alarm (“ESC” then ‘ACT”). Enlite sensors require replacement after six days.

“WEAK SIGNAL”
Scroll down to read the entire message by using the down arrow on the side of the screen. Silence the alarm (“ESC” then “ACT”).
Move the glucose monitor closer to the transmitter. If monitor does not pick up a signal in 5 minutes, go into the Sensor Menu, scroll to “Sensor Start”, “ACT”, then “Find Lost Sensor”

“LOST SENSOR”
Scroll down to read the entire message by using the down arrow on the side of the screen. Silence the alarm (“ESC” then “ACT”).
This means the monitor has not received a signal from the MiniLink transmitter for more than 40 minutes. Ensure that the MiniLink transmitter and the sensor are connected (push them together, but do not disconnect and re-connect them). Place the monitor closer to the transmitter. If this alert occurs *within 20 minutes* of starting a new sensor, go to Link to Sensor > New Sensor and press ACT. If this alert occurs *more than 20 minutes* after starting a new sensor, go to Link to Sensor > Reconnect Old Sensor and press ACT. If the sensor icon (see below) did not convert from not communicating to communicating, disconnect the transmitter from the sensor and verify the transmitter ID on the back of the transmitter is entered correctly in the monitor. Then re-connect, and activate Find Lost Sensor: Main menu>Sensor>Link to sensor >Find lost sensor.

 **Sensor icon indicating no communication**

 **Sensor icon indicates communication**

If there are any alarms or messages that are unclear, refer to the User Manual or contact study staff. Alarm Information is also available on www.medtronicdiabetes.net/support

PARADIGM VEO CONTINUOUS GLUCOSE MONITOR:
CHANGING MONITOR BATTERY

Changing the battery can be done at any time. Data will not be lost. *However, make sure that you have the replacement AAA battery with you before taking the old battery out*. If you leave a battery out for longer than 5 minutes, you may receive a BATT OUT LIMIT alarm when installing the new battery. This requires re-setting the time and date, and checking the settings (see User Manual or consult study staff).

The battery meter at the top of the monitor shows an estimate of how much power remains.

Watch the monitor or display until it shows "LOW BATTERY" alarm.

To Change The Battery:

1. Unscrew the top of battery casing with a coin

2. Remove old battery and replace with 1 AAA battery

3. Sensor will show "WARM UP". The sensor icon indicating the monitor and transmitter are communicating should display within a few minutes.

REPLACING THE ENLITE SENSOR

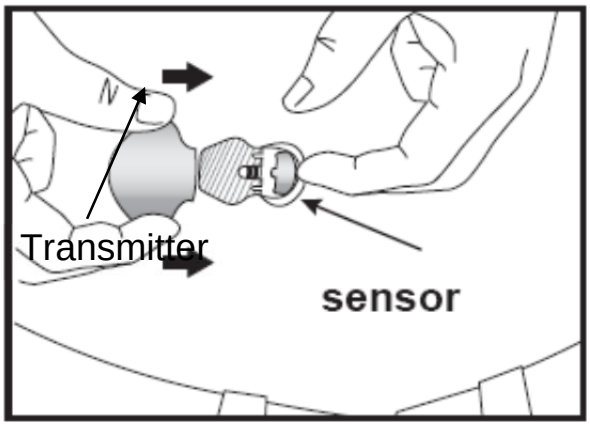
1. Ensure the sensor and packaging is intact. Check the expiration date on label.

2. Review insertion video as needed. You must be trained to insert a sensor.

3. Gather supplies:
   - Sensor with adhesive overlay. Additional transparent dressing (e.g., Tegaderm).
   - Transmitter (OK to reuse the transmitter used with the previous sensor)
   - Monitor (OK to reuse the monitor used with the previous sensor)
   - Standard skin disinfectant for your institution
   - Gloves
   - Serter (Grey insertion device)

4. Click on "Enter Sensor Information" in CHECKS. Enter required information.

5. Insert sensor per instructions using new site. Secure with adhesive overlay and transparent dressing.



6. Wait 5 minutes before attaching the transmitter.

7. Attach transmitter – slide the transmitter onto the sensor and push firmly until the notches on both sides "click" into the sensor (see figure).

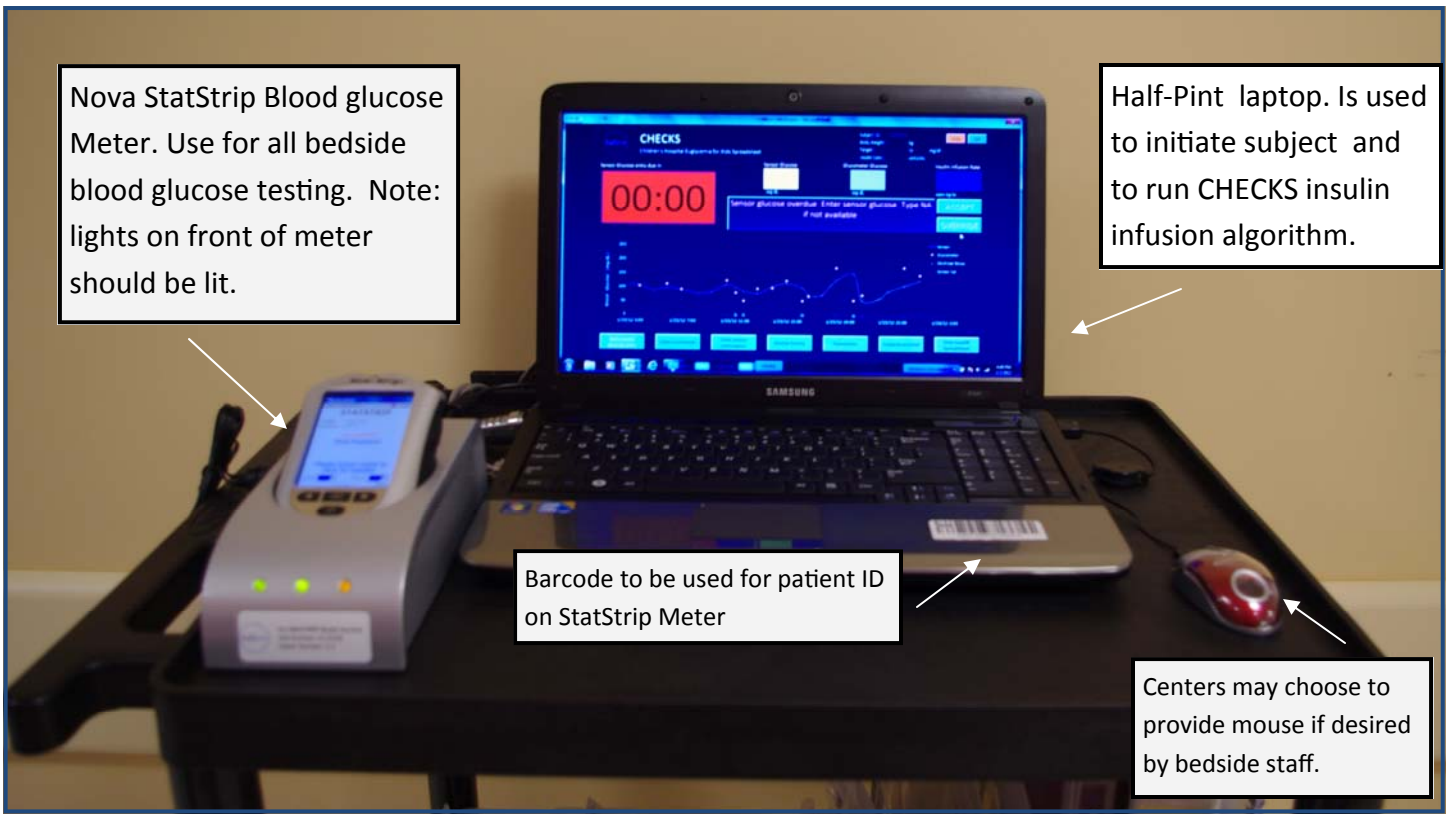
8. A GREEN LIGHT on the transmitter should flash within 20 seconds. If the transmitter does not flash, detach the transmitter, re-connect and watch for flash. If no flash is seen, refer to the MiniLink Transmitter User Guide.

9. Place transparent dressing over transmitter.

10. Activate the Paradigm Veo Monitor:
    - Go to "*Sensor*" – press "**ACT**"
    - Scroll to *"Link to Sensor"* – press "**ACT**"
    - Scroll to "*New Sensor*" – press "**ACT**"
    - Press "**ESC**" until you reach to home screen. Screen will display "Sensor Ready in 2 hours" – press "**ACT**"
    - Screen will display "Warm Up"
    - Check for "communication" (dark) antenna in approximately 10 minutes

11. The monitor will now take 2 hours to warm up. Check the monitor in 2 hours. Around this time the monitor will alert "METER BG NOW". You now need to calibrate the sensor with a blood glucose measurement (BG) (refer to the Calibration sheet in binder).

Study Cart Set-Up



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